POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Torino
Centro Congressi Lingotto
19-21 febbraio 2026

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Algoritmi terapeutici 2026: mieloma multiplo

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DICHIARAZIONE Maria Teresa Petrucci

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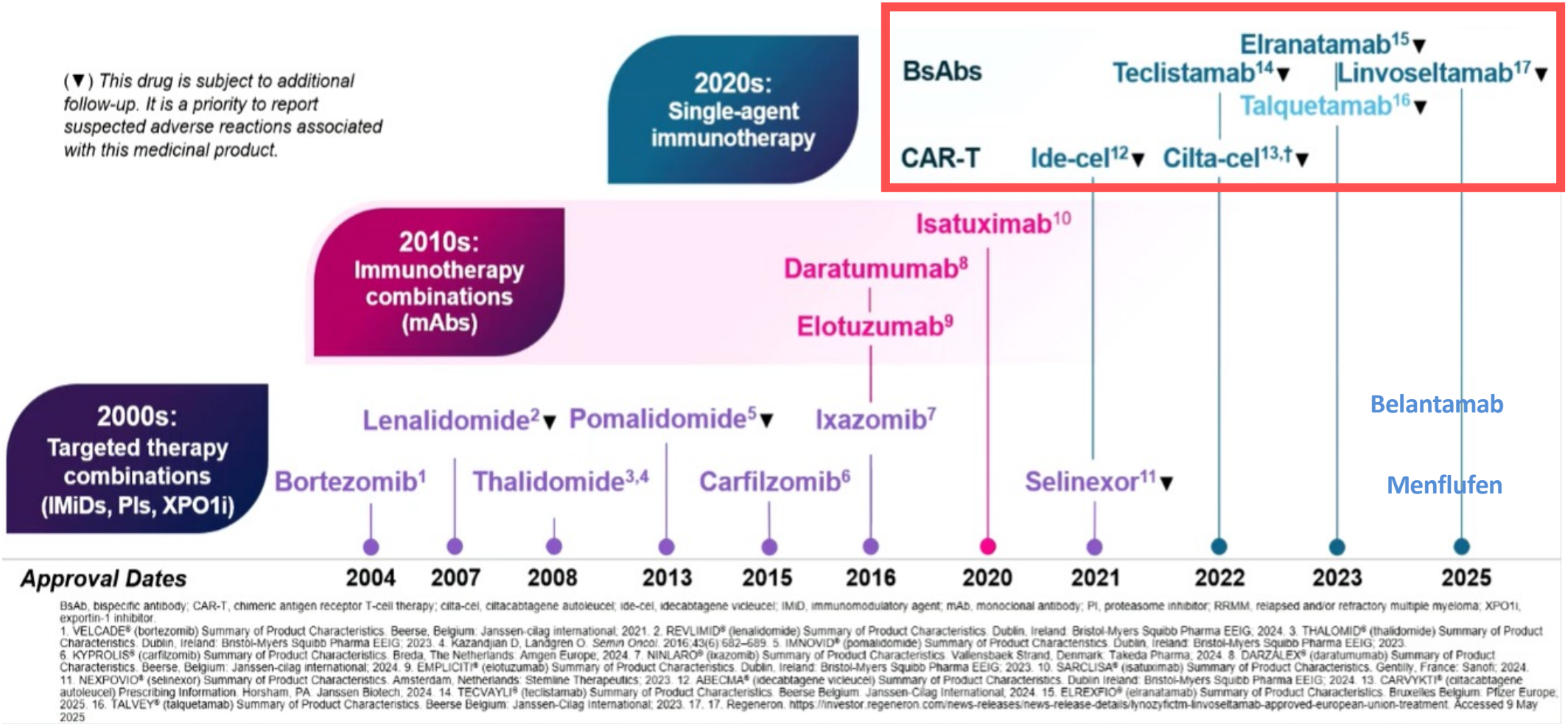
Oncopeptide	X	X
AbbVie	X	X
GSK	X	X

"The field of myeloma is **advancing so rapidly**, the use of T-cell–directed therapies is evolving in the sense of **combination therapies**; …**sequencing in the future** will actually become more complicated"

From an interview of Amrita Krishnan, MD, director of the Judy and Bernard Briskin Center for Multiple Myeloma Research at City of Hope

A New Era of Novel Immunotherapies for the Treatment of Multiple Myeloma



BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T-cell therapy; cilta-cel, ciltacabtagene autoleucel; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory agent; mAb, monoclonal antibody; PI, proteasome inhibitor; RRMM, relapsed and/or refractory multiple myeloma; XPO1i, exportin-1 inhibitor.

1. VELCADE® (bortezomib) Summary of Product Characteristics. Beerse, Belgium. Janssen-cilag international; 2021. 2. REVLIMID® (lenalidomide) Summary of Product Characteristics. Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; 2024. 3. THALOMID® (thalidomide) Summary of Product Characteristics. Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; 2023. 4. Kazandjian D, Landgren O. *Semin Oncol*. 2016;43(6):682–689. 5. IMNOVID® (pomalidomide) Summary of Product Characteristics. Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; 2023. 6. KYPROLIS® (carfilzomib) Summary of Product Characteristics. Breda, The Netherlands: Amgen Europe; 2024. 7. NINLARO® (ixazomib) Summary of Product Characteristics. Vallensbaek Strand, Denmark: Takeda Pharma; 2024. 8. DARZALEX® (daratumumab) Summary of Product Characteristics. Beerse, Belgium: Janssen-cilag international; 2024. 9. EMPLICITI® (elotuzumab) Summary of Product Characteristics. Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; 2023. 10. SARCLISA® (isatuximab) Summary of Product Characteristics. Gentilly, France: Sanofi; 2024. 11. NEXPOVIO® (selinexor) Summary of Product Characteristics. Amsterdam, Netherlands: Stemline Therapeutics; 2023. 12. ABECMA® (idecabtagene vicleucel) Summary of Product Characteristics. Dublin Ireland: Bristol-Myers Squibb Pharma EEIG; 2024. 13. CARVYKTI® (ciltacabtagene autoleucel) Prescribing Information. Horsham, PA: Janssen Biotech; 2024. 14. TECVAYLI® (teclistamab) Summary of Product Characteristics. Beerse Belgium: Janssen-Cilag International; 2024. 15. ELREXFIO® (elranatamab) Summary of Product Characteristics. Bruxelles Belgium: Pfizer Europe; 2025. 16. TALVEY® (talquetamab) Summary of Product Characteristics. Beerse Belgium: Janssen-Cilag International; 2023. 17. 17. Regeneron. https://investor.regeneron.com/news-releases/news-release-details/lynozyfictm-linvoseltamab-approved-european-union-treatment. Accessed 9 May 2025

