The Annual
National General Medical Oncology Summit

Sunday, March 24, 2024

Moderator

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Co-Moderators

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Overview

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This program will contain discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Third Annual National General Medical Oncology Summit

Agenda

Module 1: Chimeric Antigen Receptor T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates in MM — Dr Callander

Module 2: Integration of Other Novel Therapies into the Management of Newly Diagnosed and Relapsed/Refractory MM — Dr Richardson

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Chimeric Antigen Receptor (CAR) T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates in MM

Natalie S Callander, MD

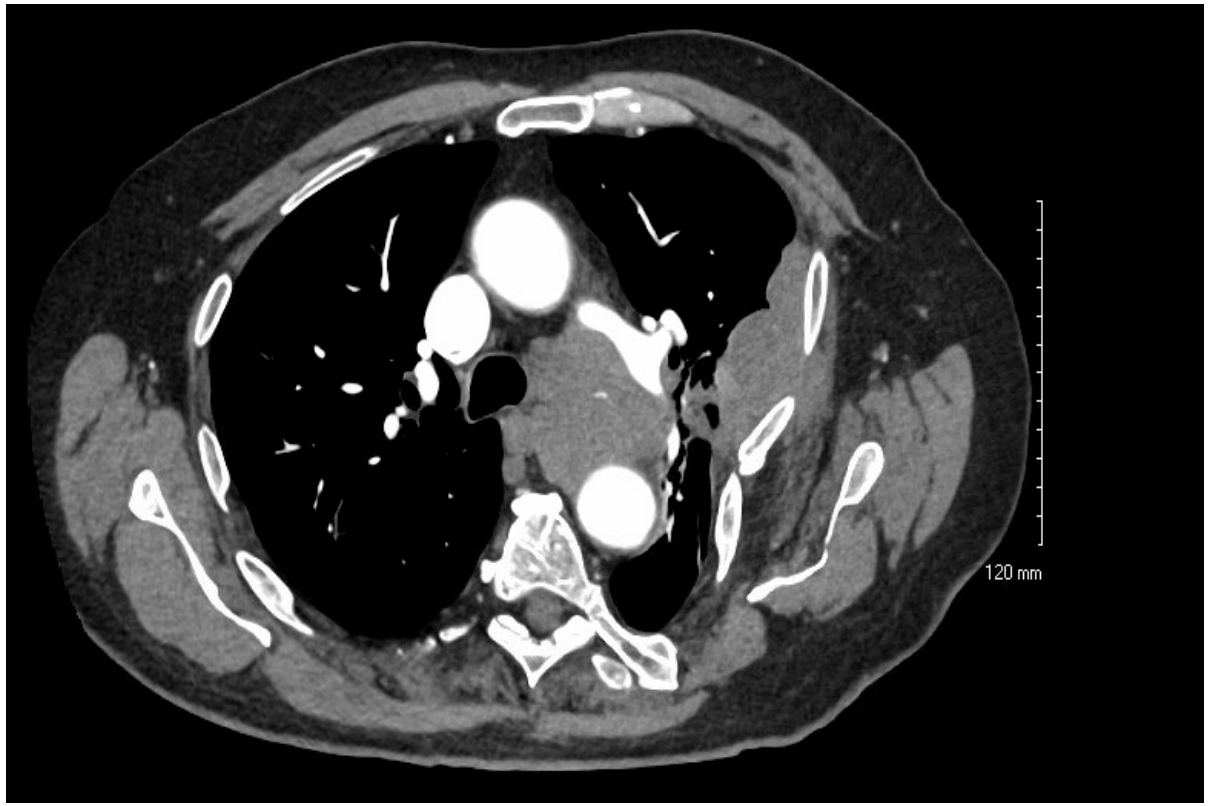
School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

Disclosure

No relevant conflicts of interest to disclose.

Case History

- 80 y.o. dx with R-ISS II IgG lambda MM 8/2020 with anemia, bone pain BMBX: FISH 1q+, t(4;14)
- VRD lite with sCR, progressed 11/22 started DPd, transient response, started KCd in 5/2023
- Called with increasing SOB, lambda 40 mg/dl

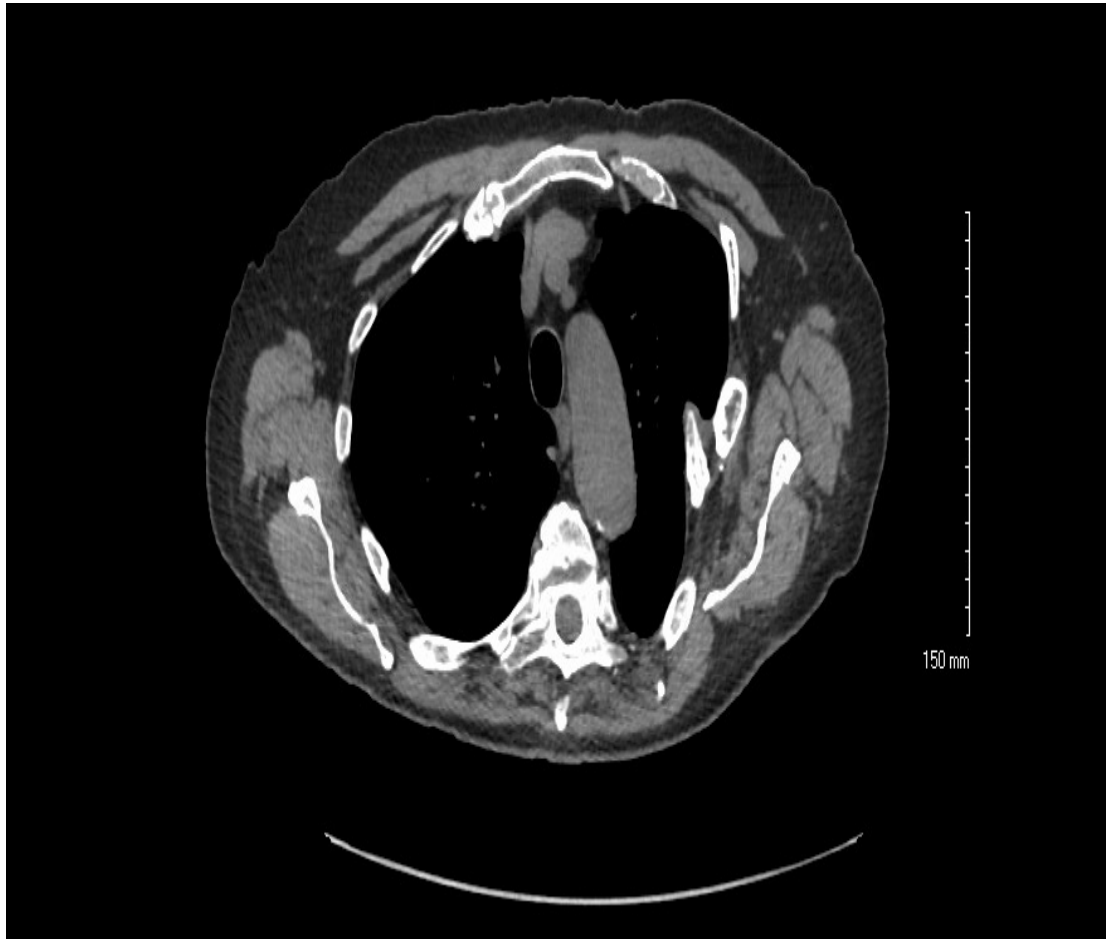


Case (continued)

- Started with teclistamab
- Quickly transitioned to q 2week dosing, then q month
- IVIG prophylaxis, PJP prophylaxis with TMP/sulfa

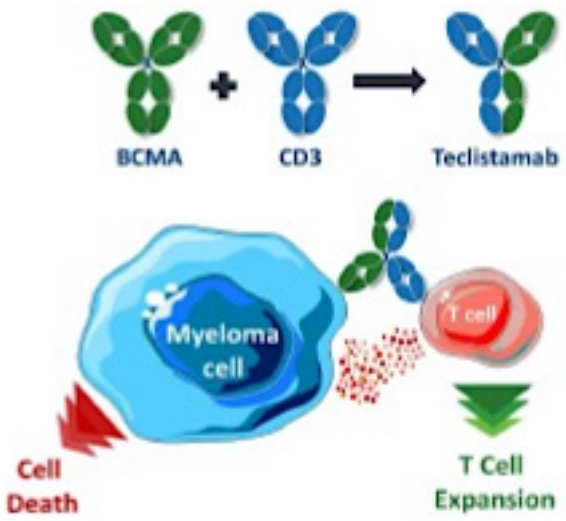
- Lambda light chains undetectable

- Admitted 12/2023 with influenza, salmonella

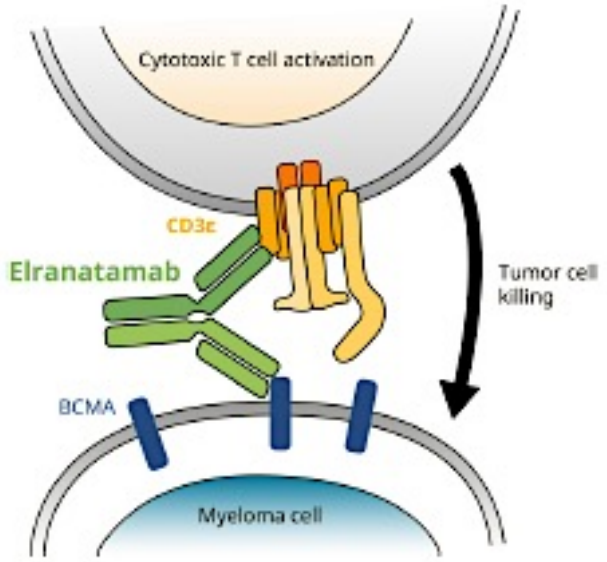


3 bispecific drugs now approved

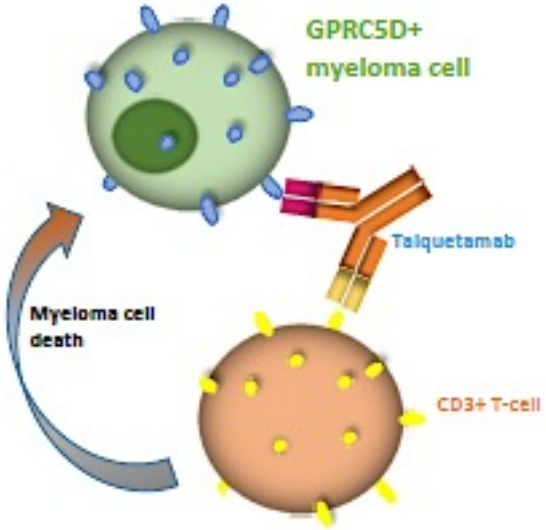
Teclistamab
Oct 2022



Elranatamab
Aug 2023



Talquetamab
Aug 2023



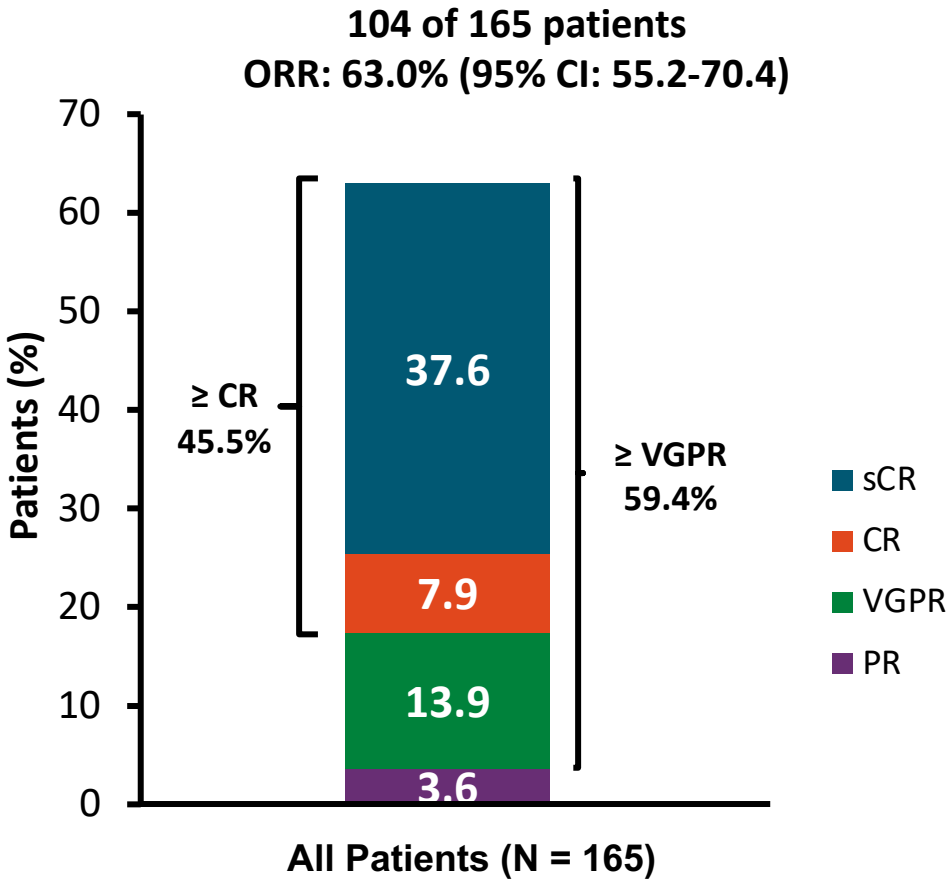
****FDA Label:**

- **Four Prior Lines of Therapy**
- **Previously treated with IMID, PI and anti-CD38 monoclonal antibody**

MajesTEC-1: Phase I/II Study of Teclistamab in R/R MM

- Patients with R/R MM after ≥3 lines of therapy, including exposure to IMiD, PI, and anti-CD38 mAb
  - 26% high-risk cytogenetics
  - Median 5 prior lines of therapy (range: 2-14)
  - 77.6% triple-class refractory; 30.3% penta-drug refractory
  - 89.7% refractory to last therapy line
- **Teclistamab**: 1.5 mg/kg SC weekly, after step-up

Patient Subgroup	ORR, % (n/N)
≤3 prior lines of treatment	74.4 (32/43)
>3 prior lines of treatment	59.0 (72/122)
High-risk cytogenetics and/or EMD	53.3 (32/60)

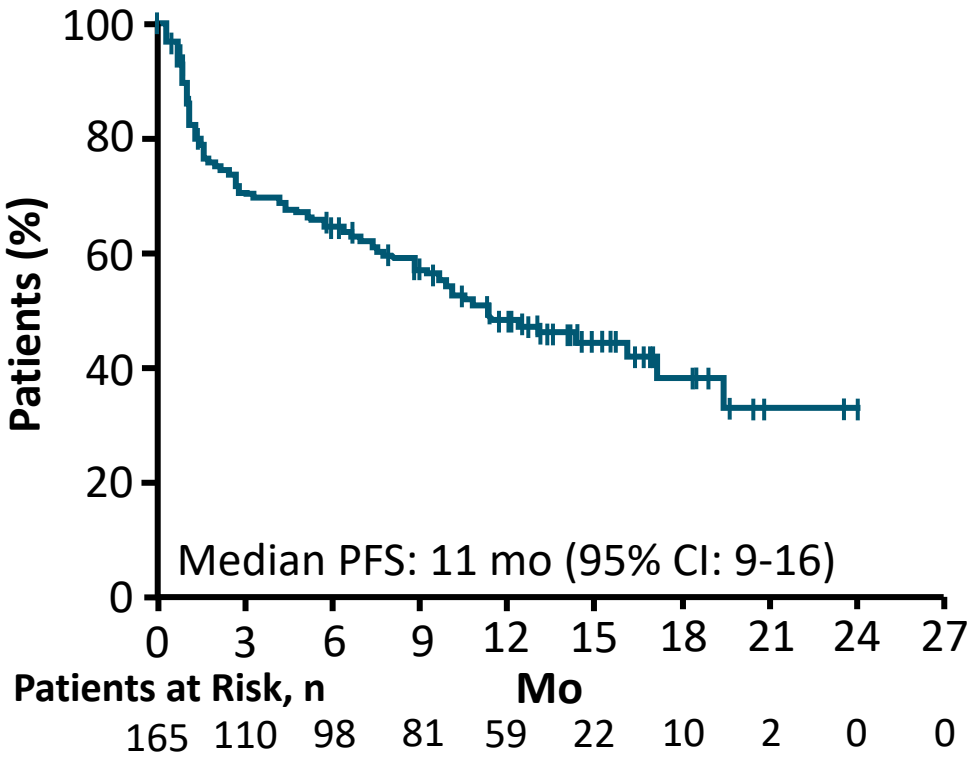


- Median follow-up: 23 mo

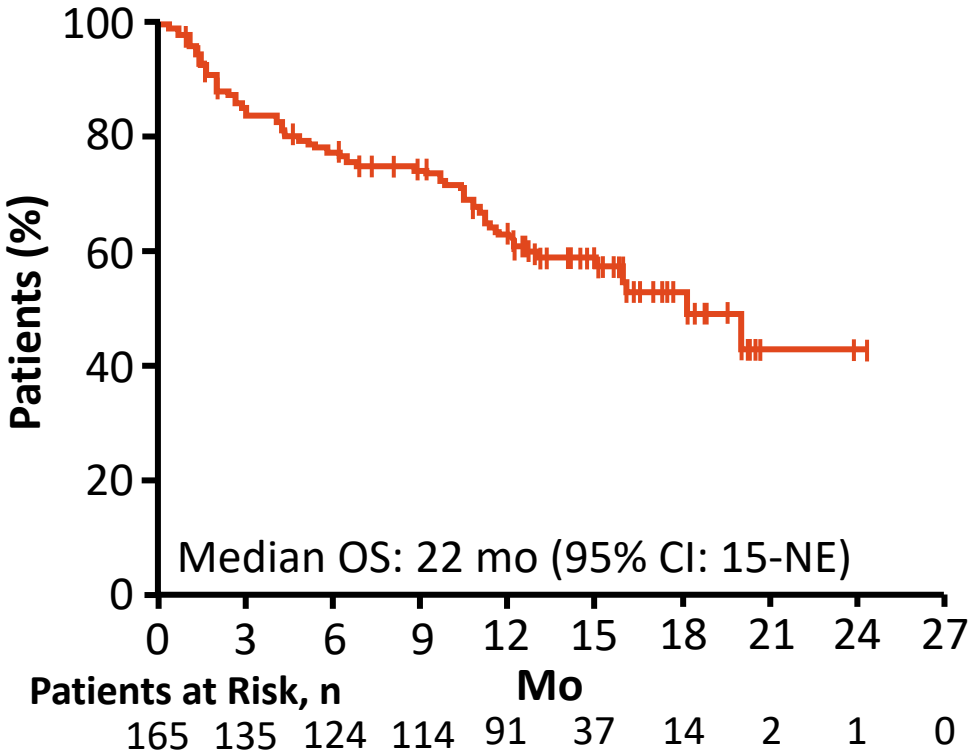
Moreau. NEJM. 2022;387:495. van de Donk. ASCO 2023. Abstr 8011.

