XII Międzynarodowa Konferencja
12th International Conference

Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku

Complex treatment of plasma cell dyscrasias in 2024

6–7 września 2024 | September 6–7, 2024
Uniwersytet Jagielloński Collegium Medicum | Jagiellonian University Medical College
Kraków, św. Anny 12

Organizatorzy składają serdeczne podziękowania Szanownemu Panu Włodzimierzowi Skleniarzowi oraz Drukarni Skleniarz za ogromną pomoc polegającą na przejęciu kosztów druku folderu.

drukarnia SKLENIARZ

Dear Colleagues,

I would like to welcome you to the 12th International Conference „Complex treatment of plasma cell dyscrasias in 2024" that will be held in old capital of Poland on September 6-7, 2024. This is a traditional scientific meeting organized by the Center of Plasma Cell Dyscrasias Department of Haematology Jagiellonian University, Myeloma Treatment Foundation Centre and Cracow Branch of the Polish Society of Hematology and Transfusion Medicine. Program of the International Conference focuses on interdisciplinary and multimodal therapy of patients with multiple Myeloma and amyloidosis.

Actually invitation to Poland has been accepted by outstanding specialists from the United States, Israel, United Kingdom, Hungary, France and Poland. I am delighted to host such widely recognized researchers in Kraków, the location of the oldest hematological centre in Poland. It is worth noting that we will be hosting the 2004 Nobel Prize winner in chemistry, prof. Aaron Ciechanover, who has Polish roots.

In addition to the science I hope that international guests will have an opportunity to enjoy the beauty of spectacular city of Kraków – place in the UNESCO list for last 45 years.

I hope that this meeting will contribute to the development of modern treatment of plasma cell dyscrasias in Poland.

Sincerely

Professor Artur Jurczyszyn MD, PhD
Plasma Cell Dyscrasias Center Department of Hematology
Jagiellonian University, Faculty of Medicine, Kraków, Poland

6 września 2024 (piątek)	
19.00	**Powitalna kolacja na Kopcu Kościuszki** (https://weselenakopcu.pl) Wyjazd z Hotelu ESTERA o godz. 18.00 (https://hotelestera.pl/en/hotel/meet-us)
7 września 2024 (sobota)	
12.00–12.10	OTWARCIE KONFERENCJI **prof. TOMASZ GRODZICKI** i **prof. ARTUR JURCZYSZYN** Uniwersytet Jagielloński, Kraków, Polska
SESJA I	Przewodniczący: **prof. Wiesław W. Jędrzejczak, prof. Lidia Usnarska-Zubkiewicz, prof. Piotr Rzepecki**
12.10–12.30	**prof. SURBHI SIDANA** Stanford University, USA **"CAR-T cell therapy in multiple myeloma: current limitations and potential strategies"**
12.40–13.00	**prof. VAISHALI SANCHOROWALA** Boston Medical Center, USA **"Advances in systemic AL amyloidosis"**
13.10–13.30	**prof. AARON CIECHANOVER** Technion-Israel Institute of Technology, Faculty of Medicine, Haifa, Izrael **"The Ubiquitine Proteolitic System: From the Bench to the Bedside"**
13.40–14.00	**prof. DAVID H. VESOLE** Myeloma Division, Myeloma Research John Theurer Cancer Center, Hackensack Meridian School of Medicine, Georgetown University, USA **"T-cell redirecting antibody in patients with relapsed or refractory multiple myeloma"**
14.15–15.00	**Przerwa kawowa**

Sponsorzy:

Johnson & Johnson · BIOKOM diagnostyka · Pfizer · GSK · 70 lat mpec kraków

SESJA II	Przewodniczący: **prof. Aleksander B. Skotnicki, prof. Bogusław Machaliński, prof. Jacek Roliński**
15.00–15.20	**prof. RAMON GARCIA-SANZ** Departament of Hematology, University Hospital of Salamanca (HUSA/IBSAL), CIBERONC, CIC-IBMCC (USAL-CSIC), Salamanka, Hiszpania **"Minimal residual disease in multiple myeloma: past, present and future"**
15.30–15.50	**prof. ELENA ZAMAGNI** Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bolonia, Włochy **"How I treat high-risk multiple myeloma"**
16.00–16.20	**prof. GABOR MIKALA** National Institute for Hematology and Infectious Disease, Budapeszt, Węgry **"The Importance of metabolism in long-term myeloma care"**
16.30–16.50	**prof. ARTUR JURCZYSZYN** Uniwersytet Jagielloński, Kraków, Polska **"Supportive care in multiple myeloma in 2024"**
17.00–17.20	**prof. ARTUR JURCZYSZYN** Uniwersytet Jagielloński, Kraków, Polska **„Ludwik Hirszfeld – polski kandydat do Nagrody Nobla"**
19.00	**Kolacja w Hotelu ESTERA** Sponsorowana przez Fundację Centrum Leczenia Szpiczaka (https://hotelestera.pl/en/hotel/meet-us)

Organizatorzy: Fundacja Centrum Leczenia Szpiczaka, Ośrodek Leczenia Dyskrazji Plazmocytowych Katedry Hematologii UJ CM, Jacek Legendziewicz JORDAN Group

Partnerzy:

Kraków

UNIWERSYTET JAGIELLOŃSKI W KRAKOWIE

UNIWERSYTET JAGIELLOŃSKI COLLEGIUM MEDICUM

Polska Grupa Szpiczakowa

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September 6, 2024 (Friday)	
19.00	**Welcome Dinner at Kopiec Kościuszki** (https://weselenakopcu.pl) Departure from ESTERA Hotel at 6.00 p.m. (https://hotelestera.pl/en/hotel/meet-us)
September 7, 2024 (Saturday)	
12.00–12.10	OPENING THE CONFERENCE **prof. TOMASZ GRODZICKI and prof. ARTUR JURCZYSZYN** Jagiellonian University, Kraków, Poland
SESSION I	Chairman: **prof. Wiesław W. Jędrzejczak, prof. Lidia Usnarska-Zubkiewicz, prof. Piotr Rzepecki**
12.10–12.30	**prof. SURBHI SIDANA** Stanford University, USA **"CAR-T cell therapy in multiple myeloma: current limitations and potential strategies"**
12.40–13.00	**prof. VAISHALI SANCHOROWALA** Boston Medical Center, USA **"Advances in systemic AL amyloidosis"**
13.10–13.30	**prof. AARON CIECHANOVER** Technion-Israel Institute of Technology, Faculty of Medicine, Haifa, Israel **"The Ubiquitine Proteolitic System: From the Bench to the Bedside"**
13.40–14.00	**prof. DAVID H. VESOLE** Myeloma Division, Myeloma Research John Theurer Cancer Center, Hackensack Meridian School of Medicine, Georgetown University, USA **"T-cell redirecting antibody in patients with relapsed or refractory multiple myeloma"**
14.15–15.00	**Coffe break**

Sponsors:

Johnson & Johnson · BIOKOM diagnostyka · Pfizer · GSK · 70 lat mpec kraków

SESSION II	Chairmen: **prof. Aleksander B. Skotnicki, prof. Bogusław Machaliński, prof. Jacek Roliński**
15.00–15.20	**prof. RAMON GARCIA-SANZ** Departament of Hematology, University Hospital of Salamanca (HUSA/IBSAL), CIBERONC, CIC-IBMCC (USAL-CSIC), Salamanca, Spain **"Minimal residual disease in multiple myeloma: past, present and future"**
15.30–15.50	**prof. ELENA ZAMAGNI** Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy **"How I treat high-risk multiple myeloma"**
16.00–16.20	**prof. GABOR MIKALA** National Institute for Hematology and Infectious Disease, Budapest, Hungary **"The Importance of metabolism in long-term myeloma care"**
16.30–16.50	**prof. ARTUR JURCZYSZYN** Jagiellonian University, Kraków, Poland **"Supportive care in multiple myeloma in 2024"**
17.00–17.20	**prof. ARTUR JURCZYSZYN** Jagiellonian University, Kraków, Poland **„Ludwik Hirszfeld – polski kandydat do Nagrody Nobla"**
19.00	**Dinner at ESTERA Hotel** Sponsored by Fundacja Centrum Leczenia Szpiczaka (https://hotelestera.pl/en/hotel/meet-us)

Organizers: Myeloma Treatment Foundation Centre, Center of Plasma Cell Dyscrasias Department of Haematology Jagiellonian University, Jacek Legendziewicz JORDAN Group

Partners:

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XII International Conference "Complex Treatment of Plasma Cell Dyscrasias in 2024"

This up-to-date and important conference has been organized by Professor Artur Jurczyszyn of the Jagiellonian University Medical College in Krakow, Poland.

There will be a Welcome Dinner on Friday, September 6, 2024, at 7:00 p.m. at Kopiec Kościuszki.

Professors Tomasz Grodzicki and Artur Jurczyszyn will open the conference at 12:00 p.m. on Saturday, September 7, 2024. The chairmen of Session I consist of Professors Wiesław W. Jędrzejczak, Lidia Usnarska-Zubkiewicz, and Piotr Rzepecki.

The first speaker is Professor Surbhi Sidana, Stanford University, USA, on "CAR-T Cell Therapy in Multiple Myeloma: Current Limitations and Potential Strategies."

Professor Vaishali Sanchorowala, Boston Medical Center, USA, will follow with a presentation on "Advances in Systemic AL Amyloidosis."

Professor Gabor Mikala, National Institute for Hematology and Infectious Disease, Hungary, will present an address entitled "The Importance of Metabolism in Long--Term Myeloma Care."

Professor David H. Vesole, Hackensack University Medical Center, New Jersey Medical School, Rutgers University, New Jersey, USA, with a presentation "T-cell Re-directing Antibody in Patients with Relapsed or Refractory Multiple Myeloma."

Following the coffee break, the chairmen of Session II are Professors Aleksander B. Skotnicki, Boguslaw Machalinski, and Jacek Roliński.

The first presentation of Session II is Professor Ramon Garcia-Sanz, Department of Hematology, University Hospital of Salamanca, Salamanca, Spain, who will speak on "Minimal Residual Disease in Multiple Myeloma: Past, Present and Future."

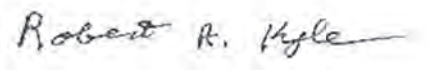
This will be followed by a presentation by Professor Elena Zamagni, Universita di Bologna, Bologna, Italy, "How I Treat High-Risk Multiple Myeloma."

The afternoon session will close with "Supportive Care in Multiple Myeloma in 2024" by the host, Professor Artur Jurczyszyn.

Of note, there will be a 10-minute discussion after each lecture.

The sessions will be followed by a dinner at Restaurant Hotel Estera at 6:00 p.m.

This conference will update the attendees on CAR-T Cell Therapy in Multiple Myeloma: Current Limitations and Potential Strategies, Advances in Systemic AL Amyloidosis, The Importance of Metabolism in Long-Term Myeloma Care, T-cell Redirecting Antibody in Patients with Relapsed or Refractory Multiple Myeloma, Minimal Residual Disease in Multiple Myeloma: Past, Present and Future, How I Treat High-Risk Multiple Myeloma, and Supportive Care in Multiple Myeloma in 2024.



Robert A. Kyle, MD, MACP
Professor of Medicine
Laboratory Medicine & Pathology
Mayo Clinic
Rochester, Minnesota

Kraków

HONORARY PATRONAGE
MAYOR OF KRAKÓW
ALEKSANDER MISZALSKI

Aleksander Miszalski
Prezydent Miasta Krakowa

obejmuje patronatem honorowym

12. Międzynarodową Konferencję „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku”

organizowaną w dniach 6-7 września 2024 r.

Z serdecznymi życzeniami powodzenia w realizacji przedsięwzięcia!

Kraków, 22 maja 2024 r.

KP-03.0054.192.2024

Patronat Honorowy
Rektor Uniwersytetu Jagiellońskiego
prof. dr hab. Piotr Jedynak

UNIWERSYTET JAGIELLOŃSKI
W KRAKOWIE

Prorektor UJ
ds. polityki kadrowej i finansowej

Kraków, dnia 9 maja 2024 roku

51.730.1.2024

Szanowny Pan

Prof. dr hab. n. med. Artur Jurczyszyn

Szanowny Panie Profesorze,

w odpowiedzi na pismo z dnia 27 kwietnia 2024 r. serdecznie dziękuję za zaproszenie Uniwersytetu Jagiellońskiego do objęcia honorowym patronatem 12-tej Międzynarodowej Konferencji „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku".

Jednocześnie pragnę przekazać, że Uniwersytet przychylił się do Państwa prośby i obejmie patronatem Państwa konferencję. Jestem przekonany, że obecność na Konferencji wielu wybitnych międzynarodowych ekspertów zaowocuje wysokim poziomem merytorycznym dyskusji oraz wymianą doświadczeń naukowych, co przyczyni się do dalszego rozwoju i postępu polskiej hematologii.

Z wyrazami szacunku,

Prorektor UJ
ds. polityki kadrowej i finansowej

Prof. dr hab. Piotr Jedynak

Pl.31-007 Kraków, ul. Gołębia 24, tel. +48(12)663 11 14, +48(12)663 10 15, fax +48(12)421 93 05
e-mail: prorektor.kadry@uj.edu.pl

Patronat Honorowy
Prorektor UJ ds. Collegium Medicum
Prof. dr hab. med. Tomasz Grodzicki

UNIWERSYTET JAGIELLOŃSKI
COLLEGIUM MEDICUM
W KRAKOWIE

Prorektor UJ ds. Collegium Medicum

Kraków, dnia 11 marca 2024 r.
115.065.16.2024

Pan
Prof. dr hab. Artur Jurczyszyn
Katedra Hematologii UJ CM

Szanowny Panie Profesorze,

w odpowiedzi na pismo z dnia 28 lutego br. uprzejmie informuję, iż wyrażam zgodę na objęcie **Patronatem Honorowym 12. Jubileuszowej Międzynarodowej Konferencji „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku", która odbędzie się w dniach 6-7 września br. w Krakowie.**
Pragnę Państwu serdecznie pogratulować cennej inicjatywy, jaką jest organizacja tego wydarzenia i z ogromną przyjemnością przyjmuję zaproszenie do objęcia go patronatem.

Z wyrazami szacunku,

Prof. dr hab. med. Tomasz Grodzicki

Pl. 31-008 Kraków, ul. św. Anny 12, tel. +48 12 422 69 22, fax +48 12 422 25 78
e-mail: prorektor.cm@uj.edu.pl, prorektor@cm-uj.krakow.pl, www.cm-uj.krakow.pl

Patronat Honorowy
Konsultant Krajowy w dziedzinie hematologii
Prof. dr hab. Ewa Lech-Marańda

Konsultant Krajowy w dziedzinie hematologii

Prof. dr hab. n. med. Ewa Lech-Marańda

Adres: Instytut Hematologii i Transfuzjologii
Ul. Indiry Gandhi 14, 02-776 Warszawa
Telefon: 22 3496176; Fax: 22 3496178; E-mail: emaranda@ihit.waw.pl

Warszawa, 5 lipca 2024 r.

Szpital [illegible] w Krakowie
[illegible] 30-688 Kraków
KANCELARIA
Wpłynęło dnia: 09. 07. 2024
Nr 17332

KKH.54.2024

Szanowny Pan

Prof. dr hab. n. med. Artur Jurczyszyn

Kierownik Ośrodka Leczenia Dyskrazji

Plazmocytowych Katedry Hematologii UJCM

Szanowny Panie Profesorze,

W odpowiedzi na pismo dotyczące objęcia patronatem honorowym 12-ej Międzynarodowej Konferencji: „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku" uprzejmie informuję, że z przyjemnością podejmę się tej funkcji.

Państwa konferencja na stałe wpisała się w kalendarz wydarzeń hematologicznych, a jej międzynarodowy charakter to doskonała możliwość wymiany doświadczeń oraz merytorycznych dyskusji.

Z poważaniem,

KONSULTANT KRAJOWY
w dziedzinie hematologii
Prof. dr hab. n. med. Ewa Lech-Marańda

OKHeMa

Patronat Honorowy
Prezes Towarzystwa Miłośników Historii
i Zabytków Krakowa prof. dr Jacek Purchla

TOWARZYSTWO MIŁOŚNIKÓW HISTORII I ZABYTKÓW KRAKOWA

ul. Św. Jana 12
31-018 Kraków
tel. 12 421 27 83

biuro@tmhzk.krakow.pl
www.tmhzk.krakow.pl

DIP.063.1.2024

Kraków, dn. 9 maja 2024 roku

Szanowny Pan
Prof. dr n. med. Artur Jurczyszyn
Collegium Medicum Uniwersytetu Jagiellońskiego

Szanowny Panie Profesorze,

Z zainteresowaniem zapoznałem się z treścią pisma od Pana Profesora z dnia 27 kwietnia 2024 roku. Cieszę się, że Alma Mater Pana Profesora – Collegium Medicum Uniwersytetu Jagiellońskiego podejmuje tak ważne inicjatywy, do których z pewnością zalicza się organizacja międzynarodowej konferencji pn. „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku" w dniach 6-7 września 2024 roku. Moja radość jest podwójna, bowiem organizację tego wydarzenia odczytuję również jako przejaw szerokiej działalności Pana Profesora, który dał się poznać nie tylko jako wybitny medyk, ale również jako członek Towarzystwa Miłośników Historii i Zabytków Krakowa aktywnie zaangażowany w działalność popularyzatorską dotyczącą historii Krakowa. Chętnie obejmę więc konferencję Honorowym Patronatem Towarzystwa.

Ufając, że konferencja pn. „Kompleksowa terapia dyskrazji plazmocytowych w 2024 roku" zainteresuje rzesze naukowców, będzie stanowić pole wymiany doświadczeń oraz przyczyni się do dalszego rozwoju terapii, łączę pozdrowienia i najlepsze myśli.

Prof. dr Jacek Purchla
Prezes Towarzystwa Miłośników Historii i Zabytków Krakowa

UNIWERSYTET JAGIELLOŃSKI
W KRAKOWIE

75.0200.27.2021

Zarządzenie nr 24
Rektora Uniwersytetu Jagiellońskiego
z dnia 17 marca 2021 roku

w sprawie: utworzenia *Ośrodka Leczenia Dyskrazji Plazmocytowych* w Katedrze Hematologii Wydziału Lekarskiego UJ CM

Na podstawie § 82 w związku z § 204 ust. 1 Statutu Uniwersytetu Jagiellońskiego zarządzam, co następuje:

§ 1

W strukturze organizacyjnej Katedry Hematologii Wydziału Lekarskiego UJ CM tworzy się *Ośrodek Leczenia Dyskrazji Plazmocytowych.*

§ 2

Szczegółowy zakres działalności Ośrodka Leczenia Dyskrazji Plazmocytowych określa regulamin, stanowiący załącznik do zarządzenia.

§ 3

Wykonanie zarządzenia powierzam Dziekanowi Wydziału Lekarskiego UJ CM.

§ 4

W zakresie uregulowanym niniejszym zarządzeniem ulega zmianie załącznik nr 4 do Regulaminu organizacyjnego Uniwersytetu Jagiellońskiego, wprowadzonego zarządzeniem nr 15 Rektora Uniwersytetu Jagiellońskiego z 28 lutego 2008 roku (z późn. zm.).

§ 5

Zarządzenie wchodzi w życie z dniem 1 kwietnia 2021 roku.

Rektor

Prof. dr hab. Jacek Popiel

Załącznik do zarządzenia nr 24 Rektora UJ z dnia 17 marca 2021 r.

Regulamin Ośrodka Leczenia Dyskrazji Plazmocytowych

§ 1

1. Ośrodek Leczenia Dyskrazji Plazmocytowych, zwany dalej „Ośrodkiem", jest jednostką organizacyjną Katedry Hematologii Wydziału Lekarskiego Uniwersytetu Jagiellońskiego – Collegium Medicum.
2. Ośrodek w kontaktach zagranicznych może posługiwać się nazwą w języku angielskim: „Plasma Cell Dyscrasia Centre".

§ 2

Celem działalności Ośrodka jest:
1) prowadzenie badań w zakresie diagnostyki, terapii i organizacji opieki nad pacjentami ze szpiczakiem plazmocytowym, amyloidozą, zespołem POEMS i innymi dyskrazjami plazmocytowymi;
2) interdyscyplinarna współpraca z ośrodkami prowadzącymi działalność w zakresie: kardiologii, transplantologii, nefrologii, ortopedii, neurochirurgii, fizjoterapii, radioterapii i innymi, prowadzącymi działalność w tym zakresie;
3) rozwijanie badawczej współpracy krajowej i międzynarodowej;
4) prowadzenie podyplomowych szkoleń krajowych i międzynarodowych;
5) organizowanie spotkań szkoleniowych;
6) aplikowanie o granty umożliwiające realizację ww. zadań;
7) współpraca z przemysłem w zakresie zaawansowanych metod diagnostyki i terapii dyskrazji plazmocytowych.

§ 3

1. Kierownikiem Ośrodka może być nauczyciel akademicki posiadający co najmniej stopień doktora habilitowanego, zatrudniony na Wydziale Lekarskim UJ CM, z zastrzeżeniem § 111 Statutu Uniwersytetu Jagiellońskiego, dla którego Uniwersytet Jagielloński jest podstawowym miejscem pracy, posiadający merytoryczne przygotowanie w zakresie hematologii.
2. Kierownika Ośrodka powołuje i odwołuje, z upoważnienia Rektora UJ, Prorektor ds. Collegium Medicum na wniosek Dziekana Wydziału Lekarskiego UJ CM, zaopiniowany przez Kierownika Katedry Hematologii Wydziału Lekarskiego UJ CM.

§ 4

1. Działalność Ośrodka finansowana jest z budżetu Wydziału Lekarskiego UJ CM.
2. Działalność Ośrodka może być finansowana również ze środków pochodzących ze źródeł zewnętrznych, a w szczególności z:
   1) grantów pozyskiwanych od grantodawców polskich i zagranicznych;
   2) środków pozyskiwanych w ramach współpracy z podmiotami zewnętrznymi;
   3) dobrowolnych dotacji podmiotów trzecich na rzecz Ośrodka;
   4) innych źródeł związanych z działalnością Ośrodka (np. fundacje, stowarzyszenia).

Rektor

Prof. dr hab. Jacek Popiel

Dr Surbhi Sidana is an Assistant Professor of Medicine at Stanford University and specializes in the treatment of multiple myeloma and related disorders. Dr Sidana leads the myeloma CAR-T/immunotherapy program at Stanford and the myeloma disease focused group in the BMT and Cell Therapy Division. She has an active clinical research portfolio and leads clinical trials, especially those focusing on CAR-T cell therapy, immunotherapies such as bispecific antibodies and transplantation in myeloma. Prior to joining Stanford University, Dr Sidana completed her Hematology/Oncology fellowship and additional training in plasma cell disorders at Mayo Clinic, Rochester, MN.

Dr Sidana has published over 80 manuscripts. She is an active member of the International Myeloma Working Group and Co-chairs the Quality-of-Life Committee. She is also the Vice-Chair of the American Society of Hematology Committee on Communications.

Stanford MEDICINE

CAR-T Therapy for MM: Current Data and Future Directions

Surbhi Sidana, MD
Associate Professor of Medicine
Stanford University

Conflict of Interest Disclosures

- Research Funding: Magenta Therapeutics, BMS, Allogene, Janssen, Novartis
- Consultancy: Magenta Therapeutics, BMS, Janssen, Sanofi, Oncopeptides, Takeda, Regeneron, Abbvie, Pfizer, BiolineRx, Legend, Kite/Arcellx

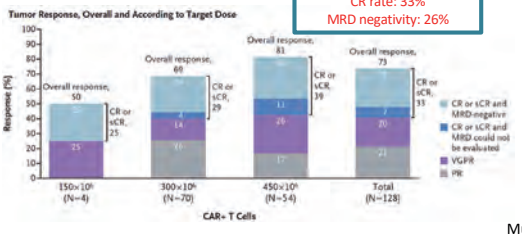
Objectives:

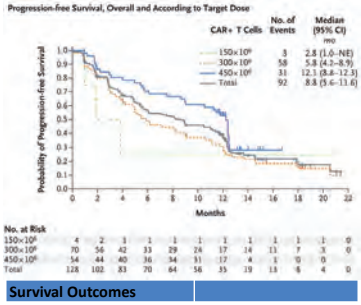
- Review data from clinical trials and real-world on safety and efficacy of BCMA directed CAR-T therapy in relapsed MM
- Review unmet needs in CAR-T therapy for MM
  - Management of unusual and late toxicities
  - Ideal sequencing of immunotherapies
  - Understanding mechanisms of relapse
- Review newer CAR-T targets in development

Idecabtagene Vicleucel (Ide-cel):
FDA Approved March 2021 in US

Baseline Characteristics	N=128
Median age	61 years
Target dose	300-450 million
Median Prior Lines	6
Triple Class Refractory	84%
Penta Refractory	26%
Bridging Therapy	88%

Overall response rate: 73%
CR rate: 33%
MRD negativity: 26%





Survival Outcomes	
Median PFS	8.8 months
Median PFS in CR	20.2 months
Median OS	19.4 months

Munshi et al. NEJM 2021;384(8):705-716

Earlier Line Use of CAR-T: Ide-cel KarMMa 3

MM patients with 2-4 prior lines of therapy

Randomized 2:1

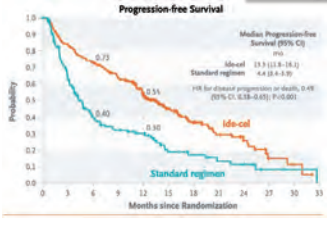
Ide-cel (N=254)

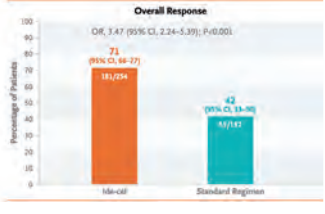
SOC treatment (5 options) (N=132)

Follow-up

Primary Endpoint: Progression Free Survival

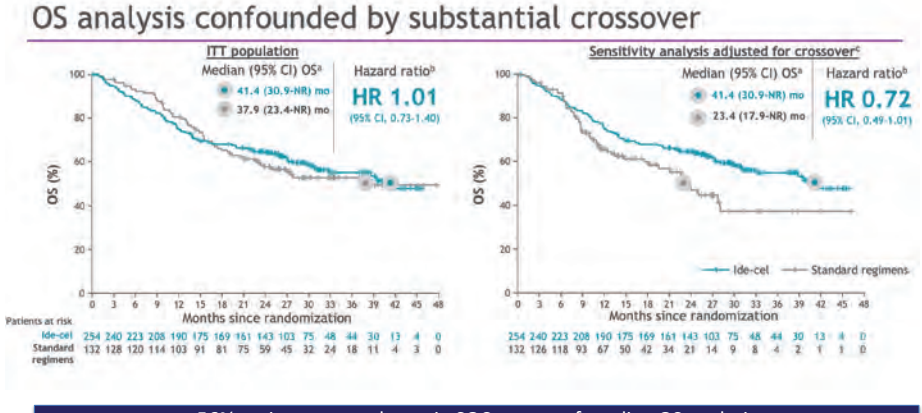
Cross-over allowed at progression in SOC arm





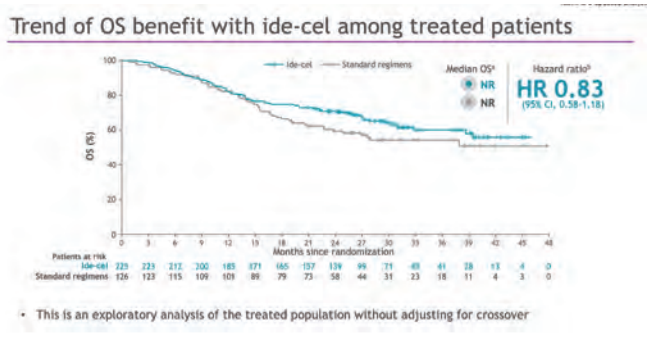
Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

OS analysis confounded by substantial crossover



56% patients crossed over in SOC arm, confounding OS analysis
Pre-specified analysis adjusted for cross-over showed improved OS with ide-cel vs SOC

Rodriguez Otero et al. ASH 2023 Abstract #1028



KarMMa-3 allowed cross-over which confounds OS interpretation
56% patients crossed over in SOC arm
Pre-specified analysis adjusted for cross-over showed improved OS with ide-cel vs SOC
Early deaths in ide-cel in patients who did not receive ide-cel- highlights need for effective bridging

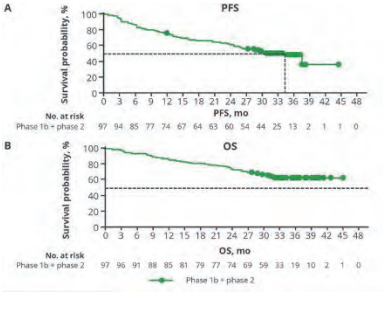
Rodriguez Otero et al. ASH 2023 Abstract #1028

Ciltacabtagene Autoleucel (Cilta-cel)

FDA Approved March 2022 in US

Baseline Features	
N	97
Target CAR-T Dose	0.75 million/kg
Median age	61 years
Median prior lines	6
Triple Class Refractory	88%
Penta Refractory	42%

Efficacy	
ORR	98%
sCR rate	83%
MRD negative rate (10^{-5})	58%[2]
PFS	34.9 months[3]
OS	3 year: 63%[3]



1. Martin et al. ASH 2021 *Blood* (2021) 138 (Supplement 1): 549.
2. Usmani et al ASCO 2021. JCO 2021;39(15_suppl):8005. 3. Lin et al ASCO 2023

Earlier Line Use of CAR-T: Cilta-cel CARTITUDE 4

MM patients with 1-3 prior lines of therapy

Randomized 1:1

Cilta-cel

SOC treatment
Dara-pom-dex
Pom-bortezomib-dex

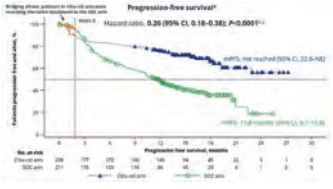
Follow-up

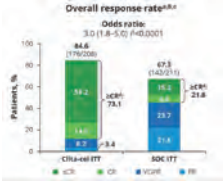
Primary Endpoint: Progression Free Survival

Earlier line compared to KarMMa-3

No crossover allowed

Median follow-up: 15.9 months





San Miguel et al. N Engl J Med 2023; Dhakal et al ASCO 2023

Real-World Evidence: Broad Applications for Clinical Decision Making

CAR-T trials have stringent eligibility criteria

RWE: Safety and efficacy data in a broad patient population in a short period of time

Populations of special interest: renal failure, alternative lymphodepletion

Data on less common AEs and optimal management

Potentially allow comparison of different products

Real-World Evidence for Ide-Cel in MM

Study Population: Patients with RRMM treated with commercial Ide-cel as SOC in United States who enrolled in the CIBMTR registry for long-term safety and effectiveness follow-up

CAR-T with conforming product and have at least 1 follow-up timepoint at day 100 (or earlier if patient was deceased before day 100)

N=821*
N=801* with data for PFS
Median follow-up: 11.6 months
(Range 1.1- 26.7 months)

Sidana et al. ASH 2023 meeting. Blood, 2023. 142(Supplement 1): p. 1027-1027.

Baseline Characteristics

	CIBMTR (N=821)	KarMMa (N=128)
Median age, years	66 years (29-90)	61 years (33-78)
Age ≥ 70 years	251 (31%)	-
Race, Black	120 (15%)	-
Ethnicity, Hispanic	55 (7%)	-
ECOG PS 0/1	728 (89%)	126 (98%)
ISS stage III	68/420 (16%)	R-ISS III: 16%
High-risk cytogenetics	196/727 (27%)	45 (35%)
Extramedullary disease	85/488 (17%)	50 (39%)
Plasma cell leukemia	13 (1.6%)	0%

High-risk cytogenetics include del17p, t(4;14) and t(14;16)

	CIBMTR (N=821)	KarMMa (N=128)
Prior lines of therapy	7 (4-21)	6 (3-16)
Triple class exposed	776 (97%)	Refractory: 84%
Penta class exposed	490 (60%)	Refractory: 26%
Prior BCMA Therapy • Prior ADC • Prior CAR-T • Prior bispecific	150 (18%) • 16 (14%) • 36 (4%) • 3 (0.4%)	0%
Bridging therapy	442/799 (54%)	112 (88%)
Lymphodepletion Flu/Cy	741 (90%)	128 (100%)

77% of real-world patients with clinically significant co-morbidity, many of which would have made many ineligible for KarMMa

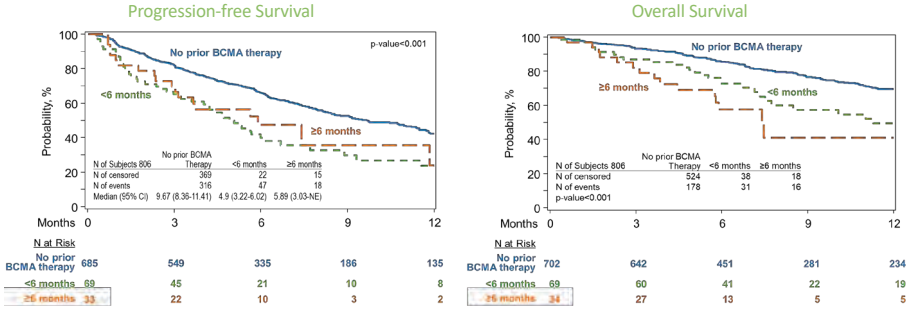
Ide-cel in MM: Real world vs. Trial Data

	CIBMTR[1] N=821	US RWE[2] N=159	KarMMa[3] N=128
CRS - Any grade Grade 3 or higher	80% 3%	82% 3%	84% 5%
ICANS– Any grade Grade 3 or higher	28% 5%	18% 6%	18% 3%
Overall response rate	73%	84%	73%
Very good partial response rate	56%	62%	52%
Complete response rate	25%	42%	33%
Progression free survival, median	9.0 months	8.5 months	8.8 months
Median follow-up	11.6 months	6.1 months	13.3 months

- Real world data: Most patients would not have met trial eligibility criteria
- 75% in the multi-center US MM consortium study did not meet eligibility criteria
- CIBMTR study: 77% had significant comorbidities

1. Sidana et al. ASH 2023. 2 Hansen et al. JCO 2023; 3. Munshi et al. NEJM 2021;384(8):705-716.

Sub-group Analysis: Prior BCMA Therapy



Prior BCMA therapy: Primarily belantamab mafodotin
This analysis excludes prior CAR-T therapy

Cilta-cel: Multi-Center Retrospective Study

Underwent apheresis from March 1, 2022-Sept 15, 2022 for SOC Cilta-cel, N=164
15 US Centers (US MM CAR-T Consortium)

Did not proceed to CAR-T infusion (n=13)*
Manufacturing failure (n=5)
Disease progression/death (n=5)
Myelodysplastic syndrome (n=1)
Declined OOS product (n=1)
Lost to follow-up (n=1)

Manufacturing failure rate
First attempt: 9% (n=15)
Overall: 3% (n=5)
Median Vein to Vein time: 71 days (36-161)

Cilta-cel infusion, N= 151 (92%)

Median follow-up: 6.9 months

- Out of Specification product (n=33, 22%)
- Lymphodepletion: Fludarabine +Cyclophosphamide (n=125, 83%); Other (n=26,17%)

1. Sidana et al. IMS 2023 presentation (Athens); unpublished data

Baseline Characteristics

	RWE Cilta-cel (N=151)	CARTITUDE-1 (N=97)
Age, median (range)	64 y (30-79)	61 y (56-68)
Age ≥ 70 years	39 (26%)	-
Race: Black	13 (9%)	17 (18%)
Ethnicity: Hispanic	15 (10%)	6 (6%)
ECOG PS, 0-1	121 (88%)	93 (96%)
High-risk cytogenetics*	56 (42%)	23 (24%)
R-ISS stage III	23 (23%)	ISS-3:14 (14%)
Extramedullary Disease	48 (32%)	13 (13%)

*High-risk cytogenetics: Del 17p, t(14;16), t(4;14)

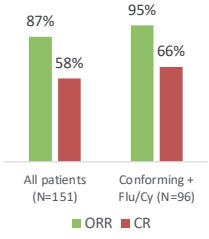
	RWE Cilta-cel (N=151)	CARTITUDE-1 (N=97)
Prior Lines of therapy	6 (3-18)	6 (4-8)
Triple Class Refractory	105 (70%)	85 (88%)
Penta-drug refractory	49 (32%)	41 (42%)
Prior BCMA Therapy	18 (12%)	0%
Bridging Therapy	117 (77%)	73 (75%)

57% of real-world patients would have been ineligible for CARTITUDE-1

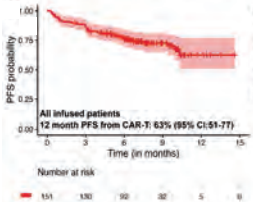
- Cytopenias (17%)
- Organ function (12%)
- Performance Status (12%)
- Prior BCMA therapy (12%)
- PCL/Amyloid/POEMS (12%)
- CNS pathology (6%)

1. Sidana et al. IMS 2023 (Athens), unpublished data; 2. Berdeja et al. Lancet 398:314-324, 2021.

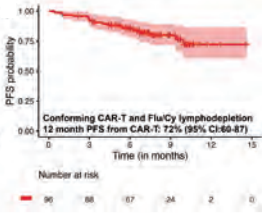
Efficacy of SOC Cilta-cel



PFS: All patients (N=151)



PFS: Conforming + Flu/Cy (N=96)



	Real-world[1] N=151	CARTITUDE-1 [2,3] N=97
ORR	87% (95%*)	98%
CR rate	58% (66%*)	83%
PFS	1 year: 63% (72%*)	34.9 months

*In patients receiving conforming CAR-T product with Flu/Cy lymphodepletion (N=96)

1. Sidana et al. IMS 2023, unpublished data ; 2. Berdeja et al. Lancet 398:314-324, 2021; 3. Martin et al. J Clin Oncol 41:1265-1274, 2023. 4. Lin et al ASCO 2023

Safety of SOC Cilta-cel

	Real-world[1] N=151	CARTITUDE-1 [2,3,4] N=97
CRS - Any grade/ ≥ Grade 3	79% (5%)	95% (4%)
ICANS – Any grade/ ≥ Grade 3	17% (6%)	17% (2%)
Delayed neurotoxicity Parkinsonism Cranial nerve palsy	13% 2% 6%	12% 6% NR*
IEC-HS/HLH	3%	~1%
Severe infections	21%	20%
Non-relapse mortality	10%**	6% ***

*Cranial nerve palsies: 6% in all CARTITUDE studies[5]

**Cause of death for NRM included infections (n=6, including PML in 1), CRS (n=3), CRS and infection (n=1), delayed neurotoxicity (n=3), IEC-HS (n=1), and ICANS (n=1).

***16 deaths due to reasons other than progression. Only 6 of 16 deaths non-myeloma related deaths attributed to cilta-cel per investigator assessment

1. Sidana et al. IMS 2023, unpublished data; 2. Berdeja et al. Lancet 398:314-324, 2021; 3. Martin et al. J Clin Oncol 41:1265-1274, 2023. 4. Lin et al ASCO 2023.
5. Van den Donk et al. ASH 2023 Blood, 2023. 142(Supplement 1): p. 3501.

Updated Cilta-cel data with 255 patients and median 1+ year follow-up to be presented at IMS 2024

Objectives:

- Review current data from clinical trials and real-world on safety and efficacy of BCMA directed CAR-T therapy in MM
- **Review unmet needs in CAR-T therapy for MM**
  - **Patient selection**
  - **Management of delayed neurotoxicities**
  - **Understanding mechanisms of relapse**
  - **Ideal sequencing of immunotherapies**
- Newer CAR-T targets in development

Patient Selection for CAR-T

Patient Characteristics: Co-morbidities

- Real world patients receiving CAR-T have more co-morbidities than patients on trials
- ~ Half to three-fourths of patients treated with SOC ide-cel and cilta-cel would be trial ineligible
- SOC CAR-T: good safety and efficacy

Prior Treatment Consideration

Avoid within 6 months of apheresis:

- Bendamustine
- Bispecific antibodies (washout unclear)
- Other BCMA targeted therapies

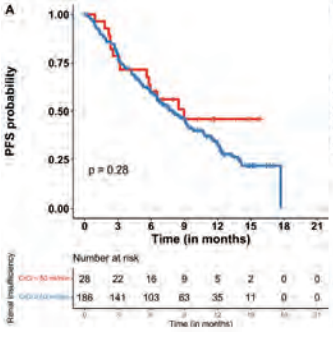
Logistics

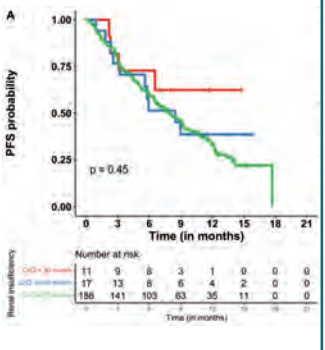
- Manufacturing availability
- Bridging
- Relocation

1. Sidana et al. ASH 2023 meeting.
2. Sidana, Patel et al. IMS 2023 meeting.
3. Hansen, Sidana et al. J Clin Oncol 41:2087-2097, 2023
4. Iacoboni et al. J Clin Oncol, 2024. 42(2): p. 205-217.
5. Ferreri et al. Blood Cancer Journal 2023

Ide-cel in Patients with Renal Impairment

- Renal Impairment: Cr Cl < 50 ml/min
- Severe renal impairment: < 30 ml/min or dialysis:
- CRS, neurotoxicity and non-relapse mortality comparable
- Longer hospital stay
- Short-term high-grade cytopenias at day 30.
- Similar response rates and PFS.