Limitations of Current Therapies → Exploring novel targets

- **Drug resistance** in proteasome inhibitors, IMiDs, anti-CD38 mAbs
- **Disease heterogeneity**
- Minimal residual disease and **relapse**

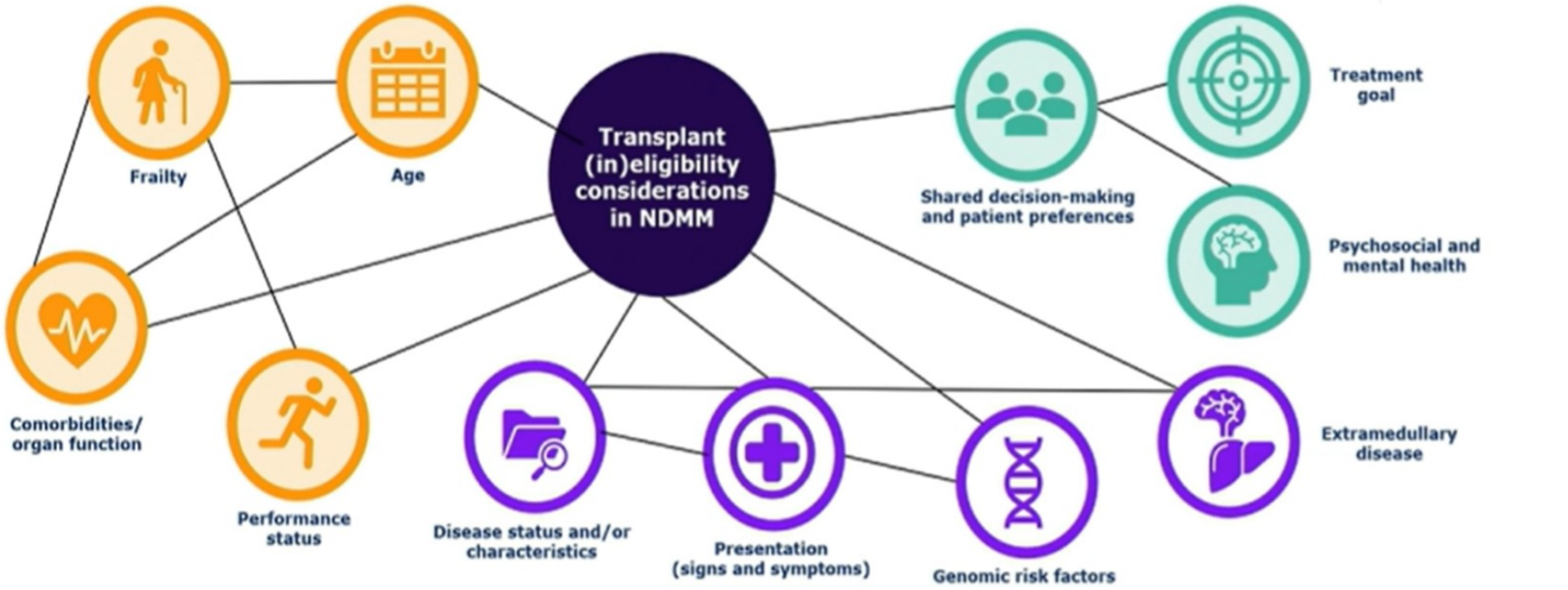
Ongoing questions regarding optimal treatment

- Is the patient eligible for more intensive treatment with/without transplant?
- How can response (MRD status) be used to assess induction efficacy and adapt subsequent treatment?
- How does disease risk/biology impact treatment selection?
- What about special populations (i.e. cast nephropathy)?

Why is age an important issue?

- Co-morbidities
  - Hypertension, Ischemic heart disease, Diabetes
  - Renal insufficiency
  - Osteoporosis
  - Psychological issues
- Frailty
- Altered drug metabolism
- Limited social support, financial issues
- Limited independence/ mobility

The decision how to treat the patient remains complex and multifaceted



All information available at diagnosis should be considered,
and **patient preference should play a key role** in determining treatment pathways in NDMM[1-7]

Goals of therapy

Rapid tumor reduction → **Reversal of myeloma defining events**

Maximum depth of response (MRD negativity)