MajesTEC-1: Survival Outcomes With Teclistamab for R/R MM After ≥3 Previous Lines of Therapy

Progression-Free Survival



Overall Survival



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

MajesTEC-1: Safety

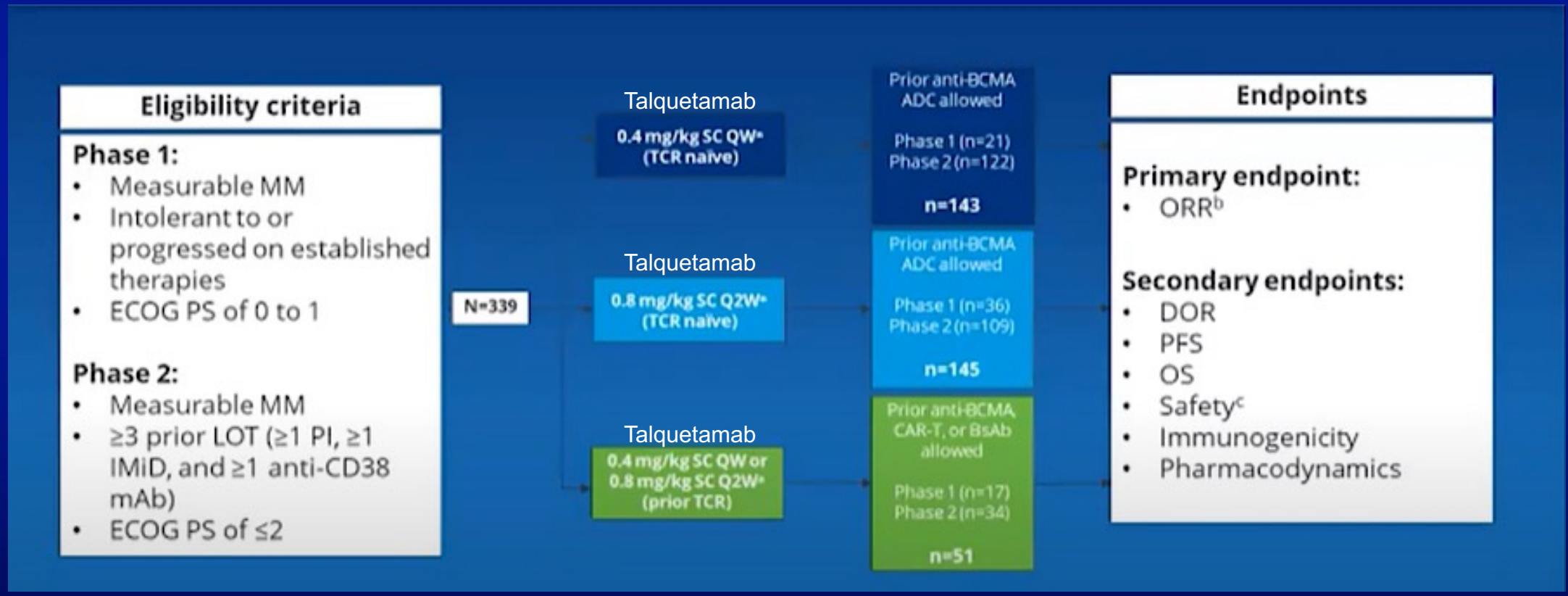
- Median treatment duration: 8.5 mo (range: 0.2-24.4)
- Median relative dose intensity: 93.7%
- 1 AE led to dose reduction
- 8 AEs led to discontinuation (5 due to infection)
- 7 treatment-related deaths (4 due to COVID-19)
- All cases of ICANS resolved
- No new safety signals

AEs, n (%)	All Patients (N = 165)	
	Any	Grade 3/4
Hematologic (≥20% of patients)		
▪ Neutropenia	118 (71.5)	108 (65.5)
▪ Anemia	90 (54.5)	62 (37.6)
▪ Thrombocytopenia	70 (42.4)	37 (22.4)
▪ Lymphopenia	60 (36.4)	54 (34.5)
▪ Leukopenia	33 (20.0)	15 (9.1)
Nonhematologic (≥20% of patients)		
▪ Infections	132 (80.0)	91 (55.2)
▪ CRS	119 (72.1)	1 (0.6)
▪ Diarrhea	56 (33.9)	6 (3.6)
▪ Pyrexia	52 (31.5)	1 (0.6)
▪ Fatigue	48 (29.1)	4 (2.4)
▪ COVID-19	48 (29.1)	35 (21.2)
▪ Nausea	45 (27.3)	1 (0.6)
▪ Cough	44 (26.7)	0
▪ Injection-site erythema	43 (26.1)	0
▪ Arthralgia	42 (25.5)	1 (0.6)
▪ Headache	40 (24.2)	1 (0.6)
▪ Constipation	36 (21.8)	0
▪ Hypogammaglobulinemia	34 (20.6)	3 (1.8)
Special interest		
▪ ICANS	5 (3.0)	0

van de Donk. ASCO 2023. Abstr 8011.

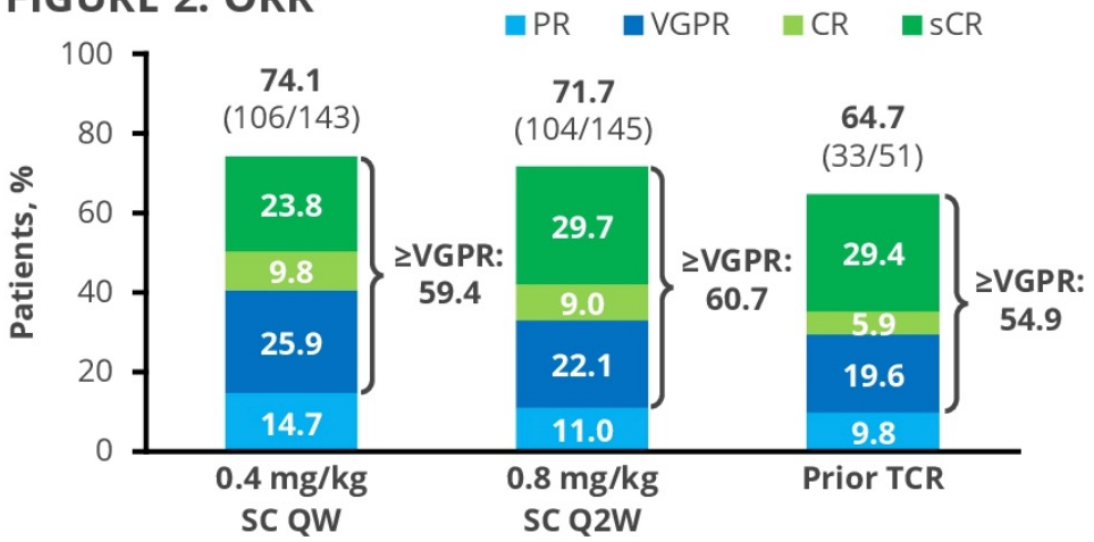
MonumenTAL-1 phase 1/2 study

- GPRC5D expressed on PCs, hair follicles, eccrine glands



Response to Talquetamab Therapy in Patients with Relapsed or Refractory Multiple Myeloma

FIGURE 2: ORR[a]



[a]Due to rounding, individual response rates may not sum to the ORR. CR, complete response; PR, partial response; sCR, stringent CR; VGPR, very good partial response.

TABLE 2: Efficacy outcomes

Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
mDOR (95% CI), mo	9.5 (6.7–13.3)	NR (13.0–NE)	11.9 (4.8–NE)
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

mDOR, median duration of response; NE, not estimable; NR, not reached.

Schinke CD et al. ASCO 2023;Abstract 8036.

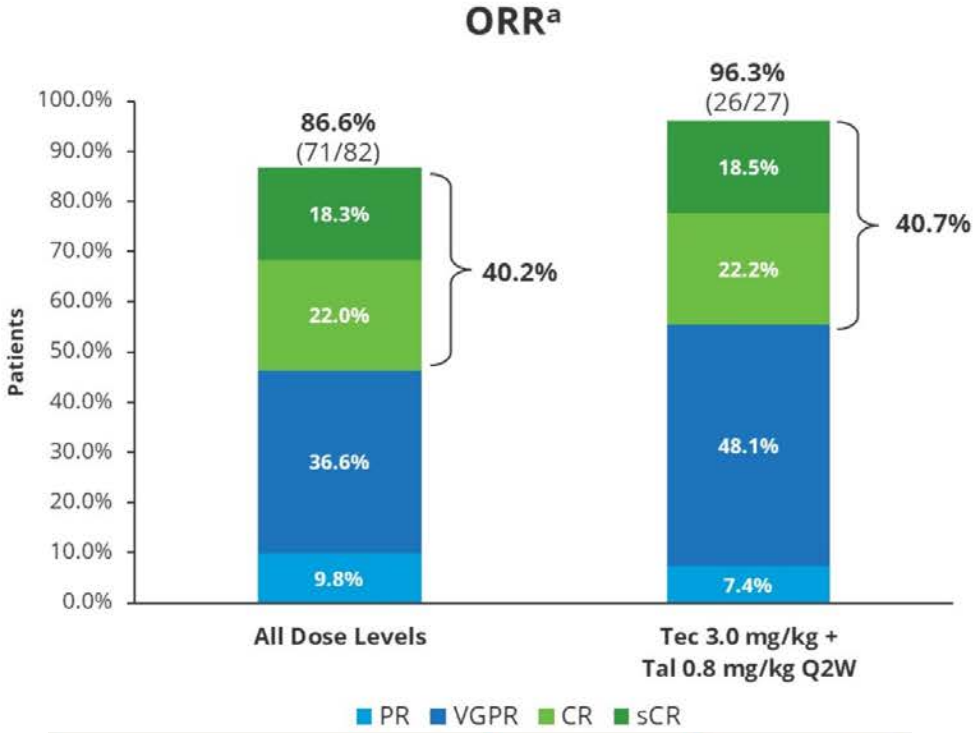
MonumenTAL-1: Talquetamab Toxicity Profile

AEs (≥20% of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=44	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs[b]	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	N/A	25 (56.8)	N/A
Nail-related AEs[c]	18 (60.0)	0	15 (34.1)	0
Rash-related AEs[d]	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0
Diarrhea	9 (30.0)	0	8 (18.2)	0
ALT increased	6 (20.0)	1 (3.3)	14 (31.8)	3 (6.8)
Decreased appetite	7 (23.3)	1 (3.3)	11 (25.0)	1 (2.3)
Headache	7 (23.3)	0	11 (25.0)	0
AST increased	3 (10.0)	0	14 (31.8)	3 (6.8)

- Overall, the most common adverse events (AEs) were CRS, skin-related events, and dysgeusia
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg QW and 38.6% at 800 µg/kg Q2W (grade 3/4: 6.7%/9.1%)
- CRS events were mostly grade 1/2 and were largely confined to the step-up doses and first full dose Dysgeusia was managed with supportive care, and at times with dose adjustments
- No patients died due to drug-related AEs

Minnema MC et al. ASCO 2022;Abstract 8015.

RedirecTT-1: COMBINATION OF TECLISTAMAB/TALQUETAMAB yields high ORR, even in EMD RRMM



- ORR was high 86.6%) across dose levels studied and 96.3% at the RP2R
- At data cutoff, 61% (57/93) of patients remained on treatment

- 81.7% with ≥1 postbaseline IgG value <400 mg/dL or hypogammaglobulinemia TEAE (all grade 1 or 2)
  - 85.3% at the RP2R
- IVIG was given to 37 patients, including 15 at the RP2R

	All Dose Levels N=93	Tec 3.0 mg/kg + Tal 0.8 mg/kg Q2W n=34
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR[b], months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response[b], months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response[b], months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS, months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

TEAE[a] (≥5% overall), n (%)	Total N=93		Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W n=34	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infections	**78 (83.9)**	**49 (52.7)**	**27 (79.4)**	**13 (38.2)**
COVID-19	31 (33.3)	9 (9.7)	14 (41.2)	1 (2.9)
Pneumonia	25 (26.9)	10 (10.8)	4 (11.8)	2 (5.9)
Upper respiratory tract infection	11 (11.8)	2 (2.2)	4 (11.8)	0
Nasopharyngitis	8 (8.6)	0	2 (5.9)	0
Rhinovirus infection	8 (8.6)	2 (2.2)	2 (5.9)	0
Oral candidiasis	7 (7.5)	1 (1.1)	2 (5.9)	0
Septic shock	7 (7.5)	6 (6.5)	1 (2.9)	1 (2.9)
Urinary tract infection	7 (7.5)	1 (1.1)	5 (14.7)	1 (2.9)
COVID-19 pneumonia	6 (6.5)	5 (5.4)	4 (11.8)	3 (8.8)
Bacteremia	5 (5.4)	2 (2.2)	1 (2.9)	0
Bronchitis	5 (5.4)	2 (2.2)	0	0
Sinusitis	5 (5.4)	0	1 (2.9)	0

ASCO 2023 Cohen Y Abstract #8002

Other Bispecific Engagers in Development

- ABBV-383[1]: 2 BCMA binding domains, Q3W to 4W dosing; no step up, short stay (24-48h); ORR 65% 11.2 mo PFS
- Alnuctamab[2]: bivalent binding, SQ dosing, step up doses d1,4, moves to monthly dosing mo 7. ORR 69% at 30 mg target dose
- Linvoseltamab[3]: 200mg IV weekly until W14; then monthly; ORR 71%, presented data in pts >75 y.o. (ORR 68%)

[1]Vij R ASH 2023 Abstract 3378; [2]Bar N ASH 2023 Abstract #2011; [3]Jagannath S 2023 ASH Abstract 4746

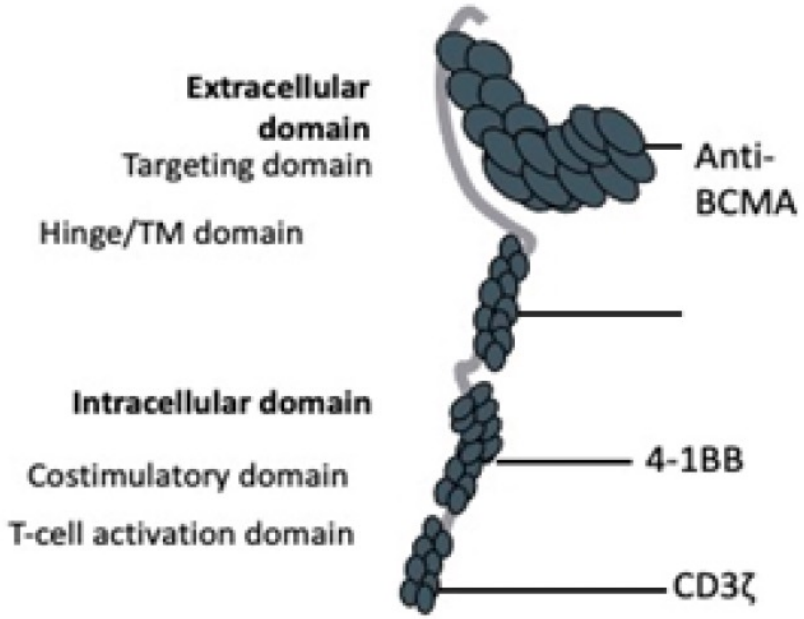
2023: two approved BCMA Directed CAR Ts

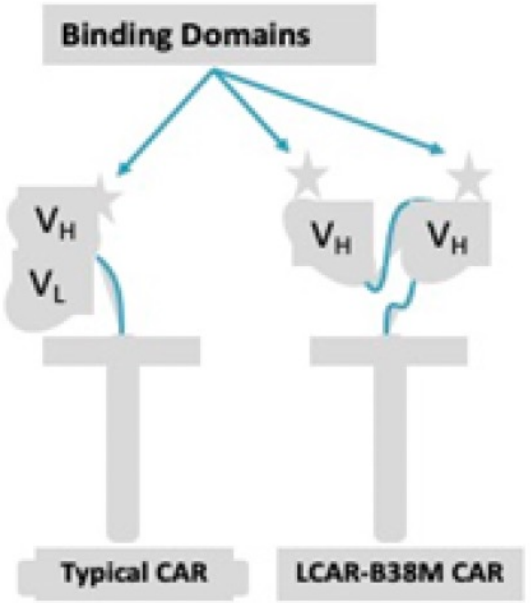
Idecabtagene Vicleucel

- Autologous T-cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: Anti-BCMA
- Costimulatory domain: 4-1BB
- T-cell activation domain: CD3 ζ

Ciltacabtagene Autoleucel

- Lentiviral vector-based + 4-1BB costimulatory domain;
- BCMA-catching domain targets 2 different epitopes simultaneously





Martino M Cancers 2021 13:2639

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KarMMa Update: Overall Response Rate

- Median follow-up: 24.8 mo (range: 1.7-33.6 mo)

Outcome	Ide-cel 150 x 10^6 (n = 4)	Ide-cel 300 x 10^6 (n = 70)	Ide-cel 450 x 10^6 (n = 54)	All Ide-cel Patients (n = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	42 (33)

Outcome by Prior Lines of Tx	3 Lines (n = 15)	≥4 Lines (n = 113)	All Ide-cel Patients (n = 128)
ORR, n (%)	73	73	73
CR/sCR, n (%)	53	30	33
VGPR	0	23	20
PR	20	20	20

Anderson. ASCO 2021. Abstr 8016.

CARTITUDE-1 Update: Efficacy Summary

Efficacy Outcome	Patients (N = 97)
ORR, % (95% CI)*	97.9 (92.7-99.7)
▪ sCR	82.5 (73.4-89.4)
Median DoR, mo (95% CI)	33.9 (25.5-NE)
Median PFS, mo (95% CI)	34.9 (25.2-NE)
Median OS	NR
▪ 3-yr OS, %	62.9

*Previously reported; assessed by IRC.

- Median f/o about 34 mo
- MRD negativity ≥12 mo in 26/49 evaluable patients
  - 20/26 had sustained MRD negative ≥ CR
- 18 patients remained MRD negative with ≥ CR 24-mo post infusion
- NEW CONCERNS: 10% risk of AML/MDS among subjects

Lin. ASCO 2023. Abstr 8009.

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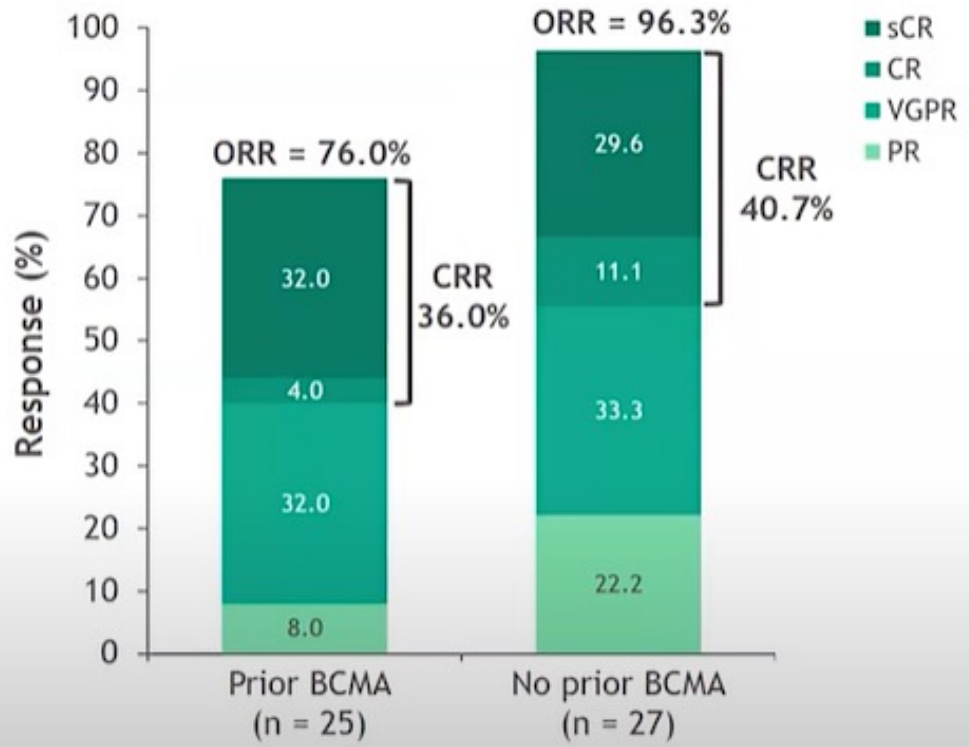
CAR-T: non-BCMA



Number of patients with prior BCMA-targeted therapy, n (%)	n = 25
CAR T-cell therapy (cilta-cel, ide-cel, orva-cel, ALLO 715, others not specified)	19 (76.0)
Non-CAR T-cell therapy (ADC, belantamab mafodotin, TCE)	8 (32.0)

BMS-986393, a GPRC5D CAR-T showed an ORR in 89.5% of pts; appears to be lower rate of mucocutaneous AEs

Bal S EHA 2023 S193

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KarMMa-3 study design (NCT03651128)

Rodriguez-Otero P et al.
ASH 2023;Abstract 1028.