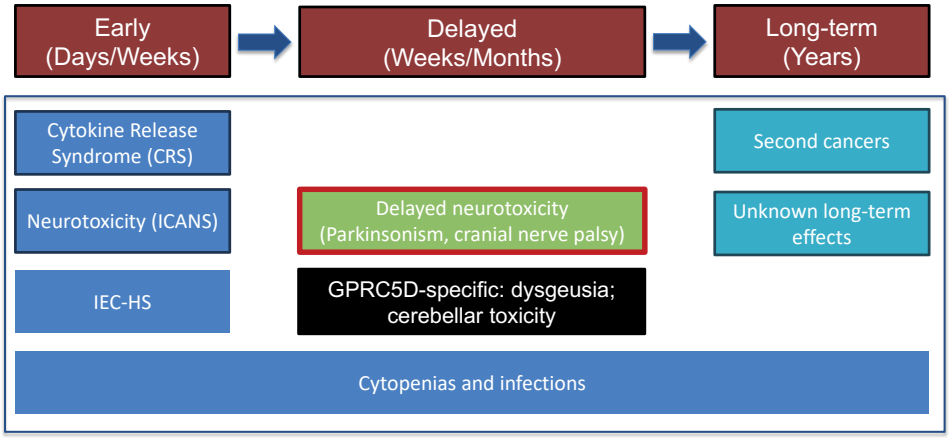




Sidana et al. Haematologica, 2024. 109(3): p. 777-786.

Management of Delayed Toxicities

Toxicities with CAR-T in Myeloma



Delayed Neurotoxicity: BCMA CAR-T

- Predominantly seen with cilta-cel, case reports with ide-cel
- Not reported with bispecific antibodies to date

- Heterogenous group: Parkinsonism, cranial nerve palsy, peripheral neuropathy, others.

	Cilta-cel (RWE)[1]	Cilta-cel (CARTITUDE-1)[2]	Cilta-cel (CARTITUDE-4)[3]
All grades	12%	12%	17%
Median onset	25 days	27 days	21 days*
Parkinsonism	**2%**	**6%**	**0.5%**

*Time to onset for cranial nerve palsy; RWE: real-world evidence

1. Sidana, Patel et al IMS 2023 presentation (Athens);2. Martin et al. J Clin Oncol 41:1265-1274, 2023; 3. San-Miguel et al. NEJM 389:335-347, 2023.

Cranial Nerve Palsies (CNP) with Cilta-cel

	Cilta-cel RWE[1]	All CARTITUDE trials[2]
Incidence	6% (n=9)	6% (n=21)
Nerves involved	All: VII nerve	All: VII nerve Additional CN in n=3
Median time to onset	21 days	22 days
Treatment	Steroids in 7 of 9	Steroids in 19 of 21
Resolution	4 of 9	19 of 21

Risk Factors: High CAR-T expansion;
CRS/ICANS were not risk factors

Management Recommendations

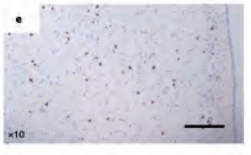
- Strongly consider brain imaging (MRI) to rule out other causes
- Consider CSF analysis on case-by-case basis
- Treatment: Low dose steroids – taper over days

1. Sidana, Patel et al IMS 2023 presentation (Athens). 2. Van den Donk et al. ASH 2023 Poster #3501. Blood 142:3501, 2023.

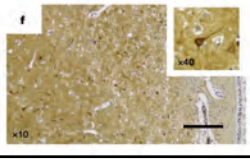
Parkinsonism with Cilta-Cel

- Risk Factors: High-tumor burden, CRS/ICANS, high CAR-T expansion
- Mechanism: potential on-target, off-tumor effect

- Parkinsonism 3 months after cilta-cel
- CAR-T persistence in blood and CSF
- Lymphocytic infiltrate in basal ganglia on autopsy
- BCMA expression on neurons and astrocytes in the patient's basal ganglia.



T cell infiltrate by IHC in basal ganglia

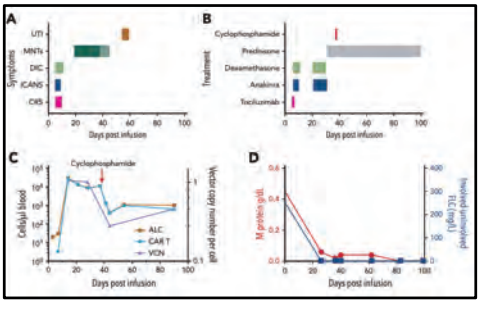


BCMA expression by IHC in basal ganglia

1. Van Oekelen O et al. *Nature medicine*. 2021;27(12):2099-2103. 2. Cohen et al. Blood Cancer Journal 12:32, 2022

Management of Parkinsonism

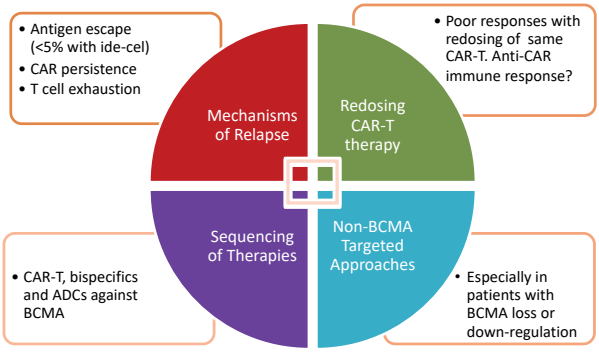
- Levodopa/carbidopa and other typical Parkinson's directed therapies are ineffective
- Some evidence suggests that decreasing CAR-T expansion with chemotherapy and steroids may be effective



Graham et al. Blood 142:1248-1252, 2023

Relapse After BCMA CAR-T Therapy

New Unmet Need



29

Sequencing of Immunotherapy

CARTITUDE-2 Cohort C: Cilta-Cel after Prior BCMA Bispecific Therapy

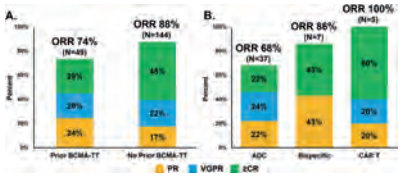
	N=20
Prior ADC Prior Bispecific	13 (1 with both BsAb and ADC) 7
Previous lines of therapy	8
BCMA as last line of therapy	30%
BCMA refractory	80%
ORR/CR	**60%/25%**
Median PFS	9 months (5 m in BCMA BsAb)

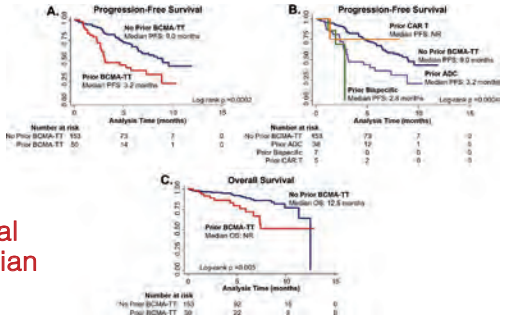
4 of 24 patients did not receive infusion due to failed manufacturing (2) or death from progression

Factors associated with response to cilta-cel were
(1) a shorter duration of the last anti BCMA treatment
(2) a longer interval between anti-BCMA treatment and cilta-cel

Cohen et al. Blood. Sept 2022

Prior BCMA therapy and Ide-cel





Prior bispecific Ab: Worst survival outcomes with ide-cel, with median PFS of ~ 3 months

Ferreri et al. Blood Cancer Journal 2023. US MM Consortium Data

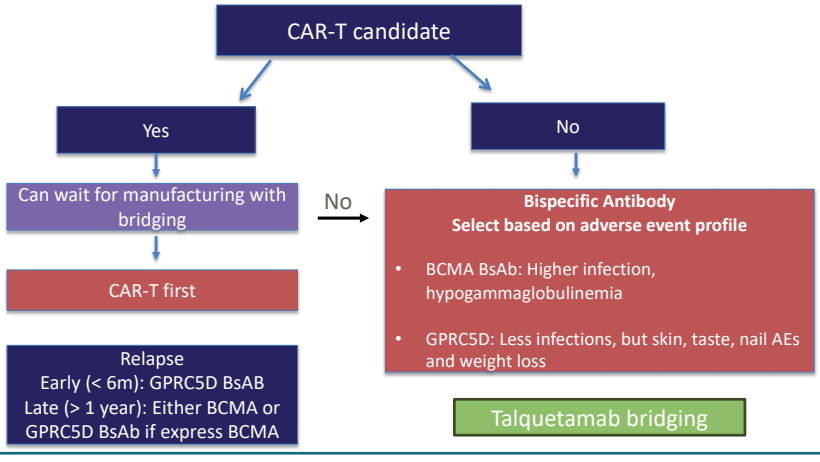
Bispecific Antibodies After BCMA Therapy

Good efficacy after prior CAR-T

	Talquetamab[1]	Elranatamab[2]	Teclistamab[3]
Target	GPRC5D	BCMA	BCMA
N	51	24% of N=55	40
Prior BCMA type	BCMA CAR-T: 36 BsAb:=18	-	ADC:73% CAR-T: 38%
Response prior BCMA	**65%**	**54%**	**53%**
Response based on prior immunotherapy	**Prior CAR-T: 75% BsAB: 44%**	**Not reported**	**Prior CAR-T: 53% ADC: 55%**

1. Schinke et al ASCO 2023; 2. Raje et al ASH 2022; 3. Touzeau et al ASCO 2022

My Sequencing Approach

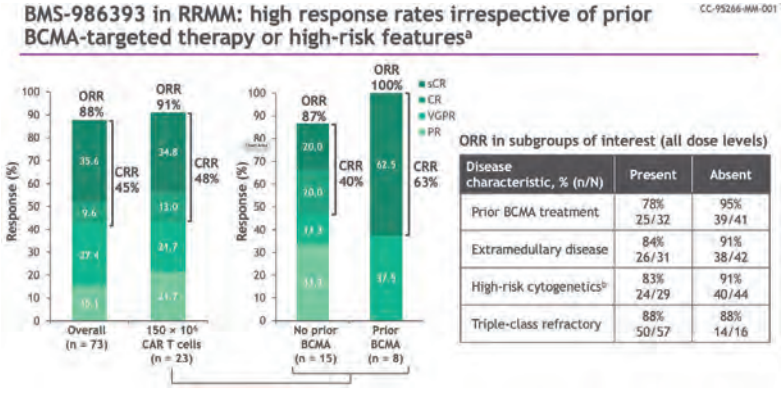


Non BCMA Targets in Development

GPRC5D
FCRH5
Others: CD38, CD138, SLAMF7

Dual targeting:
GPRC5D+BCMA
CD19+BCMA

GPRC5D CAR-T therapy: Phase 1 trial

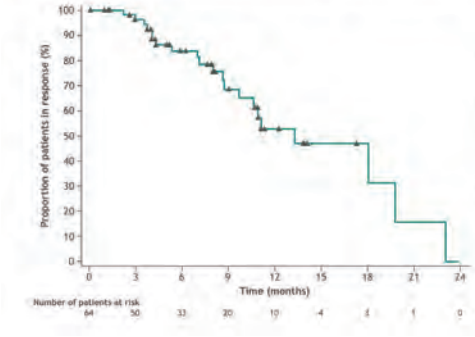


ORR in subgroups of interest (all dose levels)

Disease characteristic, % (n/N)	Present	Absent
Prior BCMA treatment	78% 25/32	95% 39/41
Extramedullary disease	84% 26/31	91% 38/42
High-risk cytogenetics[b]	83% 24/29	91% 40/44
Triple-class refractory	88% 50/57	88% 14/16

Bal et al. ASH 2023 Abstract #219

BMS-986393 in RRMM: deep and durable responses[a]



- Median duration of follow-up: 9 months (range, 1-25)
- 67% of responses are ongoing (43 of 64 efficacy-evaluable responders), yielding a median DOR of 13 months (95% CI, 10-20) at data cutoff
- 86% (12/14) of MRD-evaluable[b] patients with ≥ CR achieved MRD negativity

Additional AEs (on-target, off tumor)
Non ICANS cerebellar neurotoxicity: ~ 10%
Taste, skin and nail changes (up to 20-25%)

Bal et al. ASH 2023 Abstract #219

Summary

- BCMA targeted CAR-T is now available as SOC for relapsed MM, moving to earlier lines
- Majority of patients receiving SOC CAR-T in the US are not trial eligible
- Real world data shows promising efficacy and safety profile, even though many patients are not trial eligible
- Delayed and unusual toxicities, including neurotoxicity and SPMs remain an issue
- Early data suggests sequencing CAR-T before BsAb
- Newer CAR-T targets are in development (GPRC5D)

Stanford BMT CT Program

Stanford Myeloma Program

Trainees, APPs, nurses, and
our research team

Surbhi Sidana, MD
Michaela Liedtke, MD
Hitomi Hosoya, MD, PhD
David Iberri, MD
Lekha Mikkilineni, MD
Sally Arai, MD

Dr Vaishali Sanchorawala is the Professor of Medicine and Director of the Amyloidosis Center of Boston University Chobanian & Avedisian School of Medicine and Boston Medical Center.

Her research has led and defined the field in AL amyloidosis. She is recognized as one of the leading international experts and a key opinion leader in amyloidosis. With numerous publications and meeting presentations, she has been one of the pioneers in the field of clinical research in AL amyloidosis. Her work in the treatment of AL amyloidosis has been published in many peer-reviewed journals and has resulted in the evolution of the standard of care for these patients. She is currently heading many clinical trials in the treatment of AL amyloidosis. She has helped to create and cultivate the next generation of physician-scientists in the area of clinical research in amyloidosis, many of whom today play leadership roles in distinguished centers around the world.

She serves on the executive steering committee of the Amyloidosis Research Consortium, the board of the International Society of Amyloidosis as secretary, chair of the membership committee of the International Society of Amyloidosis and as an associate editor of *Amyloid, Journal of Protein Folding Disorders*. She has been an invited speaker and session chair nationally and internationally.

Her influence extends beyond the groundbreaking and paradigm-shifting work in the field of amyloidosis. In addition to her scientific achievements and accolades, she is a beloved teacher, a caring mentor, and a compassionate physician with exceptional clinical acumen. She has an interest in working in charity organizations. She helps cook meals for ~300 underserved individuals at a meal center in Massachusetts (1–2 times a month) and volunteer regularly at "Cradles to Crayons" charity, non-profit organization.

AMYLOIDOSIS CENTER

Advances in Systemic AL Amyloidosis

Vaishali Sanchorawala, MD
Professor of Medicine

BOSTON UNIVERSITY Amyloidosis Center
Boston University Chobanian & Avedisian School of Medicine
BOSTON MEDICAL CENTER

Disclosures

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Employee	No relevant conflicts of interest to declare
Consultant	Pfizer, Janssen, Attralus, BridgeBio
Major Stockholder	No relevant conflicts of interest to declare
Speakers' Bureau	None
Scientific Advisory Board	Proclara, Caelum, Abbvie, Janssen, Regeneron, Protego, Pharmatrace, Telix, Prothena

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Boston University Chobanian & Avedisian School of Medicine
BOSTON MEDICAL CENTER

Outline of advances in AL amyloidosis

- Patient journey
- Early diagnosis
- Pathogenesis
- Diagnostics and typing
- Staging and risk stratification
- Health disparities
- Health-related quality of life (HRQoL) measures
- Treatments
  - definitive
  - supportive

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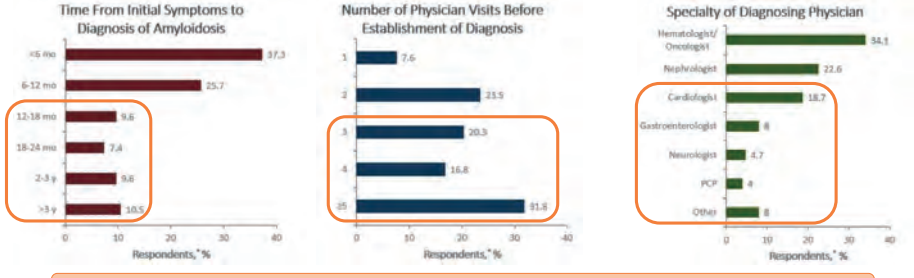
The path to diagnosis

AL amyloidosis is a rare disease with 1.2 cases per 100,000 person-years (95% CI, 0.8-1.6)



Significant delays and multiple physician visits before a diagnosis of amyloidosis is made

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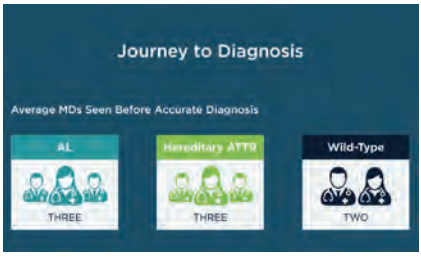
Kyle *et al*, Mayo Clin Proc 2019
Lousada *et al*, Adv Ther 2015

Amyloidosis Research Consortium (ARC) 2022 community survey results



>1200 patients and caregivers across the globe participated in this survey

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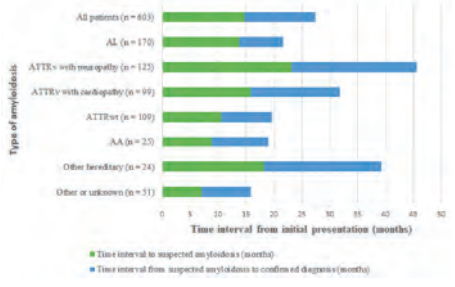
Amyloidosis from the patient perspective

Average time from symptom onset to diagnosis is **27.4 months** (all amyloidosis)

AL amyloidosis	21.7 months
hATTR amyloidosis with PN	45.6 months
hATTR amyloidosis with CM	31.8 months
ATTRwt amyloidosis	19.6 months

The French study (N = 603)



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Damy *et al*, Amyloid 2022

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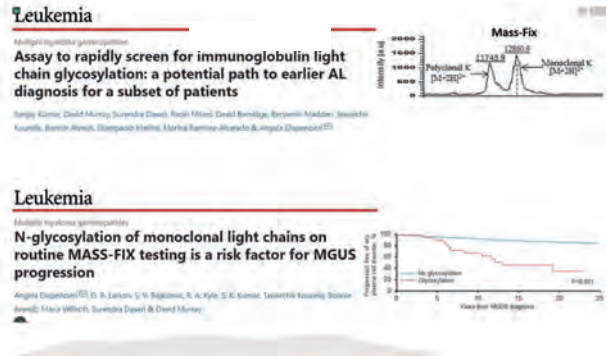
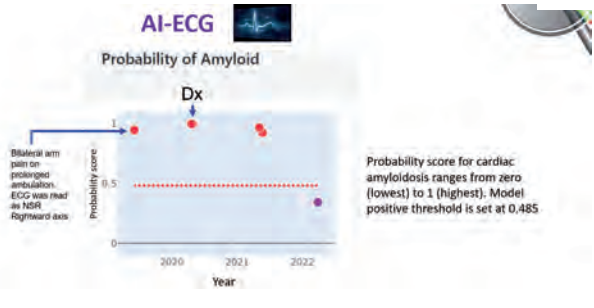
Early diagnosis



Early diagnosis

Of the patients with CA and pre diagnosis ECG studies, the AI model successfully predicted the presence of CA more than 6 months before the clinical diagnosis in 59%



Grogan *et al*, Mayo Clin Pro 2021

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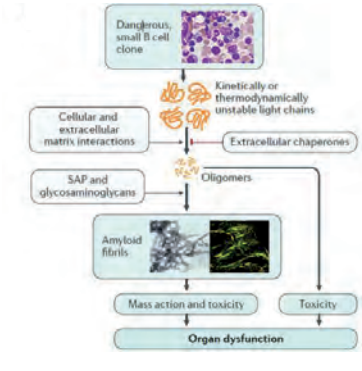
Pathogenesis of AL amyloidosis



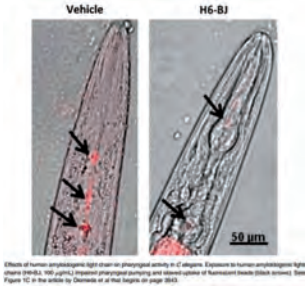
Mechanisms of organ dysfunction:

1. Deposition of amyloid fibrils in the organs
2. Direct cytotoxicity of soluble precursor proteins or oligomers

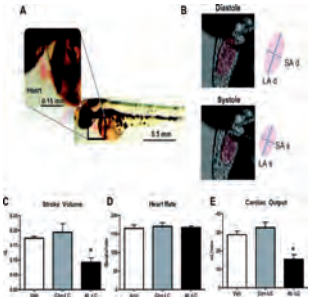
Merlini *et al*, Nature Reviews 2018

Mechanisms underlying clinical disease

Caenorhabditis elegans model for cardiac toxicity



Zebra Fish model for cardiac toxicity



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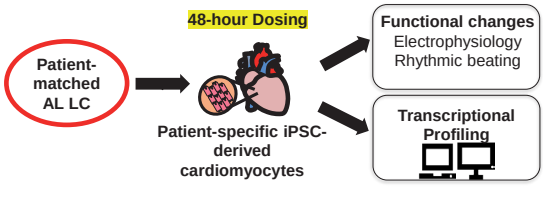
Diomede *et al*, Blood 2014; Mishra *et al*, *Am J Physiol Heart Circ Physiol* 2013

Mechanisms underlying clinical disease

Mapping the molecular mechanisms that drive amyloidogenic light chain-induced cardiotoxicity: Camille Edwards, MD



Cells exhibit a unique transcriptional response to amyloidogenic light chains leading to negative cardiac chronotropic effects:

- **Upregulation of transcripts:** cardiac hypertrophy (actin, myosin, troponin genes) and cardiac remodelling (ROCK1 and MMP genes)
- **Downregulation of transcripts:** adaptive immune response (*GPR183*, *CCL11*)

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Diagnosis: 2 steps

Tissue biopsy of target or surrogate site and Congo red staining
- ✓ Abdominal fat (75-80%)
- ✓ Bone marrow (~70%)
- ✓ Minor salivary gland (~80%)

Unequivocal identification of amyloid precursor protein
- ✓ Appropriate treatment
- ✓ Assess prognosis
- ✓ Genetic counseling (when appropriate)

Typing of amyloid deposits
- ✓ Immunohistochemistry (unreliable with commercial antibodies)
- ✓ Ultrastructural (EM) immunohistochemistry (specificity 99% even with commercial antibodies)
- ✓ Mass spectrometry based proteomics (gold standard, LCMD or MudPIT, not antibody dependent)

Satoskar *et al*, Am J Surg Path 2011; Fernandez de Larrea *et al*, Blood 2015; Vrana *et al*, Blood 2009; Brambilla *et al*, Blood 2012

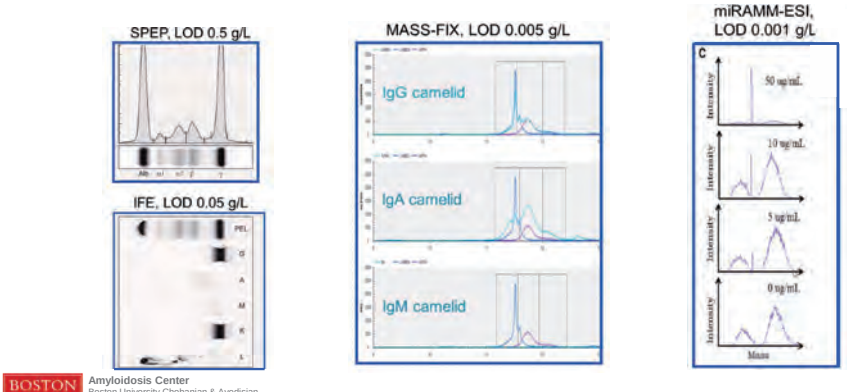
Evaluation of plasma cell dyscrasia: diagnostic sensitivity

Bone marrow plasma cell clone is usually small (*median 10%, <5% in 20% of patients*)

	Palladini Clin Chem Lab Med 2017	Akar Amyloid 2005	Katzmann Clin Chem 2009	Bochtler Haematolgica 2008
SIFE	93%	76%	87%	69%
UIFE	87%	88%	-	86%
SIFE+UIFE	94%	96%	94%	92%
FLCR	82%	75%	88%	89%
IFE+FLCR	98%	98%	98%	98%

Novel MassFix technique may increase diagnostic sensitivity

Evaluation of plasma cell dyscrasia: technics and levels of detection (LOD)



Plasma cell clone in AL amyloidosis differs from myeloma

- Clone size is smaller in AL amyloidosis
- Clonal PCs in AL amyloidosis have similar phenotypic and CNA profiles to those in myeloma
- Clonal PCs in AL amyloidosis have a similar transcriptome and GEP to normal PCs
- Cyclin D1 is a more prominent driver in AL amyloidosis than myeloma
- Circulating PCs are rare in AL amyloidosis

AL amyloidosis	Chromosomal aberration	Myeloma
19%	Gain 1q21	53%
3%	t(4;14)	26%
47%	t(11;14)	26%

Paiva *et al*, Blood 2016

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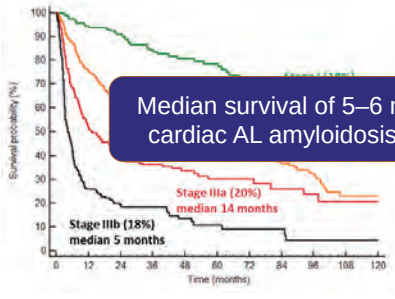
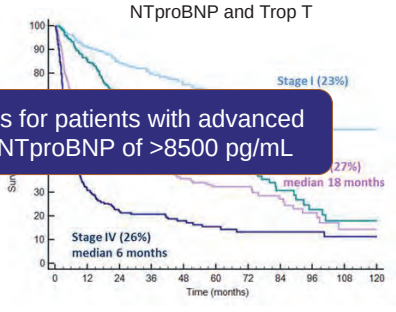
Biomarker-based staging systems

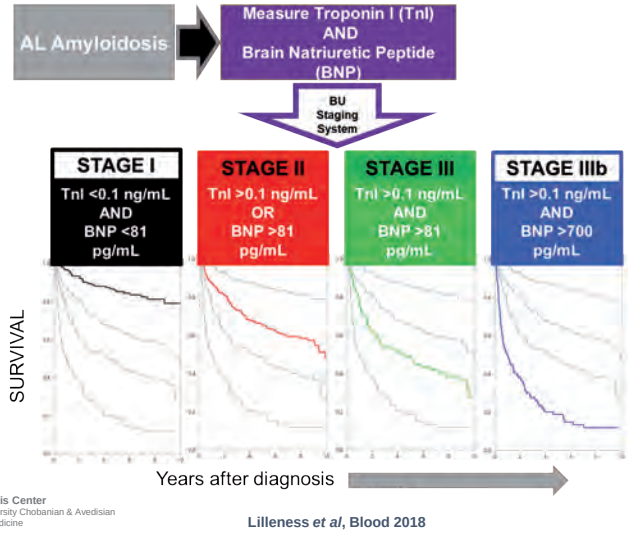
Mayo 2004/European Staging:
Elevated NTproBNP and Trop T



Mayo 2012 Staging:
dFLC >180 mg/L, elevated
NTproBNP and Trop T



Median survival of 5–6 months for patients with advanced cardiac AL amyloidosis with NTproBNP of >8500 pg/mL



Lilleness *et al*, Blood 2018

Mayo clinic 2004 vs 2012 staging systems
(n=1275; treated with bortezomib-based therapy)

Table 1. Overall survival by staging system.

	N	Median OS (95% CI)	HR (95% CI)	P*
Mayo 2012				
Stage I	199	NR	Reference	
Stage II	329	137 (137-NR)	2.26 (1.57-3.26)	<0.001
Stage III	413	37 (31-58)	4.18 (2.97-5.90)	
Stage IV	334	26 (16-34)	5.33 (3.77-7.53)	
European modification				
Stage I	219	NR (137-NR)	Reference	
Stage II	436	NR (111-NR)	2.24 (1.61-3.12)	<0.001
Stage IIIa	424	36 (31-52)	4.13 (2.99-5.69)	
Stage IIIb	196	7 (6-10)	8.22 (5.87-11.53)	

Table 2. Comparison of Mayo 2012 and European modification staging systems.

	Mayo I			Mayo II			Mayo III			Mayo IV		
European	**N**	**Median OS**	**95% CI**	**N**	**Median OS**	**95% CI**	**N**	**Median OS**	**95% CI**	**N**	**Median OS**	**95% CI**
Entire group	-	NR	-	-	137	137-NR	-	37	31-58	-	26	16-34
Stage I	125	NR	-	80	137	NR	14	83	25-NR	-	-	-
Stage II	74	NR	102-NR	159	NR	NR	144	77	49-NR	59	74	45-NR
Stage IIIa	-	-	-	90	46	31-62	181	30	19-60	153	43	29-62
Stage IIIb	-	-	-	-	-	-	74	11	8-24	122	5	3-8

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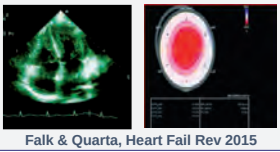
Khwaja *et al*, Haematologica 2024

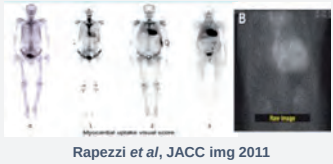
Imaging in cardiac amyloidosis

Echo with strain doppler: the cornerstone for diagnosis



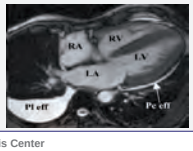
Falk & Quarta, Heart Fail Rev 2015

^{99m}Tc-PYP scan



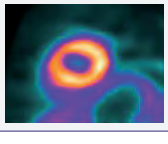
Rapezzi *et al*, JACC img 2011

Cardiac MRI – T1 map, LGE



Fontana *et al*, Circulation 2015

18F-florbetapir PET imaging



Dorbala *et al*, EJNMMI 2014

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Validated response criteria

Response	Definition of measurable disease	Criteria
Haematological[4,75,82]	dFLC >50 mg per litre	• Complete response: negative serum and urine immunofixation and normal free light chain ratio • Very good partial response: dFLC < 40 mg per litre • Partial response: dFLC decrease >50% compared with baseline
	dFLC 20–50 mg per litre	Low-dFLC response: dFLC <10 mg per litre
Cardiac[87]	NT-proBNP >650 ng per litre	NT-proBNP decrease >30% and >300 ng per litre compared with baseline
Renal[90]	Proteinuria >0.5 g per 24 hours (predominantly albumin)	Proteinuria decrease >30% compared with baseline (or is <0.5 g per 24 hours) in the absence of reduction in eGFR by >25%

AL, monoclonal immunoglobulin light chain; dFLC, difference between involved and uninvolved circulating free light chain; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal fragment of type B natriuretic peptide.

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Palladini *et al*, JCO 2012; Palladini *et al*, Blood 2014, Milani *et al*, Blood 2017

Refining hematologic response criteria

Low FLC endpoints – summary of recent studies

	UK NAC	Mayo Clinic	Pavia	BU
Time of assessment	6 months	End of therapy	6 months	6 months
Low-FLC endpoint	dFLC10	iFLC20, dFLC10	Normal iFLC, iFLC20, dFLC10	Normal iFLC, iFLC20, dFLC10
OS, low-FLC vs CR	Longer for CR+dFLC10		Longer for CR+iFLC20	Longer for CR+iFLC20
Alternative CR definition		Neg SIFE/UIFE+dFLC 10 discriminates better	Standard CR discriminates better	

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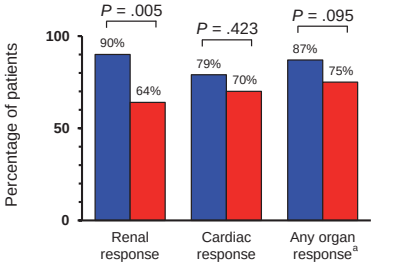
Manwani et al, Blood 2019; Muchtar et al, AJH 2020; Milani et al, BCJ 2020; Sarosiek et al, BCJ 2020

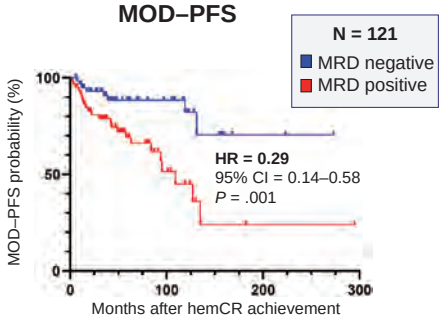
Measurable residual disease (MRD) assessment by multi parametric flow cytometry

Organ response rates

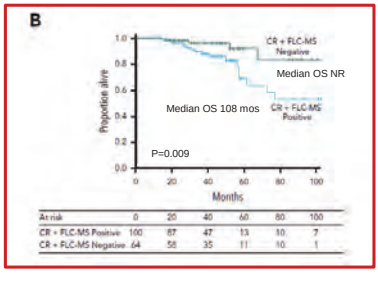


[a] heart, kidney or liver

MOD–PFS



Measurable residual disease (MRD) assessment by free light chain mass spectrometry

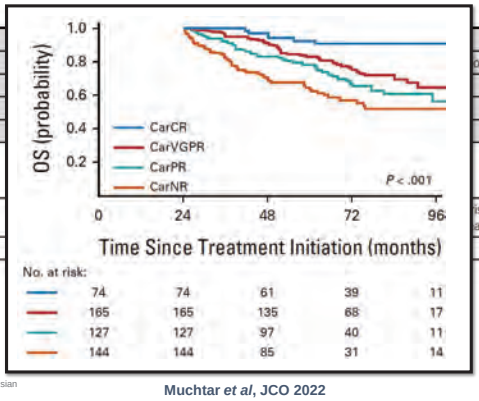


- FLC-MS can detect persistent light chains in 60% of patients with a conventional hematologic CR at 12 months
- Patients with no detectable FLC by FLC-MS have significantly better OS and organ response irrespective of conventional hematologic response

Graded cardiac response criteria

Updated criteria

Category	
Cardiac response criteria	
CarCR	
CarVGPR	
CarPR	
CarNR	
Cardiac progression criteria (adopted from Palladini et al[3])	
Any of the following	



Muchtar *et al*, JCO 2022

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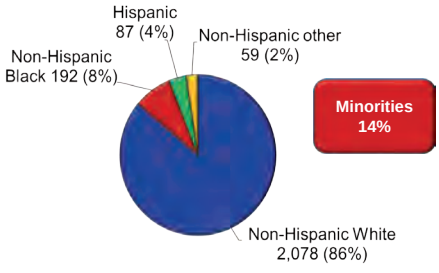
Racial/ethnic disparities in AL amyloidosis

Racial/ethnic composition of the AL amyloidosis cohort, 1990–2020 (N = 2,416)



- Younger and more advanced diagnoses were observed among NHBs and Hispanics
- Disparities in SCT utilization were driven by both sociodemographic and physiologic factors—rather than race/ethnicity itself
- Race/ethnicity did not have an independent effect on survival after controlling for disease severity and treatment use

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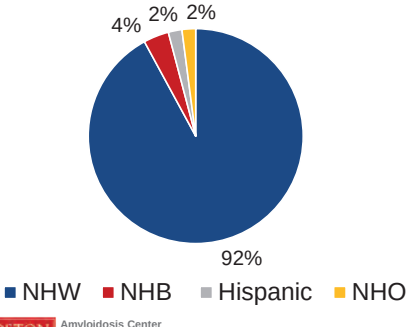
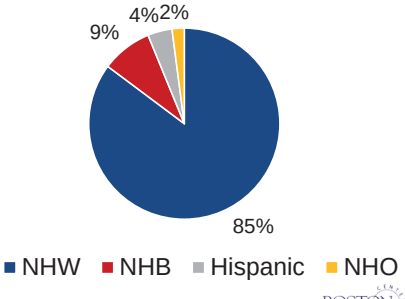
Staron *et al*, Blood Ca J. 2020

Racial/ethnic composition of participants in clinical trials for AL amyloidosis

SCT clinical trials (n=12, 8%) with 341 participants enrolled



Non-SCT clinical trials (n=24,15%) with 291 participants enrolled



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Sanchorawala *et al*, ISA 2024

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Patient Related Outcome Measures
Dovepress
REVIEW
Health-Related Quality of Life Instruments for Clinical Trials in AL Amyloidosis: Report from the Amyloidosis Forum HRQOL Working Group
Avery A Rizio[1], Michelle K White[1], Anita D'Souza[2], Kristen Hsu[3], Paula Schmitt[4], Tiffany P Quock[5], James Signorovitch[6], Isabelle Lousada[3], Vaishali Sanchorawala[7]

- **SF-36v2® Health Survey** and **PROMIS-29** were identified as relevant instruments for patients with AL amyloidosis
- Reliability and validity was evaluated with a recommendation for future work
- The context of use should drive selection of the appropriate PRO instrument to detect meaningful change and enable patient-focused drug development

Rizio *et al*, Patient related outcome measures 2023

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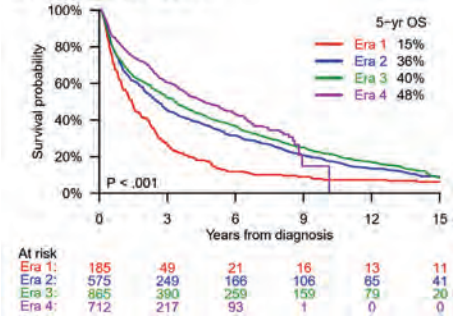
  - **definitive**
  - **supportive**

Overall survival of patients with AL amyloidosis (N = 2,337)



Stratum	Median OS, years
Era 1 1980–1989	1.4
Era 2 1990–1999	2.6
Era 3 2000–2010	3.3
Era 4 2010–2019	4.6

Staron *et al*, BCJ 2021

Therapeutic landscape

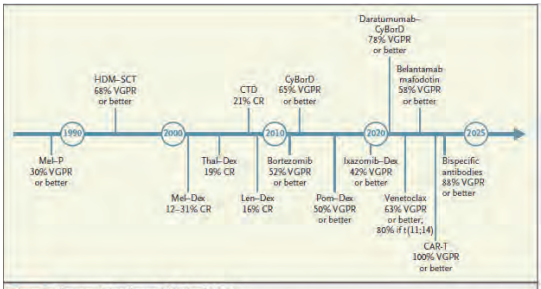
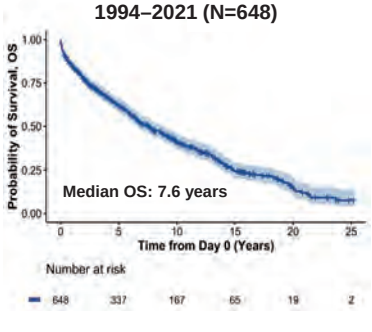


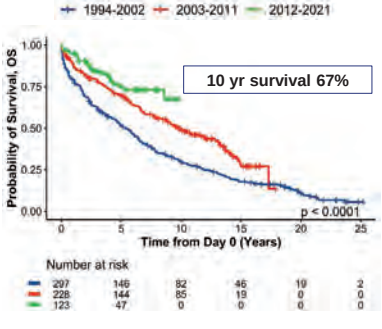
Figure 3. Therapeutic Landscape of AL Amyloidosis.

The therapeutic landscape of AL amyloidosis has seen substantial expansion in the past three decades. The majority of treatment regimens are adapted from myeloma therapies, with a focus on targeting the underlying plasma cell clone. Hematologic response has improved significantly with more effective and contemporary treatments, contributing to an overall increase in survival and a reduction in the rate of early death. CAR-T denotes chimeric antigen receptor T-cell therapy, CR complete hematologic response, CTD cyclophosphamide–thalidomide–dexamethasone, CyBorD cyclophosphamide–bortezomib–dexamethasone, HDM–SCT high-dose melphalan and stem-cell transplantation, Ixazomib–Dex ixazomib–dexamethasone, Len–Dex lenalidomide–dexamethasone, Mel–Dex melphalan–dexamethasone, Mel–P melphalan–prednisone, Pom–Dex pomalidomide–dexamethasone, Thal–Dex thalidomide–dexamethasone, and VGPR very good partial hematologic response.