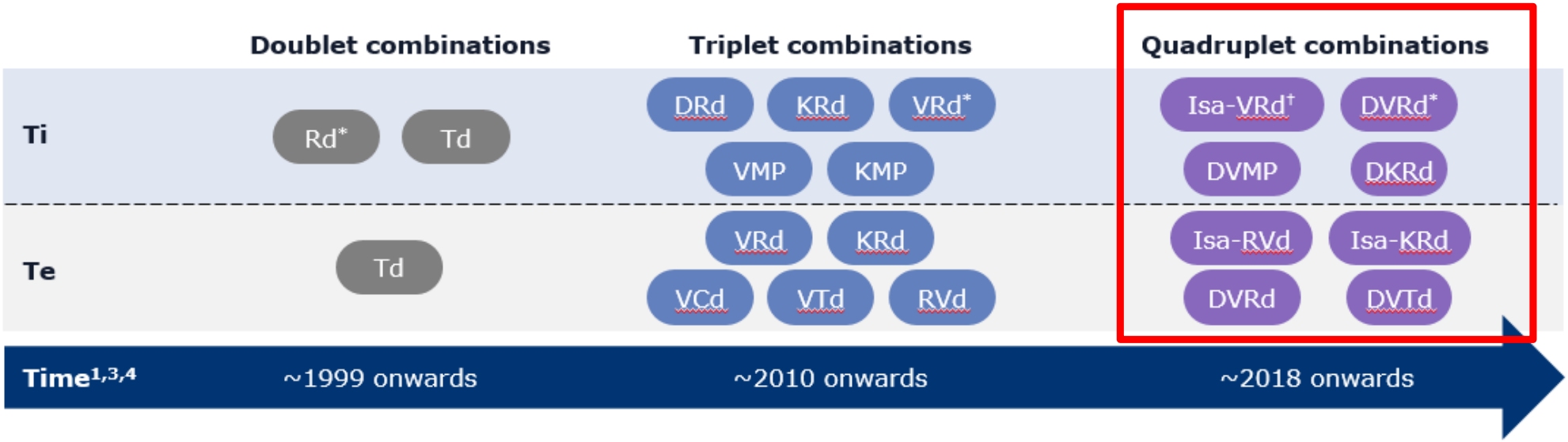
Minimize overlapping toxicities

FDA ODAC voted 12-0 to recommend MRD as a MM Endpoint

On April 12, 2024, FDA ODAC voted 12-0 in favor of using minimal residual disease (MRD) as an accelerated approval endpoint in multiple myeloma clinical trials

Conclusion: The Applicants have worked with the broader MM community to develop a novel endpoint of MRD that has the potential to expedite drug development in MM. While there are still outstanding questions on how to best use MRD, the meta-analyses conducted **(University of Miami and IMF led i2TEAMM**) represent robust assessments of MRD that support its prognostic value, provide information regarding the appropriate timing of MRD assessment, and suggest that MRD may be appropriate to use as an intermediate clinical endpoint to support accelerated approval.

Therapeutic regimens explored in Phase III NDMM trials over time



*Including transplant-eligible/deferred. †Twice-weekly and once-weekly V dosing are being explored in the IMROZ and BENEFIT studies, respectively[6,7]

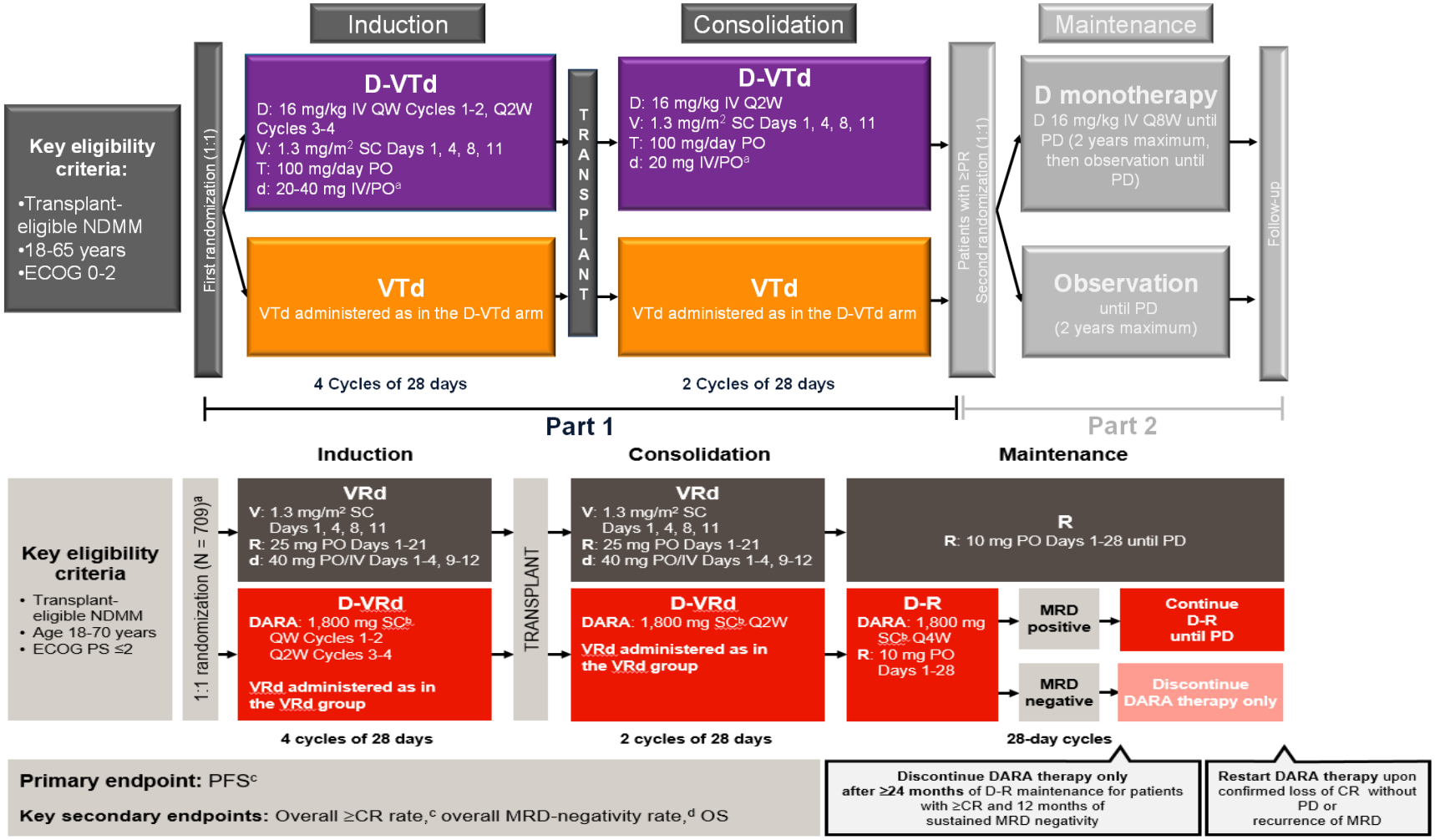
The emergence of newer agents and novel combination treatment strategies has improved patient outcomes

Quadruplet induction therapy is standard of care

Four drug induction therapy with an anti-CD38 monoclonal antibody, a proteasome inhibitor, an immunomodulatory drug (IMiD) and dexamethasone is the standard of care for a fit patient with newly diagnosed multiple myeloma:

- CASSIOPEIA (Dara VTD vs VTD)
- GRIFFIN (Dara RVD vs RVD)
- GMMG HD7 (Isa RVD vs RVD)
- ISKIA (Isa KRD vs KRD)
- Emory real world (Dara RVD vs RVD)
- PERSEUS (Dara RVD vs RVD)
- IMROZ (Isa RVD vs RVD)
- CEPHEUS (Dara RVD vs RVD)

CASSIOPEIA and PERSEUS: Study Design



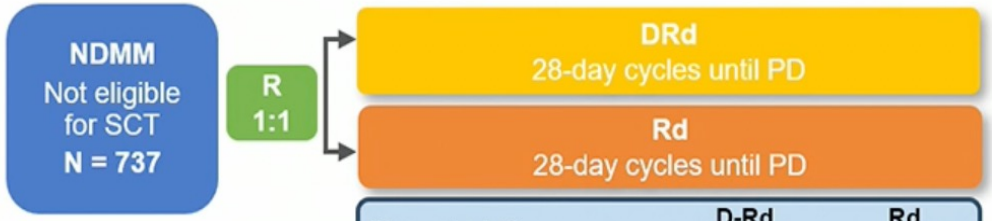
Key study design in non stem-cell transplantation NDMM

ALCYONE[1]

Primary endpoint: PFS

Characteristic	D-VMP (n = 350)	VMP (n = 356)
Median age (range), years	71 (40–93)	71 (50–91)
Age ≥ 75 years, %	30	30
ECOG PS 0/1/2, %	22/52/26	28/49/24
High-risk cytogenetics, %	17	15

MAIA[2]



Primary endpoint: PFS

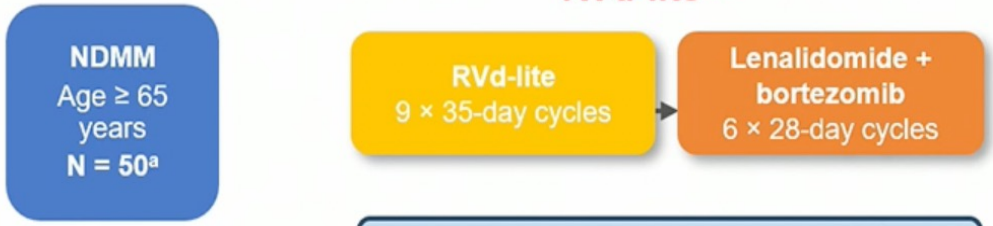
Characteristic	D-Rd (n = 368)	Rd (n = 369)
Median age (range), years	73 (50–90)	74 (45–89)
Age ≥ 75 years, %	44	44
ECOG PS 0/1/2, %	35/48/17	33/51/16
High-risk cytogenetics, %	15	14

SWOG S0777[3]

Primary endpoint: PFS

Characteristic	RVd (n = 264)	Rd (n = 261)
Median age (range), years	63 (-)	63 (-)
Age ≥ 65 years, %	38	48
ECOG PS > 1, %	12	16
High-risk cytogenetics, %	-	-

RVd-lite[4,a]



Primary endpoint: ORR

Characteristic	ITT (n = 50)
Median age (range), years	73 (65–91)
Age ≥ 75 years, %	-
ECOG PS 0/1/2, %	50/36/14
High-risk cytogenetics, %	12

These charts are provided for ease of viewing information from multiple trials.

NUOVE QUADRIPLETTE NTE NDMM

IMROZ

-Età 18-80 anni
-Non eleggibile al trapianto per età o comorbilità se età < 65 aa
-ECOG PS<2

INDUZIONE
4 x CICLI 6 SETTIMANE

3:2
- ISA VRD
- VRD

FASE CONTINUATIVA
- ISA -VRd
- RD

PRIMARY END POINT **PFS**
Trattamento fino a progressione o tossicita' inaccettabile

BENEFIT-IFM 2020-05

-Età ≥ 65-<80 anni
-Non eleggibile al trapianto e non frail
-ECOG PS < 2

INDUZIONE
12 X CICLI 4 SETTIMANE

1:1
- ISA VRD
- ISA RD

CICLO 13-18
- ISA-R
- ISA R

CICLO 19
- ISA-R
- ISA-R

PRYMARY END POINT **MRD**

Trattamento fino a progressione o tossicità inaccettabile

CEPHEUS

-Età ≥ 18 anni
-Non intento al trapianto per ≥ 65 o < 65 con comorbilità impattanti il trapianto
-ECOG PS < 2
-Frailty Index ≤ 2