KarMMa-3

386 patients

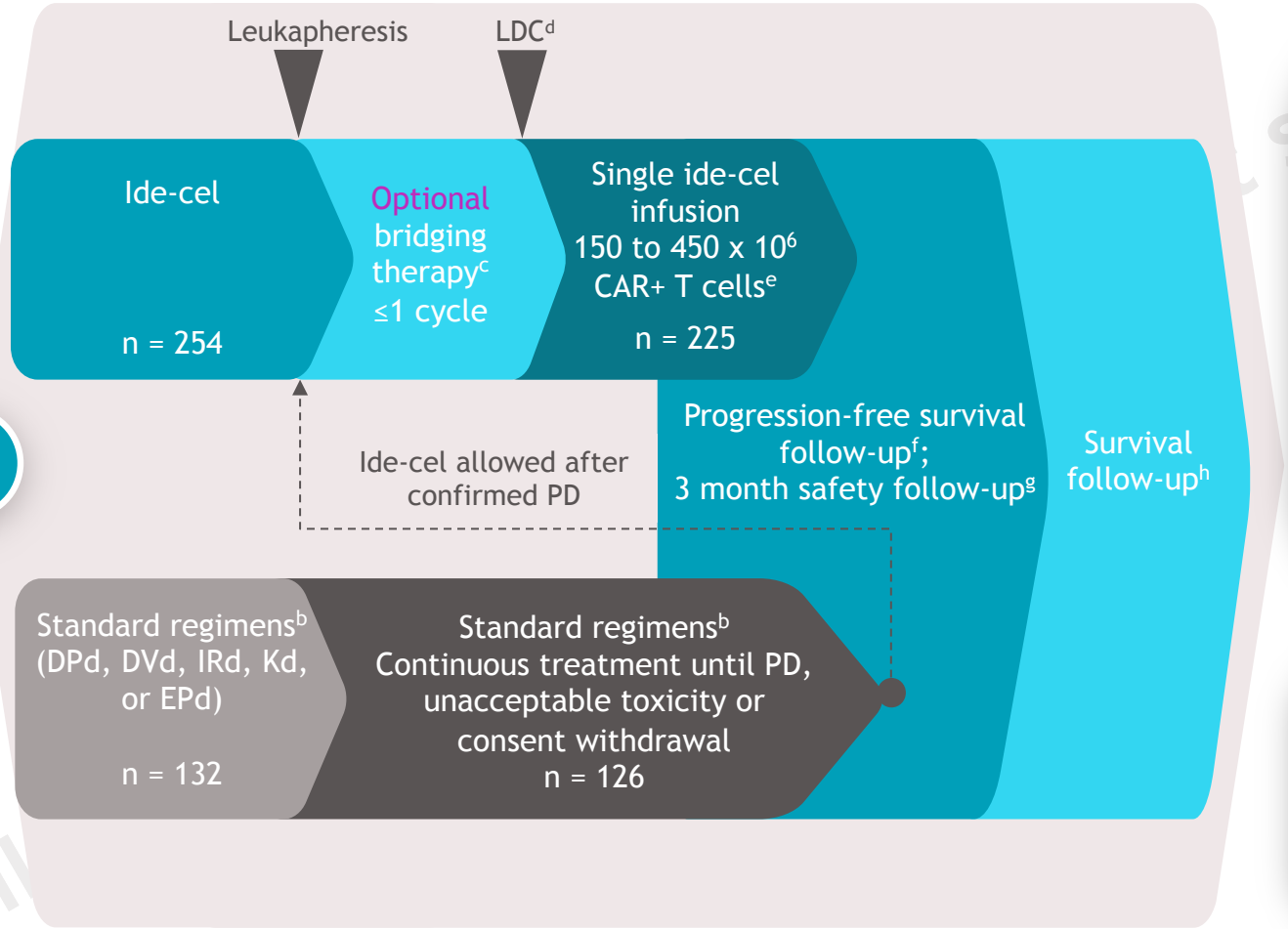
Inclusion criteria

- Aged ≥ 18 years
- ECOG performance status 0–1
- 2–4 previous regimens (including an IMiD agent, PI, and daratumumab)
- Refractory to the last regimen

Stratification factors

- Age (< 65 vs ≥ 65 years)
- Number of previous regimens (2 vs 3 or 4)
- High-risk cytogenetics (yes vs no/unknown)

R 2:1



Objectives

Endpoints

Primary endpoint

- PFS
- *Key secondary endpoints*
- ORR (by IRC), OS

Other secondary endpoints

- CRR by IRC, PFS2, EFS, TTR, MRD, TTNT
- Safety

Exploratory endpoints

- sBCMA levels

Data cutoff: April 27, 2023

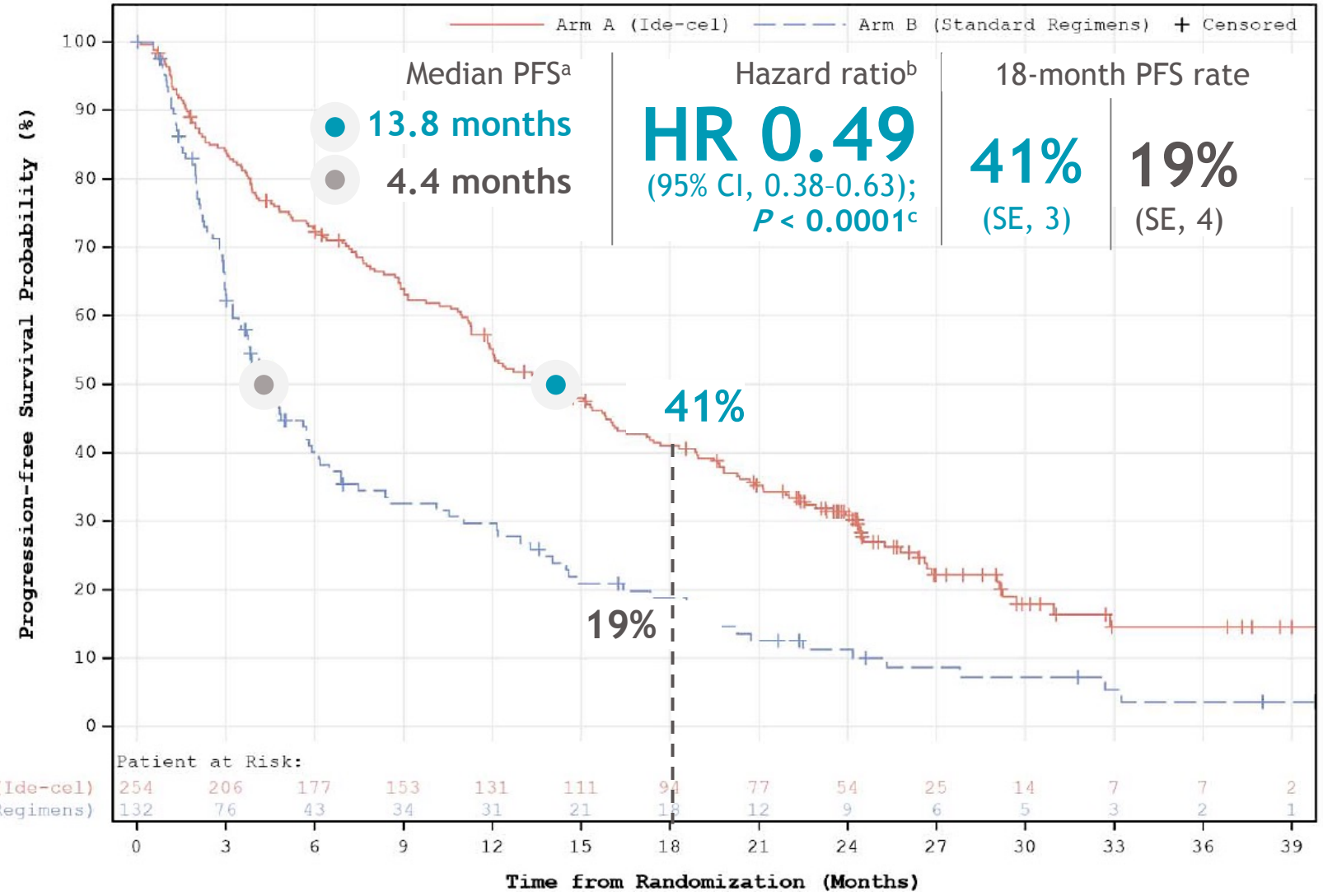
Median (range) follow-up: 30.9 (12.7-47.8) months

Ide-cel arm: treated population (patients who underwent either leukapheresis, bridging therapy, LDC, or ide-cel treatment) was used to assess AEs; the safety population (patients who received ide-cel) was used to assess TRAEs, iiNT, and CRS; standard regimens arm: the treated and safety populations included those patients who received any treatment. [a]Time from randomization to the first occurrence of disease progression or death from any cause according to IMWG criteria; [b]Based on most recent treatment regimen and investigator discretion; [c]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging therapy; [d]3 days fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2; [e]Doses ≤ 540 x 10^6 cells permitted; [f]PFS assessed monthly for patients randomized to ide-cel for 24-months then every 3 months until PD, and monthly until PD for patients randomized to standard regimens; [g]Patients randomized to standard regimens and received subsequent ide-cel therapy; [h]Every 3 months after PD until end of trial; 5 years after last patient randomized.
AE, adverse event; CRS, cytokine release syndrome; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EPd, elotuzumab/pomalidomide/dexamethasone; iiNT, investigator-identified neurotoxicity; IRC, Independent Response Committee; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; LDC, lymphodepleting chemotherapy; OS, overall survival; PD, progressive disease; R, randomization; sBCMA, soluble B-cell maturation antigen; TRAE, treatment-related adverse events.

Progression-free survival (overall ITT population)

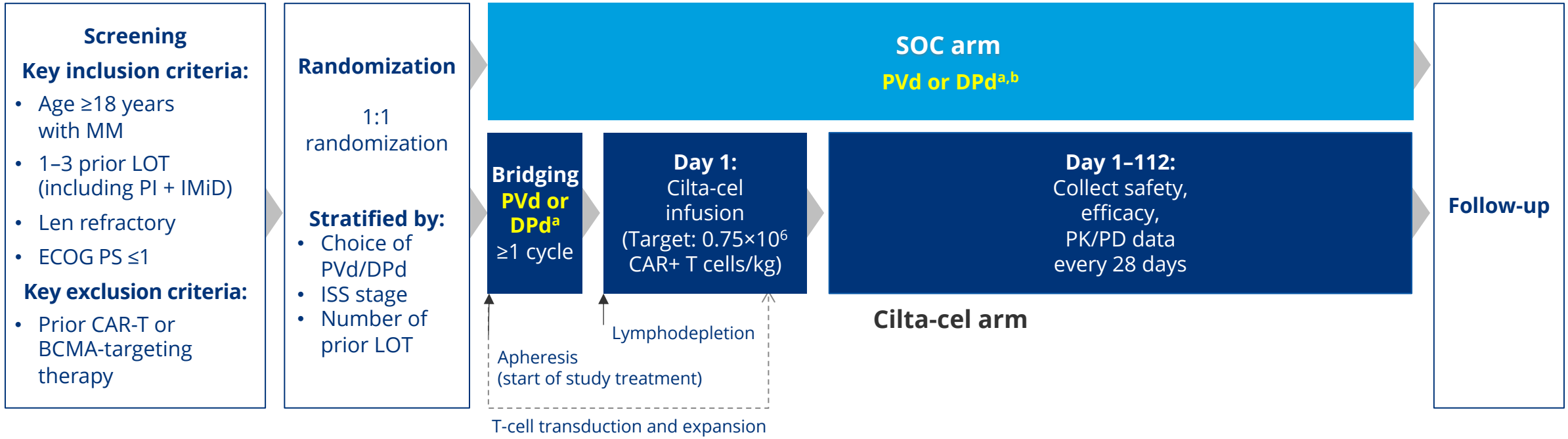
Rodriguez-Otero P et al.
ASH 2023;Abstract 1028.

HR CYTO/FISH:
44% of pts
Triple RR: 65%
EMD: 24%



PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. Final PFS analysis was planned to be conducted when a total of ~289 events had occurred to provide 94% overall power to detect a HR of 0.643 using a one-sided log rank test with an overall significance of 0.025.
PFS based on IMWG criteria per IRC. [a]Based on Kaplan-Meier approach; [b]Statified rHR based on univariate Cox proportional hazard model. CI is two-sided; [c]Based on stratified log-rank test.
CI, confidence interval; IMWG, International Myeloma Working Group; SE, standard error.

CARTITUDE-4 Study Design and Endpoints: Early use of CAR-T



Primary endpoint

- PFS[c]

Secondary endpoints

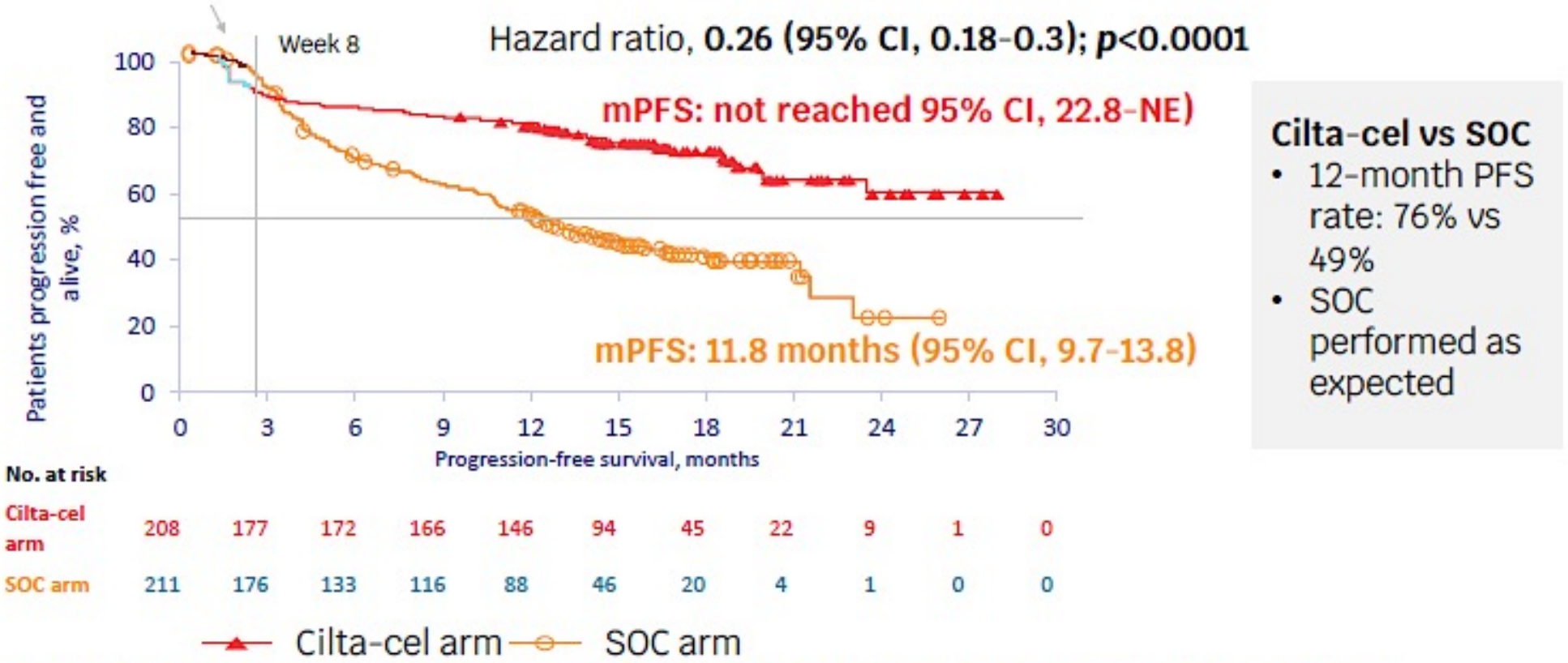
- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

Dhakal B et al. ASCO 2023;Abstract LBA106.

[a]Physicians' choice. [b]Administered until disease progression. [c]Time from randomization to disease progression/death.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; Len, lenalidomide; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; SOC, standard of care.

Even earlier use of CAR-T: 1-3 lines

CARTITUDE-4: Primary Endpoint- PFS



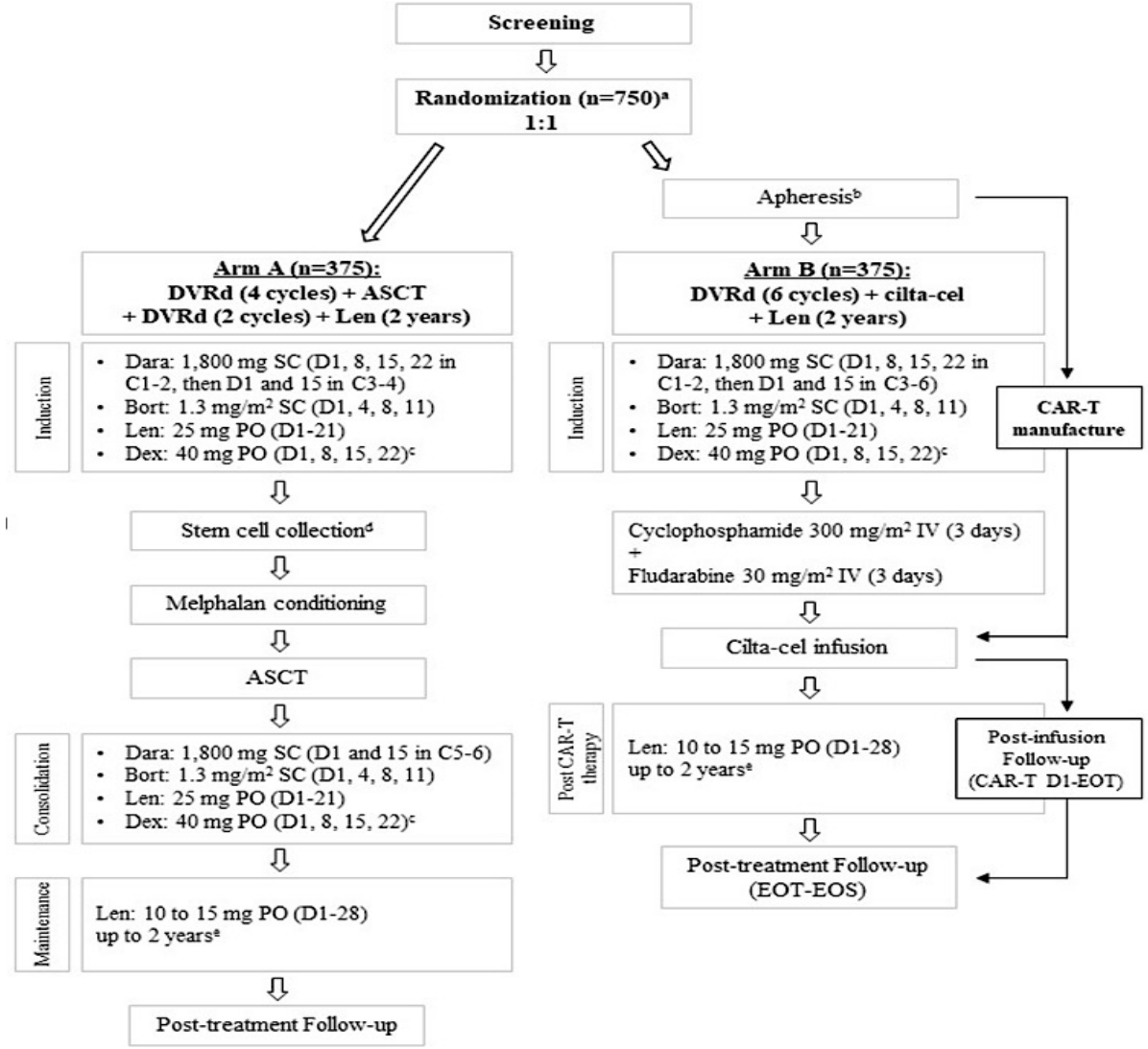
Cilta-cel vs SOC

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected

Dhakal et. al. ASCO 2023. J Clin Oncol 41, 2023 (suppl 17; abstr LBA106, San-Miguel J, Dhakal B, Yong K, et al: Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. New England Journal of Medicine 389:335-347, 2023

Dhakal B et al. ASCO 2023;Abstract LBA106.