Sanchorawala, NEJM 2024

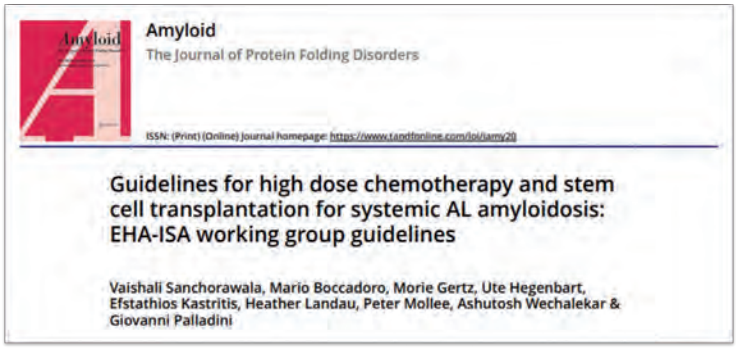
Prolonged survival with HDM/SCT: the Boston University experience





Gustine *et al*, AJH 2022

EHA-ISA guidelines



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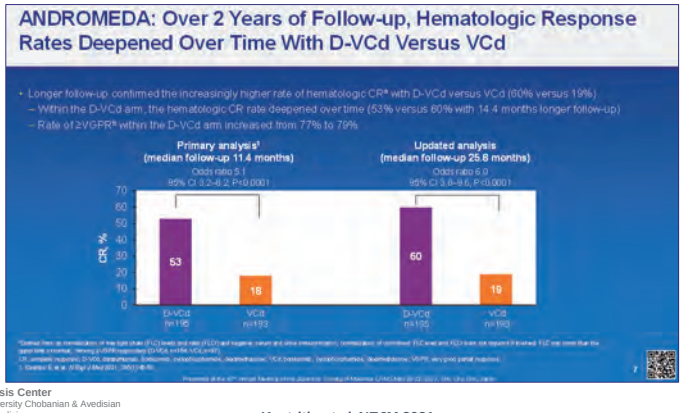
2022

VCd plus SC Daratumumab in AL amyloidosis: ANDROMEDA clinical trial



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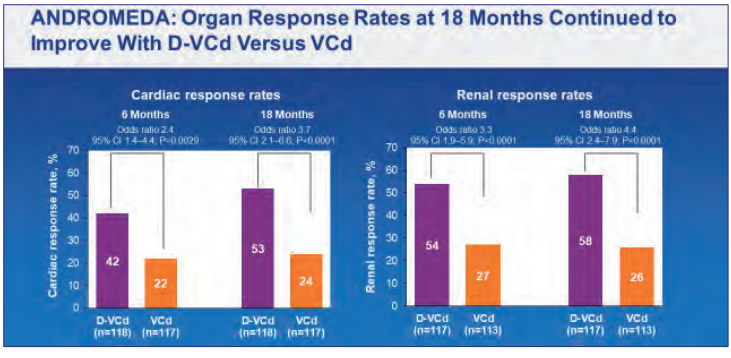
Kastritis *et al*, NEJM 2021

VCd plus SC Daratumumab in AL amyloidosis: ANDROMEDA clinical trial



Amyloidosis Center
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Kastritis *et al*, NEJM 2021

EHA-ISA guidelines

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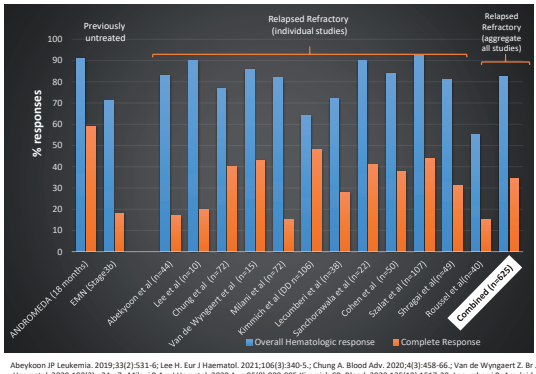
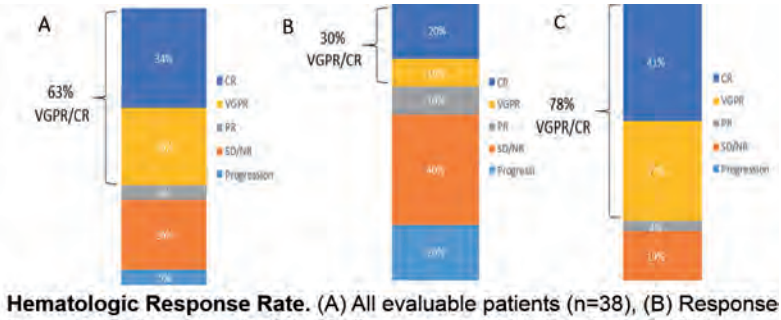
2023

Treatment for AL amyloidosis: Daratumumab



Abeykoon JP. Leukemia. 2019;33(2):531-6; Lee H. Eur J Haematol. 2021;106(3):340-5.; Chung A. Blood Adv. 2020;4(3):458-66.; Van de Wyngaert Z. Br J Haematol. 2020;188(3):e24-e7.; Milani P. Am J Hematol. 2020 Aug;95(8):900-905;Kimmich CR. Blood. 2020;135(18):1517-30.;Lecumberri R. Amyloid. 2020;27(3):163-7.;Sanchorawala V. Blood. 2020;135(18):1541-7.;Szalat RE. Am J Hematol. 2022;97(1):79-89.; Cohen OC. Amyloid. 2020;27(3):200-5.;Shragai T. 2021;106(2):184-95.; Roussel M. Blood. 2020;135(18):1531-40.

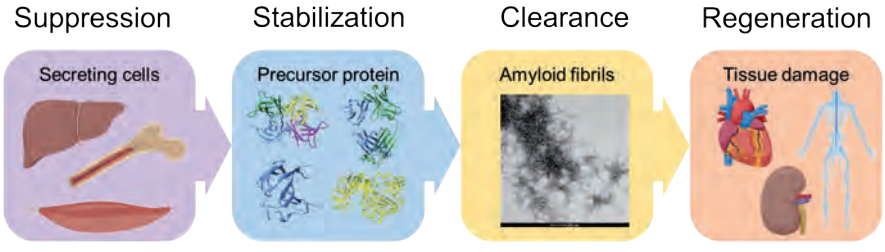
Venetoclax in AL amyloidosis



Hematologic Response Rate. (A) All evaluable patients (n=38), (B) Response in non-t(11;14) patients (n=10), (C) Response in t(11;14) patients (n=27).

Premkumar *et al*, BCJ 2021

Beyond plasma cells: combining therapies



Disease-specific

Shared mechanisms?

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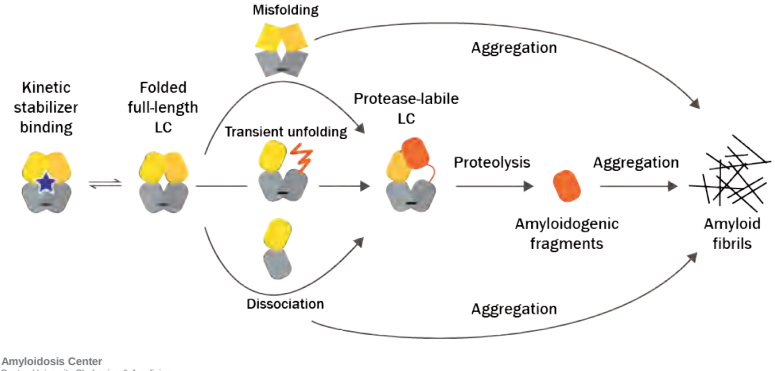
Organ images created with BioRender.com

Stabilization of light chains for AL amyloidosis



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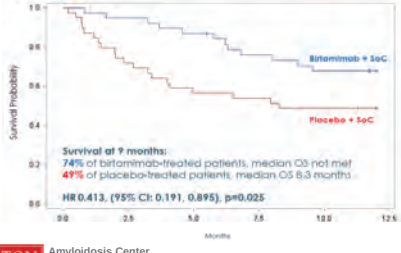
Morgan *et al*, PNAS 2019

Birtamimab (NEOD001): AFFIRM-AL trial

ClinicalTrials.gov ID NCT04973137

Phase 3 VITAL study of birtamimab vs placebo, plus SoC, in patients with AL amyloidosis: discontinued for futility

9-Month All-Cause Mortality in Patients with Mayo Stage IV (N = 77)



Secondary Endpoints, Mayo Stage IV (N=77)

SF-36v2 PCS Quality of Life	Placebo + SoC (n=39)	Birtamimab + SoC (n=38)	
Baseline score	31.2	31.1	+5 points favoring birtamimab (p=0.026)
Mean change from baseline at 9 months	−6 points	−1 point	

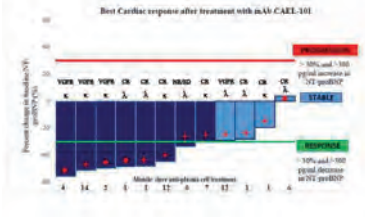
6MWT Functional Capacity	Placebo + SoC (n=39)	Birtamimab + SoC (n=38)	
Baseline distance (meters)	327.6	339.1	+27 meters favoring birtamimab (p=0.046)
Mean change from baseline at 9 months	−22 meters	+5 meters	

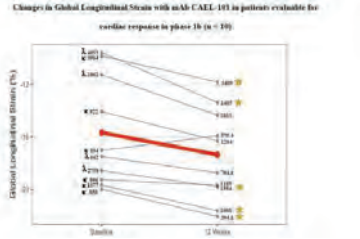
Gertz *et al*, Blood 2023

CAEL-101 (11-1F4): CARES program

ClinicalTrials.gov ID NCT04512235
ClinicalTrials.gov ID NCT04504825

In a Phase 1a/b open-label study, 15/24 (63%) patients with cardiac (67%), renal (20%), hepatic, GI or soft tissue involvement had therapeutic response by biomarkers or objective imaging modalities

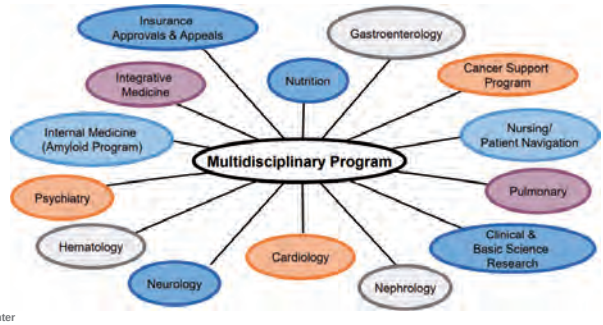




Edwards *et al*, Blood 2021

Multidisciplinary care model

Integrated care at specialized centers helps patients and physicians navigate the challenges of this rare disease



Treatments improving as understanding of disease pathophysiology grows

These results and progress in the therapeutic landscape of systemic amyloidosis are unbelievable, unprecedented, unheard of for this uniformly fatal disease, BUT they are not enough!

Future Directions:

- Improve early diagnosis (education, screening, awareness)
- Define standard of care for advanced cardiac stage patients
- Validate a definition of hematologic progression
- Evaluate new sensitive techniques (MS, MRD) to assess response
- Novel clone directed treatments
- Alternative treatment targets – LC stabilizers, anti-fibril antibodies

Acknowledgements

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BOSTON MEDICAL CENTER

Prof. Aaron Ciechanover was born in Haifa, Israel in 1947. He is currently a Distinguished Research Professor in the Faculty of medicine at the Technion – Israel Institute of Technology in Haifa, Israel. He received his M.Sc. (1971) and M.D. (1973) from the Hebrew University in Jerusalem. He then completed his national service (1973-1976) as military physician, and continued his studies to obtain a doctorate in biological sciences in the Faculty of Medicine in the Technion (D.Sc.; 1982). There, as a graduate student with Dr Avram Hershko and in collaboration with Dr. Irwin A. Rose from the Fox Chase Cancer Center in Philadelphia, USA, they discovered that covalent attachment of ubiquitin to a target protein signals it for degradation. They deciphered the mechanism of conjugation, described the general proteolytic functions of the system, and proposed a model according to which this modification serves as a recognition signal for a specific downstream protease. As a post- doctoral fellow with Dr. Harvey Lodish at the M.I.T., he continued his studies on the ubiquitin system and made additional important discoveries. Along the years it has become clear that ubiquitin-mediated proteolysis plays major roles in numerous cellular processes, and aberrations in the system underlie the pathogenetic mechanisms of many diseases, among them certain malignancies and neurodegenerative disorders. Consequently, the system has become an important platform for drug development, in particular for Multiple Myeloma and its "cousins" (proteasome inhibitors and imides). Among the numerous prizes Ciechanover received are the 2000 Albert Lasker Award, the 2002 EMET Prize, the 2003 Israel Prize, and the 2004 Nobel Prize (Chemistry; shared with Drs. Hershko and Rose). Among many academies, Ciechanover is member of the Israeli National Academy of Sciences and Humanities, The European Molecular Biology Organization (EMBO), the American Academy of Arts and Sciences (Foreign Fellow), the American Philosophical Society, the National Academies of Sciences (NAS) and

Medicine (NAM) of the USA (Foreign Associate), the Pontifical Academy of Sciences at the Vatican, the Chinese Academy of Sciences (CAS; Foreign Member), the Russian Academy of Sciences (Foreign Member), and the German Academy of Sciences (Leopoldina).

**Ubiquitin Proteolytic System:
From Basic Mechanisms thru Human Diseases
and on to Drug Development**

Aaron Ciechanover
The Rappaport Technion Integrated Cancer Center
and Faculty of Medicine,
Technion-Israel Institute of Technology, Haifa, Israel

Abstract

Between the 50s and 80s, most studies in biomedicine focused on the central dogma – the translation of the information coded by DNA to RNA and proteins. Protein degradation was a neglected area, considered to be a non-specific, dead-end process. While it was known that proteins do turn over, the high specificity of the process – where distinct proteins are degraded only at certain time points, or when they are not needed any more, or following denaturation/misfolding when their normal and active counterparts are spared – was not appreciated. The discovery of the lysosome by Christian de Duve did not significantly change this view, but gradually it has become clear that this organelle is involved mostly in the degradation of extracellular proteins, but mostly that the lysosomal proteases cannot be substrate-specific. The discovery of the complex cascade of the ubiquitin-proteasome pathway solved the enigma. It is clear now that degradation of cellular proteins is a highly complex, temporally controlled, timed and tightly regulated process that plays major roles in a broad array of basic cellular processes such as cell cycle and differentiation, communication of the cell with the extracellular environment and maintenance of the cellular quality control. With the multitude of substrates targeted and the myriad processes involved, it is not surprising that aberrations in the pathway have been implicated in the pathogenesis of many diseases, certain malignancies and neurodegenerative disorders among them, and that consequently, the system has become a major platform for drug development.

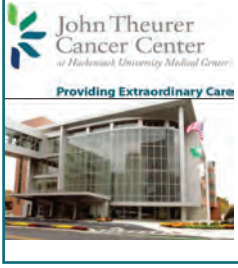
David H. Vesole, MD, PhD, FACP, is Co-Chief, Myeloma Division, Director, Myeloma Research at the John Theurer Cancer Center at Hackensack UMC; Professor of Medicine at Georgetown University School of Medicine and Hackensack Meridian School of Medicine; Director, Myeloma Program, Medstar Georgetown University Hospital. He is a Member of the Stem Cell Transplant & Cellular Immunotherapy Program at both Hackensack UMC and Medstar Georgetown University Hospital.

Dr. Vesole's research interests involve all aspects of the management of plasma cell dyscrasias (multiple myeloma, monoclonal gammopathy of undetermined significance, amyloidosis, Waldenstrom's macroglobulinemia). Dr. Vesole has had more than 30 years of clinical research experience in plasma cell dyscrasias, stem cell transplant and now effector cell therapy: he has over 250 peer reviewed publications in these areas. He is a member of the International Myeloma Working Group and listed in the IWMF Directory of WM Physicians.

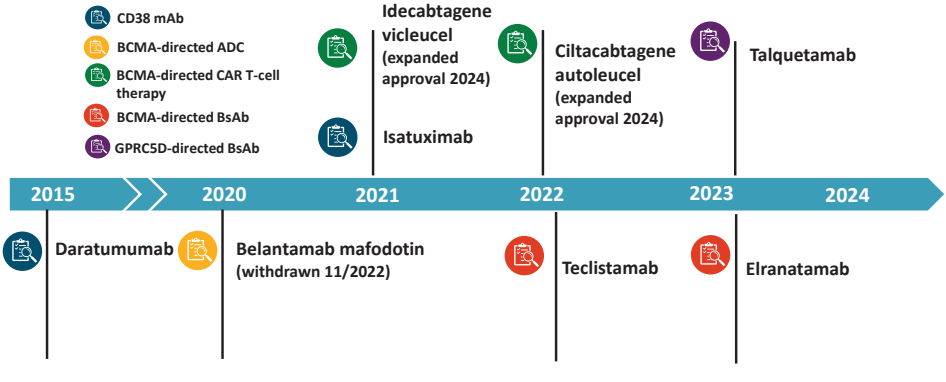
Dr. Vesole earned his bachelor of sciences degree at the University of Iowa; PhD degree in Immunology and Microbiology at the Medical University of South Carolina, his medical degree at Northwestern University and completed his hematology/oncology fellowship at the University of Iowa.

T-cell Redirecting Antibody in Patients with Relapsed or Refractory Multiple Myeloma

Co-Director, Myeloma Division
Director, Myeloma Research
John Theurer Cancer Center
Hackensack Meridian School of Medicine
Director, Myeloma Program
Interim Director, BMT Program
Professor of Medicine, Georgetown University
david.vesole@hmhn.org

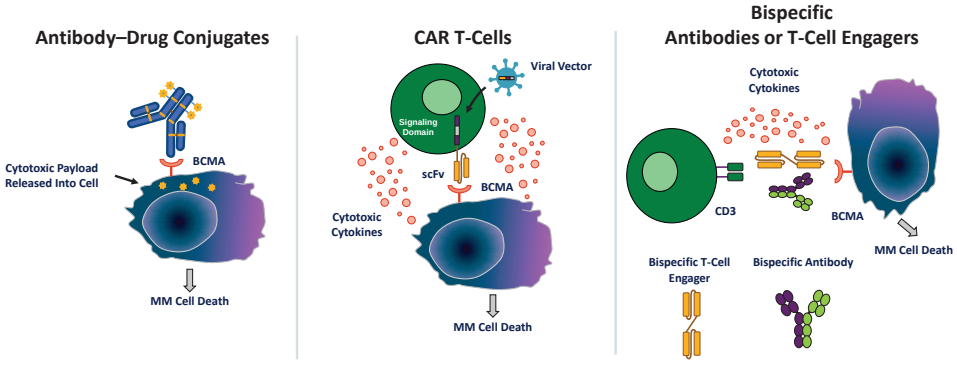


Novel Therapies in Multiple Myeloma



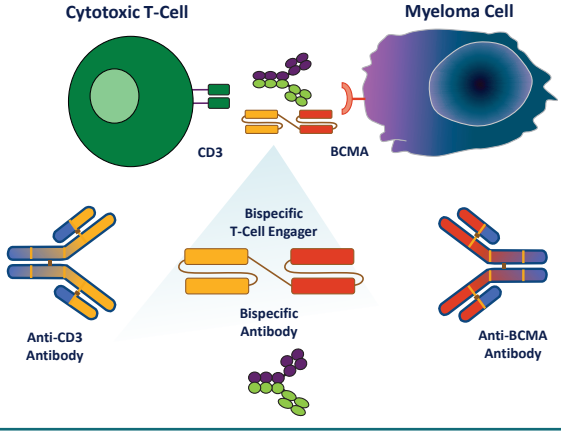
Ciltacabtagene autoleucel PI. Belantamab mafodotin PI. Daratumumab PI.
Elranatamab PI. Isatuximab PI. Idecabtagene vicleucel PI. Teclistamab PI. Talquetamab PI.

Mechanism of Action for Novel BCMA-Targeted Therapies



Cho. Front Immunol. 2018;9:1821. Su. J Hematol Oncol. 2021;14:115. Tai. Expert Opin Biol Ther. 2019;19:1143. Yu. J Hematol Oncol. 2020;13:1.

Bispecific T-Cell Antibodies in Myeloma: Mechanism of Action



O'Neill. EJHaem. 2023;4:811.

Currently Available Bispecific Antibody Therapies in R/R MM

- All indicated for R/R MM after ≥4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb

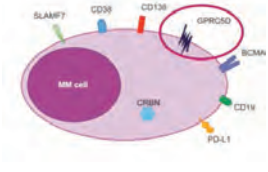
Agent	Target	Administration Route	Step-up Dosing	Target Dose
Teclistamab	BCMA x CD3	SC	Day 1: 0.06 mg/kg Day 4: 0.3 mg/kg Day 7: 1.5 mg/kg	1.5 mg/kg QW
Elranatamab	BCMA x CD3	SC	Day 1: 12 mg Day 4: 32 mg Day 8: 76 mg	76 mg QW through Wk 24, then 76 mg Q2W thereafter
Talquetamab	GPRC5D x CD3	SC	Day 1: 0.01 mg/kg Day 4: 0.06 mg/kg Day 7: 0.4 mg/kg Day 10*: 0.8 mg/kg	0.4 mg/kg QW or 0.8 mg/kg Q2W

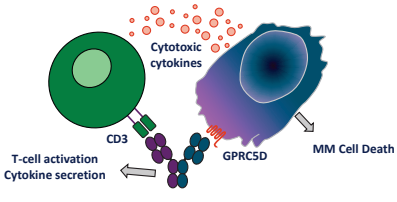
*Day 10 step-up dose only for Q2W schedule.

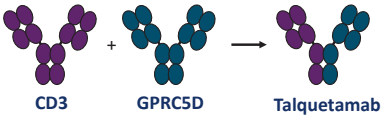
Elranatamab-bcmm PI. Teclistamab-cqyv PI. Talquetamab-tgvs PI.

Talquetamab

- GPRC5D x CD3 bispecific antibody
  - Orphan GPCR of unknown function with limited expression in healthy human tissue; primarily plasma cells and hair follicles
  - Highly expressed in MM cells and associated with poor prognostic features in MM
  - No known extracellular shedding

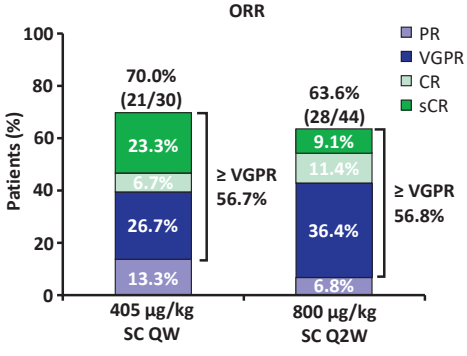






Krishnan. ASCO 2021. Abstr 8007

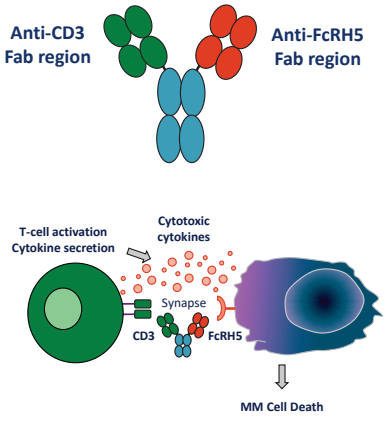
MonumenTAL-1 Trial With Talquetamab (Targets GPRC5D): Overall Response Rate



Response	405 µg/kg SC QW n=30	800 µg/kg SC Q2W n=44
Median follow-up (months), median (range)	13.2 (1.1-24.0)	7.7 (0.7-16.0)
Response-evaluable patients, n	30	44
ORR, n (%)	21 (70.0)	28 (63.6)
ORR in triple-class–refractory patients, n/N (%)	15/23 (65.2)	23/34 (67.6)
ORR in penta-drug–refractory patients, n/N (%)	5/6 (83.3)	9/12 (75.0)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.3–6.8)

Cevostamab: FcRH5 x CD3 Bispecific

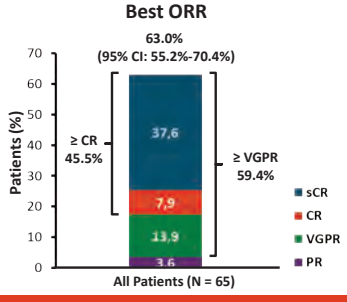
- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence
  - Also expressed on normal B-cells, but higher in myeloma and plasma cells
  - Gene located on chromosome 1
- Cevostamab BFCR4350A:
  - Humanized IgG based FcRH5 x CD3 bispecific antibody



Cohen. ASH 2020. Abstr 292.

Phase I/II MajesTEC-1: Teclistamab in R/R MM Extended 2-Yr Follow-up

- R/R MM after ≥3 lines of therapy, including an IMiD, PI, and anti-CD38 mAb
  - 26% high-risk cytogenetics
  - Median 5 prior lines of therapy (range: 2-14)
  - 78% triple-class refractory; 30% penta refractory
  - 90% refractory to last therapy line
- **Teclistamab**: 1.5 mg/kg SC weekly, after step-up



Outcomes, Mo (95% CI)	All Patients (N = 165)
Median DoR	24 (16.2-NE)
Median PFS	12.5 (8.8-17.2)
Median OS	21.9 (16-NE)

ORR by Subgroup	n/N	%
≤3 prior lines of therapy	32/43	74.4
>3 prior lines of therapy	72/122	59.0
High-risk cytogenetics and/or EMD	32/60	53.3

Median follow-up: 23 mo

Moreau. NEJM. 2022;387:495. van de Donk. ASCO 2023. Abstr 8011.

Phase I/II MajesTEC-1: Teclistamab-Related AEs

AE, n (%)	All Patients (N = 165)
CRS,*	119 (72)
▪ ≥2 CRS events	55 (33)
▪ Median onset, days (range)	2 (1-6)
▪ Median duration, days (range)	2 (1-9)
Supportive measures CRS	
▪ Tocilizumab	60 (36)
▪ Low-flow oxygen by nasal cannula	21 (13)
▪ Corticosteroids	14 (9)
▪ Single vasopressor	1 (<1)
ICANS/neurotoxicity*	24 (15)
▪ Median onset, days (range)	3 (1-13)
▪ Median duration, days (range)	7 (1-291)
Supportive measures for neurotoxicity	
▪ Tocilizumab	3 (2)
▪ Dexamethasone	3 (2)

*Events resolved without needing treatment discontinuation or dose reduction.

AE, %	All Patients (N = 165)	
	Any Grade	Grade ≥3
Hematologic		
▪ Neutropenia	72	65
▪ Anemia	54	38
▪ Thrombocytopenia	42	22
▪ Lymphopenia	35	33
Other		
▪ Infection	80	55
▪ Hypogammaglobulinemia	22	—

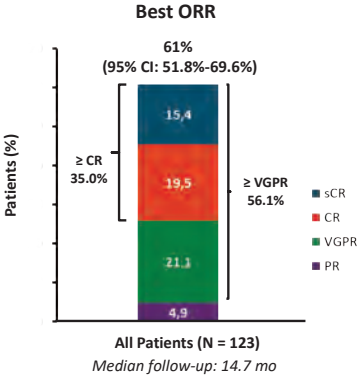
- Infection risk
  - 58% respiratory
  - 27% COVID-19 related
  - 4% *P jirovecii* pneumonia
  - 21 infection-related deaths; 18 COVID-19 related

Moreau. NEJM. 2022;387:495. Martin. Cancer. 2023;129:2035. Nooka. Cancer. 2024;130:886. van de Donk. ASCO 2023. Abstr 8011.

Phase II MagnetisMM-3: Elranatamab for BCMA-Directed Therapy-Naive R/R MM (Cohort A)

- Patients with MM refractory to ≥1, including an IMiD, PI, and anti-CD38 mAb
  - 97% triple-class refractory
  - Median 5 prior lines of therapy (range: 2-22)
  - 25% with high-risk cytogenetics
  - 32% with extramedullary disease
- **Elranatamab**: 76 mg SC weekly with priming and/or premedication to reduce CRS
  - If weekly dosing given for ≥6 cycles with achievement of ≥ PR for ≥2 mo, then dosing interval changed to every 2 wk

Outcome	All Patients (N = 123)
Median DoR, mo (95% CI)	NR (NE-NE)
Median PFS, mo (95% CI)	NR (9.9-NE)
Median OS, mo (95% CI)	NR (13.9-NE)



Lesokhin. Nat Med. 2023;29:2259.

Phase II MagnetisMM-3: Safety

AE, %	All Patients (n = 119)
CRS	56.3
▪ ≥2 CRS events	15.1
▪ Median onset, days (range)	2 (1-9)
▪ Median duration, days (range)	2 (1-19)
Supportive measures CRS	
▪ Tocilizumab	22.7
▪ Corticosteroids	8.4
ICANS	3.4
▪ Median onset, days (range)	2 (1-4)
▪ Median duration, days (range)	2 (1-6)
Supportive measures for ICANS	
▪ Tocilizumab	1.7
▪ Corticosteroids	1.7

TEAEs, %	All Patients (n = 123)	
	Any	Grade ≥3
Hematologic		
▪ Anemia	48.8	37.4
▪ Neutropenia	48.8	48.8
▪ Thrombocytopenia	30.9	23.6
▪ Lymphopenia	26.8	25.2
Other		
▪ Infection	69.9	39.8
▪ Hypogammaglobulinemia	75.5	—

- Any grade TEAE occurred in all patients; 70.7% grade ≥3 events (fewer after switch to Q2W dosing)
- Dose reduction in 28.5% and interruptions in 77.2% of patients
- Infection risk:
  - 29.3% COVID-19 related
  - 6.5% fatal
  - 4.9% *P jirovecii* pneumonia

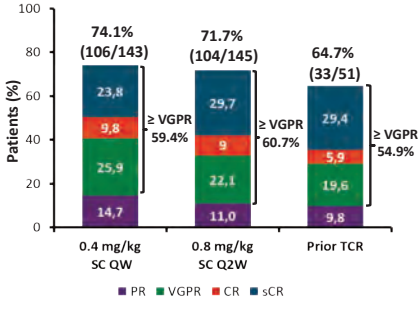
Lesokhin. Nat Med. 2023;29:2259.

Phase II MonumenTAL-1: Talquetamab in R/R MM

- Patients with R/R MM after ≥3 lines of therapy, including an IMiD, PI, anti-CD38 mAb
  - 69%-84% triple-class refractory
  - Median 5-6 prior lines of therapy across all cohorts
  - 27.1% with high-risk cytogenetics; 24.3% with EMD
- **Talquetamab**: 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W with 2-3 step-up doses and/or premedication to reduce CRS

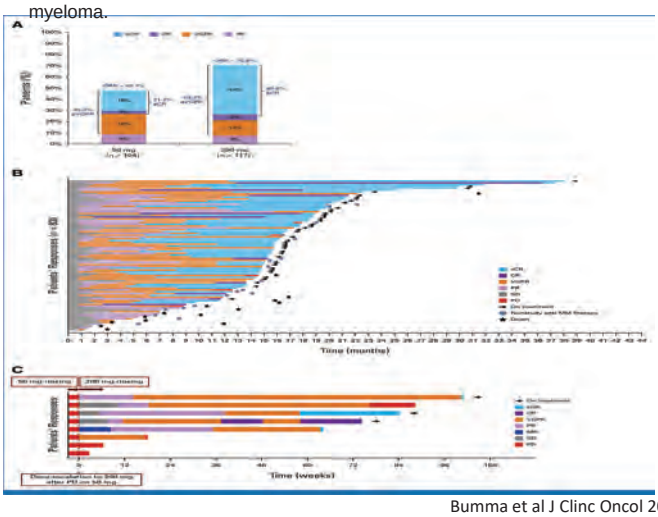
Outcome	0.4 mg/kg QW (n = 143)	0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection Tx (n = 51)
Median DoR, mo (95% CI)	9.5 (6.7-13.3)	NR (13.0-NE)	11.9 (4.8-NE)
12-Mo PFS, %	34.9	54.4	38.1
12-Mo OS, %	76.4	77.4	62.9

ORR



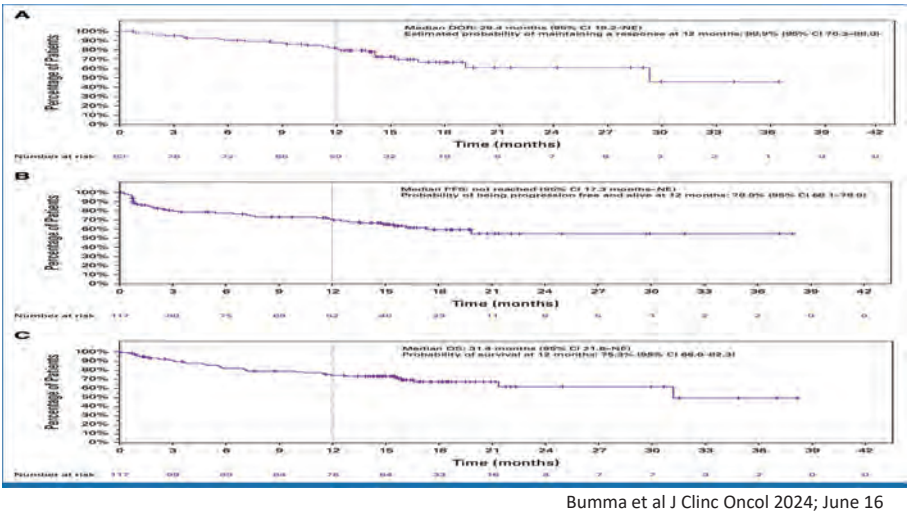
Schinke. ASCO 2023. Abstr 8036.

Overall response to linvoseltamab in relapsed/refractory multiple myeloma.



Bumma et al J Clinc Oncol 2024; June 16

KM analysis of DOR, PFS, and OS.



Bumma et al J Clinc Oncol 2024; June 16

BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response	DoR/PFS/OS, Mo
Teclistamab[1]	▪ RP2D: 1.5 mg/kg SC once weekly	165	▪ Median of 5 prior lines of tx ▪ 78% triple refractory ▪ 30% penta refractory	▪ CRS 72% (0.6% G3/4) ▪ Neurotox 14% (0.6% G3/4) ▪ ICANS 3% ▪ Infections 76%	ORR: 63% sCR/CR: 39% ≥VGPR: 59%	mDoR: 18.4 mPFS: 11.3 mOS: 18.3
Elranatamab[2,3]	▪ 215-1000 µg/kg SQ weekly or every 2 wk ▪ RP2D: 1000 µg/kg	55	▪ Median of 6 prior lines of tx ▪ 91% triple refractory ▪ 24% prior BCMA-based tx	▪ CRS 87%, no G3-4 (67% with priming and premeds) ▪ ICANS 20% ▪ ISR 56%	ORR: 64% sCR/CR: 35% ≥VGPR: 58.2%	No mature data at 10.6 mo follow-up
Linvoseltamab (REGN5458)[4,5]	▪ IV weekly, then every other wk after Wk 16 ▪ 3-800 mg dose escalation	73	▪ Median of 5 prior lines of tx ▪ 89% triple refractory ▪ 38% penta refractory	▪ CRS 38%, no G3/4 ▪ ICANS 4%	ORR (all doses): 51% ORR (200-800 mg): 75% ≥VGPR (200-800 mg): 58%	mDoR: NR at median 3 mo follow-up
ABBV-383 (TNB-383B)[6]	▪ IV fixed doses, once every 3 wk with no step dosing ▪ 0.025-120 mg dose escalation	124	▪ Median of 5 prior lines of tx ▪ 82% triple refractory ▪ 35% penta refractory	▪ CRS 57%, G3/4: 2% ▪ ICANS 2% ▪ Infections 41%	ORR (all doses): 57% ORR (60 mg exp): 59% ≥VGPR (60 mg exp): 39%	mDoR: NR mPFS: 10.4
Pavurutamab (AMG 701)[7]	▪ IV weekly ▪ 0.005-18 mg dose escalation	85	▪ Median of 6 prior lines of tx ▪ 62% triple refractory	▪ CRS 65% (9% G3) ▪ No ICANS reported ▪ 17% infection SAE	ORR (all doses): 26% ORR (3-18 mg): 36% ORR (most recent cohort): 83%	No mature data at 6.5 mo follow-up

1. Moreau. NEJM. 2022;387:495. 2. Jakubowiak. ASCO 2022. Abstr 8014. 3. Dalovisio. EHA 2022. Abstr P897. 4. Zonder. ASH 2021. Abstr 160. 5. Zonder. IMS 2022. Abstr OAB-056. 6. D'Souza. JCO. 2022;[Epub]. 7. Harrison. ASH 2020. Abstr 181.

Slide credit: clinicaloptions.com

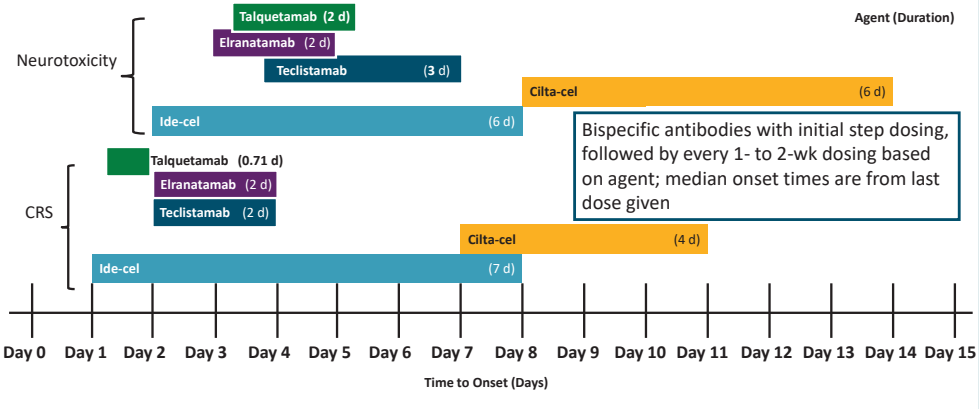
Novel Bispecific Antibodies

Therapy	Characteristics	N	Population	Safety	Response	mDoR, Mo
Talquetamab[1,2]	▪ G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody ▪ RP2D: 405 µg/kg SC once weekly or 800 µg/kg SC once every 2 wk	n = 30 (405 µg/kg QW)	▪ Median of 6 prior lines of tx ▪ 77% triple refractory ▪ 24% penta refractory	▪ CRS 78% (1.4% G3/4) ▪ Infections: 47% (405 µg/kg); 39% (800 µg/kg) ▪ Neutropenia (51%), anemia (51%), thrombocytopenia (28%)	ORR: 70% sCR/CR: 30% ≥VGPR: 57%	10.2
		n = 44 (800 µg/kg Q2W)			ORR: 63.6% sCR/CR: 20% ≥VGPR: 57%	13.0
Cevostamab (BFCR4350A)[3,4]	▪ FcRH5/CD3 bispecific T-cell engager ▪ Q3W IV infusions with single step up or double step-up expansions	161	▪ Median of 6 prior lines of tx ▪ 85% triple refractory ▪ 68% penta refractory	▪ CRS 81% (1.2% G3) ▪ ICANS 14% (0.6% G3) ▪ Neutropenia, anemia, thrombocytopenia most common heme AE	ORR: 57% at 132-198 mg; 36% at 20-90 mg dose level	11.5

1. Minnema. ASCO 2022. Abstr 8015. 2. Minnema. EHA 2022. Abstr S182. 3. Cohen. ASH 2020. Abstr 292. 4. Trudel. ASH 2021. Abstr 157.

Slide credit: clinicaloptions.com

CRS and Neurotoxicity: Median Time to Onset and Duration by CAR T-Cell or Bispecific Antibody Product



Ciltacabtagene autoleucel PI. Elranatamab PI. Idecabtagene vicleucel PI. Talquetamab PI. Teclistamab PI.

Management: Neurologic Toxicity and ICANS

Grade	CAR T-Cell Therapy		Bispecific Antibody Therapy	
	Neurotoxicity	CRS + Neurotoxicity	Neurotoxicity Without ICANS	ICANS
1	Supportive care (± corticosteroids)	Supportive care (± tocilizumab)*	Withhold until symptoms resolve or stabilize	Withhold until resolution
2	Corticosteroids (dexamethasone or methylprednisolone)	Tocilizumab + corticosteroids (dexamethasone)	Withhold until symptoms improve to grade ≤1 + supportive care	Withhold until resolution + corticosteroids + 48-hr hospitalization with next dose
3	Corticosteroids (dexamethasone or methylprednisolone)	Tocilizumab + corticosteroids (dexamethasone)	Grade 2 actions at first occurrence, grade 4 actions at reoccurrence	Grade 2 actions + supportive care + steroids at first occurrence, grade 4 actions at reoccurrence
4	High-dose corticosteroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose corticosteroids (methylprednisolone) ICU/critical care	Permanently discontinue + supportive care (dexamethasone or methylprednisolone) ICU/critical care	

*High-burden, high-risk products; older age; and comorbidities, among others.