INDUZIONE
8 x CICLI 3 SETTIMANE

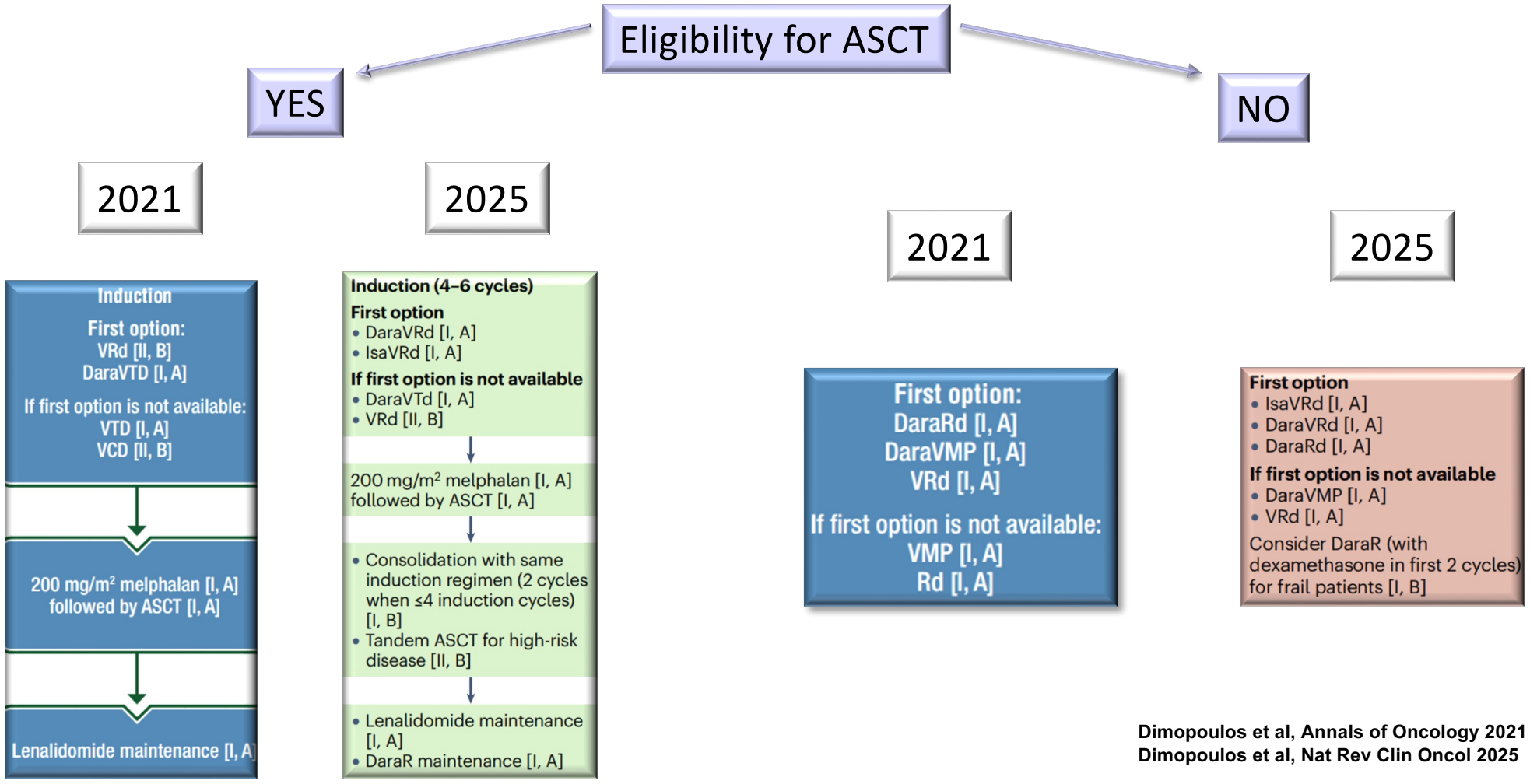
1:1
- DARA VRD
- VRD

MANTENIMENTO
- DARA Rd
- RD

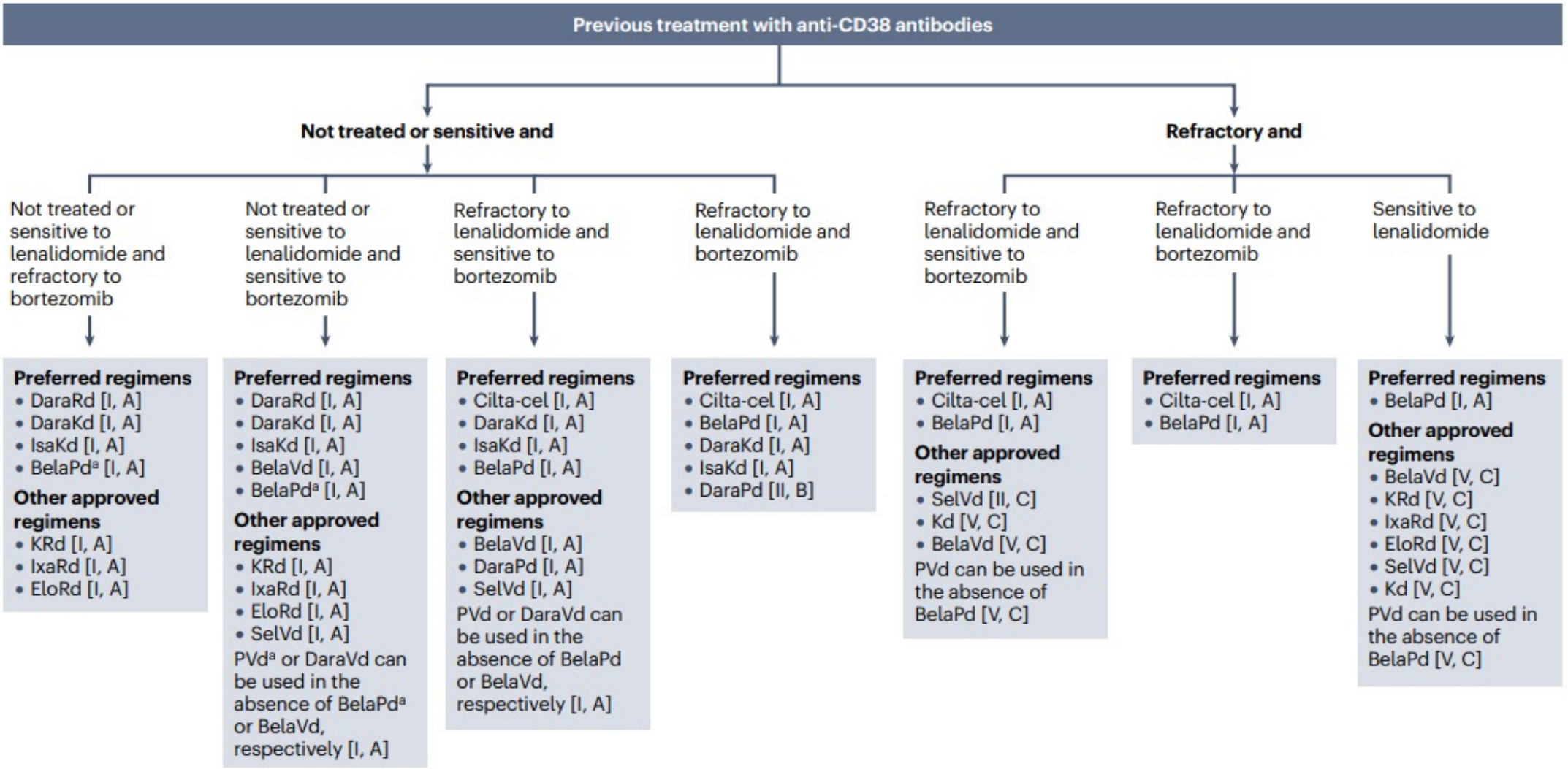
PRYMARY END POINT **MRD**

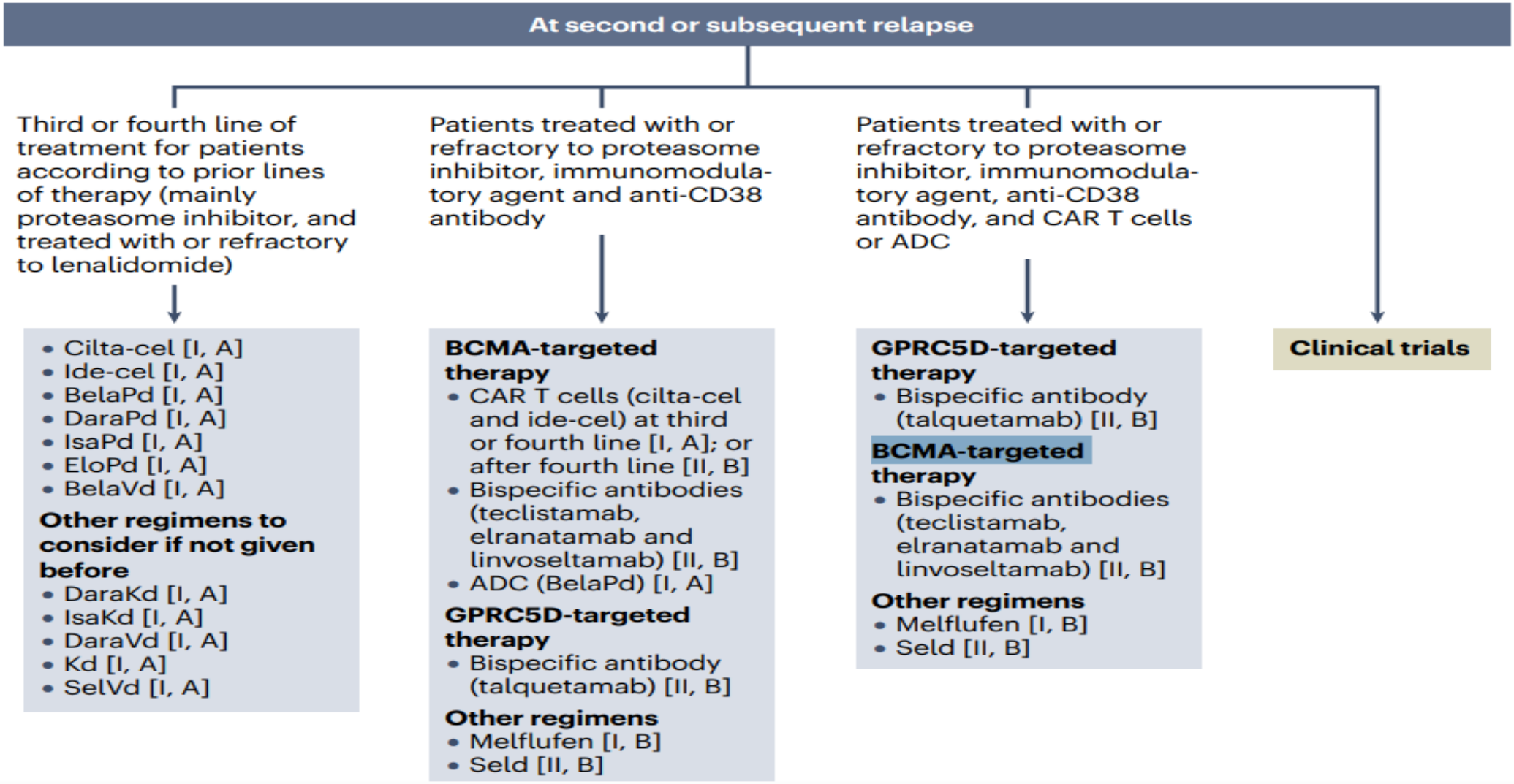
Trattamento fino a progressione o tossicità inaccettabile

GUIDELINES



Dimopoulos et al, Annals of Oncology 2021
Dimopoulos et al, Nat Rev Clin Oncol 2025


Previous treatment with anti-CD38 antibodies
Not treated or sensitive and
Refractory and
Not treated or sensitive to lenalidomide and refractory to bortezomib
Not treated or sensitive to lenalidomide and sensitive to bortezomib
Refractory to lenalidomide and sensitive to bortezomib
Refractory to lenalidomide and bortezomib
Refractory to lenalidomide and sensitive to bortezomib
Refractory to lenalidomide and bortezomib
Sensitive to lenalidomide
Preferred regimens
• DaraRd [I, A]
• DaraKd [I, A]
• IsaKd [I, A]
• BelaPd[a] [I, A]
Other approved regimens
• KRd [I, A]
• IxaRd [I, A]
• EloRd [I, A]
Preferred regimens