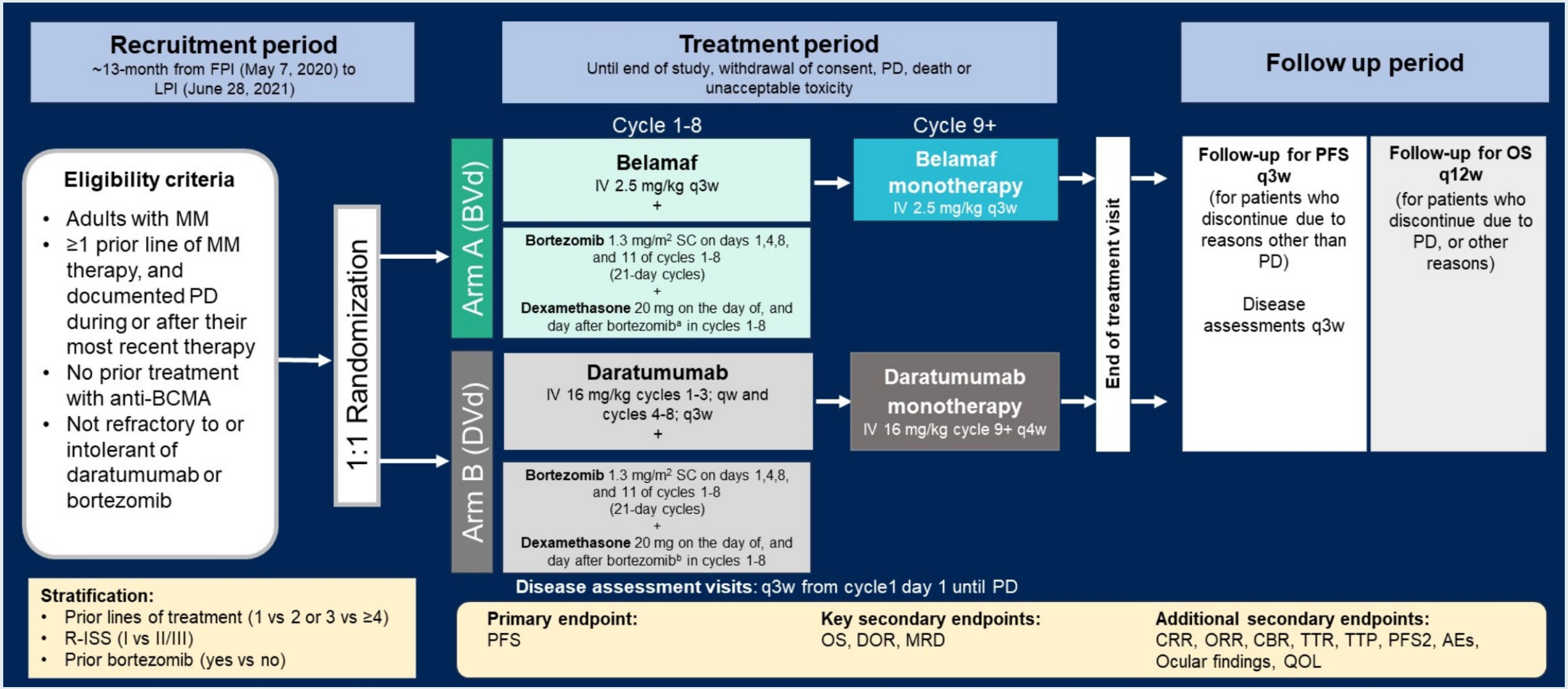
A Phase 3 Randomized Study Comparing Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) followed by Ciltacabtagene Autoleucel versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) followed by Autologous Stem Cell Transplant (ASCT) in Participants with Newly Diagnosed Multiple Myeloma who are Transplant Eligible (CARTITUDE-6)



NCT05257083

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

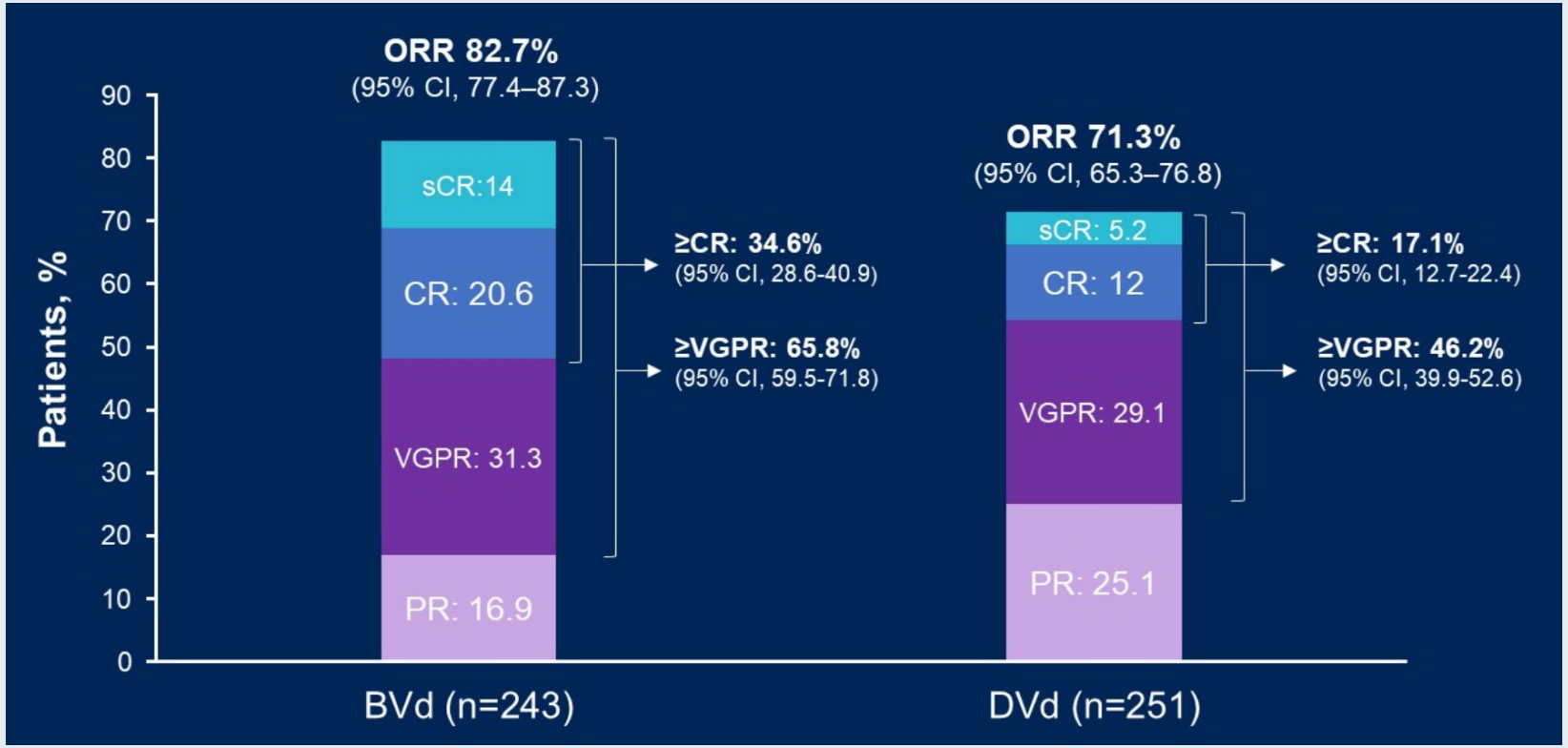
DREAMM-7: BVd vs DVd for Relapsed/Refractory MM



Mateos M-V et al. ASCO Plenary Series: February 2024;Abstract 439572.

DREAMM-7: BVd vs DVd for Relapsed/Refractory MM

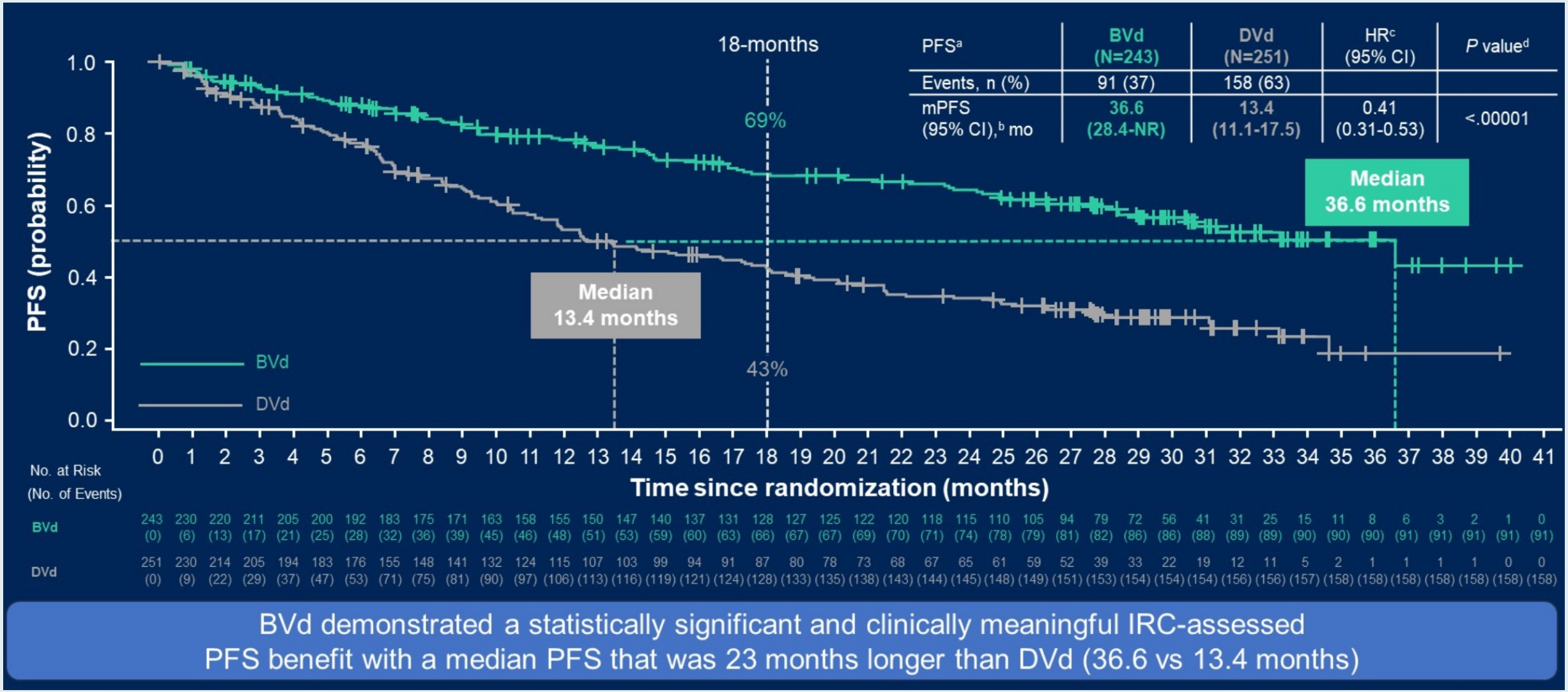
Prior treatments, n (%)	ITT population	
	BVd (N=243)	DVd (N=251)
Prior LOT		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
4+	30 (12)	27 (11)



Mateos M-V et al. ASCO Plenary Series: February 2024;Abstract 439572.

RTP RESEARCH TO PRACTICE

DREAMM-7: BVd vs DVd for Relapsed/Refractory MM



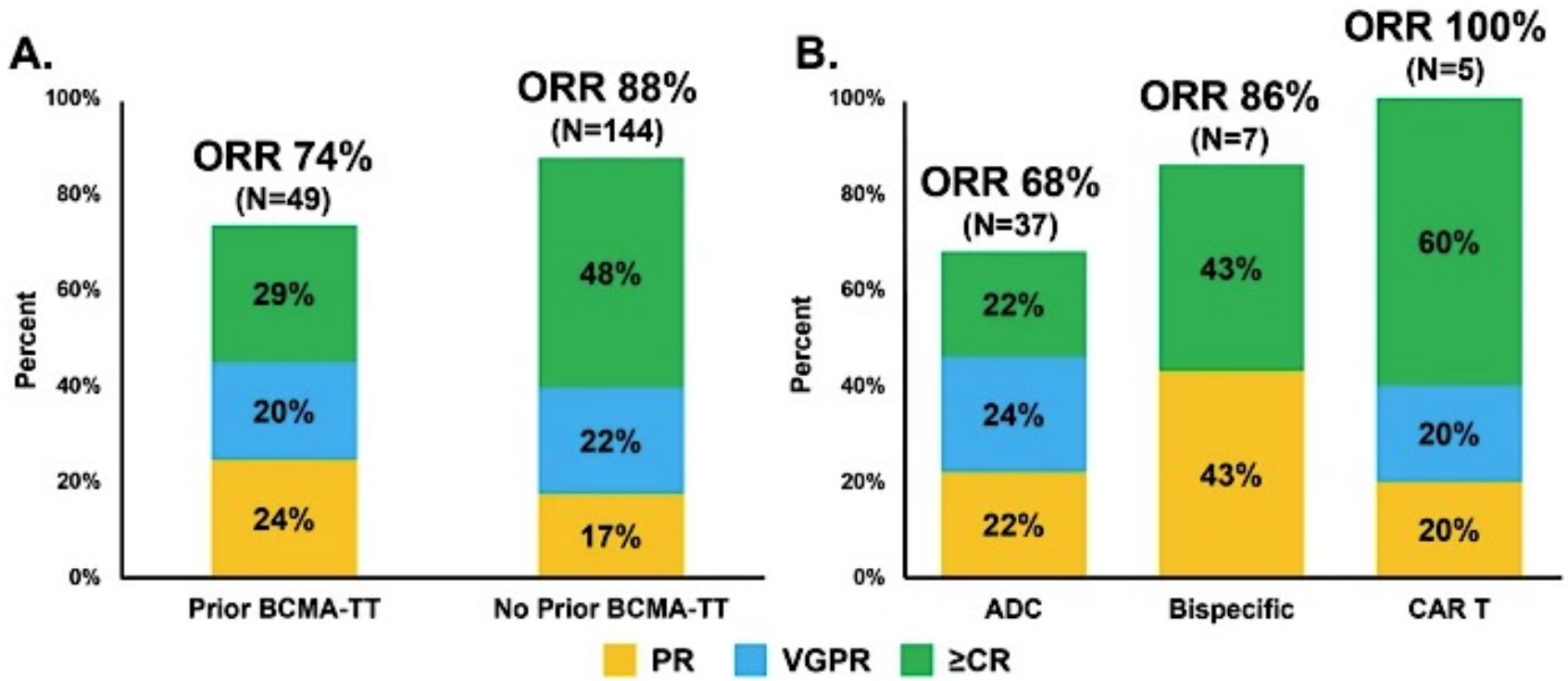
PFS[a]	BVd (N=243)	DVd (N=251)	HR[c] (95% CI)	*P* value[d]
Events, n (%)	91 (37)	158 (63)		
mPFS (95% CI),[b] mo	36.6 (28.4-NR)	13.4 (11.1-17.5)	0.41 (0.31-0.53)	<.00001

BVd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit with a median PFS that was 23 months longer than DVd (36.6 vs 13.4 months)

Mateos M-V et al. ASCO Plenary Series: February 2024;Abstract 439572.

RTP RESEARCH TO PRACTICE

Sequencing BCMA targeted therapies remains a challenge: responses to CAR-T are lower after previous BCMA targeted therapies



Overall response rate and depth of response outcomes for the prior BCMA-TT cohort compared to the no prior BCMA-TT cohort (**A**), and stratified by the specific type of prior BCMA-TT (**B**). ORR overall response rate, CR complete response, VGPR very good partial response, PR partial response.

Ferreri C et al Blood Cancer J 2023 13:117

FDA Investigating "Serious Risk" of T-Cell Malignancies for Patients Receiving CAR T-Cell Therapy

Press Release: November 29, 2023

"The FDA has launched an investigation into what it called a 'serious risk' of T-cell malignancies in patients treated with autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) or CD19.

The agency has received multiple reports of T-cell malignancies, including CAR-positive lymphomas, from clinical trials and postmarketing adverse event data sources, according to a statement posted on the FDA website. Serious outcomes of these secondary malignancies have included hospitalization and death. The notice and investigation pertain to all currently approved BCMA- and CD19-targeted CAR T-cell products.

'Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalizations and death, and is evaluating the need for regulatory action,' agency officials said in the statement. 'As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the US prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies.'"

https://www.medpagetoday.com/hematologyoncology/hematology/107569

RTP RESEARCH TO PRACTICE

- Cellular therapies are the beginning of a new chapter
- How to use these to best advantage remains to be seen
- CAR-T may not be the best first cellular therapy choice in unstable patients
- However, will early use of bispecific engagers diminish response to CAR-T?
- Optimal sequencing remains an open question
- CAR-T then anti GPRC5D bispecific, then anti BCMA therapy again
- Long term risks associated with CAR-T and bispecifics remain to be determined

Agenda

Module 1: Chimeric Antigen Receptor T-Cell Therapy, Bispecific Antibodies and Antibody-Drug Conjugates in MM — Dr Callander

Module 2: Integration of Other Novel Therapies into the Management of Newly Diagnosed and Relapsed/Refractory MM — Dr Richardson

Dana-Farber Cancer Institute

Integration of Next-Generation Novel Therapies into the Management of Newly Diagnosed and R/R MM

Paul G. Richardson, MD
RJ Corman Professor of Medicine
Harvard Medical School

Clinical Program Leader, Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Boston, Massachusetts

Sunday, March 24, 2024

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Disclosures

Advisory Committees	Bristol Myers Squibb, Celgene Corporation, GSK, Karyopharm Therapeutics, Oncopeptides, Sanofi
Research Grants	Bristol Myers Squibb, Celgene Corporation, Karyopharm Therapeutics, Oncopeptides, Takeda Pharmaceuticals USA Inc

The value of novel agent therapies in the management of MM

DFCI patient case study: 2002–2024

Patient narrative

- 76-year-old woman – originally diagnosed with MM in 2002 (aged 54 years)
- Thalidomide-Dex followed by Allo-SCT (sibling donor), with PD in 2004
- 4 additional prior lines of treatment, 2004–2021, including:
  - Lenalidomide and bortezomib (RVd)
  - Pomalidomide-based treatment
  - CD38 mAb therapy with isatuximab
  - Other protocol-directed options.

Past medical history

- SVT, CHF, cardiomyopathy, thalassemia trait.

2021–2023

- Mezigdomide-Dex, 1 year
- Belantamab mafodotin, 6 months
- SOC CyBorD, 6 months
- Remained COVID-free and not hospitalized.

July- August 2023

- SOC teclistamab
- 2 months only, as poorly tolerated with CRS, and treatment course complicated by infections, with continued PD.

August 2023 to Feb 2024

- Melflufen-Vd given per DFCI # 23-019 under a compassionate use IND.
- MR and sustained clinical improvement.
- Generally well tolerated and heme toxicity only (>6 months).

Additional pillars of treatment emerging for MM[1]

CELMoDs
- Iberdomide
- Mezigdomide

IMiDs
- Lenalidomide
- Pomalidomide

PIs
- Bortezomib
- Carfilzomib
- Ixazomib

CD38 mAbs
- Daratumumab
- Isatuximab

BCMA-targeted therapies

ADCs
- Belantamab mafodotin

CAR T cells
- ide-cel
- cilta-cel

Bispecifics
- Teclistamab
- Elranatamab

GPRC5D-targeted therapies

Bispecifics
- Talquetamab
- RG2634

CAR T cells
- MCARH109[2]
- OriCAR-017[3]

Other targeted immune therapies

Bispecifics
- Cevostamab (FcRH5)

CAR T cells
- CD38[4]
- SLAMF7[5]

- CAR NKs
- Allo CAR Ts
- Immunocytokines (TAK-573)

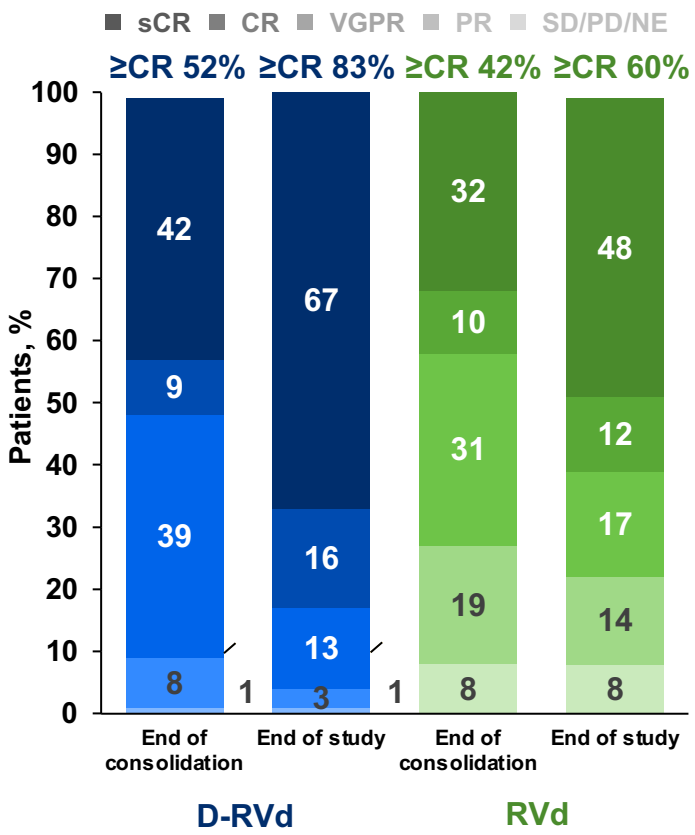
Novel / targeted therapies
- Melflufen
- Selinexor
- Venetoclax
- Panobinostat

1. Richardson PG. 4th European Myeloma Network meeting, 2023. 2. Mailankody S, et al. N Engl J Med 2022;387(13):1196–206. 3. Zhang M, et al. Lancet Haematol 2023;10(2):E107–16. 4. Glisovic-Aplenc T, et al. Blood Adv 2023;7(16):4418–30. 5. Rendo MJ, et al. Blood Lymphat Cancer 2022;12:119–36.