Add anticonvulsants
Low threshold for inpatient management (if outpatient at time of onset)
Multidisciplinary team approach

Neelapu. Hematol Oncol. 2019;37:48. Elranatamab-bcmm PI. Talquetamab-tgvs PI. Teclistamab-cqvy PI.

Management: Infection Prophylaxis and Vaccinations

- Infections (bacterial, viral, fungal), hypogammaglobulinemia, and grade ≥3 neutropenia are common TEAEs for ide-cel, cilta-cel, teclistamab, and elranatamab
- Complete outstanding vaccinations at least 2 wk prior to therapy start (eg, influenza, pneumococcal, herpes zoster, COVID-19)
  - Delay postinfusion vaccinations for 3-6 mo after chemotherapy or ASCT
  - Consider checking antibody titers
- Administer IVIG for IgG <400 mg/dL and consider preemptive treatment for high-risk patients
- Consider G-CSF in patients with severe neutropenia (avoid during step-up phase and CRS)

Antibacterial Prophylaxis	Antiviral Prophylaxis	Antifungal Prophylaxis
Recommend for patients at high risk of infection	HSV/VZV prophylaxis in all patients	▪ PJP prophylaxis recommended ▪ Other antifungal prophylaxis recommended for patients at high risk of fungal infection

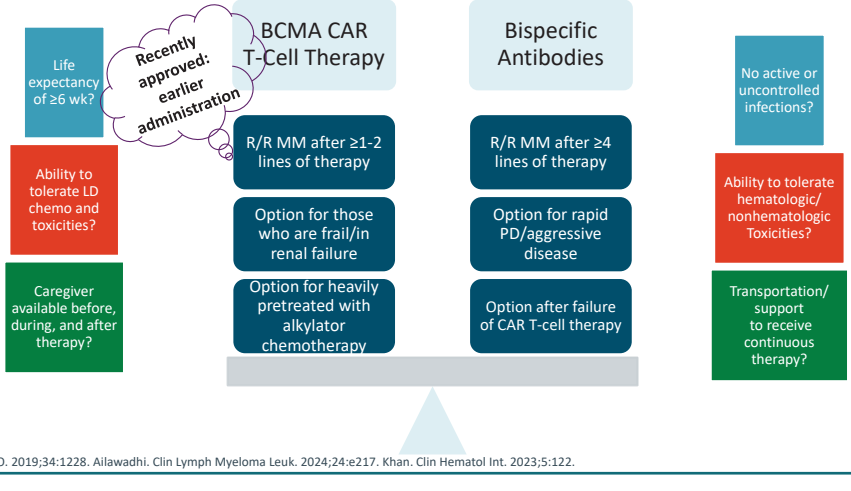
Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Teclistamab PI. Elranatamab PI. Munshi. NEJM. 2021;384:705.
Berdeja. Lancet. 2021;398:10297. Hill. Blood. 2020;136:925. Lesokhin. Nat Med. 2023;29:2259. Ludwig. Lancet Oncol. 2023;24:e255.
Moreau. NEJM. 2022;387:495. Raje. Blood Ca J. 2023;13:116. Ludwig. Am J Hematol. 2023;98:S46.

Comparing BCMA Options: Advantages/Disadvantages

	Antibody–Drug Conjugate	CAR T-Cells	Bispecific Antibody
Advantages	Off the shelf	Personalized	Off the shelf
	Targeted cytotoxicity Not dependent on T-cell health	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	No lymphodepletion No corticosteroids	Single infusion (“one and done”)	No lymphodepletion Minimal corticosteroids
	Available to any infusion center Outpatient administration	Potentially persistent	Availability for SUD not universal Outpatient administration
Disadvantages	REMS	FACT-accredited center require/REMS (hospitalization likely required)	Initial hospitalization recommended/REMS
	Ocular toxicities requiring frequent ophthalmology visits	CRS and neurotoxicity; requires ICU and neurology services	CRS and neurotoxicity possible
	Single-agent activity low in CD38-refractory patients	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires continuous administration	Requires significant social support; caregiver required	Requires continuous administration
	$$$	$$$$	$$$

Kleber. J Clin Med. 2021;10:4088. Sammartano. Cancer Drug Resist. 2023;6:169.

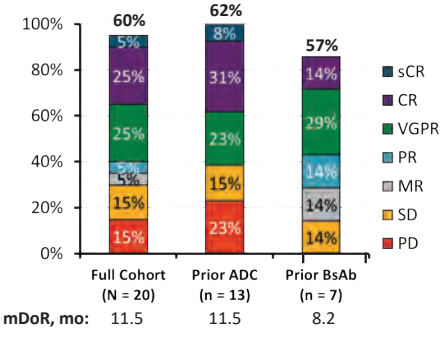
Factors to Consider When Selecting Therapies



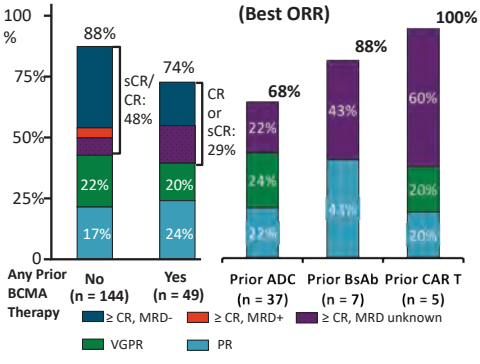
Mikhael. JCO. 2019;34:1228. Ailawadhi. Clin Lymph Myeloma Leuk. 2024;24:e217. Khan. Clin Hematol Int. 2023;5:122.

Role of Prior BCMA-Targeted Therapies on CAR T-Cell Therapy Outcomes

CARTITUDE-2 Cohort C: Cilta-Cel After PI, IMiD, CD38 mAb, BCMA-Targeted Tx (Best ORR)



Ide-Cel Retrospective RWE: 75% of Patients Met KarMMa Exclusion Criteria (Best ORR)



Cohen. Blood. 2023;141:219. Ferreri. Blood Cancer J. 2023;13:117.

Ide-Cel After BCMA-TT: Response

Response, %	Prior BCMA-TT (n = 49)	No Prior BCMA-TT (n = 144)
ORR	74	88
≥ CR	29	48
VGPR	20	22
PR	25	17

Response Stratified by Type of Previous BCMA-TT, %	ADC (n = 37)	Bispecific (n = 7)	CAR T (n = 5)
ORR	68	86	100
≥ CR	22	43	60
VGPR	24	0	20
PR	22	43	20

- Inferior outcomes with prior BCMA-TT vs those without prior BCMA-TT
  - ORR: *P* = .021
  - Best response of ≥ CR: *P* = .018

Ferreri. ASH 2022. Abstr 766.

Ide-Cel After BCMA-TT: Results by Timing of Previous BCMA-TT

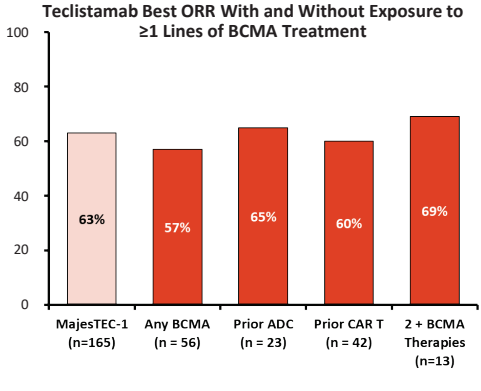
Timing	Responders (n = 36)	Nonresponders (n =13)	*P* Value by Wilcoxon Rank Sum Test
Duration of prior BCMA-TT, median days (range)	23 (1-208)	63 (1-370)	.025
Time from last BCMA-TT to apheresis, median days (range)	169.5 (30-1066)	84 (1-286)	.017
Time from last BCMA-TT to ide-cel infusion, median days (range)	209 (16-1118)	128 (32-362)	.052

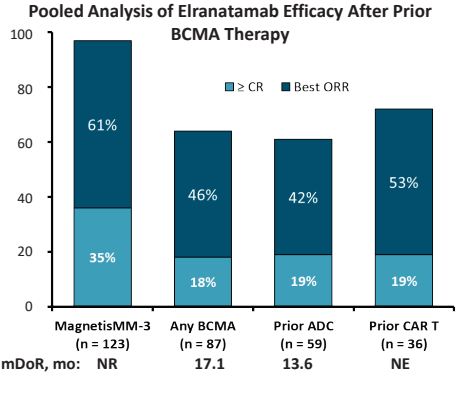
Timing	Prior BCMA-TT >6 Mo (n = 29)	Prior BCMA-TT <6 Mo (n = 20)
ORR*	24 (83)	12 (60)
▪ ≥ CR	10 (35)	4 (20)

**P* = .076 by Chi-square test.

Ferreri. ASH 2022. Abstr 766.

Outcomes With Bispecific Antibodies After Prior BCMA-Directed Therapy





Moreau. NEJM. 2022;387:495. Dima. ASH 2023. Abstr 91.
Lesokhin. Nat Med. 2023;29;2259-2267. Nooka. ASCO 2023. Abstr 8008.

Elranatamab After Previous BCMA Therapy: Efficacy Summary

Response	Any Prior BCMA tx (n = 87)	Prior ADC (n = 59)	Prior CAR-T (n = 36)
ORR, %	46.0	42.4	52.8
▪ sCR	4.6	5.1	2.8
▪ CR	13.8	13.6	16.7
▪ VGPR	24.1	20.3	27.8
▪ PR	3.4	3.4	5.6
Median DoR, mo (95% CI)*	17.1 (9.8-NE)	13.6 (6.8-NE)	NE (9.8-NE)
Median PFS, mo (95% CI)	5.5 (2.2-10.0)	3.9 (1.9-6.6)	10.0 (1.9-NE)
Median OS, mo (95%CI)	12.1 (7.5-NE)	12.1 (6.4-NE)	12.1 (6.5-NE)

*mDoR not yet mature after censoring data for 57.5% of pts (n = 23)

- Median time to response: 1.7 mo (range: 0.3-9.3)

Nooka. ASCO 2023. Abstr 8008.

TRIMM-2: Phase IB Study of Subcutaneous Teclistamab + Daratumumab in R/R MM

Characteristic, n (%)	SC Tec + Dara* (N = 65)
Median age, yr (range)	67 (40–81)
Male, n (%)	35 (53.8)
Extramedullary plasmacytomas ≥1	15 (23.1)
High cytogenetic risk† (n = 27)	12 (25.0)
Median time since diagnosis (range), yrs	6.6 (0.7–20.9)
Median prior lines of tx (range)	5 (1–15)
Prior SCT, n (%)	47 (72.3)
Exposure status	
▪ Anti-CD38‡	49 (75.4)
▪ Triple-class§	49 (75.4)
▪ Penta-drug‖	36 (55.4)
▪ BCMA-targeted therapy	8 (12.3)
Refractory status	
▪ Anti-CD38‡	41 (63.1)
▪ Triple-class§	38 (58.5)
▪ Penta-drug‖	20 (30.8)

*SC Dara 1800 mg + SC Tec (1.5mg/kg QW or 3mg/kg QW or 3mg/kg) Q2W †del(17p), t(4:14), and/or t(14;16) ‡Dara or isatuximab §≥1 PI, IMiD, and an anti CD38 mAb ‖≥2 PI, ≥2 IMiD, and ≥ 1 anti-CD38 mAb

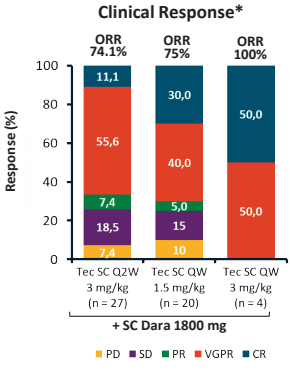
Rodriguez-Otero. EHA 2022. Abstr S188.

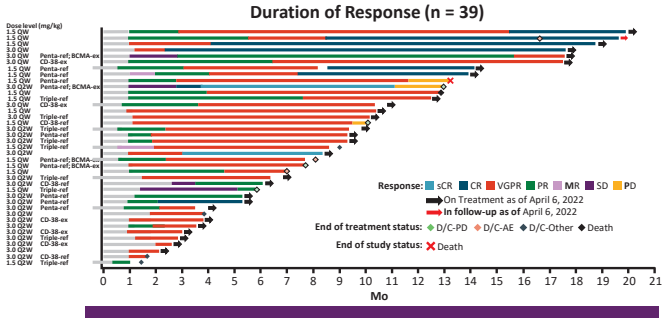
AE in ≥20% of Patients, n (%)		SC Tec + Dara (N = 65)	
		Any Grade	Grade 3/4
Hematologic	Neutropenia	32 (49.2)	27 (41.5)
	Anemia	27 (41.5)	18 (27.7)
	Thrombocytopenia	21 (32.3)	16 (24.6)
Nonhematologic	CRS	44 (67.7)	0
	Diarrhea	21 (32.3)	1 (1.5)
	Fatigue	19 (29.2)	2 (3.1)
	Pyrexia	19 (29.2)	0
	Nausea	18 (27.7)	0
	Cough	14 (21.5)	0
	Headache	13 (20.0)	1 (1.5)
	Asthenia	13 (20.0)	1 (1.5)
	Decreased appetite	13 (20.0)	0

- **Infections: 67.7% (grade 3/4: 27.7%)**
- **1 patient had grade 1 ICANS during step-up dosing that fully resolved in 1 day**

Slide credit: clinicaloptions.com

TRIMM-2: Response With Teclistamab + Daratumumab in R/R MM





- Responses were durable and deepened over time
- At median follow-up of 8.6 mo (range: 0.3-19.6), 66.7% of responders were alive and continuing on treatment

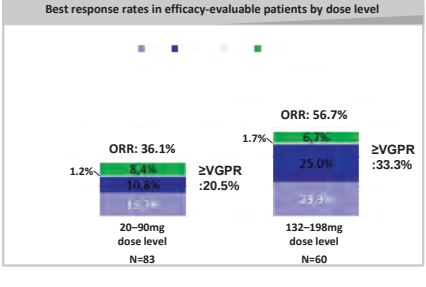
*Response evaluable patients.

Rodriguez-Otero. EHA 2022. Abstr S188.

Slide credit: clinicaloptions.com

Cevostamab (Targets FcRH5)

- Fc receptor-homolog 5 (FcRH5)
  - expressed exclusively in B-cell lineage (myeloma cells > normal B cells)
  - near ubiquitous expression on myeloma cells
- Cevostamab bispecific antibody
  - targets membrane-proximal domain of FcRH5 on myeloma cells and epsilon domain of CD3 on T cells
  - dual binding results in T-cell directed killing of myeloma cells



CR, complete response; MRD, minimal residual disease; NGS, next generation sequencing; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

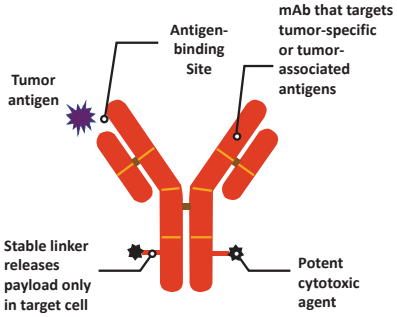
Trudel S, ASH 2021

Updates from clinical studies of bispecific antibodies for multiple myeloma

Regimen	Teclistamab	Teclistamab	Elranatamab	Linvoseltamab	F182112	Talquetamab	Teclistamab + Talquetamab	Talquetamab + Daratumumab
Disease	RRMM (without prior BCMA-directed therapies)	RRMM (with prior BCMA and GPRC5D-directed therapies)	RRMM (with and without prior BCMA-directed therapies)	RRMM (without prior BCMA-directed therapies)	RRMM (without prior BCMA-directed therapies)	RRMM (with and without prior T-cell-directed therapies)	RRMM	RRMM
Pts	165	24	123	252	16	288	63	65
mFU	22 m	1.3 m	12.8 m (range, 0.2–22.7)	2.3 m (200 mg); 4.7 m (50 mg)	3.1 m (range, 0.9–11.7)	14.9 m (QW); 8.6 m (Q2W); 11.8 m (prior T)	14.4 m (range, 0.5–21.9)	11.5 m (range, 1.0–27.3)
ORR	NA	60%	61% (objective response rate)	64% (200 mg); 50% (50 mg)	43.8% (95% CI, 19.8–70.1)	74% (QW); 73% (Q2W); 63% (prior T)	84%	78%
CR (sCR)	43%	NA	31.7%	NA	NA	NA	34%	45%
mDoR	24 m (95% CI, 16.2–NR)	NR	74.1% (95% CI, 60.5–83.6) at 12 m	NR	NA	NA	NR	NA
mPFS	12.5 m (95% CI, 8.8–17.2)	NR	57.1% (95% CI, 47.2–65.9) at 12 m	NA	NA	7.5 m (QW); 11.9 m (Q2W); 5.1 m (prior T)	NA	19.4 m
mOS	21.9 m (95% CI, 16.0–NR)	NR	62.0% (95% CI, 52.8–70.0) at 12 m	NA	NA	NA	NA	93% at 12 m
CRS	72%	41%	NA	37% (200 mg); 53% (50 mg)	81%	79% (QW); 75% (Q2W); 77% (prior T)	81%	78%
NAE/ICANS	ICANS: 3%	NAE: 13%	NA	ICANS ≥ G3: 2% (200 mg); 1% (50 mg)	NA	ICANS: 11% (QW); 11% (Q2W); 3% (prior T)	2%	5%

Belantamab Mafodotin: BCMA-Targeted ADC

- **Belantamab mafodotin (GSK2857916)**: humanized, afucosylated, IgG1 **BCMA-targeted ADC** that neutralizes soluble BCMA
  - **Cytotoxic agent** – MMAF (non–cell-permeable, highly potent auristatin)
  - **Afucosylation** – **Enhanced ADCC**
  - **Linker** – Stable in circulation
- Belantamab mafodotin FDA approved for R/R MM after ≥4 previous therapies, including an anti-CD38 mAb, a PI, and an IMiD

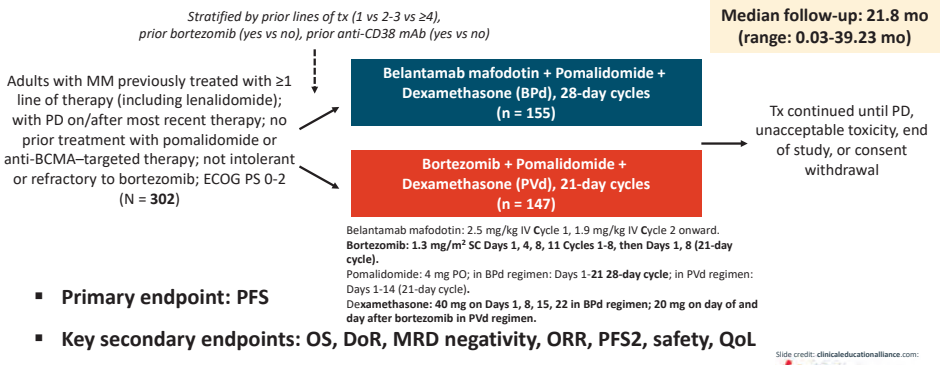


Tai. Blood. 2014;123:3128. Trudel. Lancet Oncol. 2018;19:1641. Trudel. Blood Cancer J. 2019;9:37. Belantamab mafodotin PI.

Slide credit: clinicaleducational
Slide credit: clinicaloptions.com

DREAMM-8: Study Design

- **Multicenter, randomized, open-label phase III trial**



- **Primary endpoint: PFS**
- **Key secondary endpoints: OS, DoR, MRD negativity, ORR, PFS2, safety, QoL**

Dimopoulos. **NEJM. 2024;[EPub].** Trudel AS**CO** 2024. Abstr LBA105.

Slide credit: clinicaleducationalliance.com:

DREAMM-8: Other Efficacy Endpoints

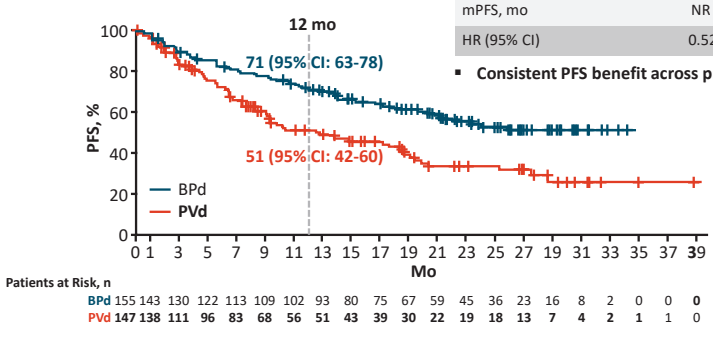
Efficacy Outcome	BPd (n = 155)	PVd (n = 147)	HR (95% CI)
ORR, %	77	72	
▪ ≥ CR	40	16	
▪ ≥ VGPR	64	38	
MRD negativity among patients with ≥ CR, %	24	5	
Median DoR, mo	NR	17.5	
▪ 12-mo DoR, %	79	61	
Median PFS2, mo	NR	22.4	0.61 (0.43-0.86)
▪ 12-mo PFS2, %	80	67	
Median OS, mo	NR	NR	0.77 (0.53-1.14)
▪ 12-mo OS, %	83	76	

Dimopoulos. **NEJM. 2024;[EPub].** Trudel AS**CO** 2024. Abstr LBA105.

DREAMM-8: PFS (Primary Endpoint)

	BPd (n = 155)	PVd (n = 147)
Patients with an event	62 (40)	80 (54)
mPFS, mo	NR	12.7
HR (95% CI)	0.52 (0.37-0.73) *P* <.001	

- **Consistent PFS benefit across prespecified subgroups**



Patients at Risk, n

BPd	155	143	130	122	113	109	102	93	80	75	67	59	45	36	23	16	8	2	0	0	**0**
PVd	**147**	**138**	**111**	**96**	**83**	**68**	**56**	**51**	**43**	**39**	**30**	**22**	**19**	**18**	**13**	**7**	**4**	**2**	**1**	1	0

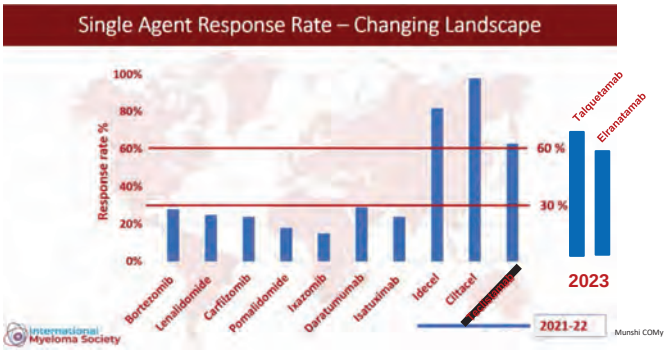
Dimpoulos. **NEJM. 2024;[EPub].** Trudel AS**CO** 2024. Abstr LBA105.

Controversies with Immunotherapy for MM

- What is the best therapeutic – Bispecific vs CAR T-cell vs ADC
- When it the best time to introduce immunotherapies?
- What is the best sequence – Bispecific ➔ CAR T-cell ➔ ADC?
- Once a therapeutic has been utilized (eg, BCMA bispecific) what's next?
  - Utilize a non-immunotherapy regimen (give the T-cells a rest)
  - Switch target BCMA➔GPRC5D➔FcRH5
  - If CAR T-cell not first therapy – when is an appropriate time to collect lymphocytes for CAR?
- What is the mechanism of resistance to CAR and bispecifics therapy?
  - Ag loss/low density on tumor cells
  - Mutations in tumor cells resulting in poor binding of therapeutic
  - T-cell exhaustion – poor T-cell function

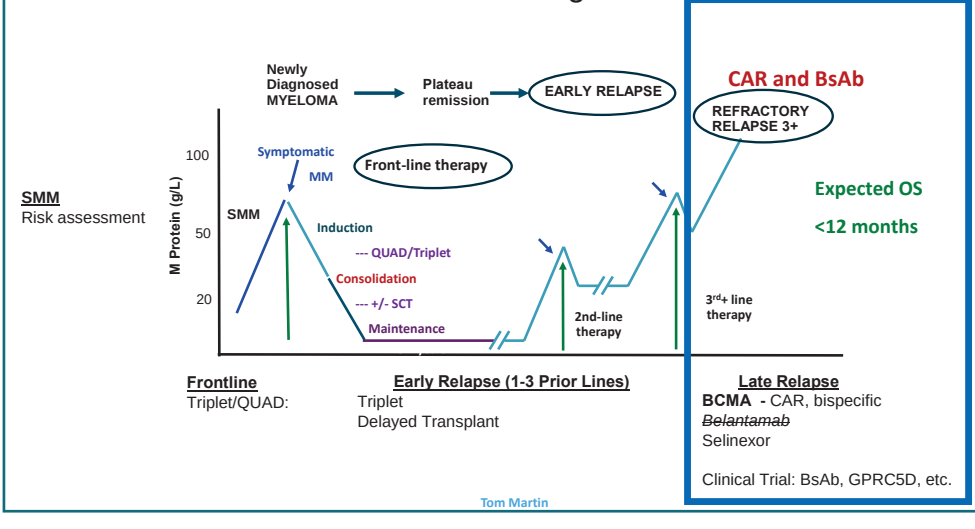
Slide credit: clinicaleducationalliance.com:
cea clinical education alliance

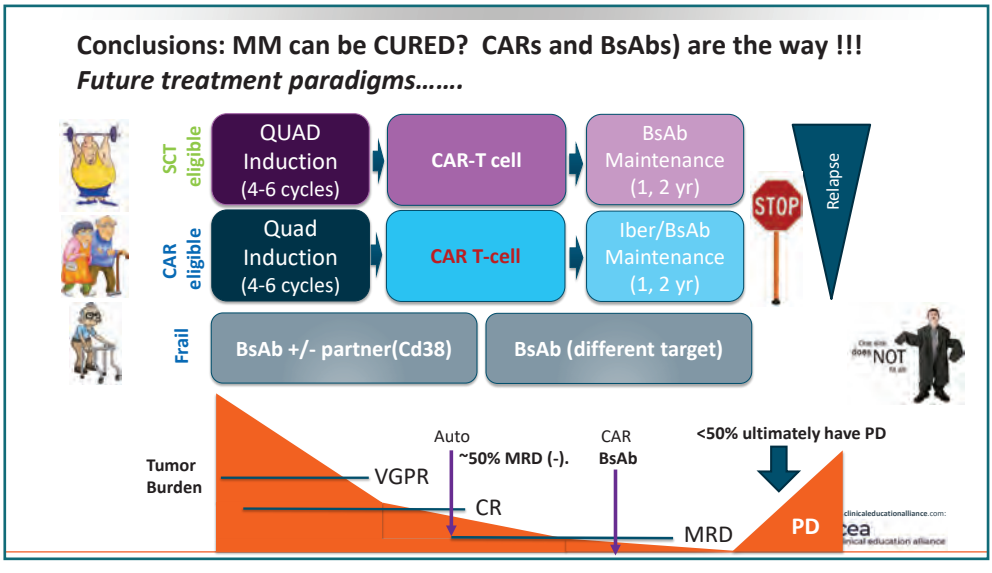
Amazing Success in Immunotherapy for MM



Right patient, right treatment, right time

Current MM Treatment Paradigm




Conclusions: MM can be CURED? CARs and BsAbs) are the way !!!
Future treatment paradigms…….
SCT eligible
QUAD Induction (4-6 cycles)
CAR-T cell
BsAb Maintenance (1, 2 yr)
CAR eligible
Quad Induction (4-6 cycles)
CAR T-cell
Iber/BsAb Maintenance (1, 2 yr)
STOP
Relapse
Frail
BsAb +/- partner(Cd38)
BsAb (different target)
NOT
Tumor Burden
VGPR
CR
MRD
Auto
~50% MRD (-).
CAR BsAb
<50% ultimately have PD
PD

Ramón García Sanz, MD, PhD, hematologist at the University Hospital of Salamanca since 1994, head of the Molecular Laboratory Unit since April 2019. Researcher at the Cancer Research Center of Salamanca since 2001. Associate professor at the School of Medicine in the University of Salamanca since 2007.

He pursued medical studies in the University of Salamanca between 1982 and 1988, and he specialized in hematology between 1990 and 1994. His PhD work was about multiple myeloma biology, and he was awarded with the Special Mention 1993/94. He also did postdoctoral studies in the Immunology Department of the Erasmus University of Rotterdam, The Netherlands, and Anthony Nola Research Institute, London, UK.

Dr. García Sanz is principal investigator and co-investigator in Multiple Myeloma, Hodgkin's Lymphoma, and Waldenström's macroglobulinemia. He also researches in blood biology and standardization in the hematology laboratory.

Ramón García Sanz has authored or co-authored more than 380 original research articles indexed in PubMed, as well as publications in Spanish, with more than 30,000 citations and an H index of 86 in google.scholar (74 in WOS). He actively participates in the Spanish groups GEM/PETHEMA and GELTAMO focusing on myeloma biology, minimal residual disease detection, and global studies in Hodgkin's lymphoma and Waldenström's macroglobulinemia. He is the current coordinator of the hematological tumors program of the CIBERONC network and the coordinator of the Hodgkin's Lymphoma subcommittee of the GELTAMO. He also participated in the board of Spanish Society of Hematology, where he was the president between 2019 and 2022.

MRD in Multiple Myeloma: past, present and future

Ramón García Sanz

Hospital universitario de Salamanca

Diagnostic criteria of Multiple Myeloma

International Myeloma Working Group (Lancet Oncol 2014; 15: e538–48)

	Monoclonal Gammopathy of uncertain significance (MGUS)	Asymptomatic Multiple Myeloma (AMM)	Multiple Myeloma (MM)
Monoclonal component	<30 g/L serum	≥ 30 g/L serum	Present (serum/urine)
	&	or	and
Bone Marrow Plasma Cells (%)	<10%	10%-60%[b,c,d]	>10%[c,d]
	y	y	y
End organ damage	Absent	Absent	Present

a) Myeloma Related Organ or Tissue Impairment (end organ damage) related to Plasma cell proliferative process: anemia with 2 g/dL below the normal level or <10 g/dL, or serum calcium level >10 mg/L (0.25 mmol/L) above normal or >110 mg/dL (2.75 mmol/L), or lytic bone lesions or osteoporosis with compressive fractures, or renal insufficiency (creatinine >2 mg/dL or 173 mmol/L),[CRAB: Calcium increase, Renal impairment, Anemia and Bone lesion] or symptomatic hyperviscosity, amyloidosis or recurrent bacterial infections (>2 episodes in 12 m).

b) treatment requirement: >60% of BMPC or a FLC involved to uninvolved ratio of at least 100 (the involved free light chain must be ≥100 mg/L); >1 focal lesions on MRI studies

c) BMPC estimation for diagnosis is based on either conventional bone marrow aspirate or biopsy examination, not FCM; If a discrepancy exists between BMPC estimation in the biopsy sample and aspirate, the higher of the two values should be used.

d) Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Response	Criteria
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in BM biopsy by IHC (κ/λ ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 PC)
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus ↓ in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% ↓ in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% ↓ in PC is required in place of M-protein, provided baseline BMPC percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% ↓ in the size (SPD) of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% ↓ of serum M-protein and ↓ in 24-h urine M-protein by 50-89%. In addition to the above listed criteria, if present at baseline, a ≥50% ↓ in the size (SPD) of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	≥1 of the following criteria: ↓ of 25% from lowest confirmed response value in ≥1 of the following criteria: Serum M-protein (absolute ↓ must be ≥0.5 g/dL); Serum M-protein ↓ ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute ↓ must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute ↓ must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, BMPC percentage irrespective of baseline status (absolute ↓ must be ≥10%); new lesion(s), ≥50% ↓ from nadir in SPD of >1 lesion, or ≥50% ↓ in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating PC (minimum of 200 cells/μL) if this is the only measure of disease

Kumar et al, Lancet of Oncology 2016

New criteria for Response

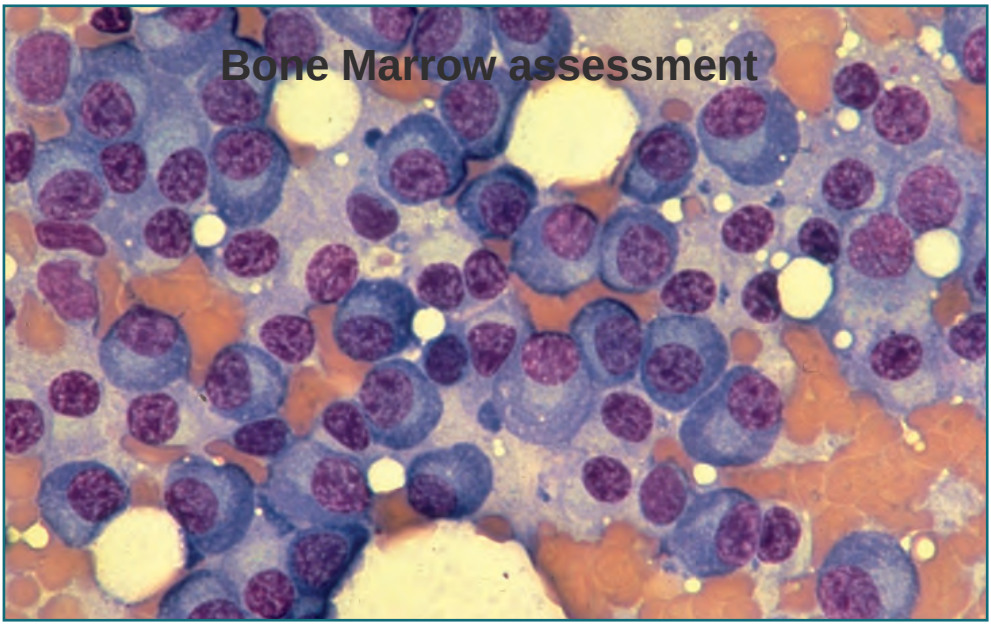
	Response Criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶

Kumar et al, Lancet of Oncology 2016

NGF, NGS & PET/CT endorsed in the IMWG MRD guidelines1 (mass spect soon)

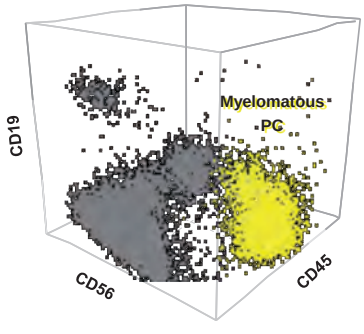
Techniques	Target	Serum	Peripheral Blood	Bone marrow	Intra- and extramedullary
Mass spectrometry	M-component	✓	-	-	-
NGF	Aberrant cells	-	✓	✓	
NGS	Clonotypic cells	-	✓	✓	
PET/CT	Active cells	-	-	-	✓

1. Kumar S, et al. **Lancet Oncol. 2016 Aug;17(8):e328-e346.**



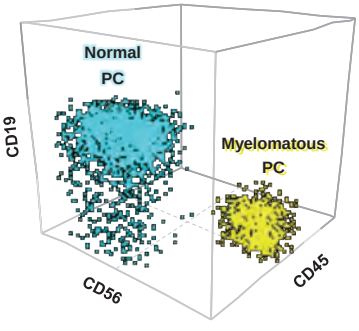
Flow cytometry
Plasma cell identification

Diagnosis



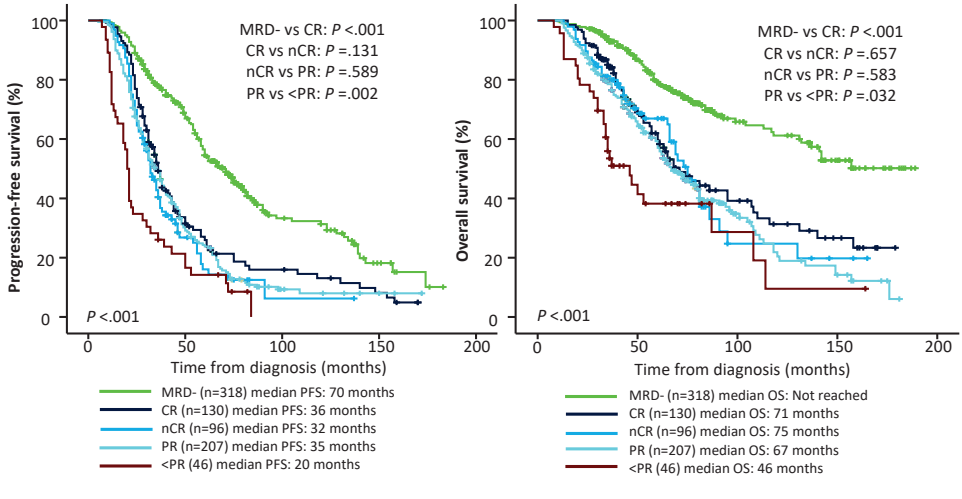
Total Bone Marrow

Post-Treatment



BM Gate CD38

MRD by flow value in MM compared to other responses



GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

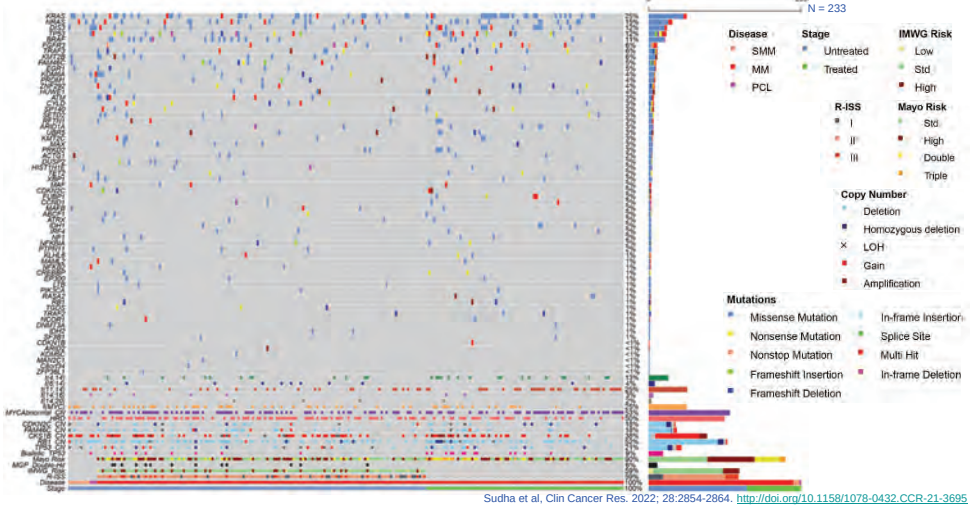
Lahuerta et al, JCO 2017 (ePud ahead of print)

Cytogenetic abnormalities in MM

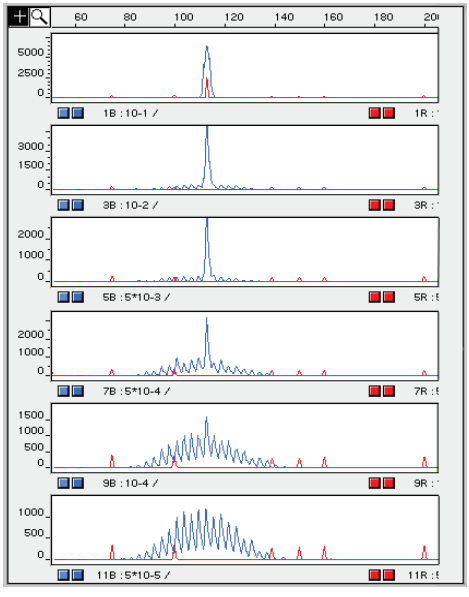
Alteration	Technique	Frequency	Molecular Consequence	Relevance
t(4;14)	**FISH**	**15%**	**Over-expression of MMSET-FGFR3**	**Poor prognosis**
del(17/17p)	**FISH**	**7%**	**Deletion of *TP53***	**Poor prognosis**
1q gain	FISH	30%	CKS1 Amplification	Poor prognosis
t(14;16)	FISH	4%	Over-expression de c-MAF	Poor prognosis
t(14;20)	FISH	1%	Over-expression de MAFB	Poor prognosis
No hyperdiploid	Karyotyping	20%	-	Poor prognosis
del(13q)	Karyotyping	10%	Rb deletion	Poor prognosis
Poor risk GEP	GEP	15%	-	Poor prognosis
del(13q)		40%	Rb deletion	Irrelevant
t(11;14)		20%	Over-expression de CCND1	Irrelevant
del(1p)		30%	Deleción de FAM46C & CDKN2C (p18)	Unknown

Sonneveld et al, 2016 Jun 16;127(24):2955-62

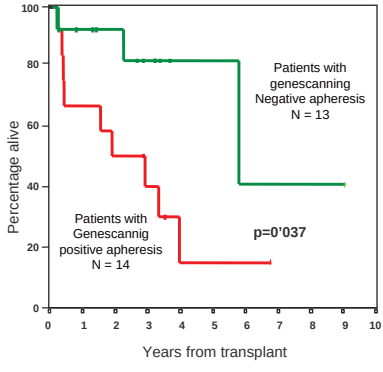
Frequency of mutations in 63 key driver genes, translocations, hyperdiploidy, and key copy number abnormalities detected by NGS



Sudha et al, Clin Cancer Res. 2022; 28:2854-2864. http://doi.org/10.1158/1078-0432.CCR-21-3695

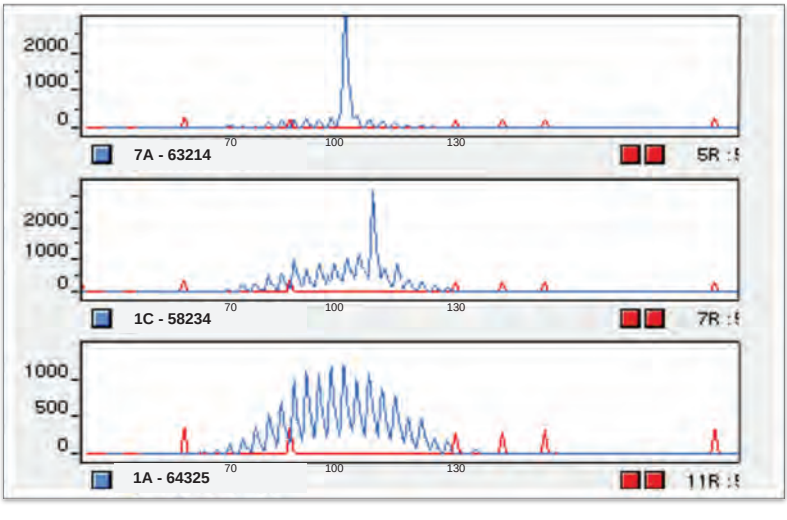


Genescanning of clonal VDJH fragments and minimal residual disease

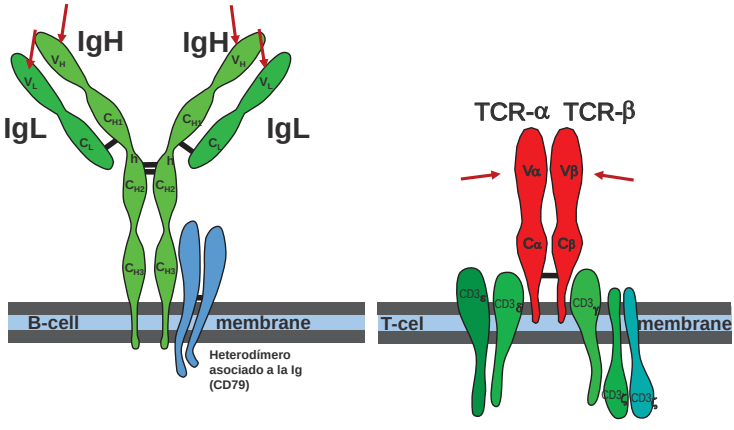


López-Pérez et al, Bone Marrow Transpl 2001, 28, 665-672

GeneScanning analysis



B & T-cell antigenic receptors

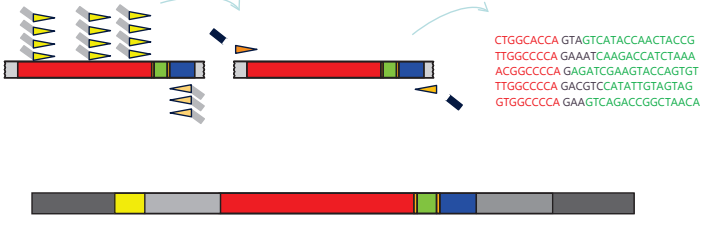


Inmunoglobulin

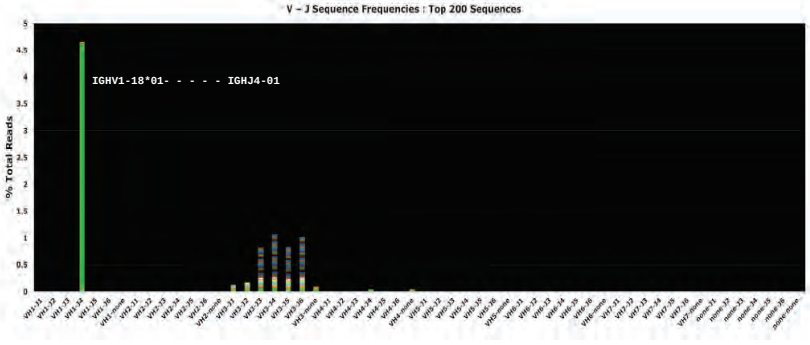
T-cell receptor

13

High throughput sequencing: Is it applicable to MRD?