• DaraRd [I, A]
• DaraKd [I, A]
• IsaKd [I, A]
• BelaVd [I, A]
• BelaPd[a] [I, A]
Other approved regimens
• KRd [I, A]
• IxaRd [I, A]
• EloRd [I, A]
• SelVd [I, A]
PVd[a] or DaraVd can be used in the absence of BelaPd[a] or BelaVd, respectively [I, A]
Preferred regimens
• Cilta-cel [I, A]
• DaraKd [I, A]
• IsaKd [I, A]
• BelaPd [I, A]
Other approved regimens
• BelaVd [I, A]
• DaraPd [I, A]
• SelVd [I, A]
PVd or DaraVd can be used in the absence of BelaPd or BelaVd, respectively [I, A]
Preferred regimens
• Cilta-cel [I, A]
• BelaPd [I, A]
• DaraKd [I, A]
• IsaKd [I, A]
• DaraPd [II, B]
Preferred regimens
• Cilta-cel [I, A]
• BelaPd [I, A]
Other approved regimens
• SelVd [II, C]
• Kd [V, C]
• BelaVd [V, C]
PVd can be used in the absence of BelaPd [V, C]
Preferred regimens
• Cilta-cel [I, A]
• BelaPd [I, A]
Preferred regimens
• BelaPd [I, A]
Other approved regimens
• BelaVd [V, C]
• KRd [V, C]
• IxaRd [V, C]
• EloRd [V, C]
• SelVd [V, C]
• Kd [V, C]
PVd can be used in the absence of BelaPd [V, C]