Dara-based quadruplet regimens for NDMM

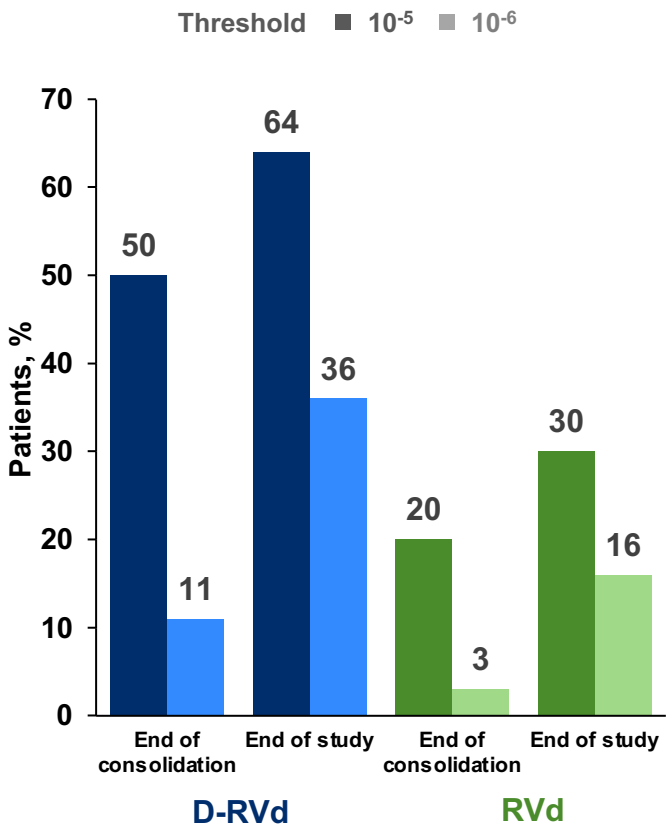
GRIFFIN:[1,2] Dara-RVd vs RVd – prolonged PFS, deepened responses

ORR



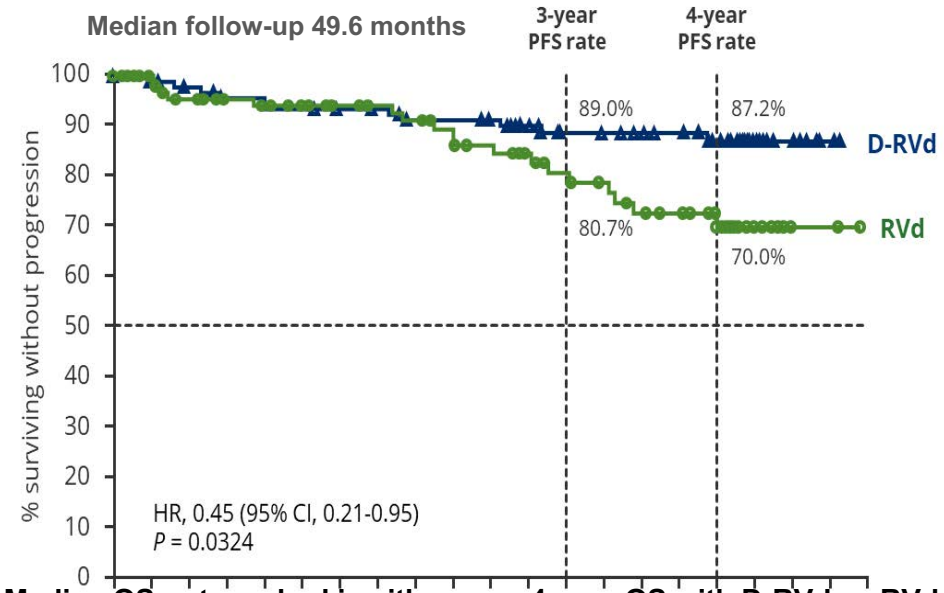
≥CR rates increased over time, with deepest responses at end of study

MRD-neg rate



14% vs 10% of patients converted from MRD-pos at end of consolidation to MRD-neg by end of study

PFS/OS in the ITT population for D-RVd versus RVd



- Median OS not reached in either arm; 4-year OS with D-RVd vs RVd: 92.7% vs 92.2% (HR 0.90)

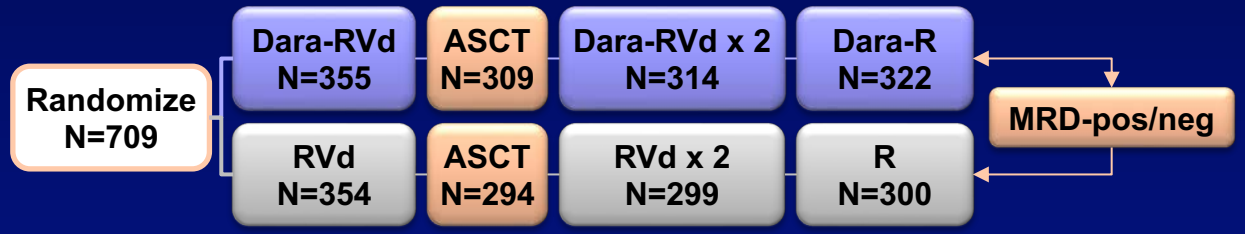
Safety data

- Hematologic Grade 3/4 AEs with D-RVd vs RVd: neutropenia (46% vs 23%), lymphopenia (23% vs 23%), leukopenia (17% vs 8%), thrombocytopenia (16% vs 9%), anemia (9% vs 6%)
- Non-hematologic Grade 3/4 AEs: PN (7% vs 9%), fatigue (7% vs 6%), diarrhea (7% vs 5%)
- AEs led to discontinuation in 33% vs 31% of patients (due to infections in 2% vs 3%)
- Minimal impact on stem cell mobilization, predictable stem cell harvesting and engraftment in all patients who underwent ASCT[3]

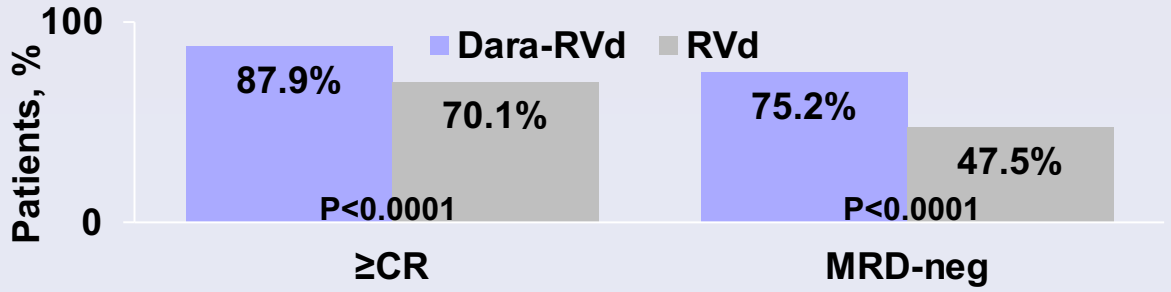
1. Voorhees PM, et al. Blood 2020;136(8):936–45. 2. Voorhees PM, et al. Lancet Haematol 2023;10(10):e825–37. 3. Chhabra S, et al. Transplant Cell Ther 2023;29(3):174.e1–10.

Dara-based quadruplet regimens for NDMM

PERSEUS: Dara-RVd vs RVd – prolonged PFS, deepened responses



Overall rates of ≥CR and MRD-neg



Safety

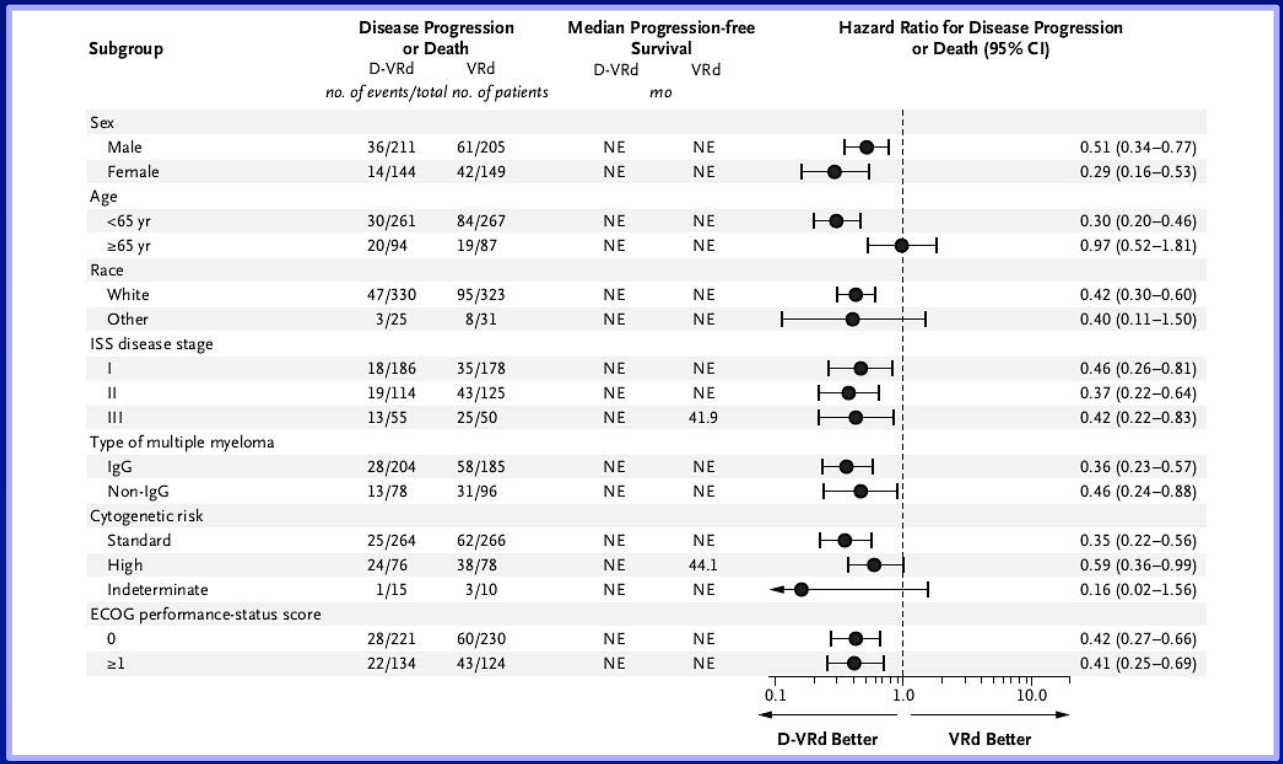
AEs, %	Dara-RVd (N = 355)	RVd (N = 354)
Grade 3/4 AEs	91.5%	85.6%
SAEs	57.0%	49.3%
AEs leading to discontinuation	8.8%	21.3%
SPMs	10.5%	7.2%

Grade 3/4 AEs, %	Dara-RVd (N = 355)	RVd (N = 354)
Neutropenia	62.1%	51.0%
Thrombocytopenia	29.1%	17.3%
Diarrhea	10.5%	7.8%
Pneumonia	10.5%	6.1%
Febrile neutropenia	9.4%	10.1%
PN	6.0%	4.9%

Sonneveld P, et al. N Engl J Med 2024;390(4):301–13.

PFS (primary endpoint), Dara-RVd vs RVd

- Median follow-up 47.5 months; 48-month PFS rate 84.3% vs 67.7%; HR 0.42 (95% CI 0.30–0.59), P<0.0001
- Generally consistent PFS benefit across subgroups including ISS III (HR 0.42) and high-risk cytogenetics (HR 0.59)
- Some differences by sex, age, and cytogenetic risk



Dara-based quadruplet regimens for NDMM

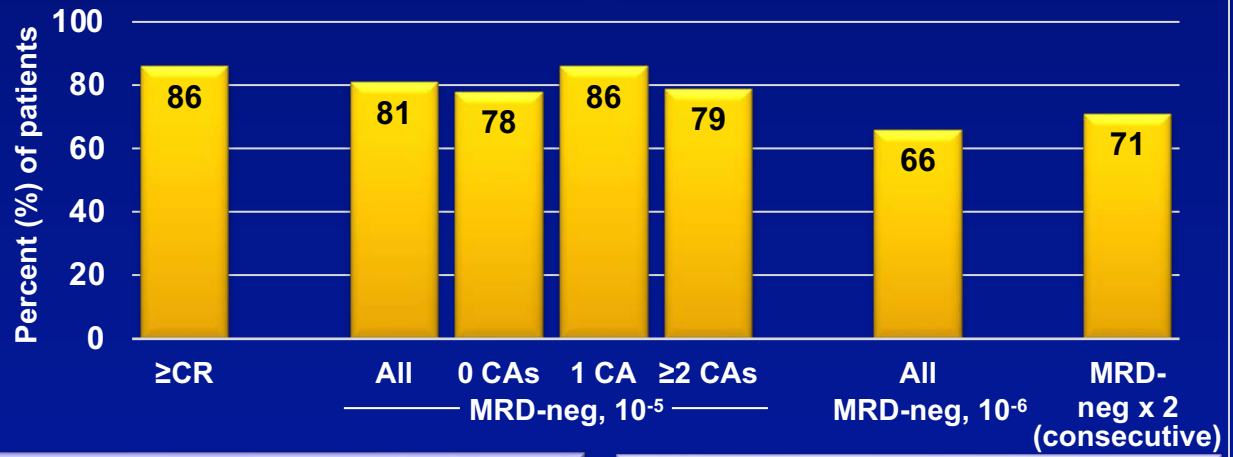
MASTER / IFM 2018-04: Dara-KRd in NDMM patients with high-risk cytogenetics

MASTER study design[1,2]

- Induction: 4 x Dara-KRd, Stem cell collection, ASCT
- Consolidation: 0, 4, or 8 x Dara-KRd according to MRD status
- Two consecutive MRD-neg results → treatment-free surveillance
- MRD-pos after consolidation → R maintenance

123 patients

- Median age 60 years (range 36–79); 24% aged ≥70 years
- 57% with high-risk cytogenetics
- 37% with 1 high-risk cytogenetic abnormality (HRCA); 20% with ≥2 HRCAs
- MRD trackable by NGS in 96%



Median follow-up 35.9 months[2]

- Older vs younger (≥70 vs <70 years)
- 3-year PFS: 86.3% vs 80.3%
- 3-year OS: 95.8% vs 88.7%

Median follow-up 42.2 months[3]

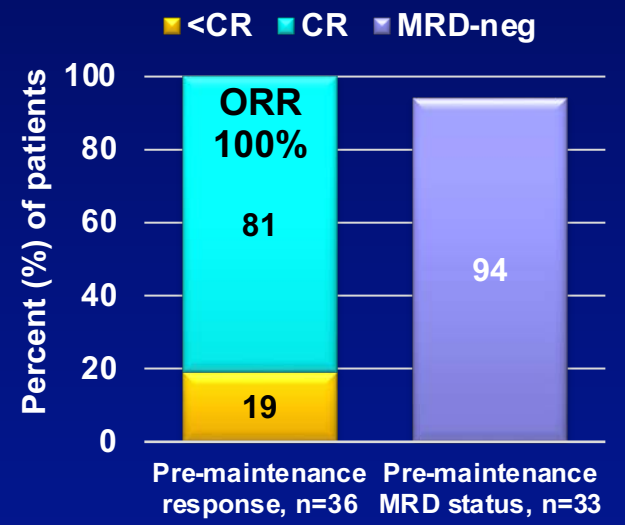
- 0 vs 1 vs ≥2 HRCA:
- 3-year PFS: 88.4%, 78.9%, 50.0%
- 3-year OS: 94%, 92%, 75%

IFM 2018-04 study design[4]

- Induction: 6 x Dara-KRd, ASCT 1
- Consolidation: 4 x Dara-KRd, ASCT 2
- Maintenance: Dara-R x 2 years

50 patients with high-risk cytogenetics

- Median age 57 years
- 40% del(17p), 52% t(4;14), 20% t(14;16)
- 50% 1q gain
- 60% with 2 abnormalities



Primary endpoint met

- 72% of patients completed ASCT 2
- MRD-neg (10^{-6}), pre-maintenance: 94% (n=31/33)

Median follow-up 32 months

- 24-month PFS: 86%; 30-month PFS: 80%
- 24-month OS: 94%; 30-month OS: 91%

Grade 3/4 AEs:

- Neutropenia 44%
- Thrombocytopenia 24%
- Anemia 22%
- Infection 14%
- GI disorders 10%

1. Costa LJ, et al. J Clin Oncol 2022;40(25):2901–12. 2. Giri S, et al. Blood 2022;140(suppl 1):abstract 1930.
3. Costa L, et al. Lancet Haematol 2023;10(11):e890–901. 4. Touzeau C, et al. Blood 2023;142(suppl 1):abstract 207.

CA, cytogenetic abnormality

Dara-based quadruplet regimens for NDMM, no ASCT

MANHATTAN:[1] Dara-KRd – high response and MRD-neg rates

Dara-KRd for 24 cycles[2] – high MRD-neg rates

MANHATTAN

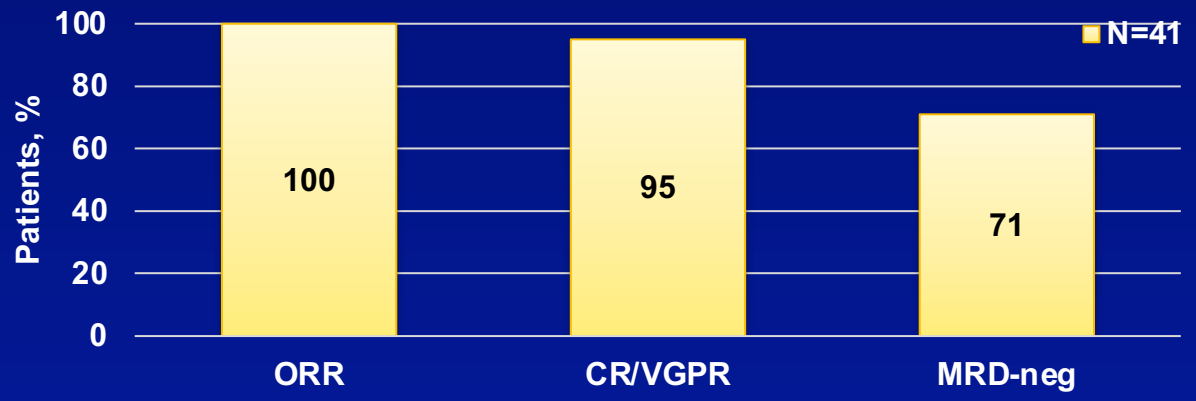
41 NDMM patients received Dara-KRd regimen for 8 cycles

- Patients could then receive ASCT (n=12) or standard-of-care maintenance

MRD-negative rate after 8 cycles: 71%

- No significant differences by age or cytogenetics
- At 1 year, 7/8 patients assessed remained MRD-negative

Responses after 8 cycles of Dara-KRd



After median follow-up of 11 months:

- 1-year PFS 98%
- 1-year OS 100%

Safety

- Common grade 3/4 AEs: 27% neutropenia, 9% rash, 7% lung infection; SAEs in 18%
- Dara infusion-related reactions in 40%

Derman et al.