Ladetto et al, Leukemia 2014; Martínez-López et al, Blood 2014



V-J Sequence Frequencies. The LymphoTrack Bioinformatics Software provides a stacked bar graph depicting the relative frequencies for the 200 most common V - J rearrangements sequenced and identified in the sample.

VH-FR2 VH-FR3 JH (consensus primer)

IGHV1-12*01 ATTTCAGGGATTGTAGAATGAATCACATTAACAAATCTGACACAGAACTTCCTCTGAATCAATCTTTGTAAACATCAATTTCCGAATCAATGTTGTAAATAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV1-14*01 GGCAGAGTCACCATGACCAGGGACACGTCCACGAGCACAGCCTACATGGAGCTGAGCAGTCAGAGATCTGAGGACATAGATGTGTACTACTGTGCGAGACAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV1-18*02 ACTATGCACAGAAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTAAGATCTGACGACACGGCCGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV1-02*02 GGCAGGGTCACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAGCTGAGCAGGCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV1-03*01 GGGCAGAGTCACCATTACCAGGGACACATCCGCGAGCACAGCCTACATGGAGCTGAGCAGGCTGAGATCTGAAGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV1-45*02 CAGGACAGAGTCACCATTACCAGGGACAGGTCTATGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACAGCCATGTATTACTGTGCAAGATGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV1-67*01 GGCAGAGTCACGATGACCAGGGACACATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCCATGTATTACTGTGGGAGAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV1-69*01 GGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCCGTGTATTACTGTGCGAGAGAGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG
IGHV1-69*09 CCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAAGGATCATCCCTATCCTGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV2-05*01 GCAGGCTCACCATCACCAAGGACACCTCCAAAAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGCCACATATTACTGTGCACACAGACGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV2-70*03 ATCTCTGAAGACCAGGCTCACCATCTCCAAGGACACCTCCAAAAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACGGCCGTGTATTACTGGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-11*01 AGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV3-13*01 GGGCCGATTCACCATCTCCAGAGAAATGCCAAGAACTCCTTGTATCTTCAAATGAACAGCCTGAGAGCCGGGGACACGGCTGTGTATTACTGTGCAAGAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV3-15*01 AGGCAGATTCACCATCTCAAGAGATGATTCAAAAAACACGCTGTATCTGCAAATGAACAGCCTGAAAACCGAGGACACAGCCGTGTATTACTGTACCACAGAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-19*01 GGGCCGATTCATCATCTCCAGAGACAATTCCAGGAACTTCCTGTATCAGCAAATGAACAGCCTGAGGCCCGAGGACATGGCTGTGTATTACTGTGTGAGAAAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-21*01 GGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-23*01 GGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-25*01 GGACCGATTCAATACTCCAGAGATAACGCCAAGAACACACTTCATCTGCAAATGAACAGCCTGAAAACCGAGGACACGGCCCTCTATTAGTGTACCAGAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV3-30*01 GGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-30*13 GGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACAGGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-32*01 GGGCAGATTCTCCATCTCCAAAGACAATGCTAAGAACTCTCTGTATCTGCAAATGAACACTCAGAGAGCTGAGGACGTGGCCGTGTATGGCTATACATAAGGTCGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-23*01 GGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-33*01 GGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-36*02 GAAGGGTCGATTCACCCTCTCCAGAGATGATGCCAAGAAATCACTGTATCTGCAAATGAACAGCGTCAGAGCCGAGGATAGGTCTGTGTATTACTGTGGTGGGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-37*02 AGACACTGAAGGGTAGATTCACCATCTCTAGAGACAATGGCAAGAACATGCTGTACTTGCAAATGAACAGCTCGAGAGATGAGGACTCGGCTGTGTGAGAGAGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-42*01 GAAAGGCAGGTTCACCATCTCAAGAGATGATTCAAAGAACACACTGTATCTGCAAGTGAATACCCTGAAAACCGAGTACACGGCCATCTATTACTGTACTAGAGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV3-43*01 GCCGATTCACCATCTCCAGAGACAACAGCAAAAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGACACCGCCTTGTATTACTGTGCAAAAGATAGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-47*01 ATGGGCCGATTCACCATCTCCAGAGACAAGCCAAGAAGTCCTTGTATCTTCATATGAACAGCCTGATAGCTGAGGACATGGCTGTGTATTATTGTGCAAGAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-23*01 GGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-48*01 GGGCCGATTCACCATCTCCAGAGACAATGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-49*03 AAGGCGATTCACCATCTCAAGAGATGATTCCAAAGCATCGCCTATCTGCAAATGAACAGCCTGAAAACCGAGGACACAGCCGTGTATTACTGTACTAGAGAGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV3-50*03 AAGGGCCGATTGACCATCTCCAGAGACAATGCCAAGAACTCCCTCTATCTGCAAGTGAACAGCCTGAGAGCTGAGGACATGACCGTGTATTACTGTGTGAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV3-23*01 GGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-53*01 AGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV3-54*02 GAGCAGATTCACCATCTCCAAAGAAATGCCAAGAACTCACTCCGTTTGCAAATGAACAGTCTGAGAGCAGAGGGCACGGCCGTGTATTACTGTATGTGAGGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-57*01 GGGCACAAATTAACAGTCCCAAGCGACACCTTTTCATGTGCAGTCTACCTTACAATGACCAACCTGAAAGCCAAGGACAAGGCTGTGTATTACTGTGAGGGAGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
IGHV3-57*02 TACAAATAAATTAACAGTCCCAAGCGACACCTTTTCATGTGCAGTCTACCTTACAATGACCAACCTGAAAGCCAAGGACAAGGCTGTGTATTACTGTGAGGGAGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
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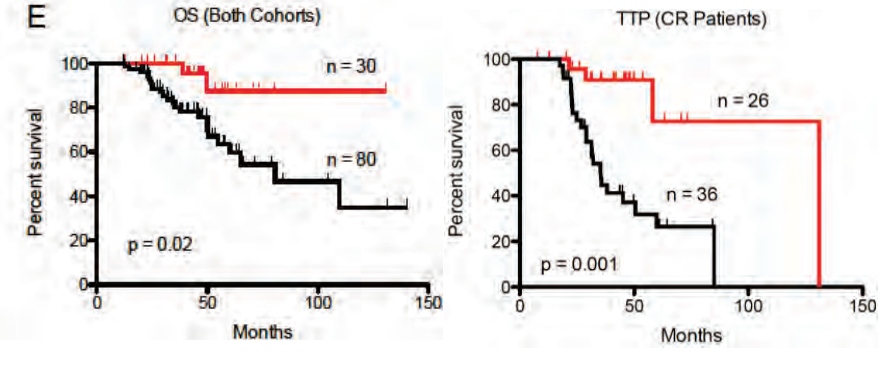
IGHV3-06*01 GGGCCGATTCACCATTTCCAGAGACAATACCAAAAACTCACTGTATCTGCAAATGAACAGACTGAGGGCAGAGGATGCAGCTGCATATGACTCTGTGAGAGAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-64*05 GGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATGTTCAAATGAGCAGTCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGTGAAAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV3-65*02 AGGTTTCACTAAAAACAAAACTAATCGTGGAACAACAGAATACGCCGCGTCTGTGAAAGGCAGATTCACCATCTCAAGCGATGATTCCAAAAGCATCGCCTATGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
IGHV3-66*04 AAGGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGCAAAGGGACCACGGTCACCGTCTCCTCAG
IGHV3-71*01 AGGCAGATTCACAATCTCAAGAGATGATTCCAAAAGCATCACCTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-73*01 AAAGGCAGGTTCACCATCTCCAGAGATGATTCAAAGAACACGGCGTATCTGCAAATGAACAGCCTGAAAACCGAGGACACGGCCGTGTATTACTGTACTAGAGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG
IGHV3-23*01 GGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG
IGHV3-74*02 AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACACGCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCAAGAGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAG

MRD evaluation by HTS in Multiple Myeloma patients: clinical value

Deep sequencing of rearranged BCR genes (Lymphosight™)

N 133 cases in CR or VGPR (sensitivity ≥10^{-5}), GEM00,05,10; Applicability 91%



Martínez-López et al, Blood 2014

MRD evaluation by HTS in Multiple Myeloma patients: clinical value

Deep sequencing of rearranged BCR genes (Lymphosight™) vs FCM & RT-PCR

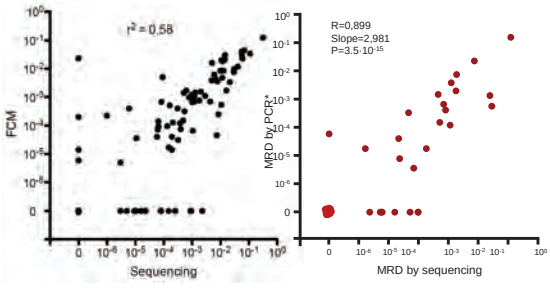
N 133 cases in CR or VGPR (sensitivity ≥10^{-5}), GEM00,05,10; Applicability 91%

HTS vs. FCM

- **62/101 (63%) & 25/45 (55%) samples were positive with both techniques**
- **22/101 (22%) & 10/45 (22%) samples were negative with two techniques**

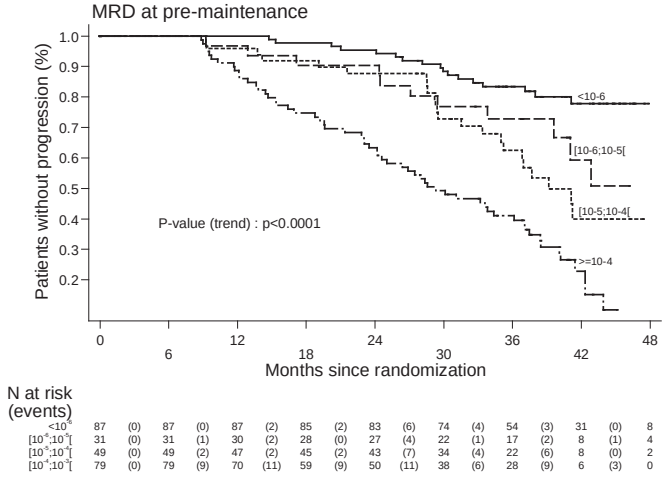
DISCORDANCIES:

- **FMC: 17/101 (17%) were discordant:**
  - **FCM+SEQ-: 5**
  - **FCM-SEQ+: 12**
- **RQ-PCR: 10/45 (22%)**
  - **PCR+SEQ-: 1**
  - **PCR-SEQ+: 9**



Martinez-Lopez et al , Blood 2014

10^{-6} MRD level is the most powerful cutoff for PFS risk-stratification



Avet-Loiseau H, et al. Blood 2015 126:191

Medina et al. *Blood Cancer Journal* (2020)10:108
https://doi.org/10.1038/s41408-020-00377-0
Blood Cancer Journal
ARTICLE Open Access

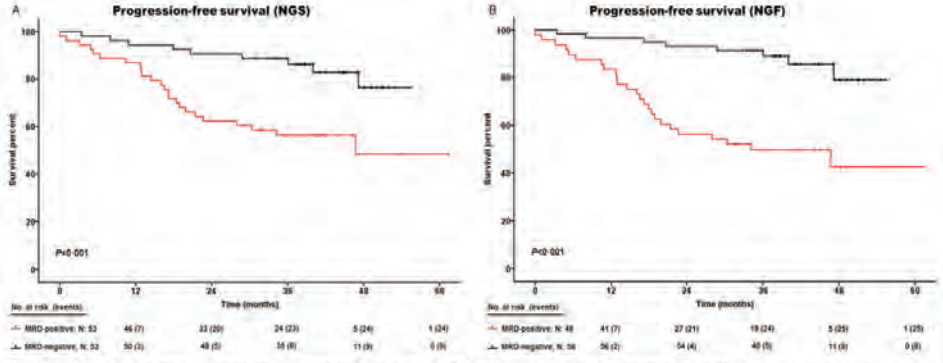
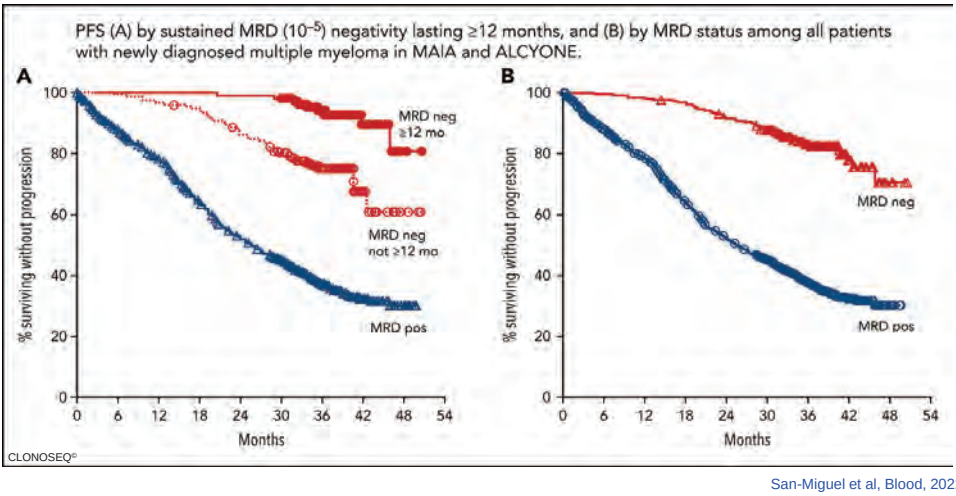


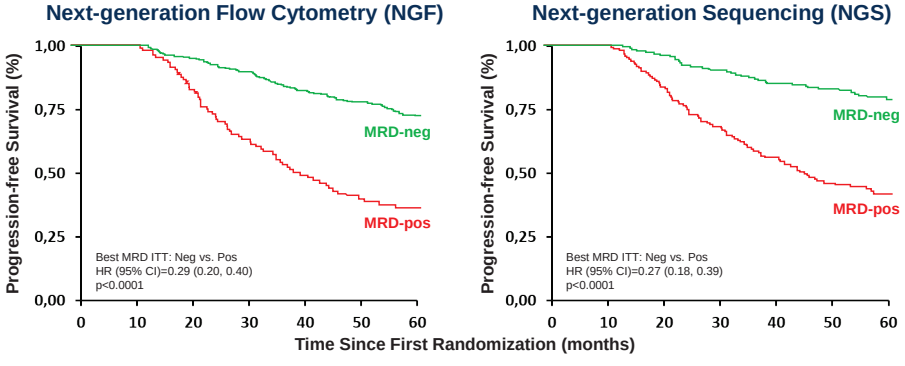
Fig. 2 Kaplan–Meier curves comparing progression-free survival of MRD-positive and MRD-negative subsets. A Progression-free survival of NGS-based results. **B** Progression-free survival of NGF-based results. Time was calculated from the time of MRD assessment, 3 months after transplantation. Negative patients are represented in black; positive patients are represented in red. Patients at risk are shown at each time point below plots; events are represented between parentheses. Median PFS of positive patients was 46.7 and 34.2 months for NGS and NGF, respectively. Median PFS was not achieved by negative patients. MRD minimal residual disease, NGF next-generation flow, NGS next-generation sequencing.

10^{-6} MRD level is the most powerful cutoff for PFS risk-stratification



San-Miguel et al, Blood, 2022,

Two interchangeable next-generation MRD methods



Oliva S, et al. EClinicalMedicine. 2023 Jun 9;60:102016.

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

	Allele-specific oligonucleotide qPCR	MFC	VDJ sequencing
Applicability	60–70%	Nearly 100%	≥90%
Need for baseline sample	Yes, requires production of patient-specific probes	Not required; abnormal plasma cells can be identified in any sample by their distinct immunophenotypic pattern vs normal plasma cells	Baseline samples required for identification of the dominant clonotype; alternatively, a stored sample from a time point with detectable disease can be used to define baseline status
Sample requirements	<1 million cells	~5 million cells	<1 million cells; higher numbers improve sensitivity
Sample processing	Can be delayed; can use both fresh and stored samples	Needs assessment within 24–48 h; requires a fresh sample	Can be delayed; can use both fresh and stored samples
Sample quality control	Not possible. Additional studies required	Immediate with global bone marrow cell analysis	Not possible. Additional studies required
Sensitivity	≥1 in 10^6	≥1 in 10^6	≥1 in 10^6
Information regarding sample composition	No further information available	Detailed information available on leucocyte subsets and their relative distribution	Information about immunoglobulin gene repertoire of B cells in the studied patient samples
Turnaround and complexity	Labour intensive; requires the development of patient-specific primers/probes; can take several days	Can be done in a few hours; automated software available	Can take several days for turnaround; requires intense bioinformatics support. Use of local laboratories could speed up this limitation
Standardisation	Has been done for other diseases (EuroMRD), can be done for myeloma as well	Standardised by the EuroFlow consortium	In process
Availability	Wide*	Most hospitals with four-colour flow cytometry. Eight or more-colour flow cytometry requires more experienced centres/laboratories. Many laboratories have adopted the EuroFlow laboratory protocols and use the EuroFlow MRD tubes	So far limited to one company/platform

*Globally, about 60 MRD laboratories are EuroMRD members and participate twice per year in the external quality assurance rounds. MFC=multiparametric flow cytometry. MRD=minimal residual disease.

Table 3: Comparison of different bone marrow minimal residual disease assessment techniques

Kumar et al; Lancet Oncol 2016; 17: e328–46

International Myeloma Working Group consensus criteria for response and minimal residual disease assesment in multiple myeloma

Respuesta	Criterio
Respuesta completa estricta	Respuesta completa como se define arriba más relación de FLC normal y ausencia de células clonales en la biopsia de médula ósea por IHC (κ / λ ≤4: 1 o ≥1: 2 para pacientes κ y λ, respectivamente, después de contar ≥100 PC)
Respuesta completa	Inmunofijación negativa en suero y orina y desaparición de cualquier plasmocitoma de tejidos blandos y <5% de células plasmáticas en aspirados de médula ósea
Respuesta parcial muy buena	Proteína M en suero y orina detectable por inmunofijación, pero no en electroforesis o reducción ≥90% en la proteína M en suero más el nivel de proteínas M en orina <100 mg por 24 h
Respuesta parcial	≥50% de reducción de la proteína M sérica más ↓ en 24 h de proteína M urinaria en ≥90% o <200 mg por 24 h; Si la proteína M en suero y orina no se puede medir, se requiere una ≥50% ↓ en la diferencia entre los niveles de FLC involucrados y no involucrados en lugar de los criterios de proteína M; Si la proteína M en suero y orina no se puede medir, y el ensayo de luz libre de suero también no se puede medir, se requiere ≥50% ↓ en PC en lugar de proteína M, siempre que el porcentaje basal de BMPC sea ≥30%. Además de estos criterios, si están presentes al inicio del estudio, también se requiere un ≥50% ↓ en el tamaño (LO) de los plasmocitoma de tejidos blandos
Respuesta mínima	≥25% pero ≤49% ↓ de proteína M sérica y ↓ en proteína M en orina de 24 h en 50-89%. Además de los criterios enumerados anteriormente, si está presente al inicio del estudio, también se requiere un ≥50% ↓ en el tamaño (SPD) de los plasmocitomas de tejidos blandos
Enfermedad estable	No se recomienda su uso como indicador de respuesta; La estabilidad de la enfermedad se describe mejor proporcionando las estimaciones del tiempo hasta la progresión. No cumple con los criterios de respuesta completa, muy buena respuesta parcial, respuesta parcial, respuesta mínima o enfermedad progresiva

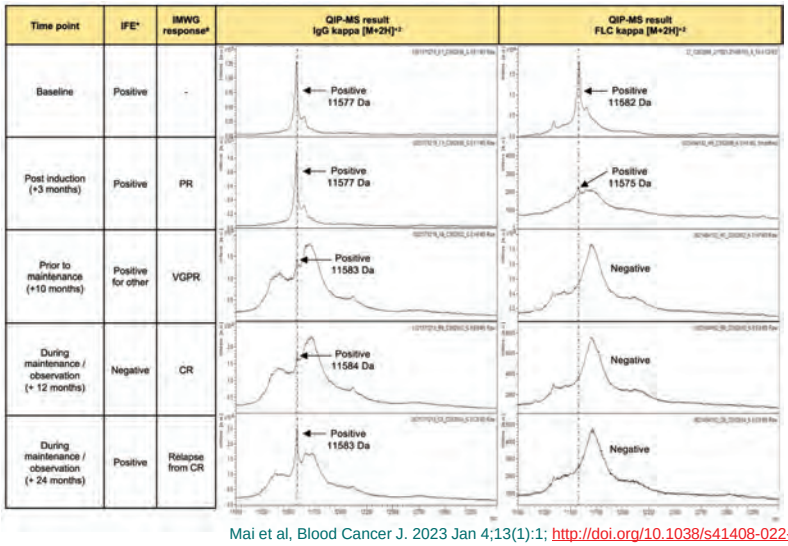
Kumar et al; Lancet Oncol 2016; 17: e328–46

International Myeloma Working Group consensus criteria for response and minimal residual disease assesment in multiple myeloma

EMR negativa por citometría	Ausencia de células plasmáticas clonales fenotípicamente aberrantes por NGF en aspirados de médula ósea utilizando procedimientos normalizados EuroFlow para detectar EMR en mieloma múltiple (o método equivalente validado) con una sensibilidad mínima de 1 en 10^5 células nucleadas o más
EMR negativa por secuenciación	Ausencia de células plasmáticas clonales por NGS en el aspirado medular en el que la presencia de un clon se define como al menos dos lecturas de secuenciación idénticas obtenidas después de la secuenciación de ADN de los aspirados de médula ósea utilizando la plataforma LymphoSIGHT (o método equivalente validado) con una sensibilidad mínima de 1 en 10^5 células nucleadas o superior

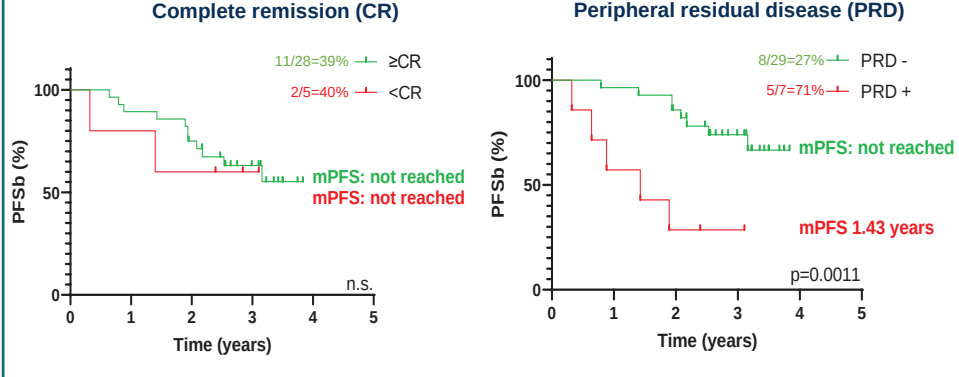
Kumar et al; Lancet Oncol 2016; 17: e328–46

QIP Mass vs. Immunofixation

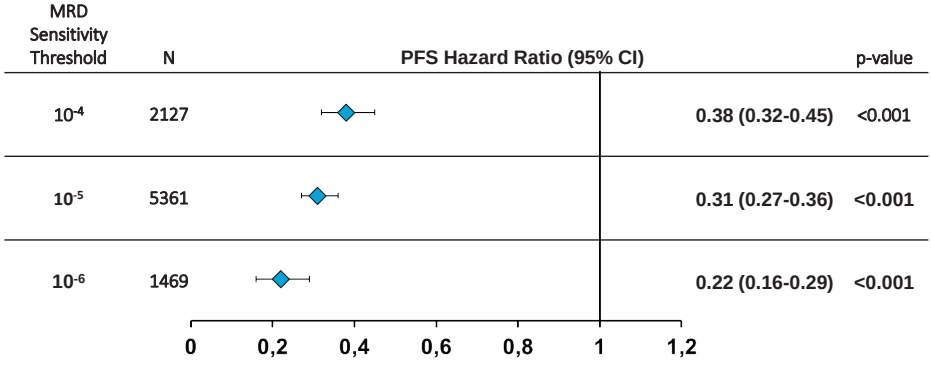


Mai et al, Blood Cancer J. 2023 Jan 4;13(1):1; http://doi.org/10.1038/s41408-022-00772-9

Improved prognostic value of MS over immunofixation

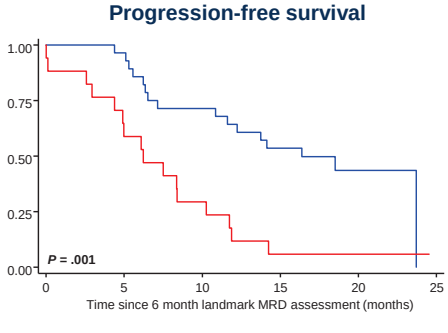


Puig et al, Haematologica 2024. Http://DOI.org/10.3324/haematol.2024.285742



Munshi NC, et al. Blood Adv. 2020 Dec 8;4(23):5988-5999.

Role of PET/CT in MRD negative patients after CAR T

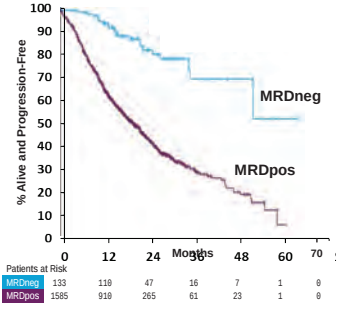


Response	Median PFS
MRDneg / NA (n = 29)	16
MRDneg / EMD (n = 17)	6

Paiva B, et al. **Blood Cancer Discov. 2023 Sep 1;4(5):365-373.**

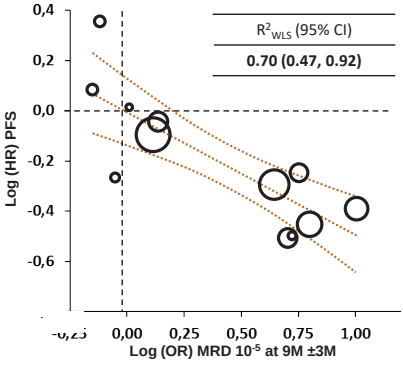
Use of MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma

Individual-Patient-Level Correlation



HR=0.24 (0.16-0.36); P-value < 0.0001

Trial-Level Correlation



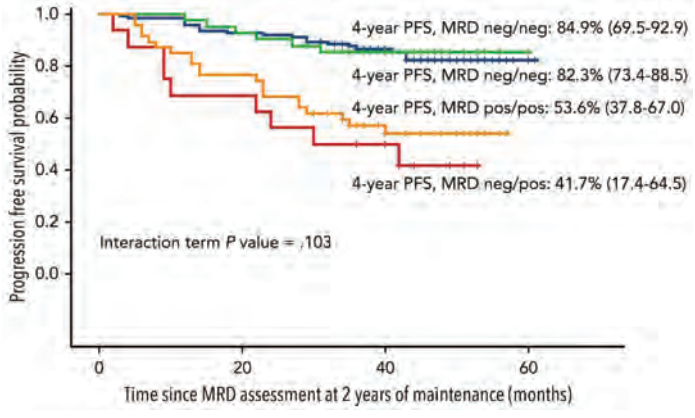
Shi Q, et al. Manuscript in preparation

MRD assessment in clinical trials[1]

- **Adhere to the IMWG guidelines[2]**
  - High-quality data with the possibility of cross-trial comparison
- **MRD negative rates in the intent-to-treat population**
  - Pre-specified time points in addition to CR to minimize missing MRD data
- **First BM pull for MRD assessment**
  - Check for hemodilution to avoid false-negative results[3,4]
- **Limit of detection (LOD) calculated in each sample and MRD threshold defined accordingly**
  - LOD depends on the quality of the sample
  - Acceptable MRD threshold if >95% of samples were analyzed with the corresponding LOD
- **MRD kinetics are more informative than a single assessment**

1. Costa LJ, et al. Leukemia. 2021 Jan;35(1):18-30.
2. Kumar S, et al. Lancet Oncol. 2016 Aug;17(8):e328-e346.
3. Puig N, et al. Cancers (Basel). 2021;13(19):4924.
4. Óskarsson JÞ, et al. Blood Cancer J. 2023 Dec 1;13(1):177.

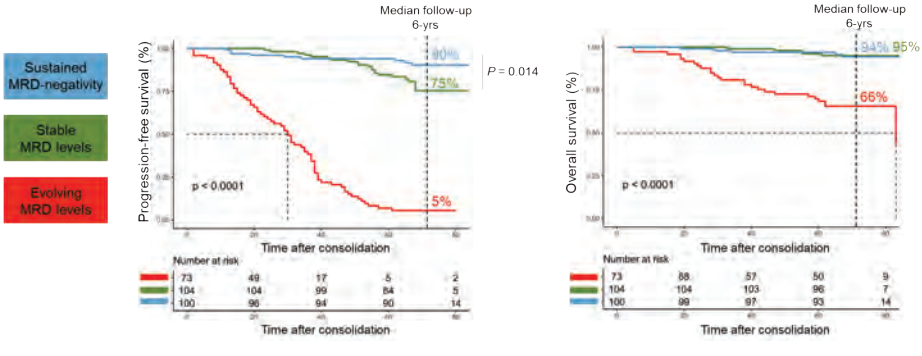
Consistent results across multiple studies[1-5]



1. Perrot A, et al. Blood. 2018;132(23):2456-2464.
2. Diamond B, et al. Lancet Haematol. 2021 Jun;8(6):e422-e432.
3. de Tute RM, et al. J Clin Oncol. 2022 Sep 1;40(25):2889-2900.
4. Paiva B, et al. Blood. 2023 Feb 9;141(6):579-591.
5. Rosiñol L, et al. Blood. 2023;142(18):1518-1528.

MRD kinetics matter

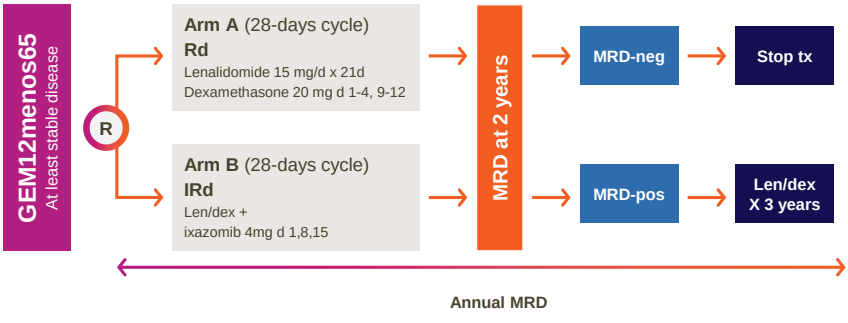
GEM2012MENOS65 – GEM2014MAIN trials: 1,759 MRD assessments



Guerrero C, et al. Blood 2023; 142 (Supplement 1): 871.

Can treatment be interrupted in some MRD negative patients?

Results from GEM2014MAIN



Rosiñol L, et al. Blood. 2023;142(18):1518-1528.

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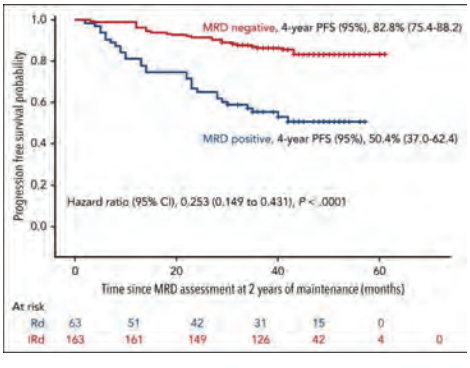

Rosiñol L, et al. Blood. 2023;142(18):1518-1528.

Can treatment be interrupted in some MRD negative patients?

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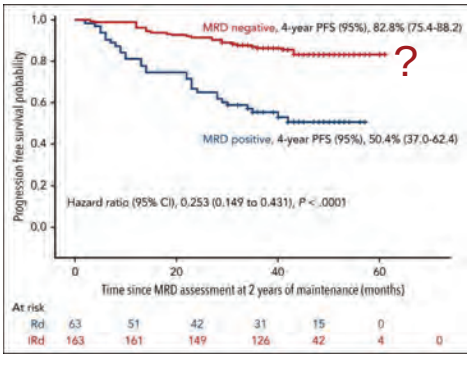
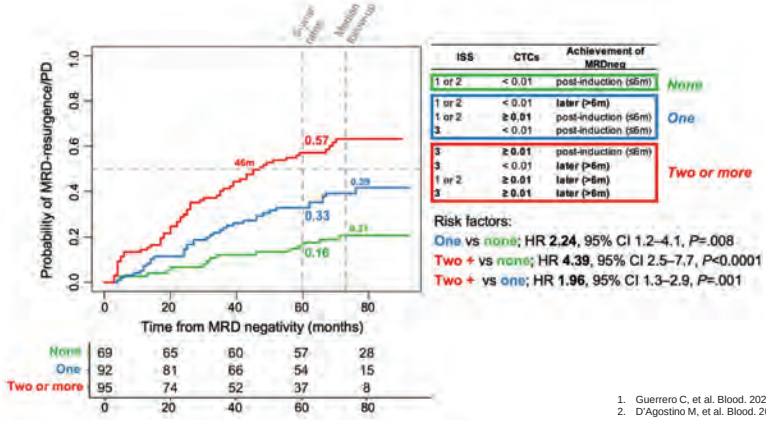


Rosiñol L, et al. Blood. 2023;142(18):1518-1528.

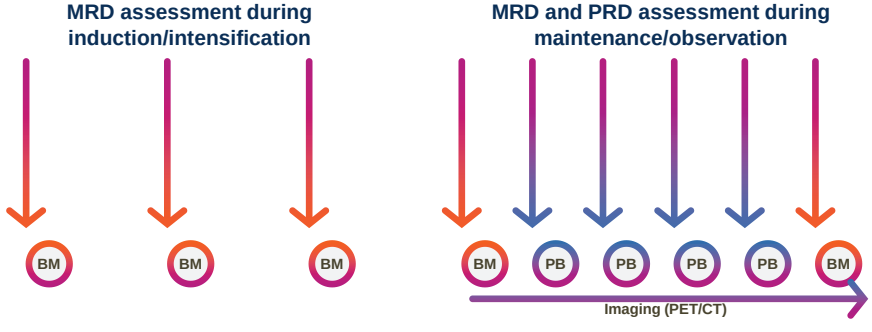
Predictors of unsustained MRD negativity in transplant-eligible patients

Reproducible results between GEM2014MAIN[1] and FORTE[2]



1. Guerrero C, et al. Blood. 2024 Feb 15;143(7):597-603.
2. D'Agostino M, et al. Blood. 2024 Feb 15;143(7):592-596.

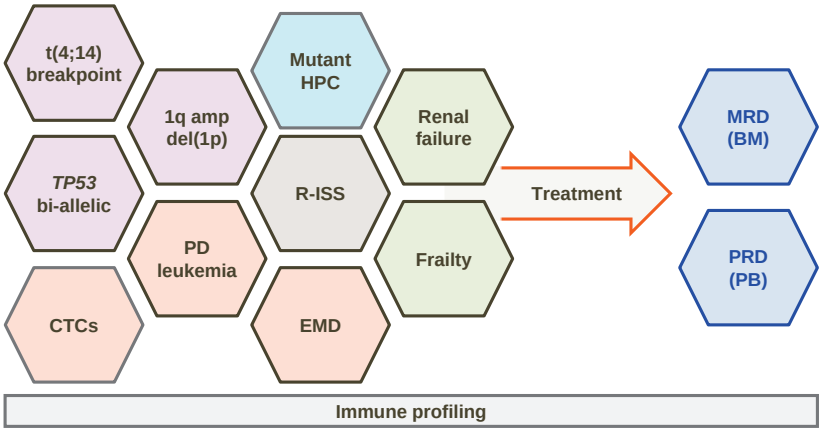
Hypothetical scenario to assess MRD and PRD



BM, bone marrow; MRD, minimal residual disease; PB, peripheral blood; PRD, peripheral residual disease.

Kindly provided by

There is no precision medicine without precision diagnostics

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GRUPO ESPAÑOL DE MIELOMA

Elena Zamagni MD, PHD, is Associate Professor of Hematology at the Bologna University, Italy. She received her medical degree from University of Bologna, where she also served her residency in haematology. She got PHD in Clinical Hematology at the University of Bologna in May 2005.