At second or subsequent relapse
Third or fourth line of treatment for patients according to prior lines of therapy (mainly proteasome inhibitor, and treated with or refractory to lenalidomide)
• Cilta-cel [I, A]
• Ide-cel [I, A]
• BelaPd [I, A]
• DaraPd [I, A]
• IsaPd [I, A]
• EloPd [I, A]
• BelaVd [I, A]
Other regimens to consider if not given before
• DaraKd [I, A]
• IsaKd [I, A]
• DaraVd [I, A]
• Kd [I, A]
• SelVd [I, A]
Patients treated with or refractory to proteasome inhibitor, immunomodulatory agent and anti-CD38 antibody
BCMA-targeted therapy
• CAR T cells (cilta-cel and ide-cel) at third or fourth line [I, A]; or after fourth line [II, B]
• Bispecific antibodies (teclistamab, elranatamab and linvoseltamab) [II, B]
• ADC (BelaPd) [I, A]
GPRC5D-targeted therapy
• Bispecific antibody (talquetamab) [II, B]
Other regimens
• Melflufen [I, B]
• Seld [II, B]
Patients treated with or refractory to proteasome inhibitor, immunomodulatory agent, anti-CD38 antibody, and CAR T cells or ADC
GPRC5D-targeted therapy
• Bispecific antibody (talquetamab) [II, B]
BCMA-targeted therapy
• Bispecific antibodies (teclistamab, elranatamab and linvoseltamab) [II, B]
Other regimens
• Melflufen [I, B]
• Seld [II, B]
Clinical trials

Second or subsequent relapses

- **Treatment selection and sequencing** become increasingly complex with the increasing number of therapeutic options

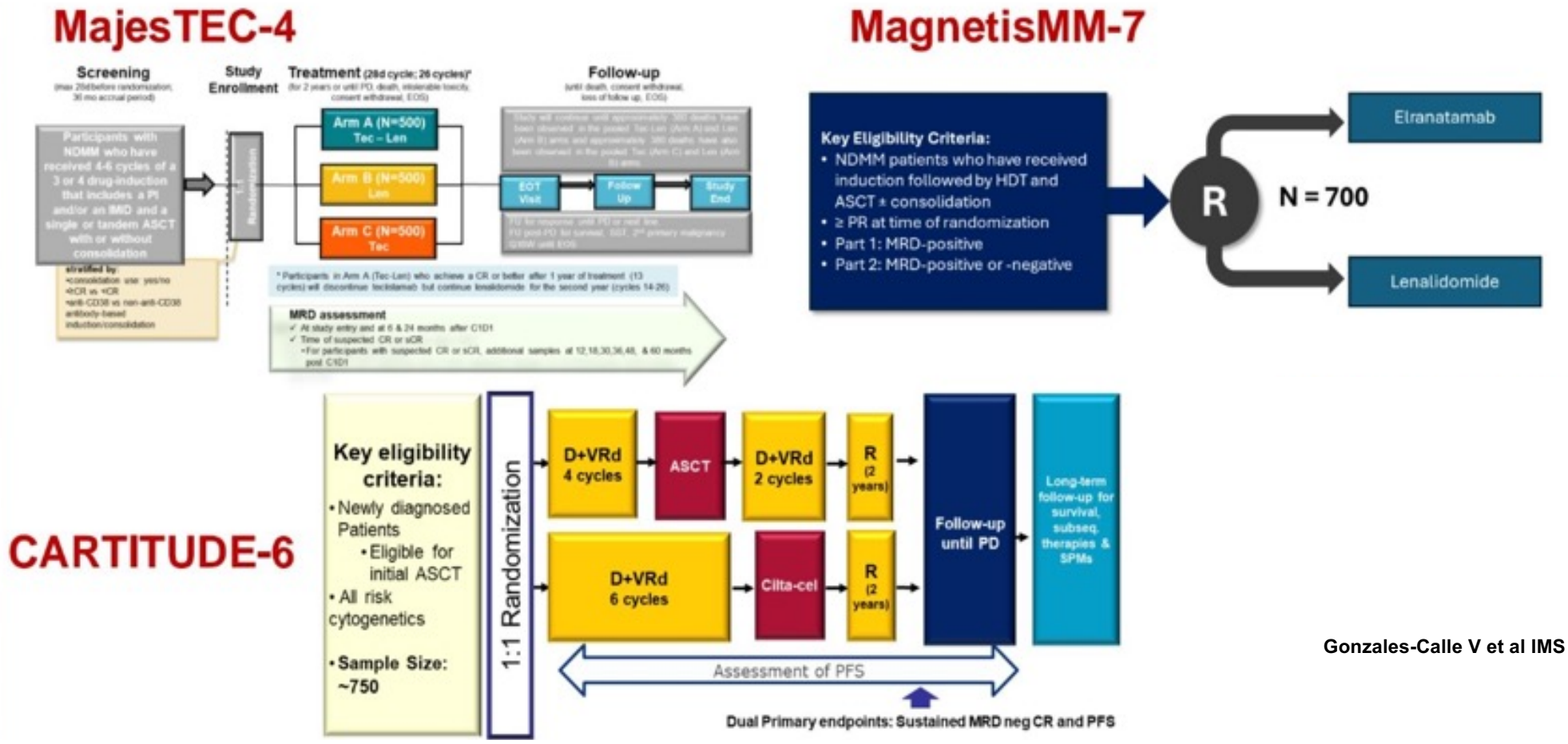
- Treatment decision is mainly driven by **drug-refractoriness/sensitivity;** the increased use of **lenalidomide and CD38 antibodies as part of first-line regimens** has major impact on treatment of first relapse

- **Treatment-related factors influencing decision:**

- Response and/or refractoriness to prior therapies
- Previous treatments received
- Single drug, dual – triple drug combinations
- Type and severity of AES related to prior therapy
- Bone marrow reserve
- Expected efficacy and toxicity of proposed therapy
- Availability, cost, and management requirements
- Patient expectations