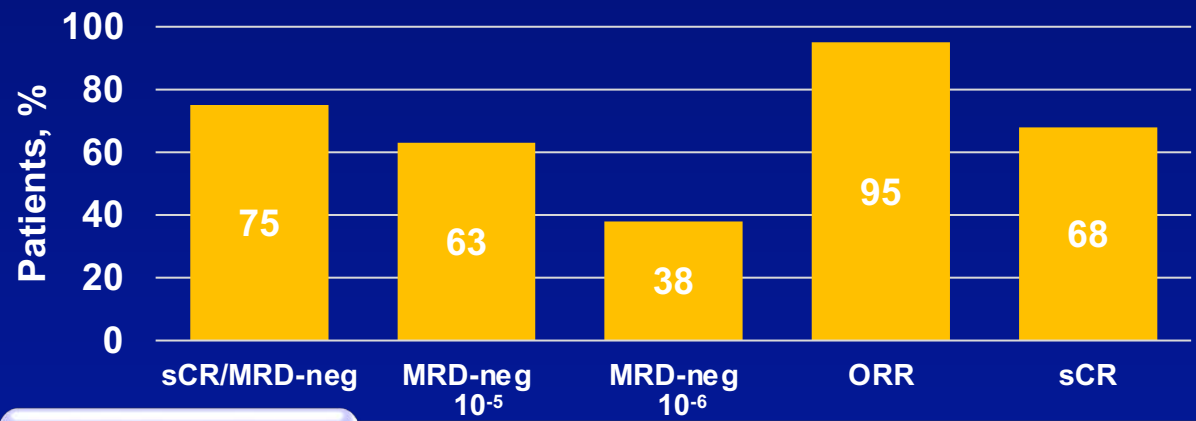
42 NDMM patients received Dara-KRd for up to 24 cycles

- Median age 58 years; 31% Black; 12% Hispanic
- 57% high-risk cytogenetics; 24% with ≥2 abnormalities

sCR/MRD-neg rate after 8 cycles: 75%

- 8% / 30% converted from MRD-pos at cycle 8 to MRD-neg at later timepoints at 10^{-5} / 10^{-6} thresholds
- 26% sustained MRD-neg (10^{-5}) for >12 months

Responses after 8 cycles of Dara-KRd



After median follow-up of 27 months:

- 50% of patients had completed all 24 cycles
- 3-year PFS 85% (100% SR, 92%/60% 1/≥2 HRCAs)
- 3-year OS 95%

Safety

- Grade ≥3 AEs: 26% thrombocytopenia, 21% neutropenia, 17% hypertension, 7% hyperglycemia, 5% diarrhea
- 45% upper respiratory infections, 38% COVID-19

1. Landgren O, et al. JAMA Oncol 2021;7(6):862–8. 2. Derman BA, et al. Blood 2023;142(suppl 1):abstract 4747.

Dara-based quadruplet regimens for NDMM, fit transplant-ineligible patients

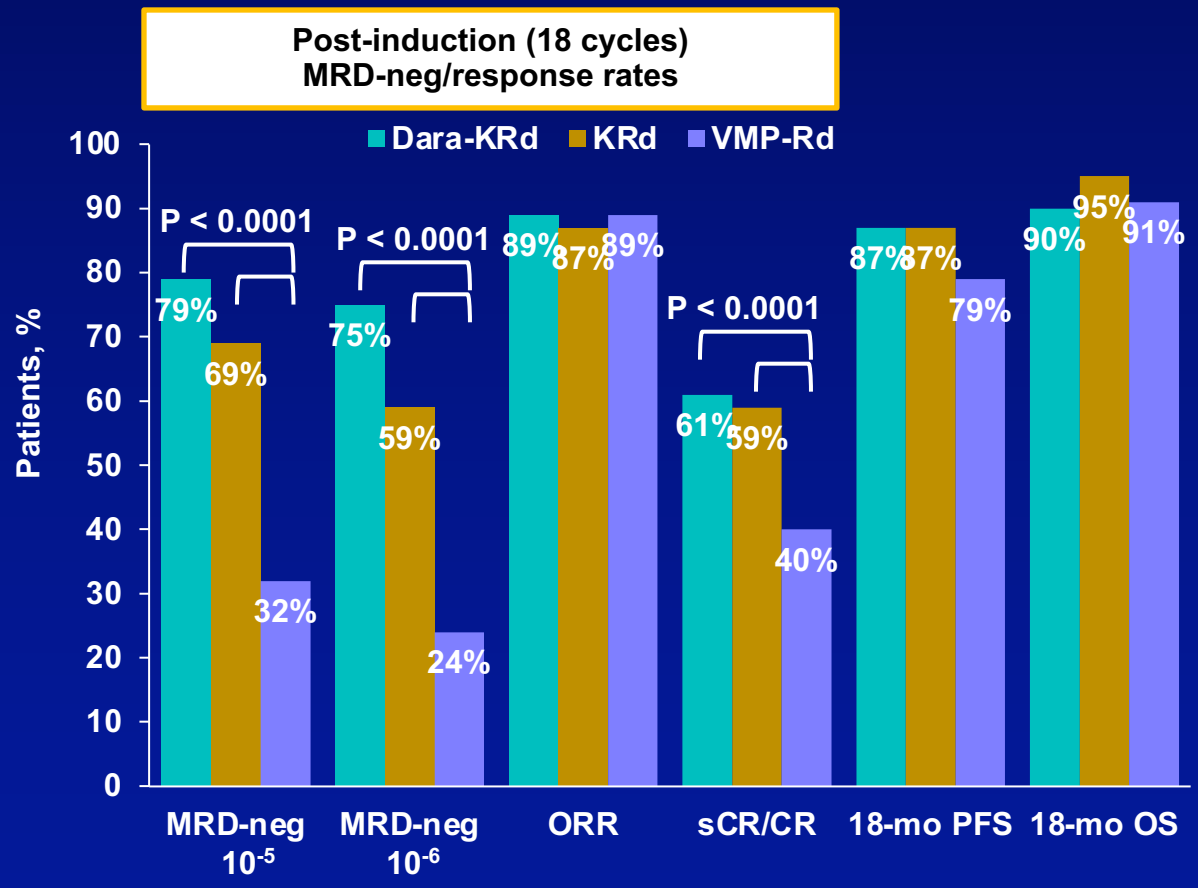
GEM2017FIT: Dara-KRd vs KRd vs VMP-Rd

GEM2017FIT study design and patients

- 'Fit' per Geriatric Assessment in Hematology scale, aged 65–80 years
- 462 patients randomized to 18 induction cycles of Dara-KRd vs KRd vs VMP-Rd (n=154 each)
- Overall median age 72 years, ~33% aged >75 years, ~33% ISS III, 15% EMD

Grade 3/4 AEs during Dara-KRd vs KRd vs VMP-Rd induction

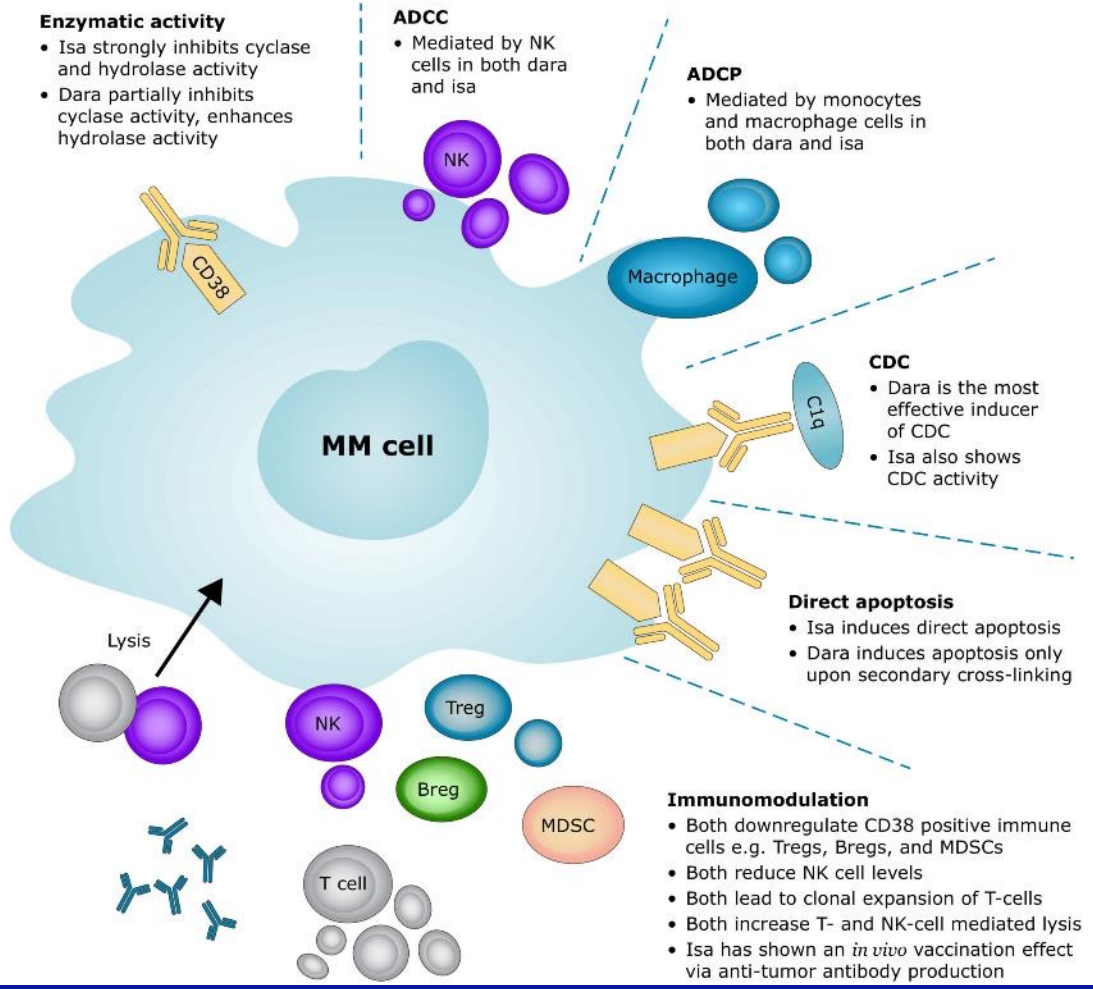
- Neutropenia 47% vs 24% vs 50%
- Thrombocytopenia 17% vs 16% vs 34%
- Infections 16% vs 15% vs 12%
- Cardiovascular AEs 14% vs 11% vs 5%

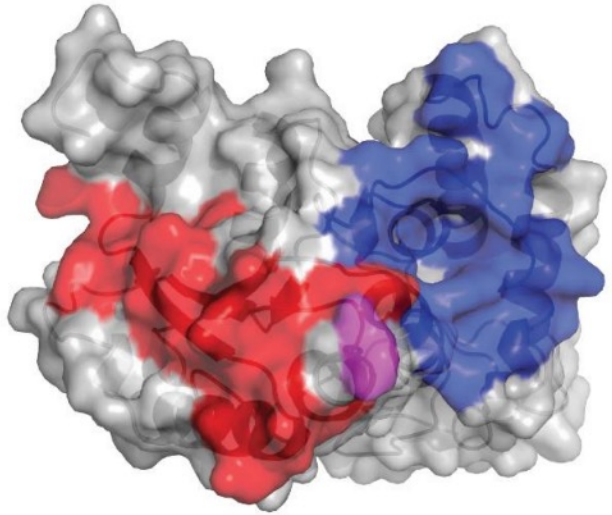


Mateos M-V, et al. Blood 2023;142(suppl 1):abstract 209.

Isatuximab: a distinct CD38 mAb vs daratumumab

Differing relative contributions to mechanisms of action of daratumumab and isatuximab[1–3]





Distinct epitopes on human CD38 interact with daratumumab (red) and isatuximab (blue), potentially contributing to distinct mechanisms of action[3]

Isatuximab epitope includes catalytic domain of CD38 – isatuximab inhibits NAD+ substrate and thus the production of immune-suppressing adenosine[4]

Distinct characteristics[3,5-7]

Isatuximab saturates membrane CD38 and can be internalized – different membrane dynamics vs daratumumab	ADCC, ADCP, CDC with isatuximab triggered at threshold of surface CD38	Isatuximab inhibits CD38 enzymatic features	Isatuximab can directly induce cell death without crosslinking[7]	Isatuximab induces NK cell activation and NK cell-mediated cytotoxicity through CD38 and CD16 crosslinking[3]

Daratumumab and isatuximab potentially valuable as complementary / alternative therapies[5]

1. Bisht K, et al. Cancer Med 2023;doi:10.1002/cam4.6619. 2. van de Donk NWCJ, et al. Blood 2018;131(1):13–29. 3. Zhu C, et al. Front Immunol 2020;11:1771. 4. Martin TG, et al. Cells 2019;8(12):1522. 5. Malavasi F, Faini AC. Clin Cancer Res 2019;25(10):2946–8. 6. Moreno L, et al. Clin Cancer Res 2019;25(10):3176–87. 7. Martino EA, et al. Expert Opin Biol Ther 2023;23(4):315–8.

Isa-based quadruplet regimens for NDMM

IsKia: Isa-KRd vs KRd in transplant-eligible NDMM patients

IsKia study design (NCT04483739)

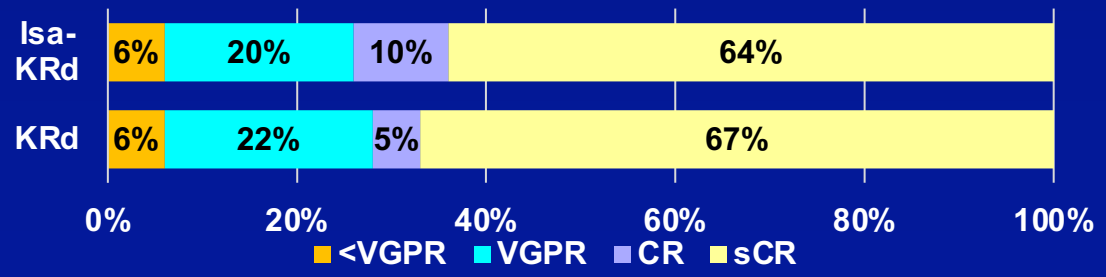
- Induction: 4 x Isa-KRd/KRd
  - MEL200+ASCT
- Consolidation: 4 x Isa-KRd/KRd → 12 x Isa-KRd/KRd light
- Maintenance: R
- Primary endpoint: MRD-neg rate post consolidation

302 NDMM patients randomized (1:1)

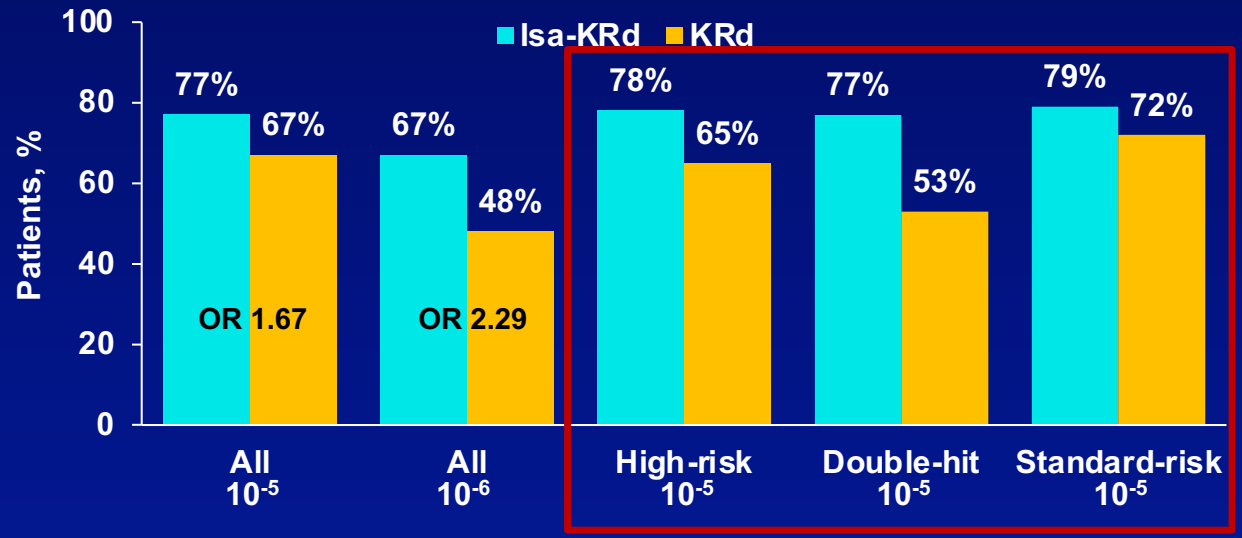
Isa-KRd vs KRd 151 vs 151

- Median age 61 vs 60 years
- 18% vs 19% high-risk cytogenetics [del17p, t(4;14), t(14;16)]
- 9% vs 11% ≥2 high-risk cytogenetic abnormalities (including gain/amp 1q) – 'double-hit'

Response rates post consolidation



MRD-neg rates post consolidation



Outcomes

- Median follow-up 20 months
- 1-year PFS 95% in both arms

Grade 3-4 AEs

- Neutropenia 36% vs 22%, thrombocytopenia 15% vs 17%
- Infections 15% vs 11%; vascular disorders 5% vs 10%

Additionally: phase 3 IMROZ trial (NCT03319667) of Isa-RVd vs RVd in transplant-ineligible NDMM has met primary endpoint of improved PFS[3]

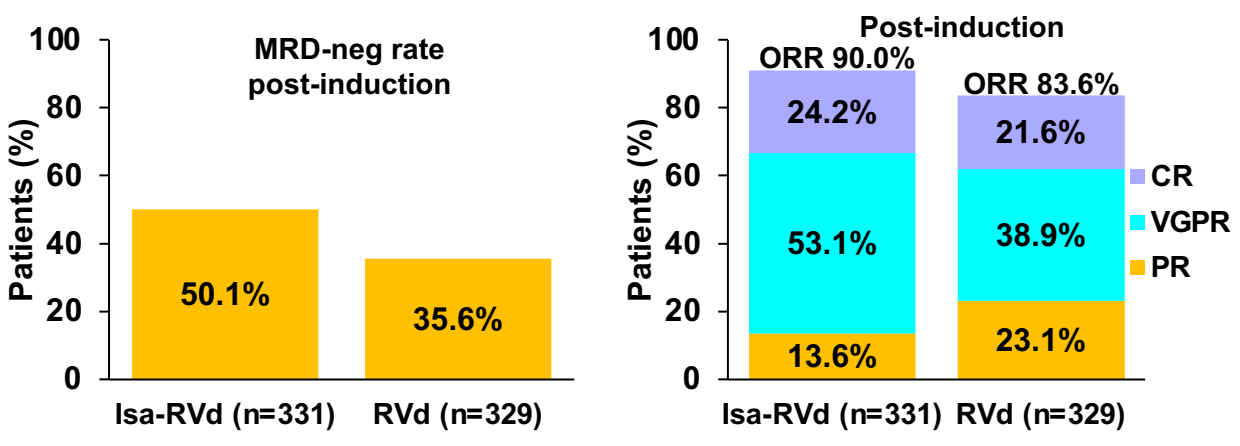
Gay F, et al. Blood 2023;142(suppl 1):abstract 4.

GMMG-HD7/SKylaRk: Isa-RVd/KRd in transplant-eligible NDMM patients

GMMG-HD7[1,2]

660 NDMM patients

- Median age 59 vs 60 years
- 24% vs 20% ISS III
- 18% vs 20% high-risk cytogenetics



Safety (induction)

- Grade 3/4 AEs 63% vs 61%
- Grade 3/4 neutropenia 23% vs 7%
- Grade 3/4 infections 12% vs 10%

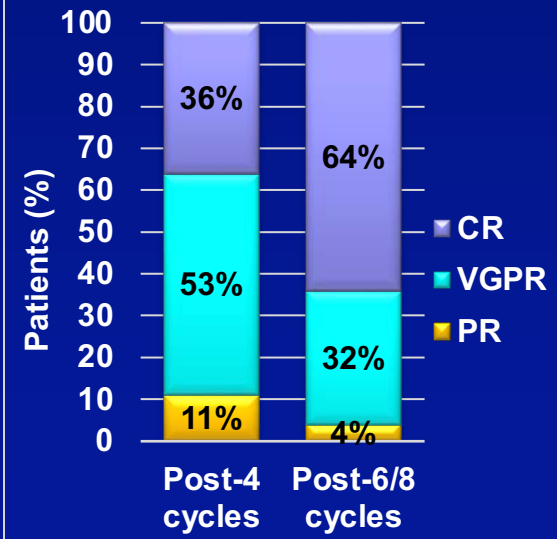
SKylaRk[3,4]

SKylarRk study design

- Induction: 4 x Isa-KRd
- Stem cell collection, ASCT or defer
- Consolidation: 2 x Isa-KRd (post-ASCT) or 4 x Isa-KRd (if ASCT deferred)
- Maintenance: R (standard-risk cytogenetics), Isa-KR (high-risk cytogenetics)

50 transplant-eligible NDMM patients

- Median age 59 years
- 46% high-risk cytogenetics
- 12% ISS III
- 4% R-ISS III



Post-4 cycles: MRD-neg (10^{-5}) 43% (n=12/28)

Post-6 cycles: MRD-neg (10^{-5}) 66% (n=27/41)

24-month PFS: 91.3%; 24-month OS: 95.8%

ASCT deferred in 89% (n=40/45)

Most common grade 3/4 AEs: neutropenia 24%, ALT elevated 10%, acute kidney injury 6%, thrombocytopenia 6%

1. Goldschmidt H, et al. Blood 2021;138(suppl 1):abstract 463. 2. Goldschmidt H, et al. Lancet Haematol 2022;9(11):E810–21.
3. O'Donnell EK, et al. Blood 2022;140(suppl 1):abstract 3239. 4. O'Donnell EK, et al. Blood 2023;142(suppl 1):abstract 4671.