Her research interests include areas related to multiple myeloma, in particular on the role of high dose therapy with stem cell support, of prognostic factors, minimal residual disease and of imaging techniques.

She has published over 150 papers in peer-reviewed journals, mainly in the field of plasma cell dyscrasia. She has contributed to the educational session of the Italian Society of Haematology (SIE) and American Society of Clinical Oncology (ASCO). She is abstracts reviewer for SIE, EHA and ASH. She is part of the editorial board of several haematological journals, including Blood Cancer Journal and Journal of Clinical Oncology. She is an active member of the board of the GIMEMA and European Myeloma Network (EMN) working party and she has cooperated in the Scientific secretary and as principal investigator in several national randomized trials in multiple myeloma. She is a member of the Italian Society of Haematology, of the International Myeloma Working Group and of the International Myeloma Society. She is served on the EHA's Scientific Program Committee from 2017 to 2021. She is part of the Scientific Program Committee for the European Society of Clinical Oncology since 2021. She is responsible for the career development committee within the International Myeloma Society since 2019 and member of the board of the IMS as European representative since 2023.

How I treat high-risk multiple myeloma

Elena Zamagni
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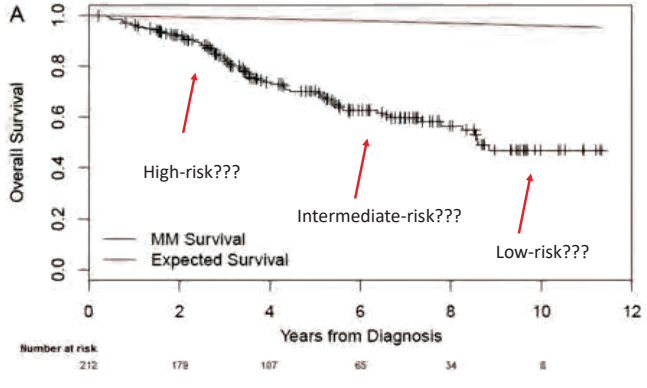
IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Italy

Multiple myeloma is a heterogeneous disease and so is the prognosis of affected patients



Ravi P, et al., *Blood Cancer Journal* 2018;8:26.

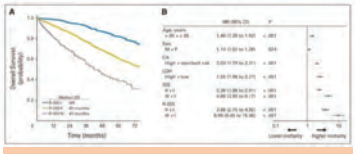
The current risk stratification model does not take into account all the known risk factors

Age

Frailty and performance status

Organ function and comorbidities

R-ISS



Albumin, B2M, LDH and cytogenetics

t(4;14), del17p and t(14;16)

Extramedullary disease

1q gain/amp del1p

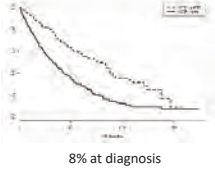
Circulating tumour cells

Plasma cell leukemia

High-risk features: cytogenetics

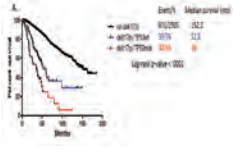
Del17p / TP53 mutation

Del17p Clonal fraction: 55% cut-off



8% at diagnosis

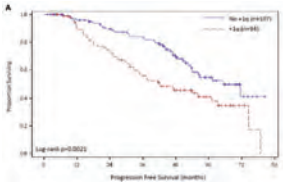
121 patients with del17p: 37% also had TP53 mutation (double hit)



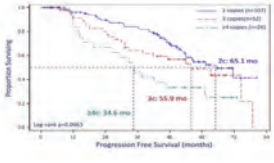
Corre J, et al., Blood 2021; Thakurta et al. Blood 2018

1q gain/amp

30-40% of MM patients carry 1q CNA



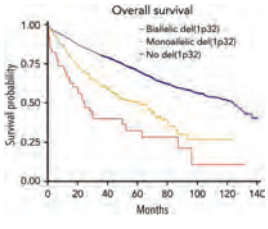
1q copy number predicts patients' outcome



Schmidt et al. Blood Cancer Journal 2019

del1p

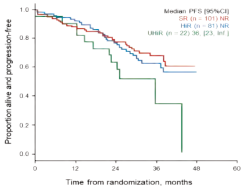
8-10% at diagnosis



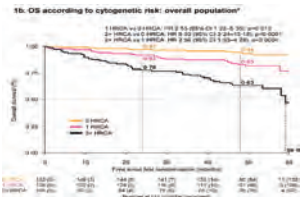
Schavgoulidze A, Blood 2022

The number of genetic lesions matters: standard risk vs high-risk vs ultra high-risk

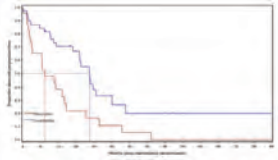
KCRD Myeloma XI



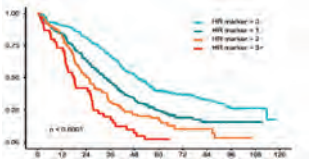
KRd-ASCT vs KRD12 vs KCd-ASCT FORTE



R maintenance Myeloma XI



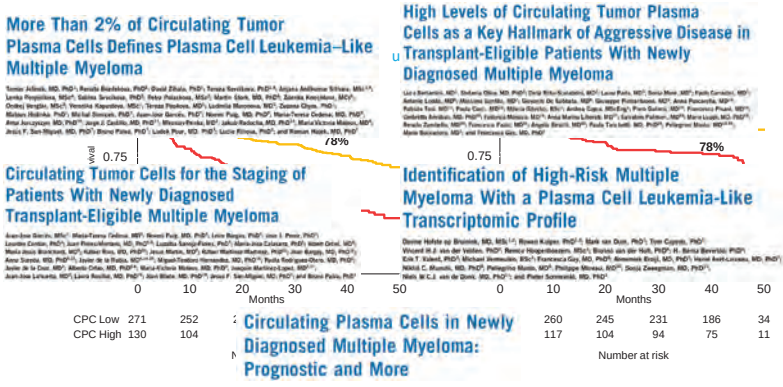
Bortezomib (GMMG-HD4/MM5)



Shah V, et al., Blood 2018, Weinhold et al., Haematologica in print, Mina et al, Lancet Oncol 2023, Croft J, et al., ASH 2019; G. Jackson GH. Et al, Lancet Oncol. 2019 Jan;20(1):57-73;

Circulating plasma cells are an indipendent risk factor

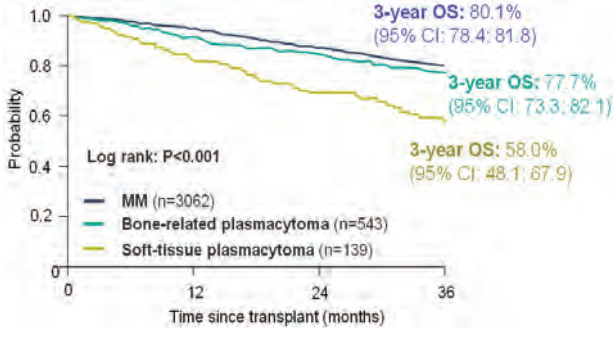
CPC evalubale population: 401/474 subjects - Median CPC 0.02% (IQR 0-0.14) - Cut-off 0.07% (5 cells/ul, 0.005 x10^9/l)



CPC, circulating plasma cells; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; p, p-value.

Bertamini L et al. ASH 2020

Extramedullary Myeloma is associated to lower probability of response and worse survival

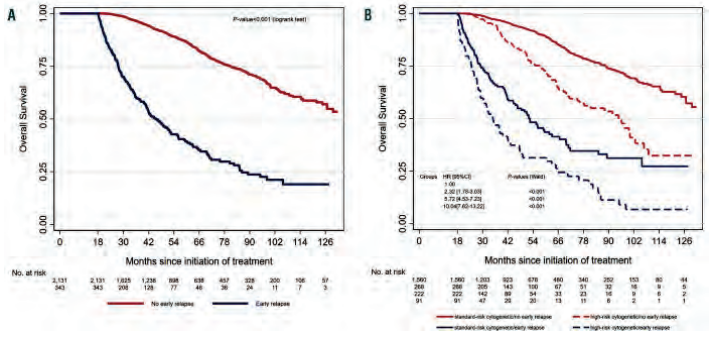


Gagelmann S, et al. Haematologica 2018;103:890–7

Functional high-risk: early relapse

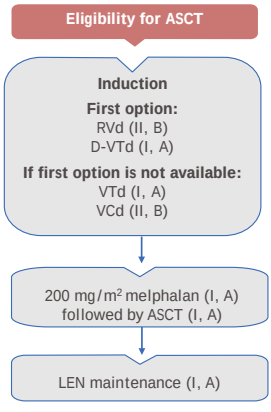
Early relapse defined as: < 18 months from treatment start or <12 months after ASCT)

19% of patients experienced early relapse; 12.5% were defined Standard risk



Corre et al., Haematologica 2020

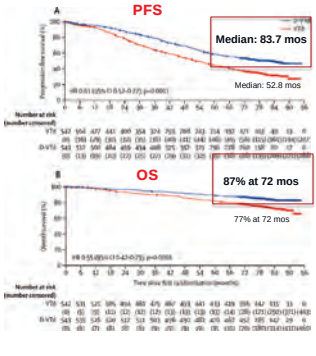
EHA-ESMO 2021 MM guidelines:
Front-line treatment of ND, TE MM patients



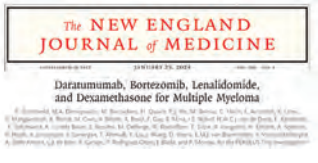
Dimopoulos MA. et al Annals of oncology 2021.

First-line treatment for Newly-diagnosed, transplant eligible myeloma patients

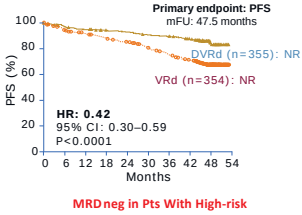
CASSIOPEIA phase III trial: Dara-VTd vs VTd + ASCT



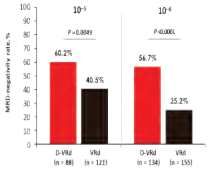
Moreau P et al, Lancet Oncology 2024



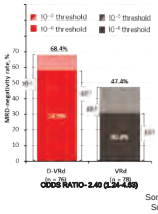
EMN28/PERSEUS phase III trial: Dara-VRd vs VRd + ASCT



MRD rate during maintenance



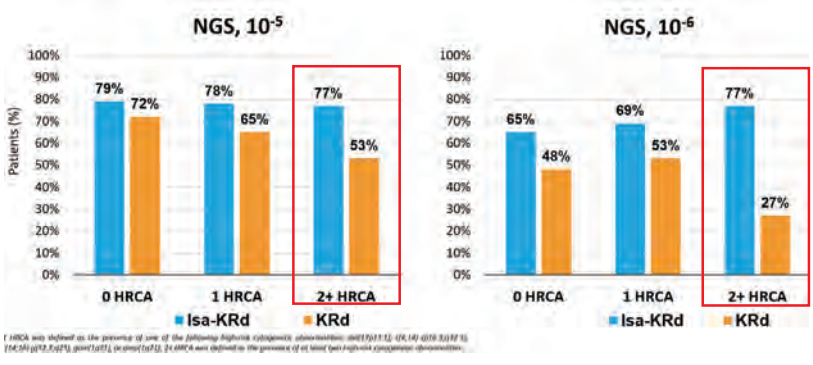
MRD neg in Pts With High-risk



Sonneveld P et al, NEJM 2024
Sonneveld P et al, EHA 2024

Isatuximab-KRd vs KRd: EMN24/ISKIA study

MRD negativity rates in ITT

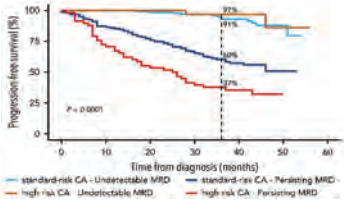


Gay F. et al ASH 2023

Reaching MRD negativity can modulate the poor prognosis of high-risk chromosomal abnormalities

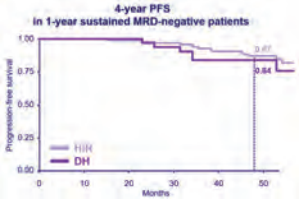
GEM2012MENOS65 trial (10^{-6})

3-year PFS
In MRD negative patients

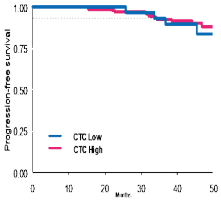


FORTE trial (10^{-5})

4-year PFS
in 1-year sustained MRD-negative patients



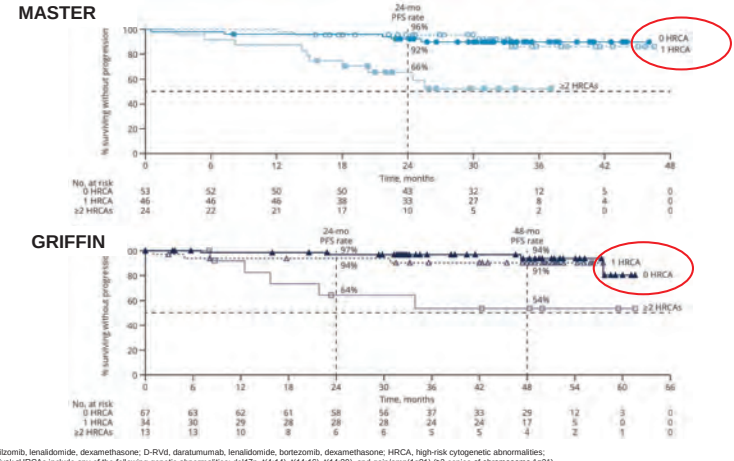
3-year PFS
in 1-year sust-MRD negative patients



CA, cytogenetic abnormalities; MM, multiple myeloma; MRD, minimal residual disease.; HiR, high risk; DH, double hit

Goicoechea I et al. Blood 2021;137(1):49-60; Mina R et al EHA 2021;abstract S182; Bertamini L. et al, JCO 2022.

MASTER (Dara-KRd) and GRIFFIN (Dara-VRd): PFS by cytogenetic risk[a]



D-KRd, daratumumab, carfilzomib, lenalidomide, dexamethasone; D-RVd, daratumumab, lenalidomide, bortezomib, dexamethasone; HRCA, high-risk cytogenetic abnormalities; PFS, progression-free survival; [a]HRCAs include any of the following genetic abnormalities: del17p, t(4;14), t(14;16), t(14;20), and gain/amp(1q21) (≥3 copies of chromosome 1q21). Patients were grouped into categories: standard risk (0 HRCA), high risk (1 HRCA), or ultra–high risk (≥2 HRCAs).

Callander N et al. ASH 2022;abstract 4557 (poster presentation)

Tandem autologous transplant for high-risk patients: still a standard?

EHA-ESMO 2021 guidelines: «a tandem ASCT is recommended for patients with genetically defined high-risk disease»

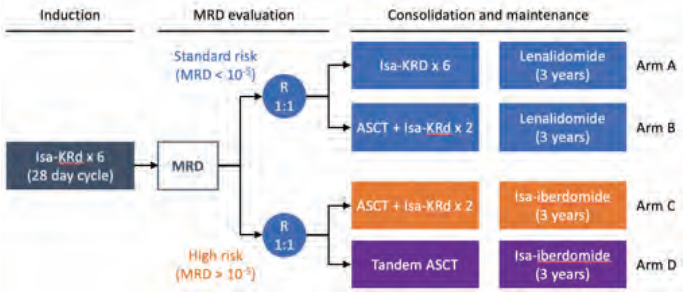
	EMN02 study[1,2]		STAMINA study[4,5]	
	Data	p	Data	p
Total number of patients[1]	702		758	
Design[1]	Double vs single ASCT		Double vs single ASCT	
High-risk definition[1]	Del(17p) or t(4;14) or t(14:16)		Del(17p) or t(4;14) or del 13 by K or hypodiploid by K	
Number of high-risk patients[1]	135 (19%)		223 (29%)	
PFS[2]	Median = 46.0 vs 26.7 mo	0.060	@6 years = 43.6 vs 26%	0.03
OS[3]	@60 mo = 61.3 vs 54.7%	0.32		
OS in patients with del(17p)[3]	@60 mo = 80.2 vs 57.1%	0.066		

ASCT, autologous stem cell transplant; mo, months; OS, overall survival; PFS, progression-free survival

1. Cavo M et al. Lancet Haematol 2020;7(6):e456–e468
2. Dimopoulos MA et al. Ann Oncol 2021; 32(3):309–22
3. Caro J et al. ASCO Educational Book 2021:41:291–309
4. Hari P et al. JCO 2020;38(15S):8506
5. Stadtmauer EA et al. J Clin Oncol 2019;37(7):589–597

MRD as endpoint vs modifying treatment based on MRD – examples from clinical trials

The role of Autologous transplant in standard and HR MM: the MIDAS[1] study



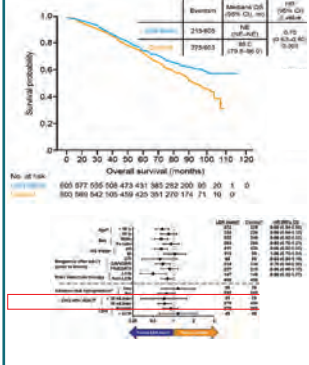
ASCT, autologous stem cell transplant; Dara, daratumumab; HDM, high-dose melphalan; Isa, isatuximab; KRd, carfilzomib, lenalidomide, dexamethasone; MRD, minimal residual disease; PD, progressive disease; R, lenalidomide; VRd, bortezomib, lenalidomide, dexamethasone

1. ClinicalTrials.gov/NCT04934475

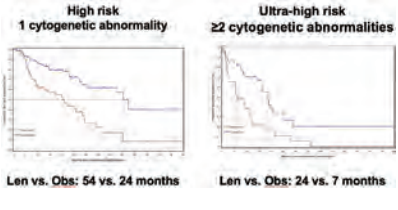
Maintenance therapy: can we do better?

Lenalidomide maintenance according to FISH risk

Overall survival



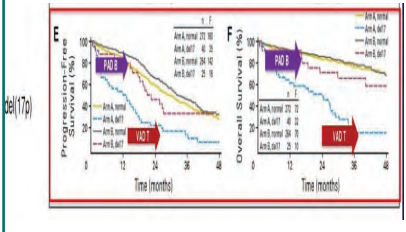
Myeloma XI study: lenalidomide versus observation



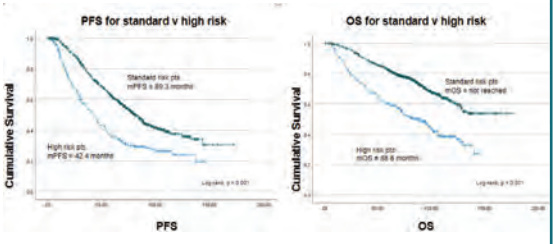
McCarthy et al. J Clin Oncol 2017; 35(29):3279-3289; G. Jackson GH. Et al, Lancet Oncol. 2019 Jan;20(1):57-73. Pawlin C. et al ASH22

Lenalidomide and proteasome inhibitor maintenance

Bortezomib vs thalidomide
HOVON65



VRd maintenance in the Emory Cohort



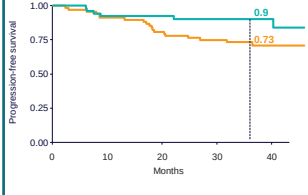
Sonneveld P et al. JCO 2012
Nisha J. et al. JCO 2020

Carfilzomib-lenalidomide vs lenalidomide (FORTE trial) maintenance FISH subanalysis

KR vs. R

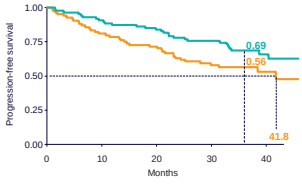
3-year progression-free survival from random 2
Median follow-up from Random 2: 37 months (IQR 33-42)

Standard risk (N=120)



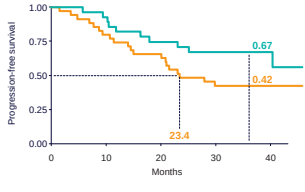
KR vs. R: HR 0.4, p=0.05

High risk (N=172)



KR vs. R: HR 0.6, p=0.04

Double hit (N=105)



KR vs. R: HR 0.53, p=0.1

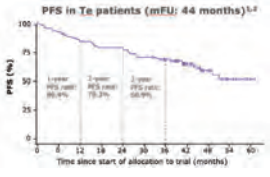
Mina R. et al. Lancet Oncol 2023

Random 2, second randomization (maintenance treatment); IQR, interquartile range; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value.

Treatment of HR patients: what's next?

GMMG-CONCEPT STUDY

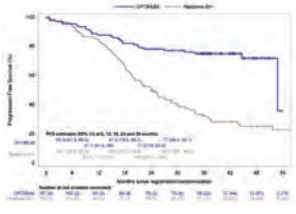
68% of TE patients were MRD negative 10^{-5} post-induction



36-month PFS: 69%

OPTIMUM MUKnine STUDY

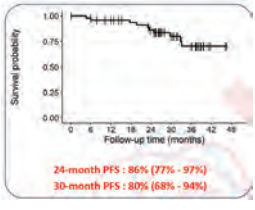
64% of patients were MRD negative 10^{-5}



30-month PFS: 77%

IFM 2018-04

94% of patients were MRD negative 10^{-6}



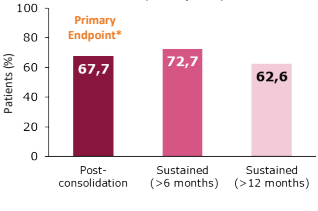
30-month PFS: 80%

Leypoldt L et al, JCO 2024; Kaiser M. et al, ASH22; Touzeau C. et al. ASCO22

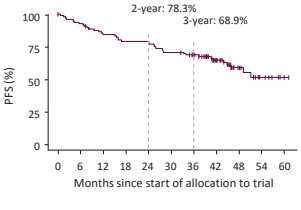
Multi-drug regimens exploring efficacy in exclusively high-risk Te NDMM populations

GMMG-CONCEPT
Phase II; Isa-KRd (N=125)

MRD– in Te population (n=99)
(10^{-5} by NGF)



PFS in Te population (n=99)
mFU: 44 months



HR definition: ISS II or III plus ≥1 of del(17p), t(4;14), t(14;16) and/or amp(1q)

Grade ≥3 AEs in Te population, %	Isa-KRd (n=97)
Neutropenia	39.2
Infection	27.8
Neuropathy	2.1
Cardiac	2.1
Hypertension	10.3

Isa-KRd induced high rates of sustainable MRD– in difficult-to-treat high-risk Te NDMM patients, translating into a median PFS that was not yet reached after 44 months

sanofi

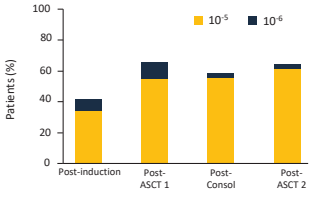
*Evaluated in interim analysis MRD population (n=93). AE, adverse event; C, cyclophosphamide; d, dexamethasone; D, daratumumab; FU, follow-up; Isa, isatuximab; K, carfilzomib; m, median; MRD, minimal residual disease; NGF, next-generation flow cytometry; PFS, progression-free survival; R, lenalidomide; Te, transplant-eligible; V, bortezomib

Leypoldt L, et al. J Clin Oncol 2024;42:26–37

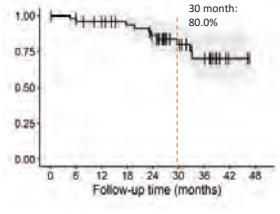
Multi-drug regimens exploring efficacy in exclusively high-risk Te NDMM populations

IFM 2018-04
Phase II; DKRd + tandem ASCT (N=50)

MRD– (by NGS) in ITT (N=50)
mFU: 33 months



PFS in ITT
mFU: 33 months



HR definition: 1 of del(17p), t(4;14), t(14;16)

Grade 3/4 AEs, %	DKRd post-induction (n=50)	DKRd + tandem ASCT (n=42)
Neutropenia	32.0	14.0
Infection	4.0	5.0
PN	0	0

DKRd induction/consolidation with tandem transplant resulted in high MRD– rates and a PFS that was not reached in high-risk Te NDMM patients

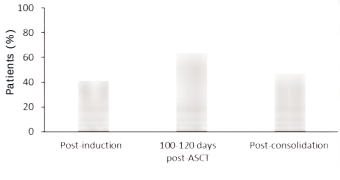
AE, adverse event; C, cyclophosphamide; d, dexamethasone; D, daratumumab; FU, follow-up; Isa, isatuximab; ITT, intention to treat; K, carfilzomib; m, median; MRD, minimal residual disease; NGS, next-generation sequencing; R, lenalidomide; PFS, progression-free survival; PN, peripheral neuropathy; Te, transplant-eligible; V, bortezomib

Touzeau C, et al. Blood 2024. Online ahead of print.

Multi-drug regimens exploring efficacy in exclusively high-risk Te NDMM populations

OPTIMUM/MUKnine
Phase II; DCVRd (N=107)

MRD–
(10^{-5} by NGF)



Primary endpoint: PFS*
mFU: 41.2 months

Ultra HR definition: ≥2 of t(4;14), t(14;16), t(14;20), del(1p), gain(1q), and del(17p), GEP high-risk

Grade ≥3 AEs during consolidation,* %	DCVRd (n=80)
Neutropenia	44
Infection	15
PN	3

DCVRd induction/consolidation with transplant resulted in high rates of MRD– and PFS in high-risk Te NDMM patients

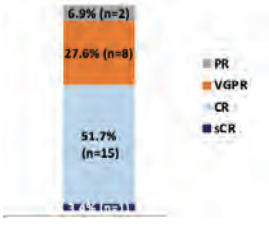
*In patients who completed ≥1 cycles. AE, adverse event; C, cyclophosphamide; d, dexamethasone; D, daratumumab; FU, follow-up; GEP, gene expression profile; Isa, isatuximab; K, carfilzomib; m, median; MRD, minimal residual disease; NGF, next-generation flow sequencing; R, lenalidomide; PFS, progression-free survival; PN, peripheral neuropathy; Te, transplant-eligible; V, bortezomib

Brown S, et al. BMJ Open 2021;11:e046225; Kaiser M, et al. Clin Oncol 2023;41:3945–55

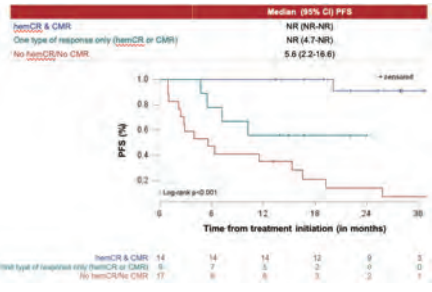
Daratumumab-VCd +/- ASCT in patients with extra-medullary MM: EMN19 phase II

40 patients with ND or RR (1 prior line) MM
41% paraosseous plasmocytoma – 62% extraosseous plasmocytoma

Response rates in NDMM patients: 90%



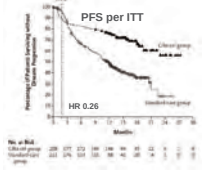
Progression-free survival according to response
Median follow-up 23 months



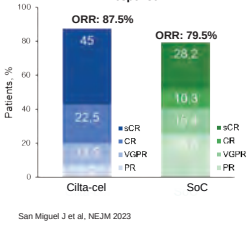
Beksac M. et al ASH 2023

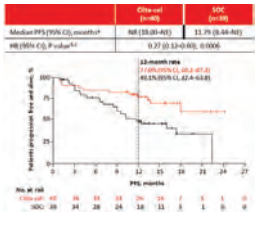
Immunotherapy moving earlier: CART in functional high-risk patients

CARTITUDE-4 phase III trial: cilta-cel vs SOC in RRMM 1-3 prior LOT



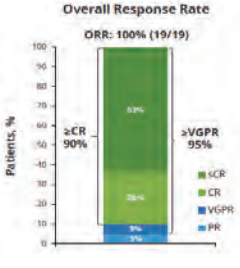
Results in patients with 1 prior LOT and functional high risk
(PD ≤18 months after ASCT or the start of initial therapy in pts with no ASCT)





San Miguel J et al, NEJM 2023

CARTITUDE-2 Cohort B:
Cilta-cel in patients with early relapse after initial therapy (n=19)
Progression ≤12 months from ASCT or induction therapy.



Median DOR was NR
12-month PFS rate was 89.5%

Hillengass J, et al. ASH 2023

OLTRE IL MIELOMA
PANORAMICA SUI DISORDINI PLASMACELLULARI RARI

Outcomes of BCMA-Directed CART Therapy in Patients with RRMM with EMD-para-skeletal

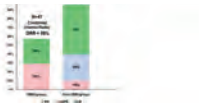
RESEARCH ARTICLE

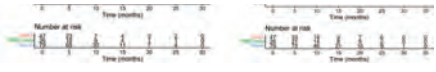
Blood Science

OPEN

Pomalidomide improves the effectiveness of CAR-T treatment in the relapsed and refractory multiple myeloma or B-cell leukemia/lymphoma with extramedullary disease

Jie Zhao[a,b], Hui Yang[a], Junnan Ge[c], Linyu Li[a], Qiong Yao[a], Shaolong He[a,b], Qiujuan Zhu[a], Ruiui Ren[a], Chunrui Li[b], Liangming Ma[a], Weiwei Tian[a,b,d,*], Jia Wei[a,b,d,e,*]



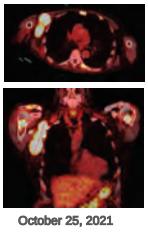


Dima M et al, BCJ 2024

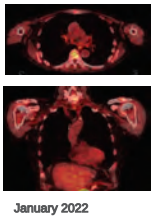
Targeting 2 Ags to prevent resistance: the way to go in EMD?

Tec + Tal RedirecTT-1 study

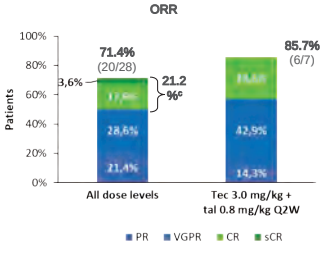
- 74-year-old male, penta refractory, 6 prior LOT including ASCT, belantamab mafodotin, and prior RT to humerus, with EMD at study entry



October 25, 2021



January 2022

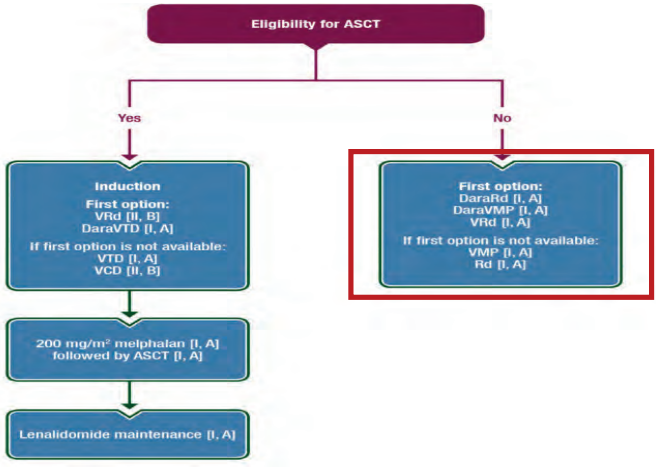


- At the RP2R (n=11):
  - Median follow-up, 7.2 mo
  - 85.7% (6/7 evaluable) ORR
  - 28.6% (2/7 evaluable) ≥CR

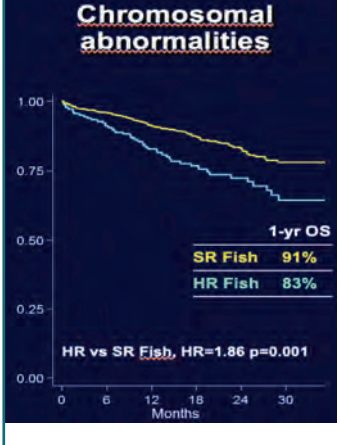
	All dose levels (N=35)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (N=11)
Median DOR,[f] months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS,[g] months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

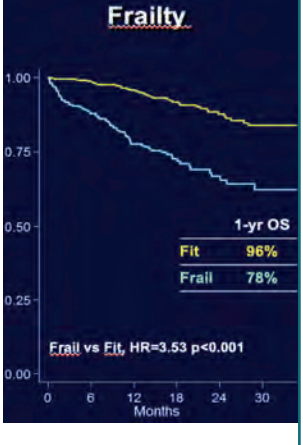
Cohen YC, et al. ASCO 2023. Oral 8002

Front-line treatment options for NTE patients 2021 ESMO guidelines



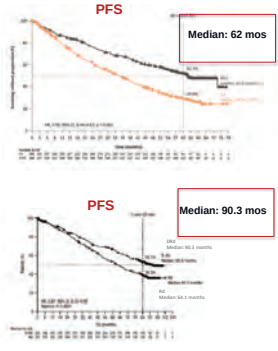
Risk has two faces in older myeloma patients



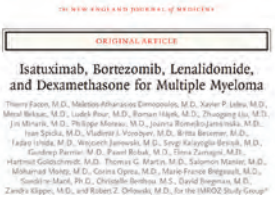


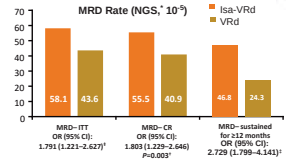
Anti -CD38 MoAbs in I line treatment of ND-NTE-MM: significantly extended survival

MAIA phase III trial: Dara-Rd vs Rd

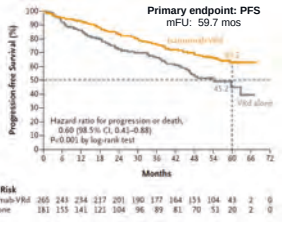


Facon T et al, NEJM 2019
Facon T et al, EHA 2024





IMROZ phase III trial: Isa-VRd vs VRd

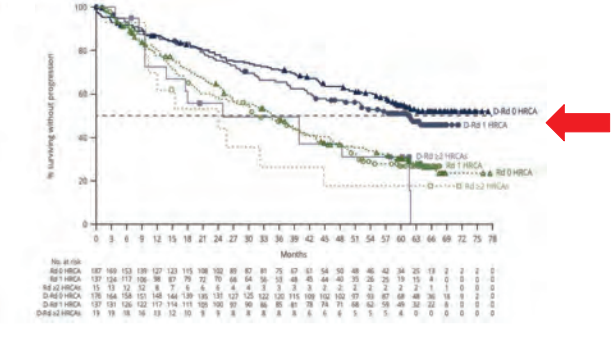


Facon T et al, NEJM 2024

MAIA cytogenetic risk subgroups: PFS

Median follow-up of 64.5 months

Subgroup analysis of PFS among patients with revised standard cytogenetic risk (0 HRCA), 1 HRCA, or ≥2 HRCAs[1]



Median PFS in:

Standard risk: NR

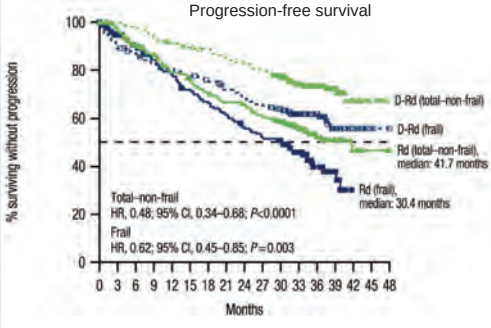
1 HRCA: 61 months

2+ HRCAs: 25 months

D-Rd, daratumumab, lenalidomide, dexamethasone; HRCA, high risk cytogenetic abnormalities; PFS, progression-free survival; Rd, lenalidomide, dexamethasone.
1. Moreau P et al. ASH 2022 (Abstract 3245 – poster).

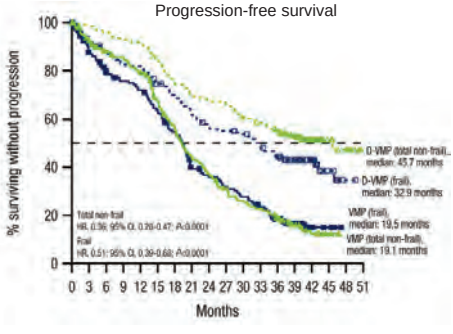
Frailty subgroup analysis of MAIA and ALCYONE studies

DRd Vs Rd
Progression-free survival



Median follow-up 36.4 months

DVMP Vs VMP
Progression-free survival



Median follow-up 40.0 months

DRd, daratumumab, lenalidomide, dexamethasone; DVMP, daratumumab, bortezomib, melphalan, prednisone; Rd, lenalidomide, dexamethasone; VMP, bortezomib, melphalan, prednisone;

Facon T et al. Leukemia 2022;doi:10.1038/s41375-021-01488-8;
Mateos MV et al. Clin Lymphoma Myeloma Leuk 2021;21(11):785-798

Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with NDMM

Rd INDUCTION
9 cycles
R: 25 mg/day PO d 1-21
d: 20 mg PO once weekly

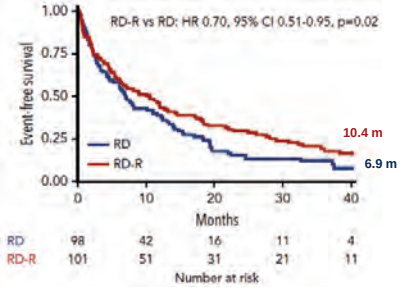
R MAINTENANCE
until PD/intolerance
R: 10 mg/day PO d 1-21

R

CONTINUOUS Rd
until PD/intolerance
R: 25 mg/day PO d 1-21
d: 20 mg PO once weekly

	Rd-r	Rd	P value
PFS median, mos	20.2	18.3	0.16
OS, at 3ys, %	74	63	0.06
ORR, %	78	68	0.15
G≥ 3 hematol AEs	26%	20%	0.40
G≥ 3 non hematol AEs	33%	43%	0.15
R dose reduction	45%	62%	0.01
Dex dose reduction	17%	31%	-
R Discontinuation	24%	30%	0.42

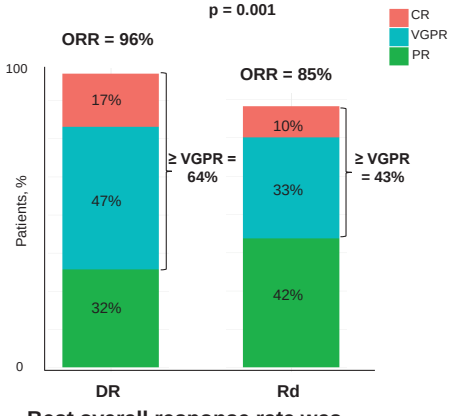
Primary end point: event-free survival (EFS)
(progression/death from any cause, lenalidomide discontinuation, or hematologic gr 4 or nonhematologic gr 3-4 adverse event)



Comparable efficacy
Potential improved tolerance/feasibility

Larocca et al. Blood. 2021;137(22):3027–3036

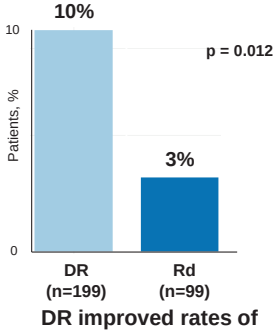
Steroid sparing regimen including daratumumab for frail MM patients IFM 2017-03 *Dara-R vs Rd*



Best overall response rate was significantly higher with DR

MRD at 10^{-5} by NGS, in ITT analysis

MRD assessed for patients with at least a VGPR at 12 months. Patients with missing data were considered MRD positive



DR improved rates of MRD negativity at 10^{-5} *vs.* Rd

Manier S et al; Abs 569 ASH 2022,

Conclusions

- Risk status requires a comprehensive evaluation of: tumor burden, cytogenetic/molecular lesions, clinical presentation (circulating plasmacells, extramedullary disease, renal failure), age, comorbidities and fitness.
- Continuous assessment of biological and clinical predictors of high risk disease should be performed as risk status may change.
- The achievement of sustained MRD negativity could be the key to overcome baseline high-risk factors such as chromosomal abnormalities, ISS and CPC

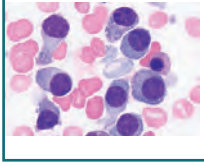
How to deal with high-risk MM in clinical practice

- Use the best induction treatment available (quadruplet with IMiD, PI and anti-CD38 Moab)
- Tandem ASCT in high-risk FISH could be recommended until something better is available
- Early access to immunotherapies may improve the outcomes of HR patients
- Lenalidomide until progression is the standard of care; the role of intensive/new fashion maintenance is under investigation
- Treatment should be adapted upon biological risk but also frailty in the elderly population

Prof. Gabor Mikala graduated with honors in 1991 at Semmelweis University, Budapest as a medical doctor. From 1991 to 1997 worked at the University of Cincinnati, Institute of Molecular Pharmacology and Biophysics, as a Program of Excellence Fellow. Upon returning to Hungary, he worked at Imre Haynal University as a clinical resident, received board certification in internal medicine and hematology. Received a PhD degree in 2000 from Semmelweis University, Program of Molecular Physiology. Has had a joint appointment as professor of anatomy, physiology and cell biology at Semmelweis University School of Health Sciences. Presently Head of Division for Lymphoma and Myeloma Care at South Pest Central Hospital, National Institute for Hematology and Infectious Diseases. His major interest is in plasma cell dyscrasias, authored more than 150 publications with more than 4500 citations. He is a governing board member of the Hungarian Society of Hematology, member of the International Myeloma Working Group, International Myeloma Society, serves as an editorial board member of several scientific journals. Co-author of the Hungarian myeloma treatment guidelines.