FUTURO

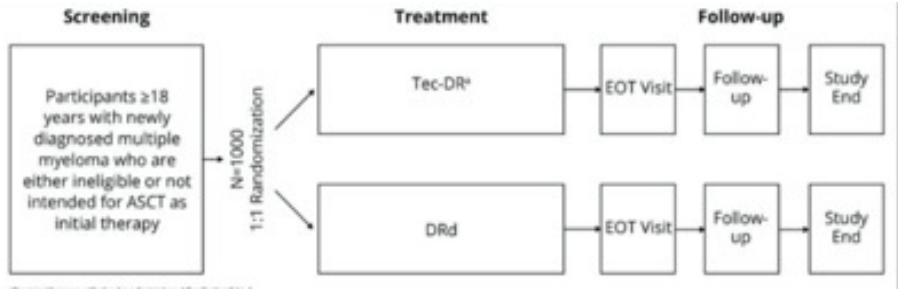
Frontline Immunotherapies for TE-NDMM Patients



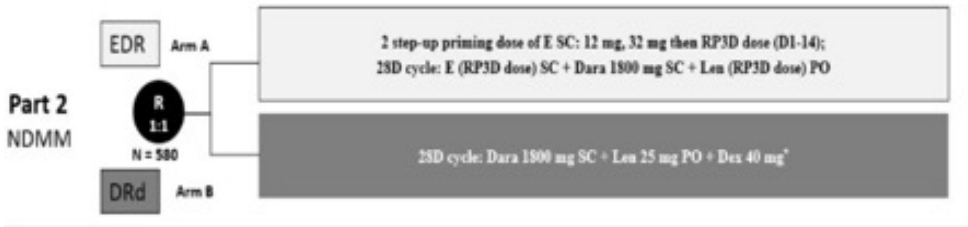
Gonzales-Calle V et al IMS 2024

Frontline Immunotherapies for TI-NDMM Patients

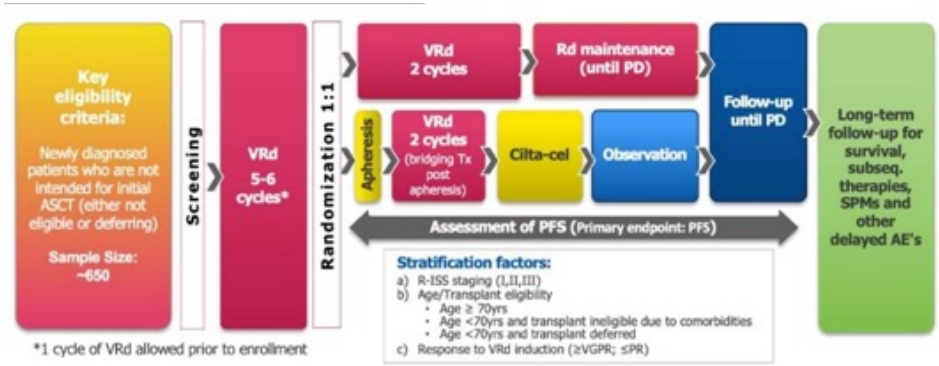
MajesTEC-7



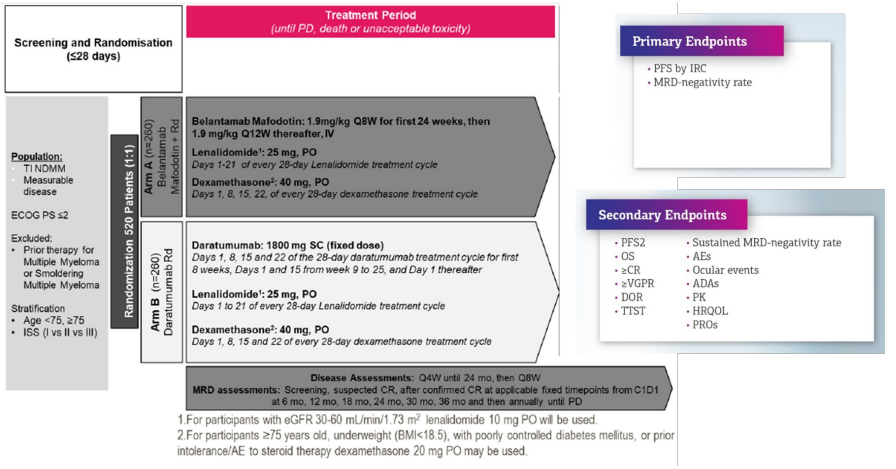
MagnetisMM-6



CARTITUDE-6



DREAMM-10



Considerazioni

- **Superiorità dei regimi con quadruplette rispetto alle triplette (>CR, >MRD neg., >PFS) anche per i pazienti non eleggibili a ASCT (pazienti fit)**

- **ASCT al momento rimane il trattamento elettivo per i pazienti eleggibili, in attesa di valutare la possibile non inferiorità/superiorità dei regimi alternativi in studio almeno per i pazienti a rischio standard o MRD negativi.**

- **I regimi di mantenimento con combinazioni di farmaci (lenalidomide + Dara, or + 2nd generation PI, or + anti-BCMA BiAbs) sarà la terapia standard in un future non lontano in attesa di identificare anche i pazienti in cui sospendere la terapia.**

- **Possibilità di eseguire trattamenti a durata fissa sulla base della negatività sostenuta della MRD**

Considerazioni

- Superiorità dei regimi con quadruplette rispetto alle triplette (>CR, >MRD neg., >PFS) anche per i pazienti non eleggibili a ASCT (pazienti fit)
- ASCT al momento rimane il trattamento elettivo per i pazienti eleggibili in attesa
- I regimi di mantenimento con combinazioni di farmaci (lenalidomide + Dara, or + 2nd generation PI, or + anti-BCMA BiAbs) sarà la terapia standard in un future non lontano in attesa di identificare anche i pazienti in cui sospendere il mantenimento .
- Possibilità di eseguire trattamenti a durata fissa sulla base della negatività sostenuta della MRD

Necessità di categorizzare bene i pazienti soprattutto quelli non eleggibili al ASCT

Grazie!!