Isa-based quadruplet regimens for NDMM

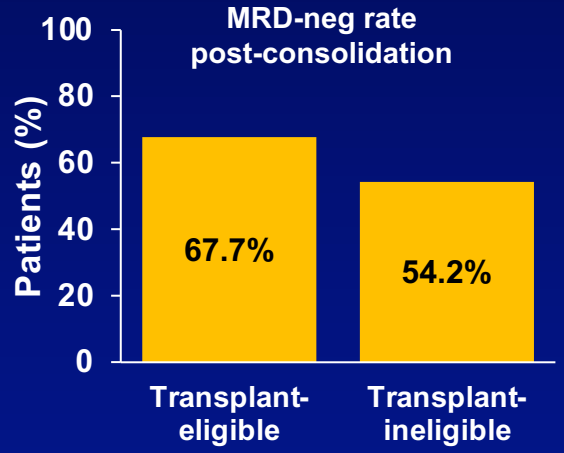
GMMG-CONCEPT: Isa-KRd in high-risk NDMM

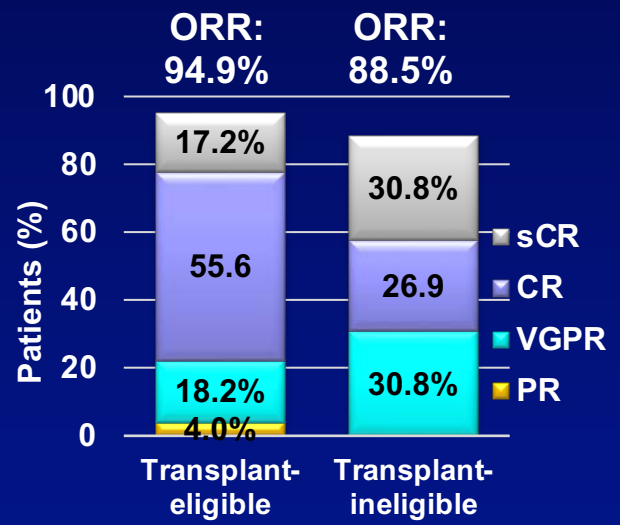
GMMG-CONCEPT study design

- Induction: 6 x Isa-KRd
  - Transplant-eligible: ASCT
  - Transplant-ineligible: 2 x Isa-KRd
- Consolidation: 4 x Isa-KRd
- Maintenance: 26 x Isa-KR

125 NDMM patients: 99 transplant-eligible, 26 transplant-ineligible

- Median age (transplant-eligible/ineligible) 58/74 years
- 100% high-risk cytogenetics
  - 44%/42% del(17p)
  - 42%/23% t(4;14)
  - 17%/8% t(14;16)
  - 31%/54% >3 copies 1q21
  - 31%/27% >1 abnormality





Among transplant-eligible/-ineligible patients:			
82%/69% MRD-neg at any point	Sustained (≥1 year) MRD-neg in 63%/46%	3-year PFS 68.9%/58.4%	2-year OS 83.9%/71.0%

Grade ≥3 AEs (transplant eligible/ineligible): 78.4% / 72.0%

Common grade ≥3 AEs

- Neutropenia 39.2% / 28.0%
- Thrombocytopenia 26.8% / 16.0%
- Anemia 14.4% / 12.0%
- Infections 27.8% / 28.0%

Leypoldt LB, et al. J Clin Oncol 2024;42(1):26–37.

Isa-based standard-of-care triplet regimens for RRMM

Isa-Pom-dex (ICARIA-MM)[1–3]

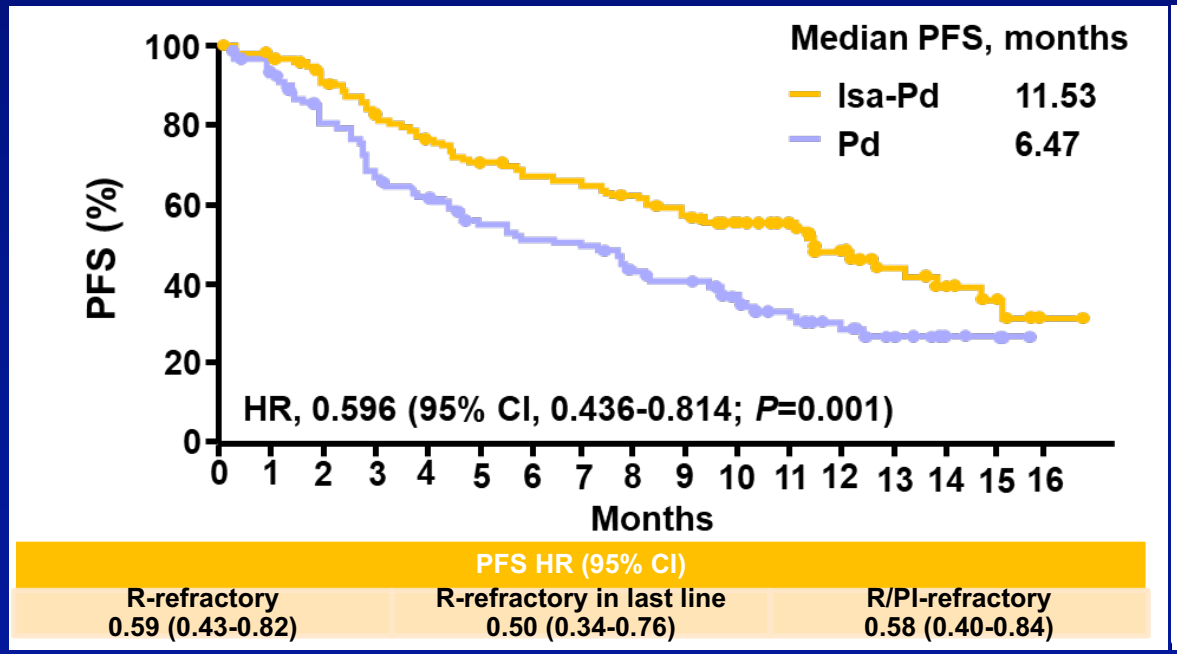
Isa-Pom-dex group

- 3 prior lines of treatment
- 94% lenalidomide-refractory (60% in last line)
- 77% PI-refractory
- 72% double-refractory

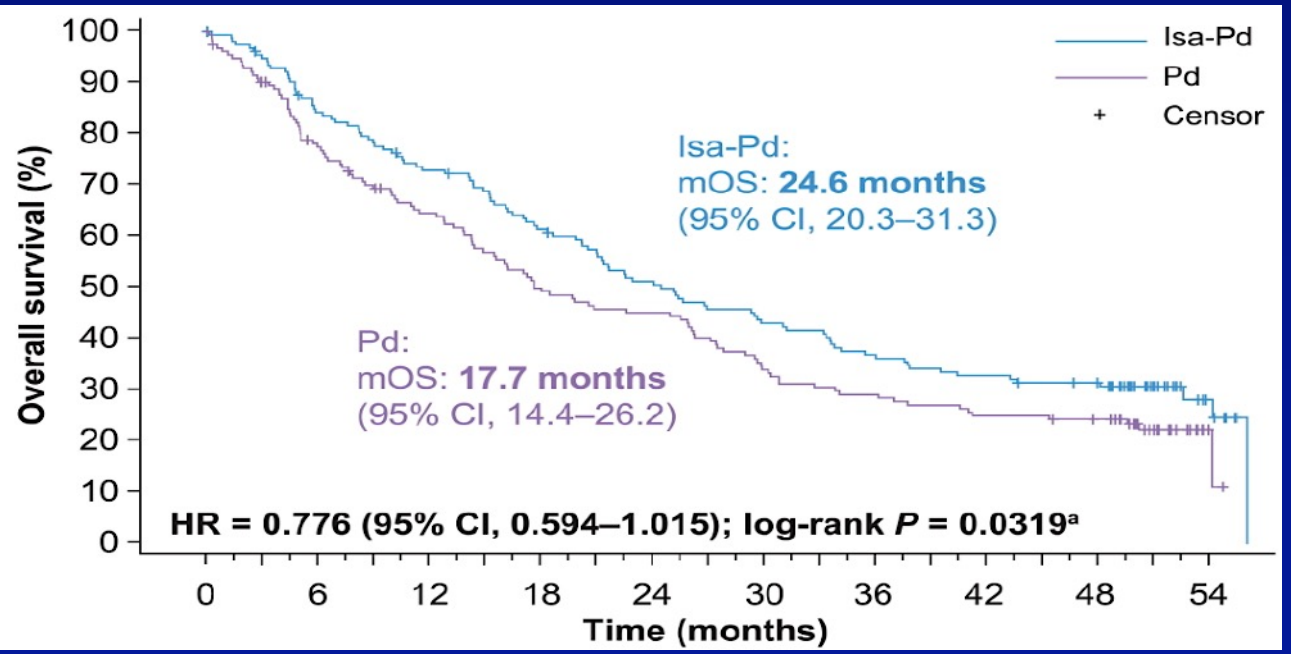
Response	Pd	Isa-Pd
ORR, %	35	60
sCR	<1	0
CR	1	5
VGPR	7	27
PR	27	29
Median DOR, months	11.1	13.3
Median follow-up	11.6 mos	

Safety

- Grade ≥3 neutropenia in 50% vs 35%
- SAEs in 73% vs 60%



PFS HR (95% CI)		
R-refractory	R-refractory in last line	R/PI-refractory
0.59 (0.43-0.82)	0.50 (0.34-0.76)	0.58 (0.40-0.84)

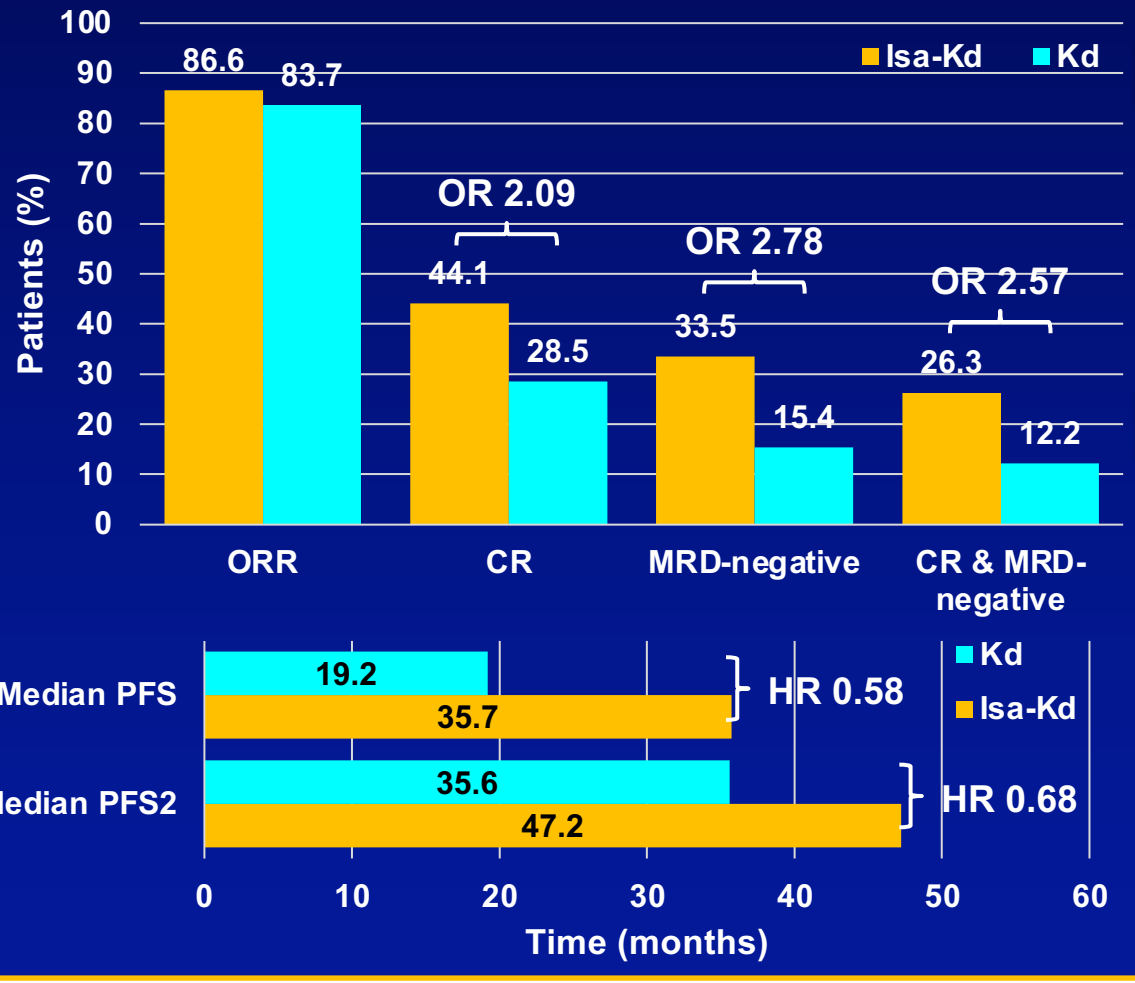


1. Attal M, et al. Lancet 2019;394(10214):2096–107. 2. Richardson PG, et al. Lancet Oncol 2022;23(3):416–27.
3. Richardson PG, et al. Haematologica 2024;doi:10.3324/haematol.2023.284325.

DOR, duration of response; OS, overall survival.

Isa-based standard-of-care triplet regimens for RRMM

Isa-Kd (IKEMA): updated analysis and subgroup analyses



Updated analysis of IKEMA[1]

- Median follow-up 44 months
- Median time to next treatment 44.9 vs 25.0 months (HR 0.55)
- OS HR 0.78
- Grade ≥3 AEs 84% vs 73%; Serious AEs 70% vs 60%
- AEs leading to discontinuation: 12% vs 18%
- Non-hematologic grade ≥3 AEs: hypertension 23% vs 23%, pneumonia 19% vs 12%

Subgroup analyses of IKEMA

- PFS benefit with Isa-Kd vs Kd in both MRD-negative (HR 0.58) and MRD-positive (HR 0.67) patients[2]
- PFS benefit (HR 0.27) and higher rate of complete renal responses (52% vs 31%) with Isa-Kd vs Kd in patients with renal impairment[3]
- Improved PFS (HR 0.36) and rates of CR (38.5% vs 23.5%) and MRD-negative response (23% vs 12%) with Isa-Kd vs Kd in elderly (≥70 years) patients[4]
- PFS benefit seen regardless of:
  - Number of prior lines (1: median PFS 38.2 vs 28.2 months, HR 0.72; >1: median PFS 29.2 vs 17.0 months, HR 0.45)[5]
  - Being refractory (HR 0.60), lenalidomide-refractory (HR 0.69), or bortezomib-refractory (HR 0.38),[6] or having early or later relapse[7]
  - Presence of 1q21 abnormalities (with PFS shorter in both arms)[8]
  - East Asian ethnicity[9]

Matching adjusted indirect comparison analysis, IKEMA vs Dara-Rd (POLLUX), suggested significant PFS benefit and trend for OS benefit with Isa-Kd[10]

1. Martin T, et al. Blood Cancer J 2023;13(1):72. 2. Martin T, et al. Blood Adv 2022;6(15):4506–15. 3. Capra M, et al. Haematologica 2022;107(6):1397–409. 4. Facon T, et al. Hematol Oncol 2022;40(5):1020–9. 5. Capra M, et al. Blood 2022;140(suppl 1):abstract 3176. 6. Dimopoulos MA, et al. Am J Hematol 2023;98(1):E15–19. 7. Facon T, et al. Haematologica 2024;109(2):604–16. 8. Facon T, et al. J Clin Oncol 2023;41(16_suppl):abstract 8029. 9. Kawano Y, et al. Clin Lymphoma Myeloma Leuk 2023;23(10):e360–7. 10. Richter J, et al. Blood 2023;142(suppl 1):abstract 6734.

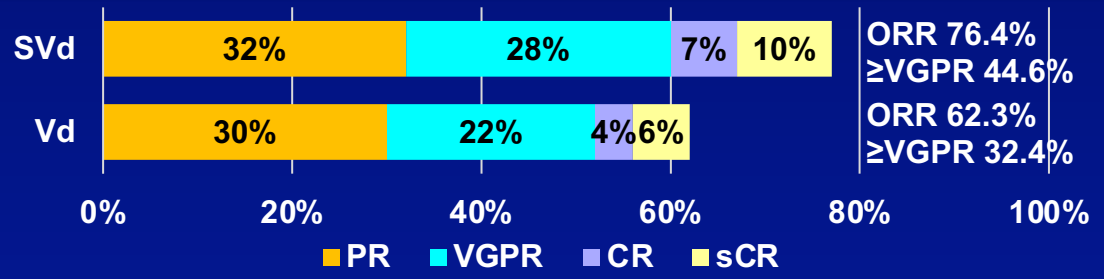
Selinexor – XPO1 inhibitor – plus PI regimens for RRMM

BOSTON trial: Selinexor-Vd vs Vd in patients with RRMM

Phase 3 trial (N=402)

- 195 SVd vs 207 Vd, median of 2 prior therapies (range 1–3)
- Median age 66 vs 67 years
- 11% vs 8% del(17p); 41% vs 34% 1q21 amp
- 69% vs 70% prior bortezomib; 39% vs 30% prior ASCT

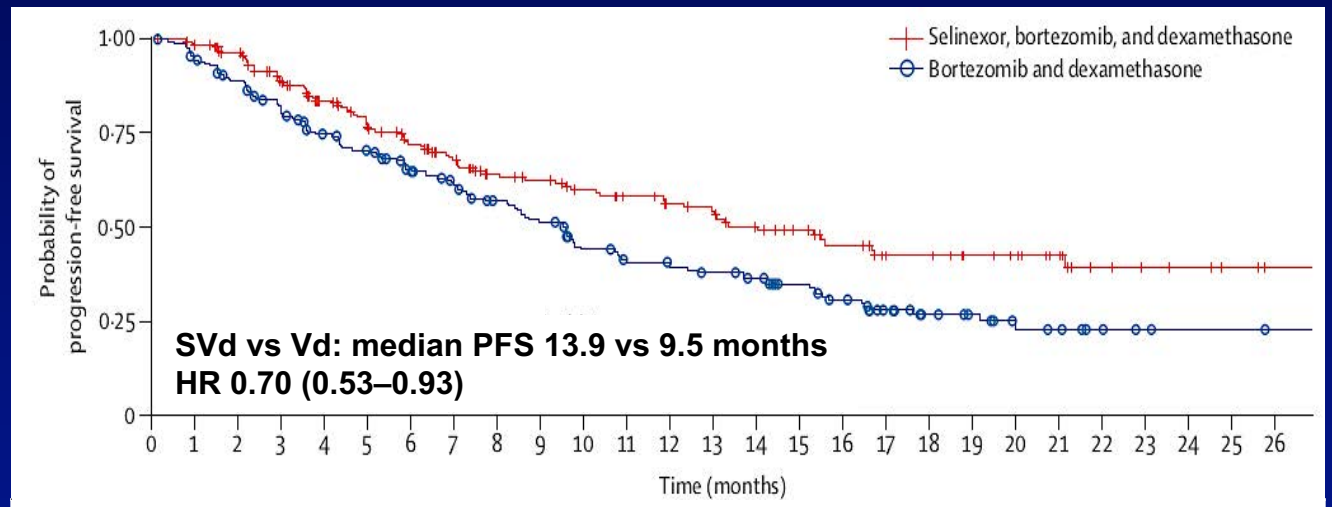
Efficacy



- Median DOR 20.3 vs 12.9 months

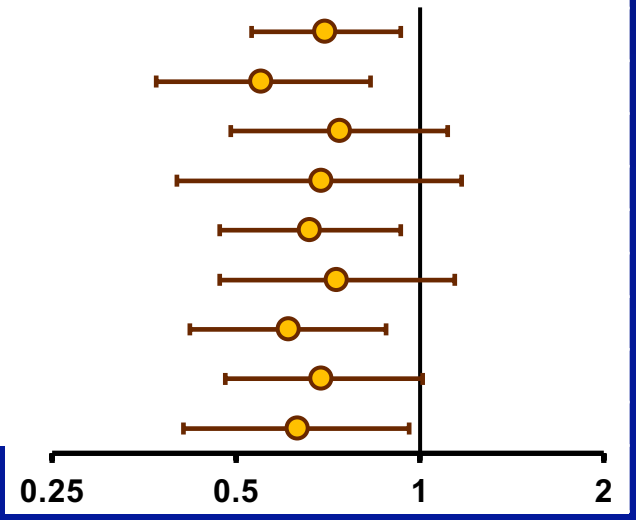
Safety

- Higher rates of grade 3-4 thrombocytopenia (39% vs 17%), anemia (16% vs 10%), neutropenia (9% vs 3%), fatigue (13% vs 1%), and cataracts (9% vs 1%) with SVd vs Vd
- Significantly lower rate of PN (32% vs 47%) and grade ≥2 PN (21% vs 34%)
- Grade ≥3 PN: 4.6% vs 8.8%



Median PFS, mos

Subgroup	SVd	Vd	HR
All[1]	13.9	9.5	0.70
Age ≥65 years[2]	21.0	9.5	0.55
Age <65 years[2]	12.2	9.4	0.74
Frail[2]	13.9	9.5	0.69
Non-frail[2]	13.2	9.4	0.66
High-risk[3]	12.9	8.6	0.73
Standard-risk[3]	16.6	9.5	0.61
≥2 prior lines[4]	11.8	9.4	0.69
1 prior line[4]	16.6	10.7	0.63



1. Grosicki S, et al. Lancet 2020;396:1563–73. 2. Auner HW, et al. Am J Hematol 2021;96(6):708–18.
3. Richard S, et al. Am J Hematol 2021;96(9):1120–30. 4. Mateos MV, et al. J Hematol Oncol 2021;14(1):59.