The Importance of metabolism in long-term myeloma care

Gabor Mikala
South-Pest Central Hospital, National Institute for Hematology and Infectious Diseases,
Budapest, Hungary



DÉL-PESTI CENTRUMKÓRHÁZ
ORSZÁGOS HEMATOLÓGIAI
ÉS INFEKTOLÓGIAI INTÉZET

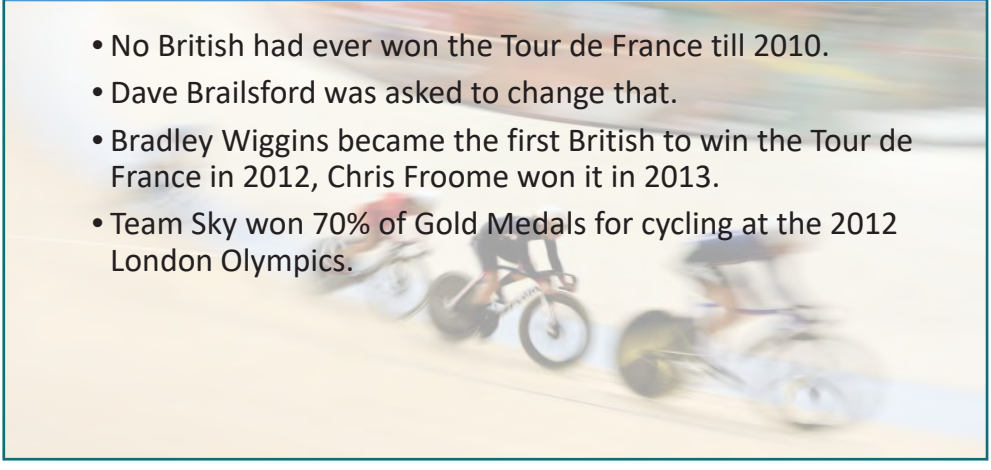
Our goal is to **cure** myeloma

» HOWEVER

- In most cases we fail in the curative attempt
- We enter a demanding (ultra)Marathon race
- Every little help counts along the way…

- Survival of our myeloma patients largely depends on the available (innovative) therapies
- Most patients ask: what can I do to support the efficacy of my myeloma therapy?
- What can we, physicians suggest for them?

Team Sky and British Cycling



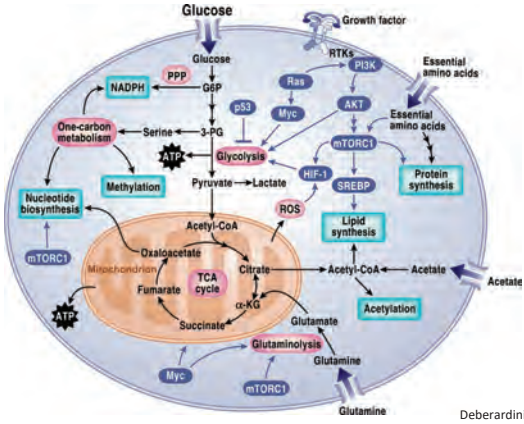
- No British had ever won the Tour de France till 2010.
- Dave Brailsford was asked to change that.
- Bradley Wiggins became the first British to win the Tour de France in 2012, Chris Froome won it in 2013.
- Team Sky won 70% of Gold Medals for cycling at the 2012 London Olympics.

Team Sky and British Cycling and the idea of **marginal gains**

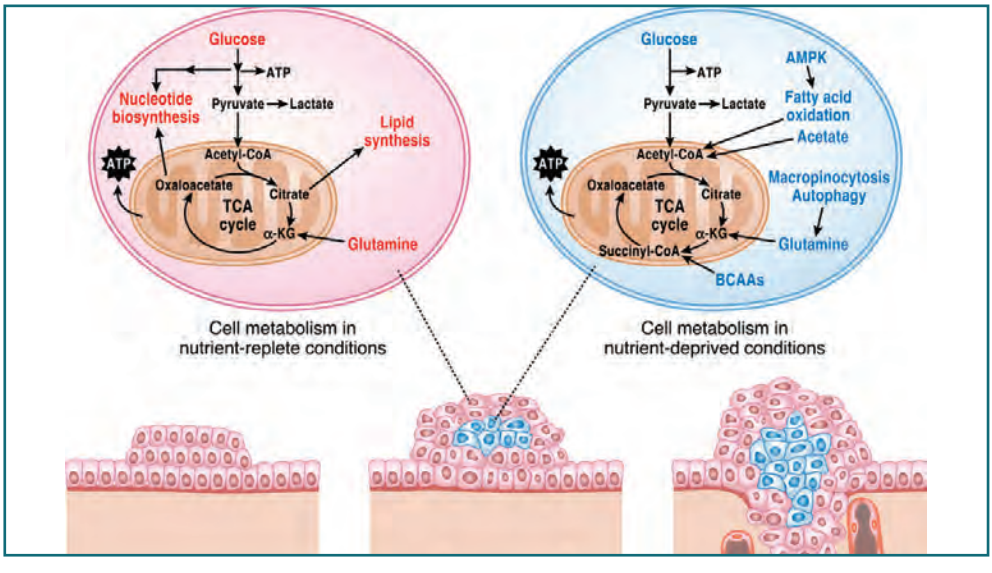
Examples: rubbing alcohol on tyres to improve grip, electrically heated overshorts to maintain muscle temperature and a ban on bikini waxes to prevent saddle sores…

- Understanding the metabolic pathways of myeloma can offer some possibilities for those marginal gains…

Signaling and metabolism in tumor cells



Deberardinis et al, Science Advances, 2016



How this basic tumor biology may be applicable to multiple myeloma?

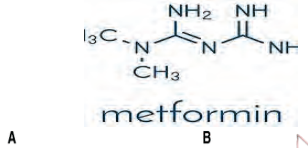
- Myeloma cells need two major essential nutrients
  - **Glucose**
  - **Glutamine**
- Can we influence these?
- Can we limit myeloma cell access to these?

Glucose

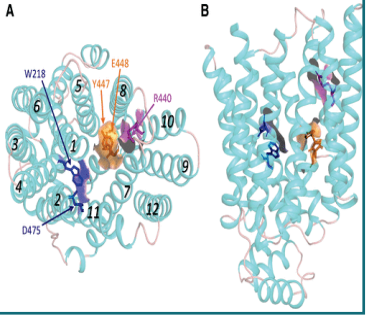
- Myeloma cells „love glucose”
- But can survive with low levels
- Hyperglycaemia és hyperinsulinaemia are supportive for myeloma growth – to be avoided
- Ketogenic diet has an effect on some tumors, but not on myeloma
- The effect of prolonged/**intermittent fasting** is currently tested in an ongoing clinical trial
- Avoiding foods with a high glycemic index is a safe advice

Use certain antidiabetic agents?

- Population studies support the beneficial effect of metformin and SGLT2 inhibitors
- Metformin decreases the risk of progression to MM
- Metformin use may increase the PFS after ASCT
- Metformin activity **requires OCT-1** to enter the cell
- Metformin is an inhibitor of mitochondrial oxidative phosphorylation (Complex I)
- AMP signaling pathway is activated

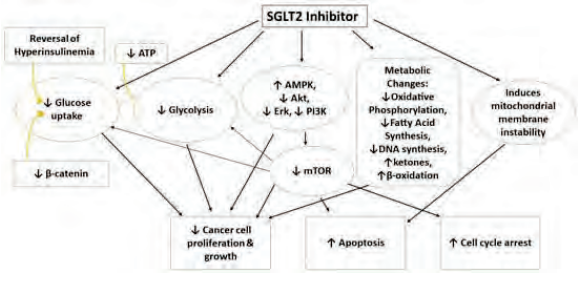


metformin



Use certain antidiabetic agents?

- **SGLT2 inhibitors** may decrease the growth of cancer cells
- Canagliflozin and dapagliflozin promotes AMPK-dependent cell growth arrest



Canagliflozin inhibits mitochondrial OxPhos complex I and ATP synthetase

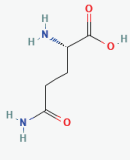
Basak et al, Biomedicines, 2023

Use certain antidiabetic agents?

- Diabetic patients treated with **GLP-1 agonists** exhibit 65% risk reduction in progression from MGUS to MM
- More profound effects on overweight patients
- Controversial effects of T-cell immune functions

Grandhi et al, Cancer Res, 2023

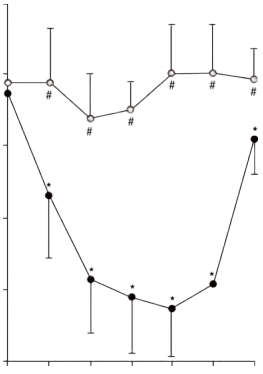
Glutamine



- The amino acid present at the highest concentration in the bodily fluids
- Glutamine is critical for mitochondrial anaplerosis
- Myeloma cells rely on external glutamine
- Glutamine is present in all kinds of foodstuff
- Its intake cannot be effectively limited
- Most glutamine from food is retained in the intestinal mucosa
- Can we safely and effectively limit myeloma cell access to glutamine?

Best way to limit myeloma glutamine access: physical exercise

- Glutamine levels are largely controlled by skeletal muscle cells
- 45 minutes of exercise may show a 30-40% decrease in serum glutamine level that may last more than 2 hours
- More prolonged exercise may have a 6-9 hour glutamine decreasing effect
- Exercise may also be important to preserve muscle mass
- Glutamine transport inhibitors are developmental anticancer agents
- Metabolic competition for glutamine may exist in the tumor microenvironment (T cells)



Coqueiro et al, Nutrients, 2019

Regular aspirin use?

- Health Professionals Follow-up Study
- 436 MM patients
- Regular aspirin use decreased MM-specific **mortality** with HR 0.61 and overall mortality with HR 0.63
- Regular aspirin use may decrease MM incidence by 39%

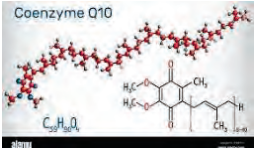
Marinac et al, Cancer Epidemiol, 2022

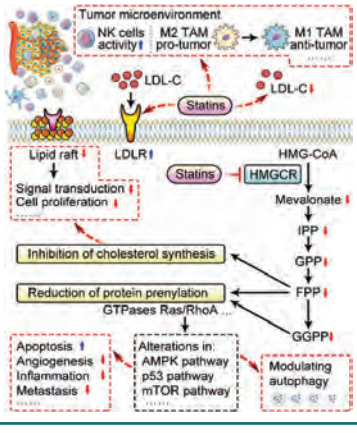
Statin use may also be helpful

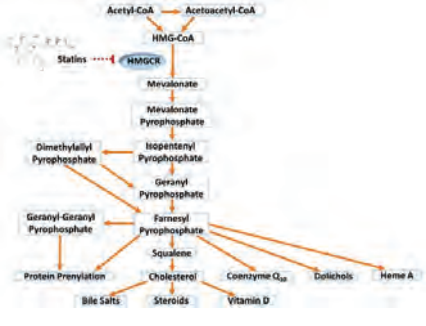
- Swedish study of 4315 MM patients
- MM specific mortality with HR 0.61 is statins are taken for at least 6 months
- MM-specific mortality decreased with increased statin intensity
- Not all statins may be the same?

Branvall et al, Am J Hematol, 2020

Statins have pleiotropic effects: limiting CoQ synthesis may be of importance in MM







A few words about the microbiome connection to metabolism

- The microbiome regulates adipose tissue biology and glucose homeostasis
- Microbial propionate induces insulin resistance, and plasma propionate decreases with weight loss
- Metformin use modifies intestinal microbiome
- Exogenous interventions to modify the microbiome currently are not durable

Thank you very much for your attention

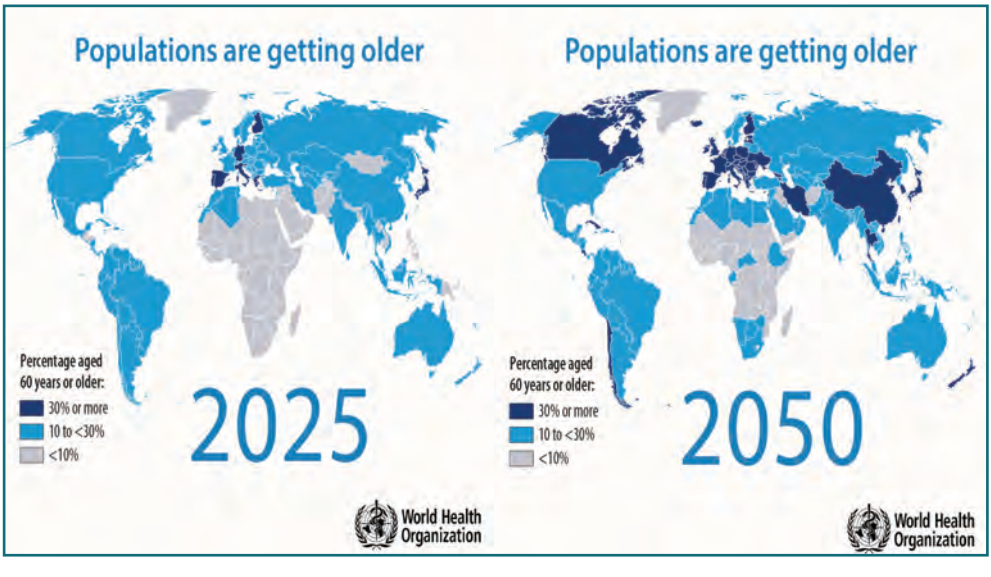
Prof. Artur Jurczyszyn, MD, PhD, Professor, specialist in internal medicine and hematology, professor at the Department of Hematology, Jagiellonian University Medical College In Kraków and Head of the Plasma Cell Dyscrasias Center. His present clinical and research activities center around the treatment of plasma cell dyscrasia. Author of more than 250 research papers with cumulative Impact Factor >700; Hirsch Index 23; scientific editor of seven monographs on clinical hematology. For many years he has been constantly cooperating with over a dozen clinical centers from around the world, which is reflected in numerous publications. President of the Board at the Polish Myeloma Working Group affiliated by the Polish Society of Hematology and Transfusion Medicine, International Myeloma Working Group (IMWG), International Myeloma Society (IMS), European Hematology Association (EHA), and American Society of Hematology (ASH).

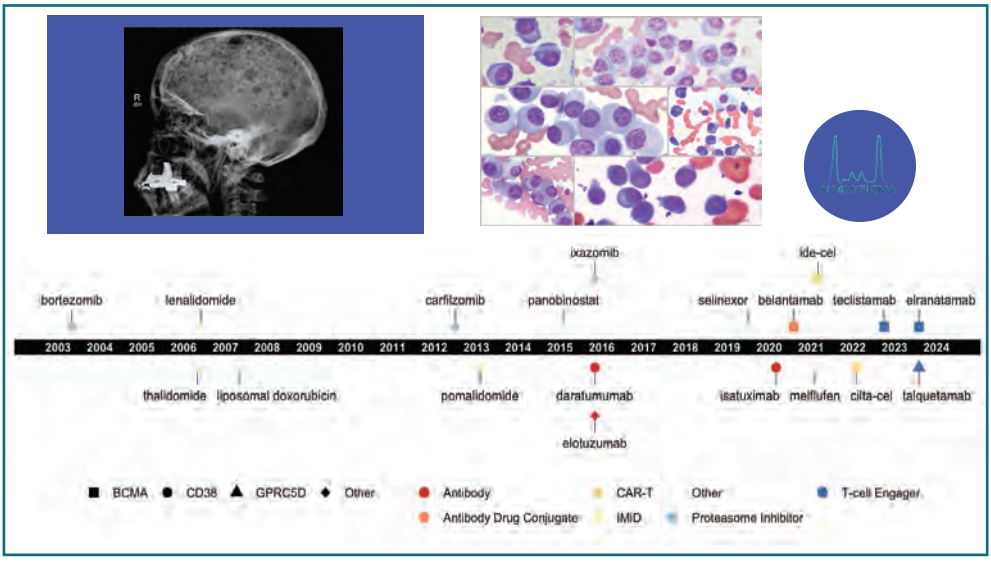
In 1996, graduated from the Faculty of Medicine, Jagiellonian University. In 2003, awarded with the doctor's degree for his research on the role of cytokines in pathogenesis of multiple myeloma. In 2016, awarded with the title of associate professor in medicine for the cycle of publications about the biology and treatment of plasma cell myeloma. Described the largest groups of patients with a rare cutaneous form of multiple myeloma and central nervous system involvement by multiple myeloma. Author of clinical reports presenting very rare patients with secondary plasma cell leukemia and patients who developed multiple myeloma before 30 years of age. Completed internships at John Theurer Cancer Institute in Hackensack (2012), Dana Farber Cancer Institute in Boston (2014) and Hammersmith Hospital in London (1998).

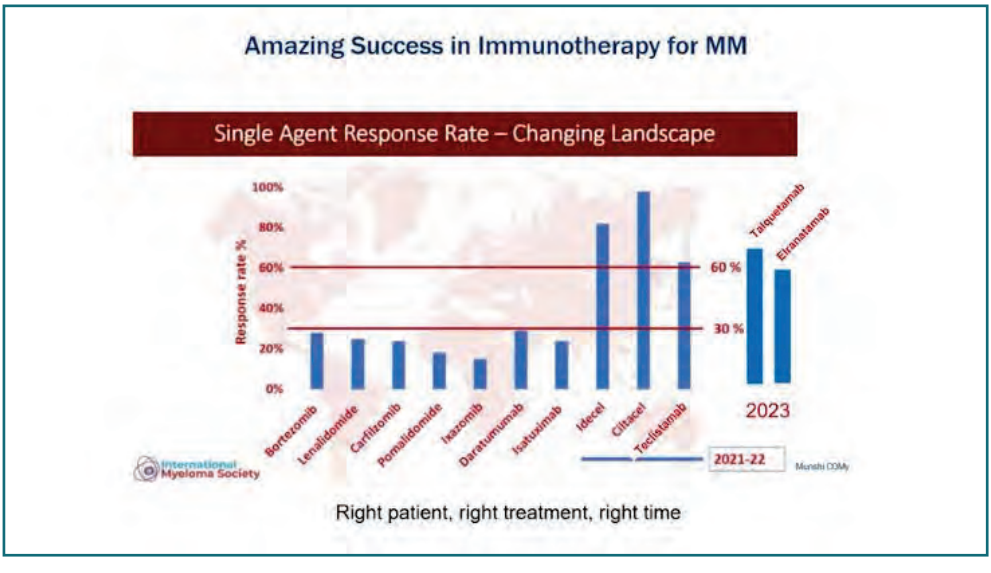
In 2015, granted a 650th Anniversary Medal of the Jagiellonian University, for his long-year clinical and research service. Co-founder and president of the Myeloma Treatment Foundation Center, a registered charity established in 2008. In 2016,

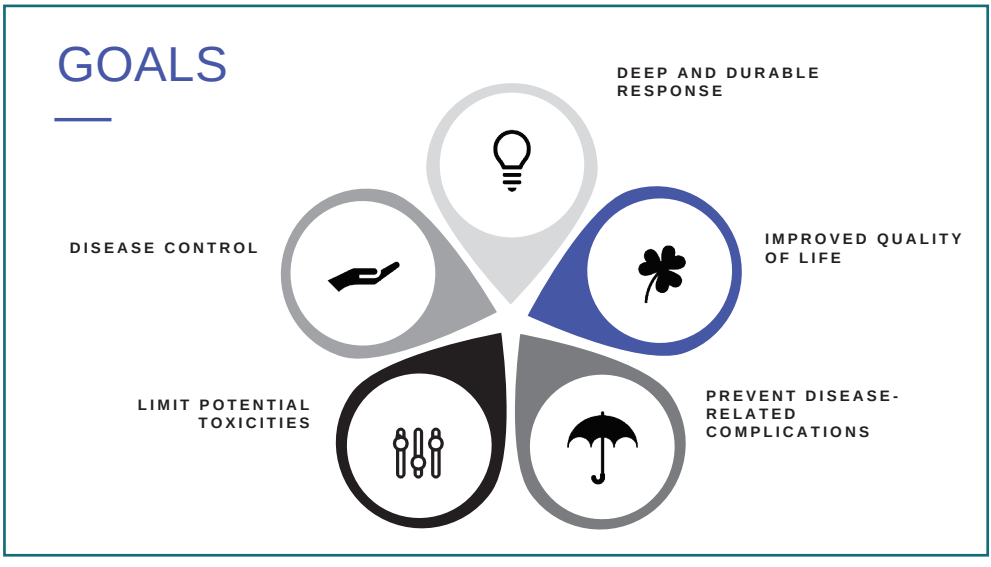
granted „Amicus Hominum" award from Małopolska Provincial Office, for individuals acting for the other's good in the field of health promotion and health protection. In 2017, received the first-degree award for research achievements from the Minister of Health and Higher Education. In 2018, presented with Tadeusz Browicz award from the Polish Academy of Arts and Sciences for the development of an original prognostic index in primary plasma cell leukemia. In 2021 received the Individual award of the Minister of Education and Science for significant achievements in the field of scientific activity. Since 2017, Chairmen at the Cracow Branch of the Polish Society of Hematology and Transfusion Medicine.

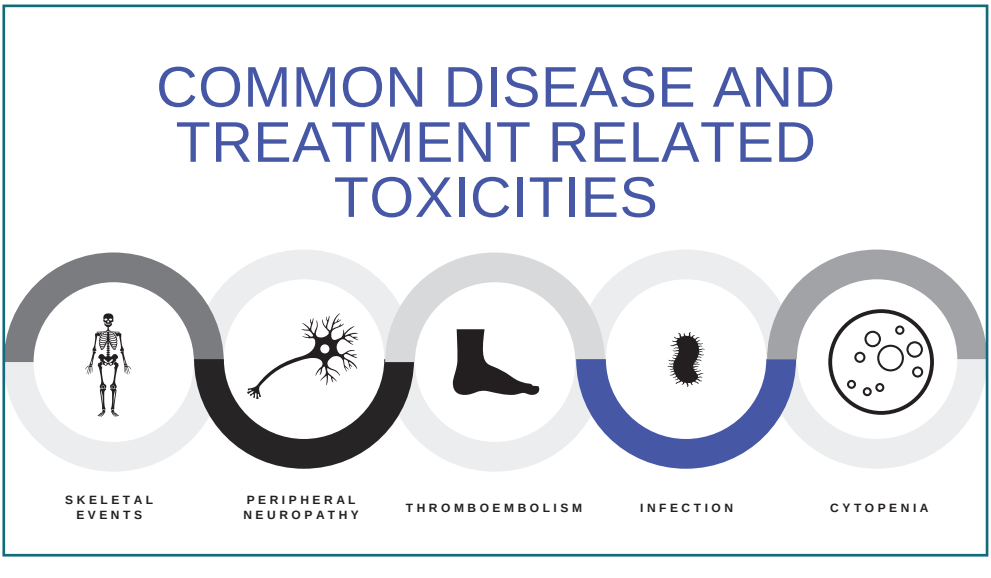

Polska Grupa Szpiczakowa
ALL4MYELOMA
POLSKIE TOWARZYSTWO HEMATOLOGÓW I TRANSFUZJOLOGÓW
prof. ARTUR JURCZYSZYN
Ośrodek Leczenia Dyskrazji Plazmocytowych
Katedra Hematologii Wydział Lekarski
Collegium Medicum Uniwersytetu Jagiellońskiego
12th International Conference
Complex treatment of plasma cell dyscrasias in 2024
September 6-7, 2024
CONFERENCE PROGRAM
Supportive care in multiple myeloma in 2024


Populations are getting older
Percentage aged 60 years or older:
30% or more
10 to <30%
<10%
2025
World Health Organization
Populations are getting older
Percentage aged 60 years or older:
30% or more
10 to <30%
<10%
2050
World Health Organization

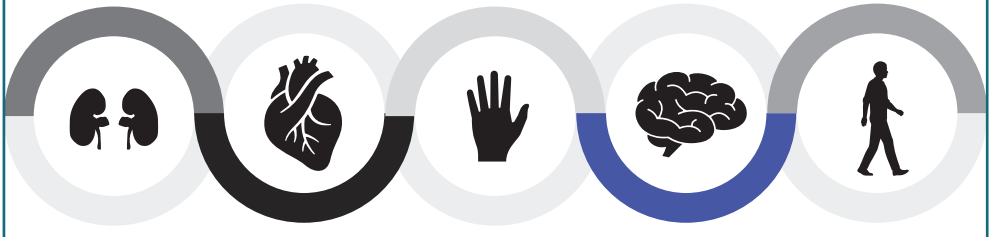

bortezomib
lenalidomide
carfilzomib
panobinostat
ixazomib
selinexor
belantamab
ide-cel
teclistamab
elranatamab
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
thalidomide
liposomal doxorubicin
pomalidomide
daratumumab
elotuzumab
isatuximab
melflufen
cilta-cel
talquetamab
BCMA
CD38
GPRC5D
Other
Antibody
Antibody Drug Conjugate
CAR-T
IMiD
Other
Proteasome Inhibitor
T-cell Engager


Amazing Success in Immunotherapy for MM
Single Agent Response Rate – Changing Landscape
Response rate %
100%
80%
60%
40%
20%
0%
60 %
30 %
Talquetamab
Elranatamab
2023
2021-22
Bortezomib
Lenalidomide
Carfilzomib
Pomalidomide
Ixazomib
Daratumumab
Isatuximab
Idecel
Cilta-cel
Teclistamab
International Myeloma Society
Munshi COMy
Right patient, right treatment, right time


GOALS
DEEP AND DURABLE RESPONSE
IMPROVED QUALITY OF LIFE
PREVENT DISEASE-RELATED COMPLICATIONS
LIMIT POTENTIAL TOXICITIES
DISEASE CONTROL


COMMON DISEASE AND TREATMENT RELATED TOXICITIES
SKELETAL EVENTS
PERIPHERAL NEUROPATHY
THROMBOEMBOLISM
INFECTION
CYTOPENIA

COMMON DISEASE AND TREATMENT RELATED TOXICITIES



RENAL INSUFFICIENCY | HEART HEALTH | RASH | FATIGUE | FUNCTIONING LIMITATIONS

BONE HEALTH

Osteolytic bone disease is the main complication of myeloma

BONE LESIONS

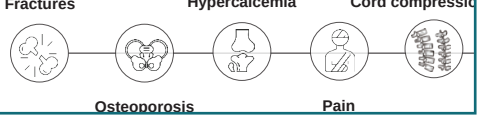
- Present in 70-80% of patients at diagnosis

OSTEOLYTIC LESIONS

- Come from imbalance of osteoclasts and osteoblasts in bone

HYPERCALCEMIA

- Comes from bone resorption and concern 25% of patients



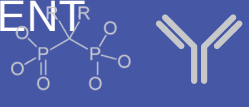
Bisphosphonates **should be used in combination with antimyeloma therapy as they reduce bone resorption**

- ZOLEDRONIC ACID may be preferred over pamidronate due to a significant reduction in the mortality rate
- ZA is also indicated for the treatment of MM-related hypercalcemia, and it is superior to pamidronate in this setting
- SMM & MGUS patients require monitoring and obtain treatment at diagnosis of osteoporosis

Denosumab **is a bone anti-resorptive monoclonal antibody, treats osteoporosis and various bone-related disorders**

- Denosumab is equivalent to zoleandric acid in terms of delaying the time to first skeletal-related event
- Denosumab may prolong PFS among NDMM patients with bone disease who receive ASCT

BONE-TARGETED TREATMENT

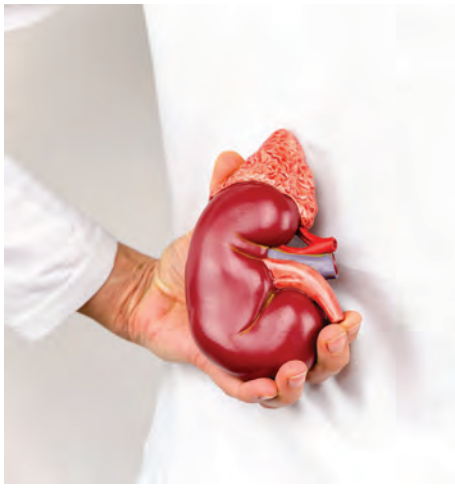


Terpos E et al. Lancet Oncol. 2021;22(3):e119-e130.
Mhaskar R et al., Cochrane Database Syst Rev. 2017;12(12):CD003188.
Raje N et al., Lancet Oncol. 2018;19(3):370.
Terpos E et al. Blood 2018:132(suppl_1): abstract 1969 and poster

RENAL DISEASE

EPIDEMIOLOGY

Renal disease is present in 25% of patients
at diagnosis and with time its frequency increases to 50%



73%

PARAPROTEIN -ASSOCIATED CHANGES

25%

NON-PARAPROTEIN ASSOCIATED CHANGES

Nasr SH et al. Am J Kidney Dis. 2012;59(6):786-94

INITIAL WORK-UP OF PATIENTS WITH RENAL INSUFFICIENCY

• Selective proteinuria, light chains predominance • serum FLC ≥500 mg/L	• Non-selective proteinuria, substantial albuminuria • serum FLC <500 mg/L	• No proteinuria
MYELOMA CAST NEPHROPATHY	**GLOMERULAR OR TUBULAR PATHOLOGY**	**CONSIDER ALTERNATIVE DIAGNOSIS**
Kidney biopsy unnecessary but might be helpful in patients with comorbidities	• AL amyloidosis • Monoclonal immunoglobulin deposition disease • Other condition	Kidney biopsy necessary

Dimopoulos MA et al. Lancet Oncol 2023;24:293-311.

Received: 19 January 2022 | Revised: 14 March 2022 | Accepted: 1 April 2022
DOI: 10.1002/ajh.26566

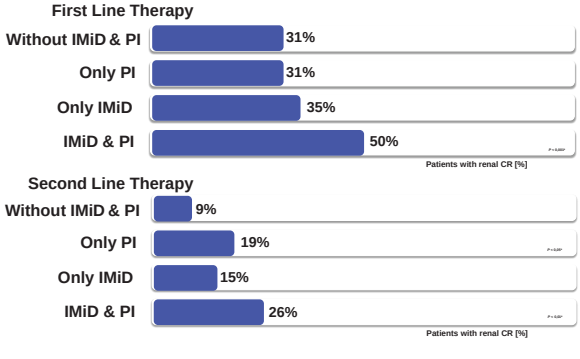
RESEARCH ARTICLE

AJH WILEY

Monoclonal gammopathy of renal significance (MGRS): Real-world data on outcomes and prognostic factors

Alessandro Gozzetti[1] | Andrea Guarnieri[2] | Elena Zamagni[3,4] | Elena Zakharova[5] | Daniel Coriu[6] | Max Bittrich[7] | Tomáš Pika[8] | Natalia Tovar[9] | Natalia Schutz[10] | Sara Ciofini[1] | Camila Peña[10] | Serena Rocchi[3] | Michael Rassner[11] | Irit Avivi[12] | Anna Waszczuk-Gajda[13] | Saurabh Chhabra[14] | Lidia Usnarska-Zubkiewicz[15] | Verónica González-Calle[16] | Maria-Victoria Mateos[16] | Monica Bocchia[1] | Flavia Bigi[3] | Hannah Füllgraf[10] | Bhavna Bhasin-Chhabra[14] | Massimo Gentile[17] | Julio Davila[18] | David H. Vesole[19] | Michele Cavo[3] | Bicky Thapa[14] | Edvan Crusoe[20] | Hermann Einsele[6] | Wojciech Legiec[21] | Grzegorz Charliński[22] | Artur Jurczyszyn[23]

- Amyloidosis is the most prevalent type of MGRS consisting around 2/3 of all cases
- MIDD is the most common type of non-amyloidosis MGRS
- Most patients received treatment (86%)
- PI-based regimes were most commonly used
- Patients with non-amyloidosis MGRS more frequently received transplant than amyloidosis MGRS patients
- Hematologic response didn't always equal the renal
- Percent of patients with renal response decreases with the quality of hematologic response
- Patients with amyloidosis MGRS had worst survival compared to patients with non-amyloidosis MGRS
- Increased mortality in the MGRS-A can be associated with heart disesese
- Achievement of complete hematologic response was a predictor of survival
- Treatment effectiveness justifies the biopsy procedure
- There are a few predictors of survival in patients with amyloidosis MGRS, but only age predicts OS in non-amyloidosis MGRS.



BORTEZOMIB-BASED REGIMENS ARE THE STANDARD OF CARE

Mikhael J et al. Blood Cancer J. 2021;11: 99.

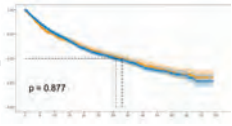
BORTEZOMIB DOSAGE MATTERS

CONSIDER ONCE WEEKLY BORTEZOMIB AS STANDARD-OF-CARE REGIMEN

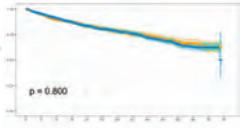
Bortezomib is administered twice weekly; however, comparable efficacy and less peripheral neuropathy occurs with once-weekly dosing

- Twice weekly
- Once weekly

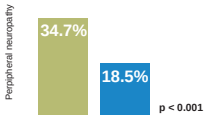
Similar PFS



Similar OS



Better safety



Hoff FW et al. Blood Cancer J. 2024;14(1):52.

ANTI-MYELOMA TREATMENT FOR RENAL INSUFFICIENCY

CARFILZOMIB	IXAZOMIB	LENALIDOMIDE	POMALIDOMIDE
safe and effective in patients with RRMM and RI (grade A for CrCl ≥15 ml/min; grade B for CrCl <15 ml/min) without need for dose adjustments. Close monitoring is important for early identification and prompt management of carfilzomib-related renal complications.	can be safely administered in combination with lenalidomide and dexamethasone in patients with RRMM and CrCl ≥30 ml/min (grade A). A lower starting dose of 3 mg is indicated for individuals with CrCl <30 mL/min (grade B).	effective and safe in RI (grade B). Lenalidomide should be administered with dose adjustments according to CrCl (grade B).	safe and effective including patients on dialysis (grade A for CrCl ≥45 ml/min; grade B for CrCl <30 ml/min).

Dimopoulos MA et al. Lancet Oncol 2023;24:293-311.

ANTI-MYELOMA TREATMENT FOR RENAL INSUFFICIENCY

HIGH DOSE DEXAMETHASONE

recommended for the first cycle: 40 mg/day (20mg for patients ≥75 years), 4 days on/4 days off for three pulses during the first cycle of therapy; then according to the treatment protocol (grade B).

PI + IMID + DEX

in the upfront setting and at first relapse in patients with CrCl <50mL/min improve renal response and survival (grade B).

ANTI-CD38 BASED TRIPLETS

safe and effective in RRMM patients with moderate/severe or moderate RI

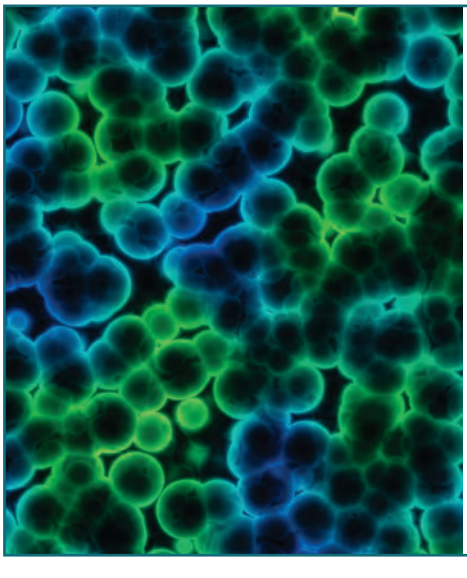
OTHER TREATMENTS

HDM/ASCT is safe and effective in fit NDMM patients with stable RI.

Belantamab mafodotin is well tolerated and effective in RRMM patients with moderate RI (grade C).

Selinexor-based regimens are well tolerated and effective in RRMM patients with moderate/severe RI (grade C).

Dimopoulos MA et al. Lancet Oncol 2023;24:293-311.



INFECTION

Infection remains the leading cause of death in patients with multiple myeloma

PERIODS OF DANGER

The periods of highest infectious risk are during the first three months after diagnosis and when treating RRMM

PATHOGENS

Most infections are caused by viruses and bacteria. Bacterial infections manifest, most commonly as pneumonia and bacteremia. Viral infections present typically as seasonal viruses particularly influenza, SARS-CoV-2 and herpes zoster.

PREVENTION

Newly diagnosed patients have higher rates of potentially preventable infections (e.g., Streptococcus pneumoniae, Haemophilus Influenzae).

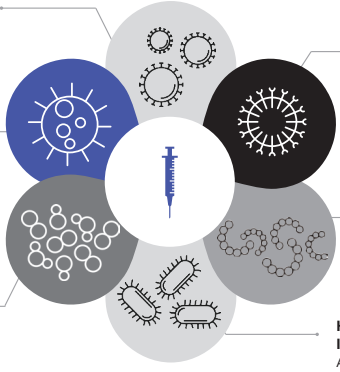
Raje N, et al. Lancet Haematol 2022;9:143-61

VACCINATION

COVID-19
All patients.

HERPES ZOSTER
All patients.

MENINGOCOCCI
Patients with asplenia, complement deficiency, recurrent episodes of bacterial infections



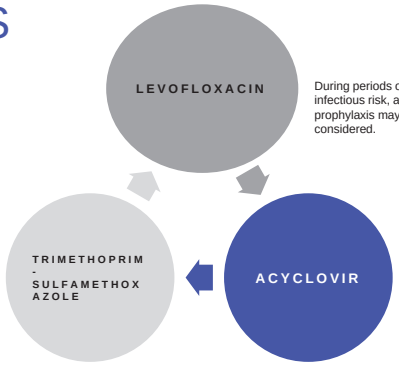
INACTIVATED INFLUENZA VACCINE
All patients. Preferably with a two-dose series of high-dose influenza vaccine

S. PNEUMONIAE VACCINES
PCV13 or PCV20 followed by PPSV23 every two years

HAEMOPHILUS INFLUENZAE
All patients.

Ludwig H et al. Leukemia. 2021;35(1):31-44.

PROPHYLAXIS FOR INFECTIONS

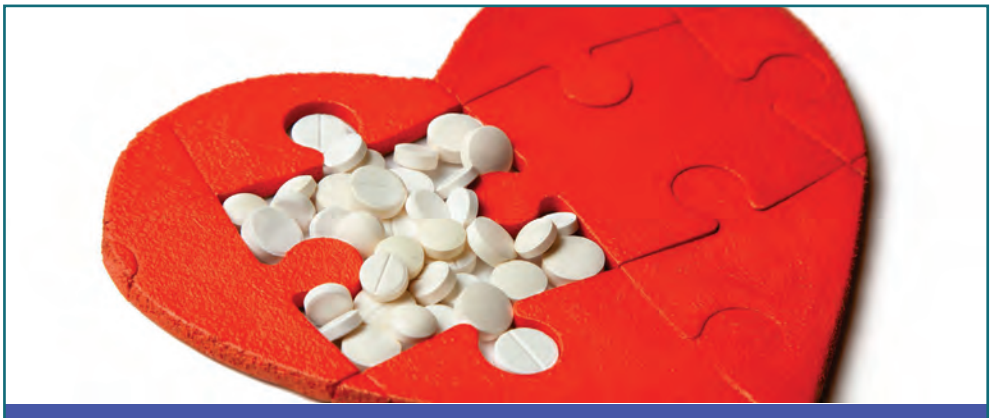


During periods of increased infectious risk, antibacterial prophylaxis may be considered.

Used for patients who are seropositive for herpes simplex virus and varicella zoster virus if tested. We also use acyclovir prophylaxis for patients treated with proteasome inhibitors or MM-targeted monoclonal antibodies, specifically anti-CD38

Only for patients at risk of Pneumocystis jirovecii pneumonia (RRMM or receipt of high doses of dexamethasone such as ≥ 40mgs/day for 4 days/week). Alternatives such as dapsone may be considered for patients with sulfa allergies.

Raje N, et al. Lancet Haematol 2022;9:143-61



Several large studies using combination therapy for MM have demonstrated an increased risk of serious CV adverse event

	Hypertension	Hyperglycemia / Diabetes	Heart Failure	Atrial fibrillation	Myocardial infraction	Venous thromboembolism	Pulmonary hypertension	Arterial thromboembolism
Thalidomide								
Lenalidomide								
Pomalidomide								
Bortezomib								
Carfilzomib								
Daratumumab								
Elotuzumab								
Isatuksimab								

Rare: <0,1% | Uncommon: 0.1-1% | Common: 1-10% | Very common: >10%

MM DRUG-RELATED CARDIOVASCULAR TOXICITIES

Lyon et al. Eur Heart J. 2022;43(41):4229-4361

SELECTED RECOMMENDATIONS FOR BASELINE RISK ASSESSMENT AND MONITORING

BLOOD PRESSURE

- BP measurement is recommended for patients treated with PI at every clinical visit.
- Home monitoring of BP weekly during the first 3 months and monthly thereafter should be considered for patients treated with PI.

CARDIAC BIOMARKERS

- Measurement of NP is recommended prior to PI in high- and very high-risk patients
- In patients receiving carfilzomib or bortezomib, measurement of NP should be considered at baseline and every cycle during the first 6 cycles

TRANSTHORACIC ECHOCARDIOGRAPHY

- Baseline echocardiography, including assessment for AL-CA, is recommended in all patients with MM scheduled to receive PI.
- Echocardiography surveillance every 3 cycles should be considered in high- and very high-risk patients receiving carfilzomib

VTE PROPHYLAXIS

- Therapeutic doses of LMWH are recommended in patients with MM with previous VTE
- Prophylactic doses of LMWH are recommended in patients with MM with VTE-related risk factors at least during the first 6 months of therapy
- Low doses of apixaban or rivaroxaban may be considered as an alternative to LMWH (or aspirin)

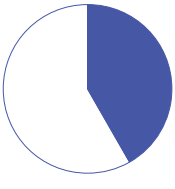
Lyon et al. Eur Heart J. 2022;43(41):4229-4361

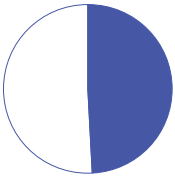
Patients with multiple myeloma experience a high burden of disease and treatment-related symptoms that impact upon their quality of life

PROM	Characteristics			MCID	Validated in		
	Number of items	Completion Time	Paper + Electronic		MM	BMT	Languages
EQ-5D-3L	5	<10 min	yes	yes	yes	no	>150
EORTC QLQC30	30	<10 min	yes	yes	yes	yes	110
EORTC MY20 *	20	12 min	yes	yes	yes	yes	50
FACT-MM (BMT)	41	10–15 min	no	yes	yes	yes	9
MDASI-MM	26	5 min	yes	no	yes	no	30
MyPOS	30	7 min	no	no	yes	no	2
HM-PRO	42	7 min	yes	yes	yes	yes	11

HOW TO MEASURE QOL?

Lacas E et al. Cancers 2022;15:5764





QoL evaluation

Only 40% of RCTs planned to assess QoL (118/286).

In RCTs planned to assess QoL only in 33% protocols was available (39/118)

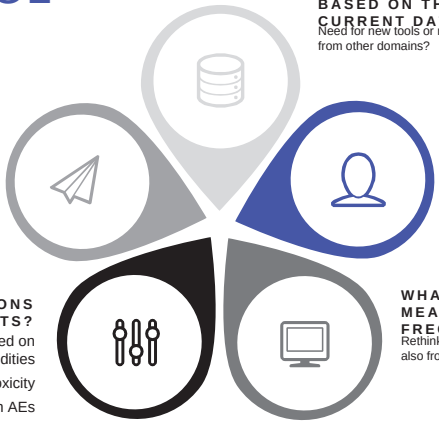
QoL reporting

Only in half of studies planning QoL assessment reported the outcome (58/118)

DO WE MEASURE QOL IN TRIALS?

Salek S et al. Cancers (Basel). 2022;14(23):6007.

GAPS IN QOL



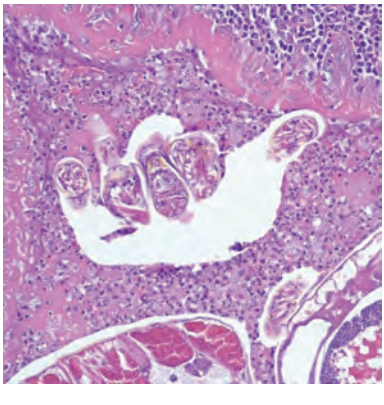
WHAT DO WE KNOW BASED ON THE CURRENT DATA?
Need for new tools or re-purpose tools from other domains?

DOES TIME SPEND ON HEALTHCARE MATTER?
Decrease in QoL in earlier timepoints, then improvement on CAR-T cell therapy

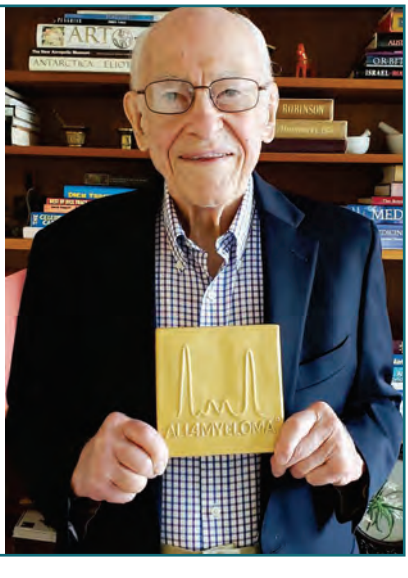
IS THIS WHAT WE MEASURE IMPORTANT?
Need for new tools or re-purpose tools from other domains?

WHAT ARE THE LIMITATIONS OF CURRENT ASSESSMENTS?
Assessments based on comorbidities
Delayed neurotoxicity
Low-grade but long-duration AEs

WHAT SHOULD WE MEASURE AND HOW FREQUENT?
Rethink current tools and gain consensus also from patients



THANK YOU



Historia Ludwika Hirszfelda to opowieść o wybitnym lekarzu, bakteriologu i immunologu, założycielu polskiej szkoły immunologicznej, twórcy podstaw nauki o grupach krwi.

Był też wybitnym humanistą, doskonale odnajdującym się w roli przewodnika i nauczyciela pokoleń lekarzy i naukowców.

„Kto chce być szczęśliwy, niech nie szuka szczęścia, niech szuka życia”

„Wiedza - moją nadzieją i ukojeniem, bez niej nie wytrzymam”

Początek

1884

Początek
Ludwik Hirszfeld urodził się w Warszawie
w łódzkiej zasymilowanej rodzinie żydowskiej; wychowywał się w otoczeniu naukowców m.in. Aleksandra Rajchmana i Ludwika Rajchmana

1902

Studia medyczne
Rozpoczął w Wurzburgu, a dwa lata później zaczął studiować filozofię w Berlinie

Ludwik Hirszfeld (1884-1954)

Praca zawodowa

1905

Ślub z Hanną Kasman

1907

Tytuł doktora medycyny i chirurgii
(*Badania nad aglutynacją krwi i ich podstawy fizykalne*)

(exima cum laude)

1907-1911

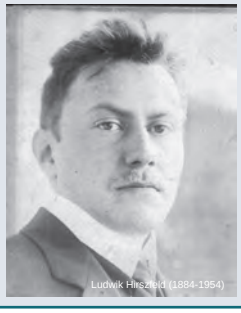
Asystentura
Instytut Badania Raka
na Uniwersytecie w Heidelbergu

Ludwik Hirszfeld (1884-1954)

Hirszfeld uważał pobyt w Heidelbergu za najbardziej twórczy okres swojego życia

- Znane były prace Karla Landsteinera z lat 1900-1902 na temat grup krwi
- Zrodziło się pytanie, czy są one dziedziczne? Hirszfeld z Emilem von Dungernem zbadali grupy krwi osób z rodzin pracowników Instytutu
- Odkryli, że grupy krwi dziedziczy się zgodnie z prawami Mendla, przy czym grupy A i B są dominujące, a O recesywna
- Badacze wprowadzili nazwy grup krwi: A, B, AB i O (Karl Landsteiner oznaczał je cyframi rzymskimi)
- Oznaczenie grup krwi: 0, A, B, AB przyjęto na całym świecie w roku 1928
- Gdy w 1930 r. Karl Landsteiner otrzymał Nagrodę Nobla za odkrycie grup krwi, w swojej mowie noblowskiej stwierdził: „*w badaniach nad dziedziczeniem grup krwi najważniejsze wyniki uzyskali von Dungern i Hirszfeld*".


Emil von Dungern (1867-1961)


Ludwik Hirszfeld (1884-1954)

Przed I Wojną Światową

1912
Kontynuacja asystentury w Zurychu

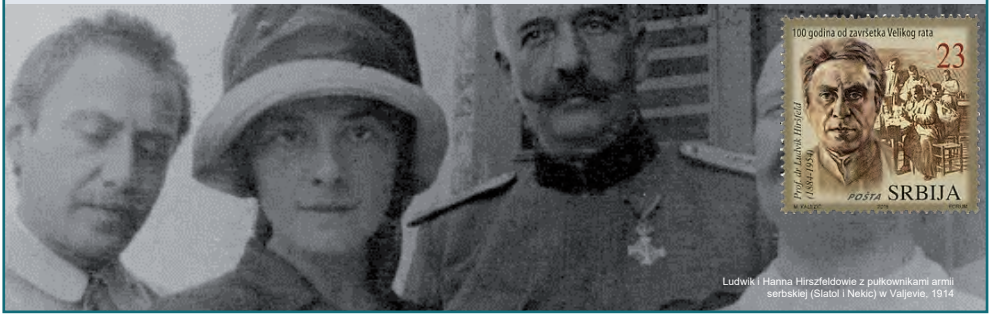
1914
Habilitacja
(*Anafilaksja i anafilatoksyna i ich związek z procesem krzepnięcia*)

1915-1920
Armia Serbska
Polowe centralne laboratorium bakteriologiczne; epidemia duru plamistego, duru rzekomego oraz zimnicy oraz prace nad seroantropologią

Ludwik Hirszfeld (1884-1954)

Lekarska i humanitarna powinność w czasie I Wojny Światowej

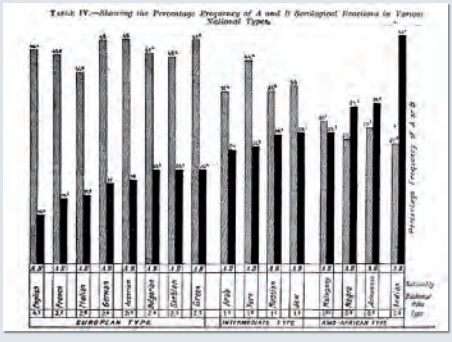
- Hirszfeldowie nie chcieli wspierać krajów walczących przeciw Polsce.
- W Serbii uczestniczyli w organizacji tamtejszej służby zdrowia wspierającej armię serbską walczącą z przeważającymi siłami austriackimi.
- Pracując na Bałkanach Hirszfeld odkrył pałeczkę duru rzekomego, nazwaną *Salmonella hirschfeldii*.
- W podzięce za te wszystkie dokonania wdzięczny rząd serbski odznaczył go Orderem Św. Sawy, późniejszy zaś rząd jugosłowiański Orderem Orła Białego.



Ludwik i Hanna Hirszfeldowie z pułkownikami armii serbskiej (Slatol i Nekic) w Valjevie, 1914

Przełomowa praca w skrajnie trudnych warunkach

- Różnorodność etniczna żołnierzy skłoniła Hirszfeldów do przeprowadzenia badań na częstością występowania grup krwi układu ABO u osób o różnych narodowościach
- Zakrojone na dużą skale badanie, z udziałem 8000 osób, nie zostało opublikowane przez lata; argumentowano, że nie jest interesujące dla lekarzy.
- Ostatecznie artykuł ukazał się w czasopiśmie Lancet w 1919 r.



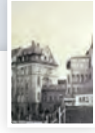
Czerwiński M, Glensk U. Kosmos 2019;68(2):145-156.
Hirszfeld L, Hirszfeld H. Lancet 1919;194:675-679.

Fotografia: Hanna Hirszfeld (siedzi w środku) i jej mąż Ludwik jako lekarze wojenni, ok. 1916, wł. Piotr Kiełbasiński

Powrót do Polski

Po 17 latach spędzonych za granicą Hirszfeldowie wrócili po wojnie do Polski.

w ojczyźnie ma się i przeszłość, i teraźniejszość, i przyszłość,
a na emigracji tylko teraźniejszość.



Nowe wyzwania zawodowe

Ludwik Hirszfeld zajął się organizowaniem Zakładu Badania Surowic, który wkrótce został połączony z Centralnym Zakładem Epidemiologicznym, tworząc jedną instytucję naukowo-medyczną o nazwie Państwowy Zakład Higieny (PZH). Hanna Hirszfeld swoje doświadczenie wykorzystywała w tworzonej Warszawie klinice pediatrycznej przy ulicy Litewskiej

Ludwik Hirszfeld w PZH (lata trzydzieste)

Lata międzywojenne

- Na stanowisku dyrektora PZH, Hirszfeld zastąpił swojego kuzyna Ludwika Rajchmana
- W PZH przystąpiono do monitorowania zagrożeń epidemiologicznych, bo świadomość higieniczna pozostawiała wiele od życzenia.
- Hirszfeld kierował pracą naukowców, którzy zajmowali się bakteriologią, wirusologią, immunologią, badaniem nad rakiem, a także szukali nowych sposobów rozpoznawania chorób zakaźnych.
- Kontynuowano prace nad grupami krwi, m.in. określano częstość występowania grup krwi w Polsce, czyli kontynuowano prace rozpoczęte w Serbii.
- Określanie grup krwi wykorzystywał również z badaniach kryminologicznych, a udział w procesach sadowych przyniósł mu rozpoznawalność społeczną (Hirszfeld L., O wykorzystaniu grup krwi do badań kryminologicznych. *Czasopismo Sądowo-Lekarskie*, 1936;2).
- Ludwik Hirszfeld podróżował i brał aktywny udział w życiu naukowym Europy.
- W 1931 r. Hirszfeld otrzymał profesurę tytularną na Uniwersytecie Warszawskim. Zamieszkał w domu na Saskiej Kępie (ulica Obrońców 27).

Ludwik Hirszfeld (1884-1954)

Maszyna do pisania profesora Ludwika Hirszfelda

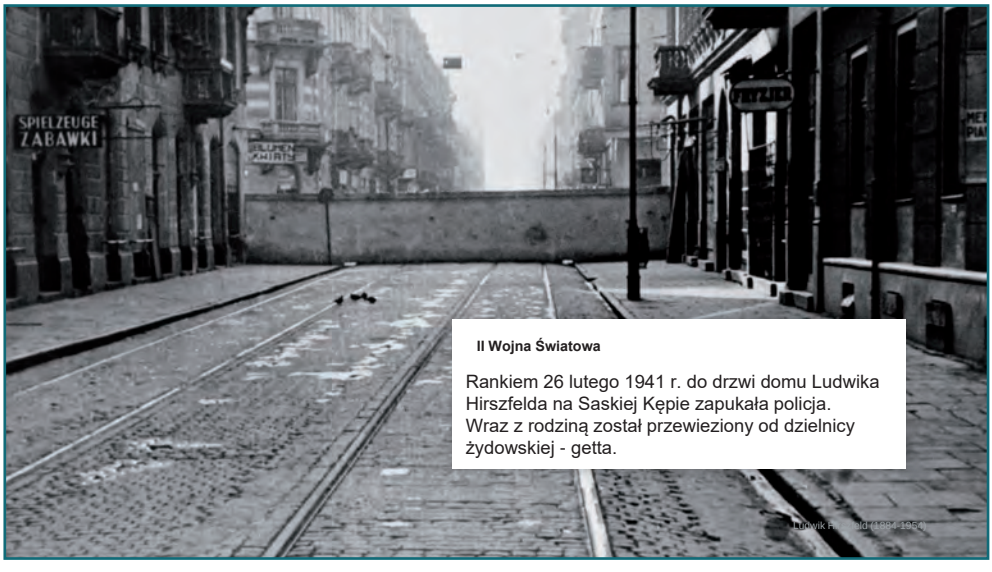
Sprawa Gorgonowej

Proces w sprawie morderstwa Lusi Zarembiny w Brzuchowicach był głośnym wydarzeniem medialnym dwudziestolecia międzywojennego. Była to historia brutalna, poruszająca, z mocnym wątkiem obyczajowym i skandalicznym posmakiem.

O zbrodnię została oskarżona guwernantka, Rita Gorgonowa. Zabezpieczone na chusteczce ślady krwi były innej grupy niż grupa krwi Gorgonowej. Hirszfeld wraz ze współpracownikami wykazali, że chusteczka była dotykana przez wiele osób w czasie śledztwa, jest przesycona antygenami grupowymi i grupy krwi nie można precyzyjnie ustalić. Te ustalenia doprowadziły Hirszfelda wstrząsnęły opinią publiczną i zaufaniem do sądu oraz do konfliktu z mającym odmienne zdanie słynnym lekarzem sądowym Janem Stanisławem Olbrychtem.

Rita Gorgonowa została skazana na karę więzienia i nigdy nie przyznała się do zarzucanej jej zbrodni.

Łazarewicz Cezary, Koronkowa robota: sprawa Gorgonowej, Wołowiec: Wydawnictwo Czarne, 2018, sygn.: 1.019.369.



II Wojna Światowa

Rankiem 26 lutego 1941 r. do drzwi domu Ludwika Hirszfelda na Saskiej Kępie zapukała policja. Wraz z rodziną został przewieziony od dzielnicy żydowskiej - getta.

Ludwik H... ...ld (1884-1954)

Życie w getcie

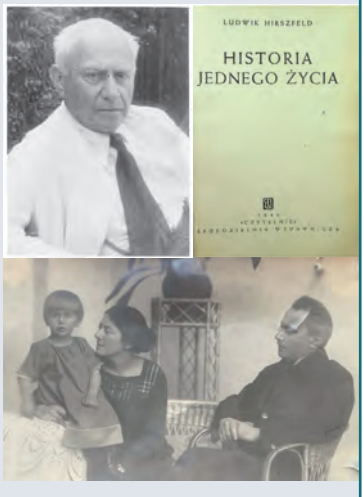
Hirszfeld został usunięty z zajmowanych stanowisk. W getcie czuł się wyobcowany. Doskwierał mu brak pracowni. Mimo to, angażował się w pracę naukową i dydaktyczną, m.in.:

- Leczył chorych na tyfus przemyconą do getta szczepionką Rudolfa Weigla,
- Przygotowywał zaległe prace naukowe, pisał autobiografię,
- Prowadził kursy przysposobienia sanitarnego, które w rzeczywistości były nauczaniem medycyny na poziomie uniwersyteckim.

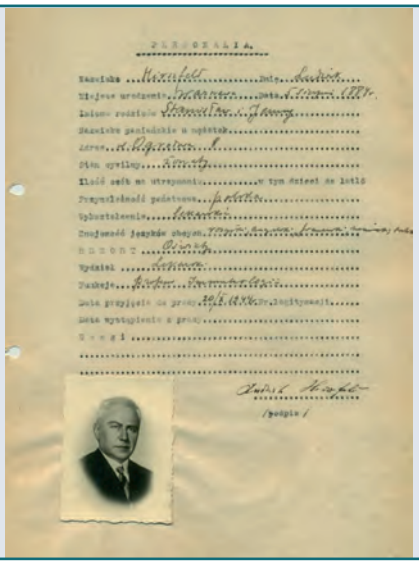
Ludwik Hirszfeld (1884-1954)

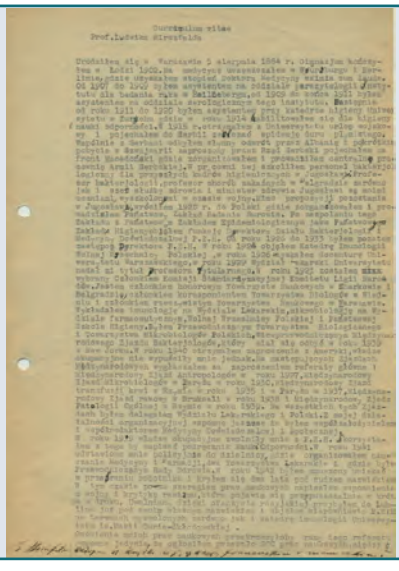
Okres II Wojny Światowej i lata powojenne

- 1939; ośrodek przetaczania krwi w Warszawie
- 1941; Narodowa Rady Zdrowia
- 1942; ucieczka z getta, ukrywanie się
- 1943; śmierć córki Hirszfeldów, Marii
- 1944; Lublin, Uniwersytet im. Marii Skłodowskiej-Curie
- 1945; Uniwersytet Wrocławski
- 1946; pierwsze wydanie *Historii Jednego Życia*, autobiografii Ludwika Hirszfelda

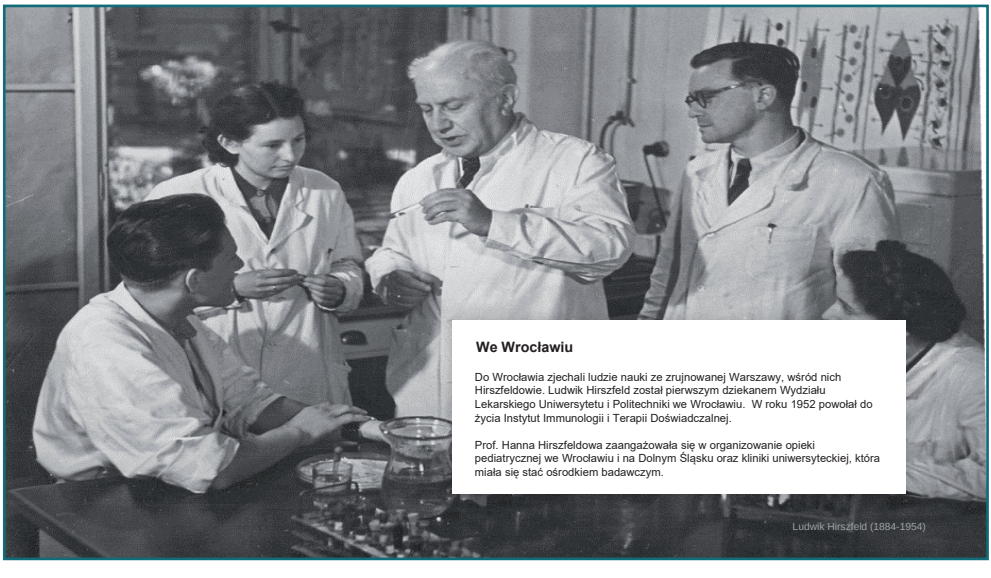


Zdjęcia dzięki uprzejmości prof. Urszuli Glensk z Wrocławia






JUDE
Fragebogen zur erstmaligen Meldung der Heilberufe.

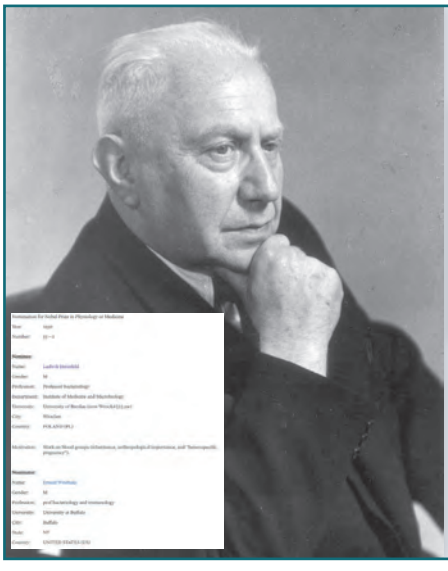


We Wrocławiu

Do Wrocławia zjechali ludzie nauki ze zrujnowanej Warszawy, wśród nich Hirszfeldowie. Ludwik Hirszfeld został pierwszym dziekanem Wydziału Lekarskiego Uniwersytetu i Politechniki we Wrocławiu. W roku 1952 powołał do życia Instytut Immunologii i Terapii Doświadczalnej.

Prof. Hanna Hirszfeldowa zaangażowała się w organizowanie opieki pediatrycznej we Wrocławiu i na Dolnym Śląsku oraz kliniki uniwersyteckiej, która miała się stać ośrodkiem badawczym.

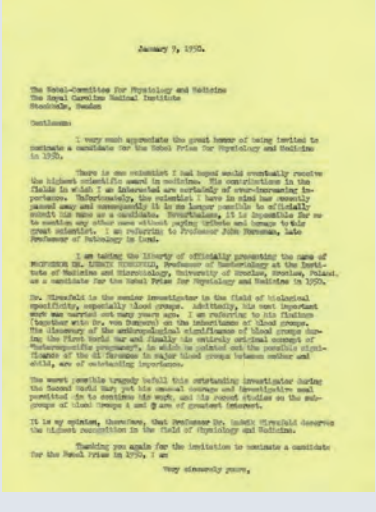
Ludwik Hirszfeld (1884-1954)



Ludwik Hirszfeld (1884-1954)

Zagadka konfliktu serologicznego

Hirszfeld odkrył przyczynę konfliktu serologicznego oraz opracował zasady przetaczania krwi co uratowało i nadal ratuje życie wielu noworodkom. W 1950 był za to i wcześniejsze odkrycia nominowany do nagrody Nobla.



January 9, 1950.

The Nobel-Committee for Physiology and Medicine
The Royal Caroline Medical Institute
Stockholm, Sweden

Gentlemen:

I very much appreciate the great honor of being invited to nominate a candidate for the Nobel Prize for Physiology and Medicine in 1950.

There is one scientist I had hoped would eventually receive the highest scientific award in medicine. His contributions in the fields in which I am interested are certainly of ever-increasing importance. Unfortunately, the scientist I have in mind has recently passed away and consequently it is no longer possible to officially submit his name as a candidate. Nevertheless, it is impossible for me to mention any other name without paying tribute and homage to his great intellect. I am referring to Professor John Donsmus, late Professor of Pathology in Lund.

I am taking the liberty of officially presenting the name of PROFESSOR DR. LUDWIK HIRSZFELD, Professor of Bacteriology at the Institute of Medicine and Bacteriology, University of Wrocław, Wrocław, Poland, as a candidate for the Nobel Prize for Physiology and Medicine in 1950.

Dr. Hirszfeld is the senior investigator in the field of biological specificity, especially blood groups. Additionally, his most important work was carried out many years ago. I am referring to his findings together with Dr. von Dungern on the inheritance of blood groups. The discovery of the anthropological significance of blood groups during the First World War and finally his entirely original concept of "heterogenetic pregnancy", in which he pointed out the possible significance of the AB Isogroups in major blood groups between mother and child, are of outstanding importance.

The worst possible tragedy befell this outstanding investigator during the Second World War but his unusual courage and investigative zeal permitted him to continue his work, and his recent studies on the subgroups of blood Isogroups A and B are of greatest interest.

It is my opinion, therefore, that Professor Dr. Ludwik Hirszfeld deserves the highest recognition in the field of Physiology and Medicine.

Thanking you again for the invitation to nominate a candidate for the Nobel Prize in 1950, I am

Very sincerely yours,

Polska Wydział Humanistyczny
Uniwersytet we Wrocławiu
L.1508/50.

Wrocław, dnia 27 października 1950 r.

Do
Ob. Prof.Dr Hanny i Prof.Dr Ludwika Hirszfeldów
we Wrocławiu
ul. Chełmońskiego 4

Rada Wydziału Humanistycznego Uniwersytetu Wrocławskiego na posiedzeniu w dniu 13 października 1950 r. jednomyślnie uchwaliła wyrazić serdeczne podziękowanie Wielce Szanownym Państwu za dotychczasową wspaniałomyślność jak i za dalsze udzielenie stypendium imienia Ich Córki ś.p. Marii Hirszfeldówny studentce Wydziału Humanistycznego.

Ze swej strony Rada Wydziału przedstawia na to stypendium nową kandydatkę, ob. Irenę Bonecką, studentkę III-go roku Filologii francuskiej.

Łączę wyrazy głębokiej czci

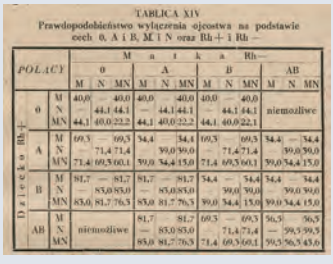
Bronisław Biliński
p/o Dziekan
Polska Wydział Humanistyczny
Uniwersytet we Wrocławiu

Odkrycia o wielkim znaczeniu

Odkrycie dziedziczenia grup krwi ABO przyczyniło się do rozwoju transfuzjologii, genetyki, kryminalistyki i wspierało ustalanie ojcostwa.

Badania zapoczątkowane na Bałkanach stworzyły seroantropologię, naukę o różnicach serologicznych między ludźmi z różnych grup etnicznych, mogącej służyć do ustalenia pokrewieństwa i pochodzenia ludzi z różnych krajów i kontynentów.

Dziś w przypadku występowania konfliktu serologicznego między matką a płodem stosuje się terapię antygenową. Ludwik Hirszfeld, razem z położnikiem prof. Kazimierzem Jabłońskim, opracowali inną terapię opartą na transfuzji wymiennej krwi, która uratowała życie wielu noworodkom. Z inicjatywy Hirszfelda rozpoczęto wówczas oznaczanie czynnika Rh w badanej krwi.



TABLICA XIV

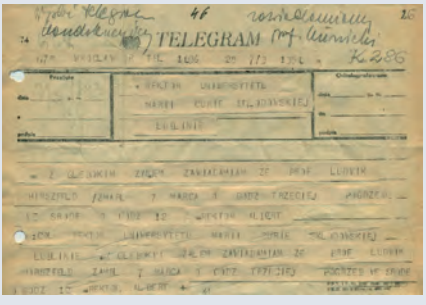
Prawdopodobieństwo wyłączenia ojcostwa na podstawie cech 0, A i B, M i N oraz Rh + i Rh —

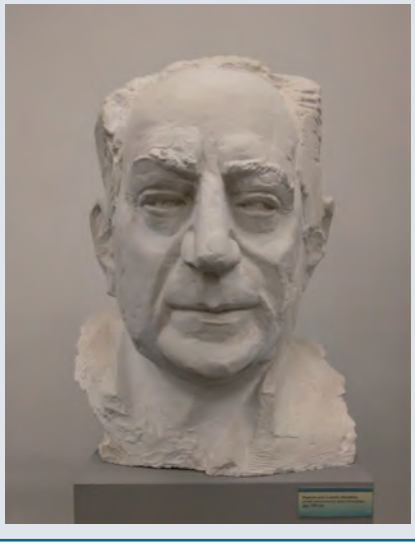
Dziecko Rh+	POLACY	M	0 M	0 N	0 MN	A M	A N	A MN	B M	B N	B MN	AB M	AB N	AB MN
0	M	40,0	—	40,0	40,0	—	40,0	40,0	—	40,0				
	N	—	44,1	44,1	—	44,1	44,1	—	44,1	44,1	niemożliwe			
	MN	44,1	40,0	22,2	44,1	40,0	22,2	44,1	40,0	22,1				
A	M	69,3	—	69,3	34,4	—	34,4	69,3	—	69,3	34,4	—	34,4	
	N	—	71,4	71,4	—	59,0	59,0	—	71,4	71,4	—	59,0	59,0	
	MN	71,4	69,3	60,1	59,0	34,4	15,0	71,4	69,3	60,1	59,0	34,4	15,0	
B	M	81,7	—	81,7	81,7	—	81,7	34,4	—	34,4	34,4	—	34,4	
	N	—	85,0	85,0	—	85,0	85,0	—	59,0	59,0	—	59,0	59,0	
	MN	85,0	81,7	76,3	85,0	81,7	76,3	59,0	34,4	15,0	59,0	34,4	15,0	
AB	M				81,7	—	81,7	69,3	—	69,3	56,5	—	56,5	
	N	niemożliwe			—	85,0	85,0	—	71,4	71,4	—	59,5	59,5	
	MN				85,0	81,7	76,3	71,4	69,3	60,1	59,5	56,5	45,6	

Hirszfeld L. Dochodzenie ojcostwa w świetle nauki o grupach krwi. Państwowy Instytut Naukowo-Wydawniczy, 1948 Wrocław.

Ludwik Hirszfeld zmarł we Wrocławiu 7 marca 1954 r. Wraz z żoną Hanną (1884-1964) spoczywa na cmentarzu św. Wawrzyńca.

Ludwik Hirszfeld (1884-1954)


TELEGRAM



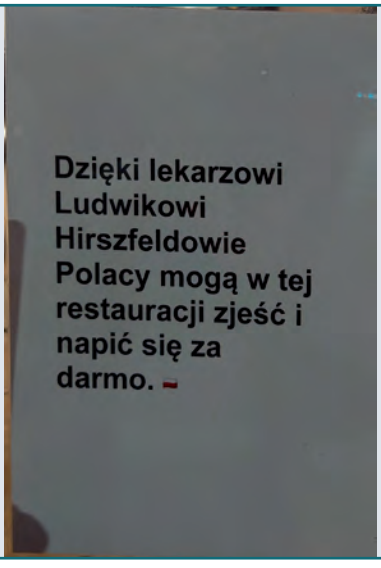
Pomnik Ludwika Hiszfelda w Belgradzie


VNIVERSITAS CAROLINA PRAGENSIS
LVDOVICVS HIRSZFELD
HONORIS CAVSA
MEDICINAE VNIVERSAE DOCTOREM

Ulubiony fotel Ludwika Hirszfelda w którym umarł w 1954 roku

“MENSCH to historia doktora Ludwika Hirszfelda, wyjątkowego lekarza, jego wiary w naukę i chęci niesienia pomocy. To świadectwo niepoddawania się w trudnych czasach wojny, walki o osiągnięcia naukowe, które będą służyć ludzkości. To jednak także film o prawdziwej historii miłości dwojga lekarzy, o wsparciu na ciernistej drodze dla tych, którzy najbardziej potrzebują pomocy.”


PIZZERIA


Dzięki lekarzowi
Ludwikowi
Hirszfeldowie
Polacy mogą w tej
restauracji zjeść i
napić się za
darmo.

ZAPROSZENIE

Prof. dr hab. n. med. **Artur Jurczyszyn**

Przewodniczący Społecznego Komitetu
ds. upamiętnienia postaci Prof. Ludwika Hirszfelda

oraz

Dariusz Piotrowski

Dyrektor Regionalnego Centrum
Krwiodawstwa i Krwiolecznictwa
w Warszawie

mają zaszczyt zaprosić do wzięcia udziału
w uroczystości odsłonięcia tablicy pamiątkowej
poświęconej upamiętnieniu wybitnego naukowca
Prof. Ludwika Hirszfelda

Uroczystość odbędzie się dnia 7 marca 2024 r. (czwartek)
o godz. 15:00 przed budynkiem siedziby RCKiK w Warszawie
od strony ul. Alfreda Nobla 2

Jednocześnie zapraszamy na projekcję filmu biograficznego
poświęconego postaci Ludwika Hirszfelda pt. MENSCH"
w reżyserii Pawła Wysoczańskiego

Pokaz filmu odbędzie się w Sali konferencyjnej RCKiK w Warszawie

Partnerzy projektu:

PRZEKAŻ 1,5% PODATKU FUNDACJI CENTRUM LECZENIA SZPICZAKA

FUNDACJA MA STATUS ORGANIZACJI POŻYTKU PUBLICZNEGO KRS: 0000317005

Fundacja Centrum Leczenia Szpiczaka z Krakowa jest organizacją pożytku publicznego, która została utworzona w 2008 roku. Fundacja współpracuje z Ośrodkiem Leczenia Dyskrazji Plazmocytowych Katedry Hematologii Uniwersytetu Jagiellońskiego Collegium Medicum, Szpitalem Uniwersyteckim w Krakowie, Polskim Towarzystwem Hematologów i Transfuzjologów, Międzynarodową Grupą Roboczą ds. Szpiczaka, International Myeloma Foundation oraz International Myeloma Society.

W ostatnich 20 latach na świecie zarejestrowano kilkanaście innowacyjnych leków przeznaczonych do leczenia szpiczaka plazmocytowego – nie ma drugiej jednostki chorobowej, w której widoczny jest tak ogromny postęp w diagnostyce i terapii. Dzięki działaniom Fundacji wiele z nich jest dostępnych w Polsce, niemniej wciąż pracujemy nad optymalizacją refundacji. Pomysłodawcą stworzenia Centrum Leczenia Szpiczaka jest prof. dr hab. n. med. Artur Jurczyszyn, prezes zarządu Fundacji. To najlepsze rozwiązanie celem kompleksowej i specjalistycznej opieki w hematologii nad tą grupą chorych. Fundacja Centrum Leczenia Szpiczaka regularnie aktywnie pomaga pacjentom, wspomaga szpitale w zakupie sprzętu medycznego oraz wspiera działalność naukowo-badawczą w Polsce.

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Organizuje cyklicznie spotkania naukowe oraz międzynarodowe konferencje dla lekarzy i pacjentów, jak również działa w sferze promocji i ochrony zdrowia. Od 15 lat prowadzi także stronę internetową www.szpiczak.org, gdzie są publikowane aktualne dane na temat diagnostyki i terapii szpiczaka plazmocytowego. Fundacja wydała wiele monografii i publikacji naukowych: *Szpiczak mnogi – kompleksowa diagnostyka i terapia, Szpiczak mnogi – wybrane zagadnienia, Szpiczak mnogi – przypadki kliniczne, Szpiczak mnogi – poradnik dla pacjentów, Kuchnia i medycyna XXI wieku – żywienie w przebiegu nowotworów, Amyloidoza – poradnik dla pacjentów, Szpiczak mnogi – praktyczny przewodnik dla pacjentów, Dwanaście tygodni, Wszystkie twarze szpiczaka, All Faces of Multiple Myeloma, Notre Dame de Cracovie – o medycynie i sztuce, Covidowe twarze szpiczaka*, *Profesor Tadeusz Tempka. Pionier polskiej hematologii*, *Być lekarzem w Krakowie* oraz poradniki *Jak aktywnie żyć z nowotworem* oraz *Szpiczak plazmocytowy. Praktyczny przewodnik*.

Na zaproszenie Fundacji z wykładami pod Wawel przybyli m.in. profesorowie: Robert A. Kyle, Pieter Sonneveld, Paul Richardson, David H. Vesole, Ruben Niesvizky, Giampaolo Merlini, Enrique Ocio, Evangelos Terpos, Xavier Leleu, Alessandro Gozzetti, Sundar Jagannath, Shaji Kumar, Roman Hajek, Morie A. Gertz, Ashraf Badros, Steven Treon, Jens Hillengass, Irene Ghobrial, Ashutosh Wechalekar, Heinz Ludwig, Jo Caers, Saad Usmani, Giovanni Palladini, Jorge J. Castillo, Robert Orłowski, Kenneth Anderson, Meral Beksac, Laurent Garderet, Leo Rasche, Samir Parekh, Ajay K. Nooka, Noopur Raje, Joseph Mikhael, Suzanne Lentzsch, Christian Buske, Georg Hess i Piere Luigi Zinzani.

Optymalizacja diagnostyki i leczenia dyskrazji plazmocytowych w Polsce to główny cel i zadanie Fundacji. Wspieramy wszelkie działania zmierzające do wprowadzania innowacyjnych leków i terapii przeciwnowotworowych, rekrutacji pacjentów do badań klinicznych oraz publikacji rzetelnych materiałów naukowych. Nasze starania wspiera grono przyjaciół i ludzi dobrej woli, za co bardzo dziękujemy, szczególne za 1,5% podatku co roku przekazywanego na nasze konto. Cały czas dążymy, aby naszym podopiecznym stworzyć jak najlepsze warunki i wydłużyć życie z trudnym nowotworem. Liczymy, że szpiczak plazmocytowy w niedalekiej przyszłości stanie się w pełni uleczalny, a wiemy, że już dziś jest schorzeniem przewlekłym i kontrolowalnym.

Zarząd Fundacji Centrum Leczenia Szpiczaka

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INFARMA

Certyfikat nr 8269

Wydarzenie:

12 th International Conference " Complex treatment pf plasma cell dyscrasias in 2024"

Odbywające się w: Kraków
W dniu: 7 września 2024

spełnia standardy etyczne wynikające
z Kodeksu Dobrych Praktyk INFARMA

Dyrektor Generalny INFARMA

Michał Byliniak

WYDARZENIE INFARMA 8269 CERTYFIKOWANE

Związek Pracodawców INFARMA reprezentuje 24 działających w Polsce wiodących firm sektora farmaceutycznego, prowadzących działalność badawczo-rozwojową i produkujących leki innowacyjne. INFARMA jest członkiem międzynarodowych organizacji zrzeszających innowacyjną branżę farmaceutyczną (EFPIA), a także Pracodawców RP oraz Krajowej Izby Gospodarczej.