PN, peripheral neuropathy, SVd, Selinexor, bortezomib, dexamethasone.

Selinexor + Pomalidomide + Dexamethasone (XPd)

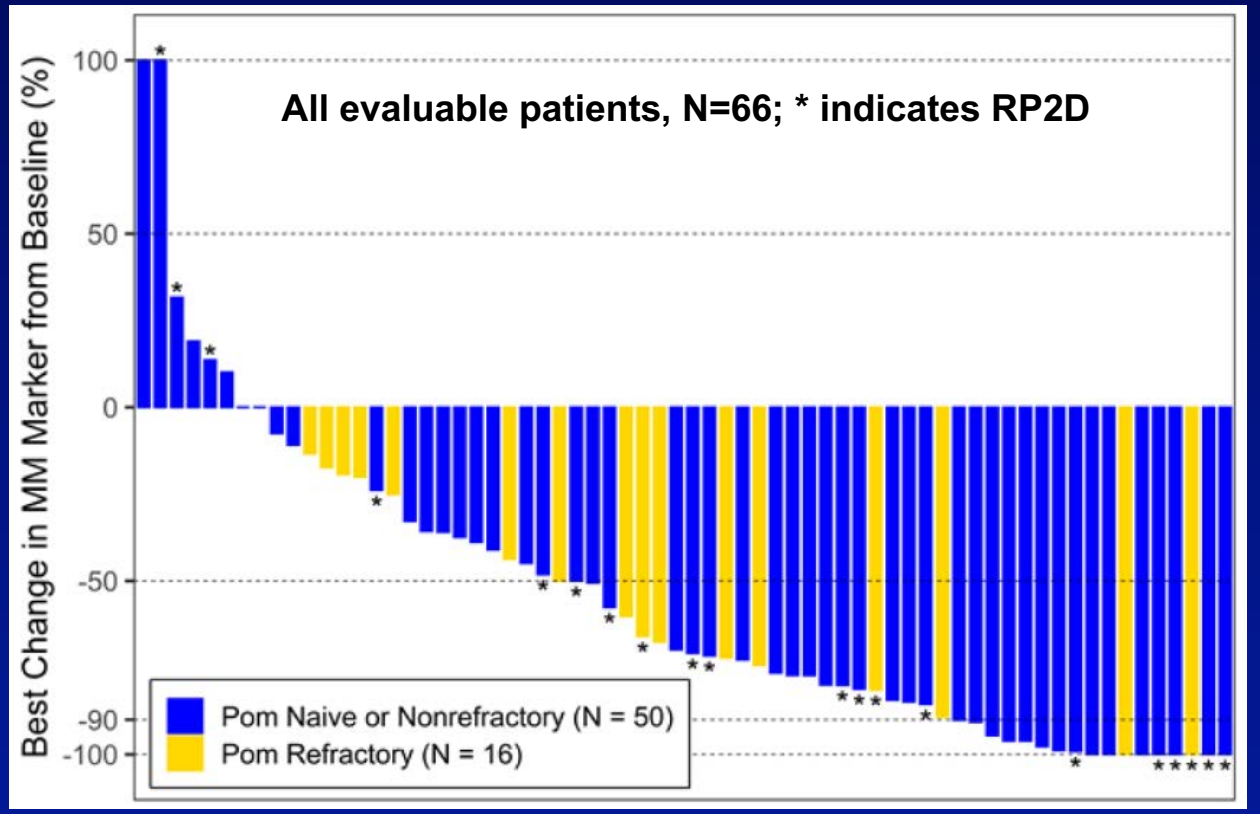
STOMP: Selinexor and Backbone Treatments Of Multiple Myeloma Patients

Phase 1b/2 trial (N=72 / n=20 at RP2D)

- Median age 64.0 / 65.5 years
- ISS Stage III 13.9% / 15.0%
- Median prior regimens (range) 4 (1–12) / 3.5 (1–12)
- Lenalidomide-refractory 80.6% / 80.0%
- Pomalidomide-refractory 26.4% / 15.0%
- Bortezomib-refractory 50.0% / 45.0%
- Carfilzomib-refractory 37.5% / 50.0%
- CD38 mAb-refractory 27.8% / 25.0%
- Prior ASCT 80.6% / 70.0%

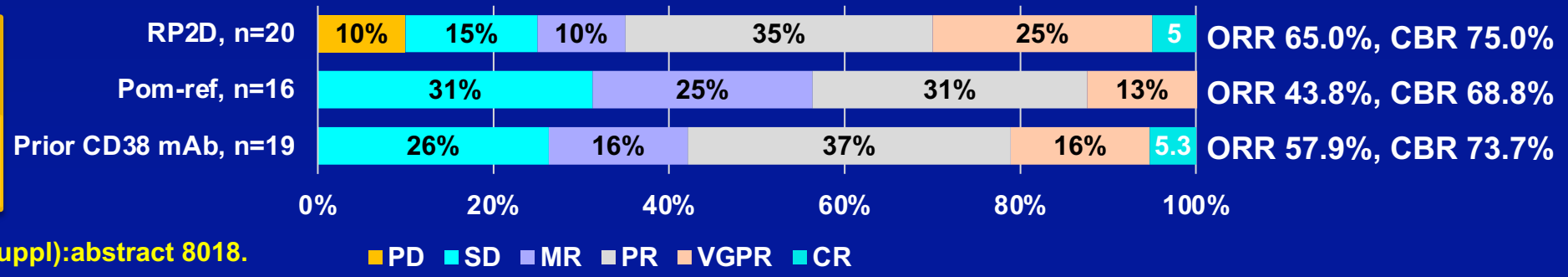
Safety (N=72 / n=20 at RP2D)

- Grade 3/4 neutropenia 52.8% / 60.0%, anemia 29.2% / 25.0%, thrombocytopenia 27.8% / 25.0%
- Any-grade nausea 61.1% / 70.0%, decreased appetite 41.7% / 30.0%, diarrhea 29.2% / 25.0%, vomiting 22.2% / 20.0%



Best response in evaluable patients

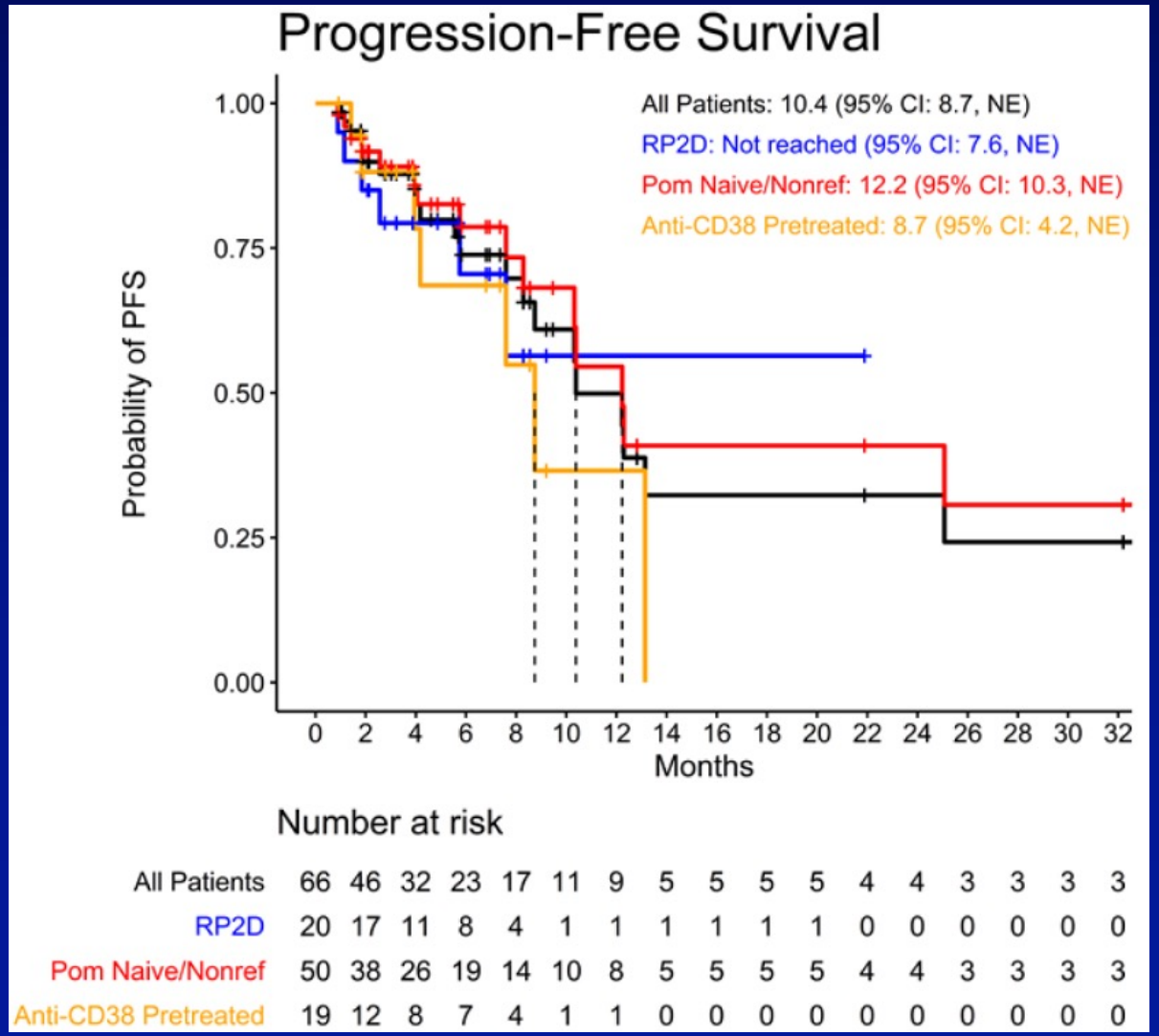
RP2D = Selinexor 60 mg QW, pomalidomide 4 mg	Pom-ref = pomalidomide-refractory patients

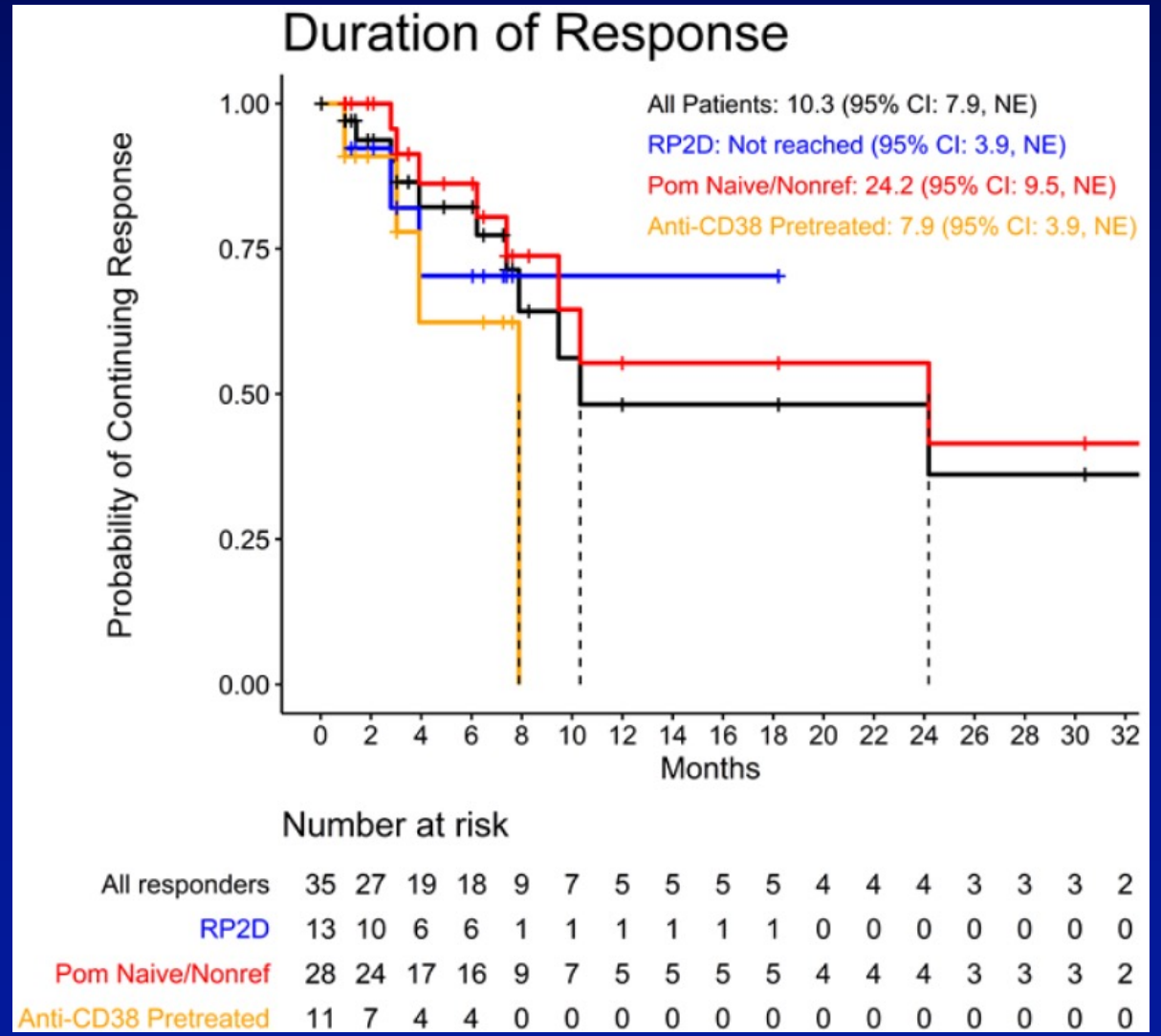


White DJ, et al. J Clin Oncol 2021;13(15_suppl):abstract 8018.

Selinexor + Pomalidomide + Dexamethasone (XPd)

STOMP: Selinexor and Backbone Treatments Of Multiple Myeloma Patients





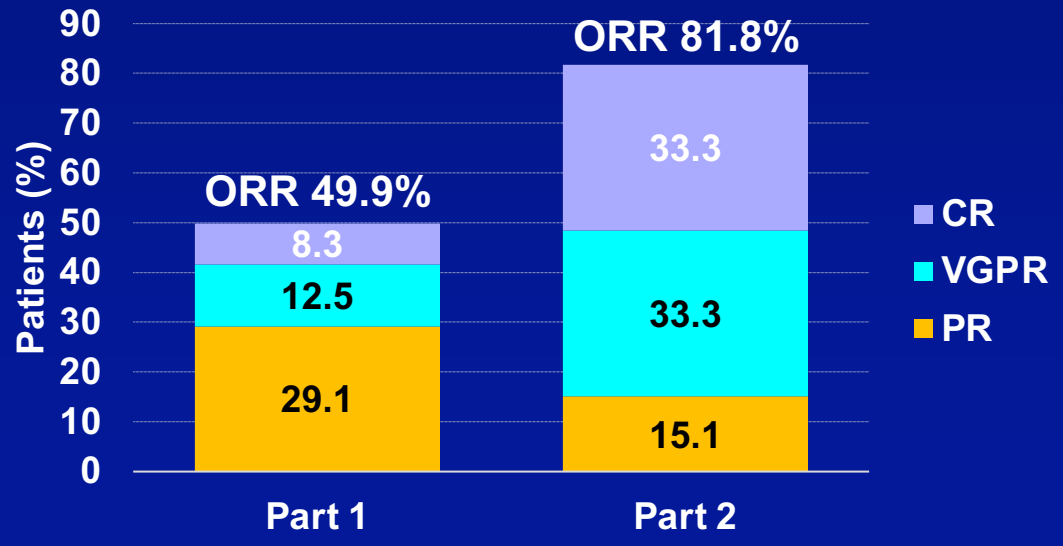
White DJ, et al. J Clin Oncol 2021;13(15_suppl):abstract 8018.

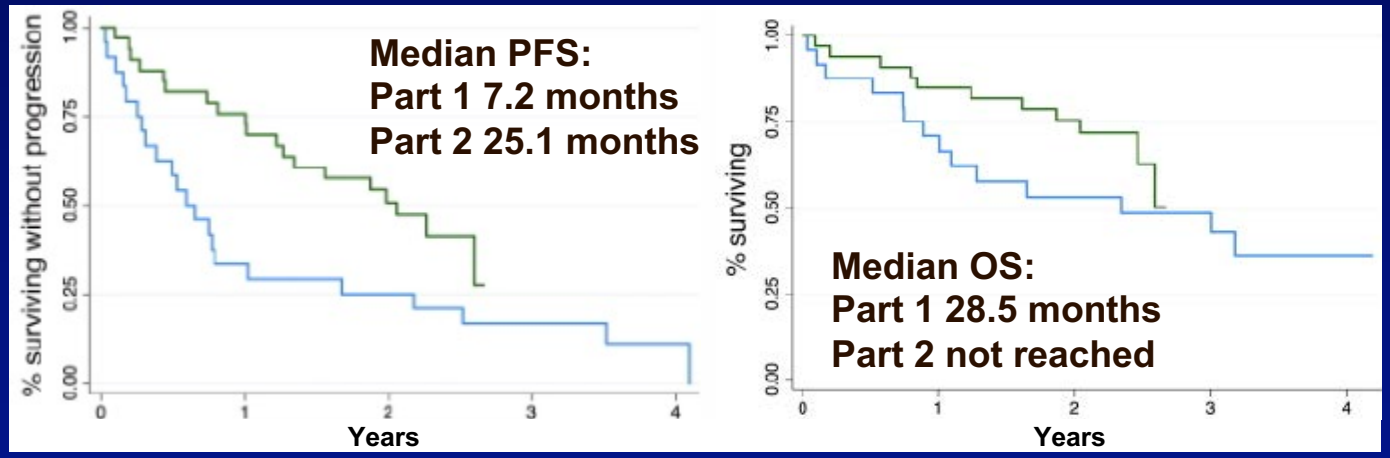
Selinexor – XPO1 inhibitor – plus PI regimens for RRMM

GEM-SELIBORDARA: quadruplet therapy for RRMM

Phase 2 study: selinexor + Dara-Vd in patients with RRMM

Part 1	Part 2
• 24 patients	• 33 patients
• Median age 66 years	• Median age 69 years
• Median 3 prior lines	• Median 1 prior line
• R-ISS III 16%	• R-ISS III 16%
• High-risk cytogenetics 26%	• High-risk cytogenetics 19%
• R-refractory 96%	• R-refractory 46%
• PI-refractory 71%	• PI-refractory 15%
• R/PI-refractory 71%	• R/PI-refractory 12%





Common TRAEs, %	All grade	Grade ≥3
Any hematologic TRAE	82	60
Thrombocytopenia	70	46
Neutropenia	39	30
Anemia	30	12
Non-hematologic TRAEs		
Infection	74	32
Fatigue/asthenia	44	14
Diarrhea	39	4
Nausea or vomiting	35	9

González-Calle V, et al. Haematologica 2024;doi:10.3324/haematol.2023.284089

Venetoclax – BCL-2 inhibitor – combinations for RRMM

Venetoclax + Dex (CANOVA) / Vd (BELLINI) / Kd / Dara-dex

Potent selective inhibitor of BCL-2

Oncogene *BCL-2* located on chromosome 11

t(11;14) (in ~20% of MM patients) activates BCL-2 overexpression; also more common in PCL

BELLINI: Venetoclax + Vd (n=194) vs placebo-Vd (n=97)[1]

- 1–3 prior therapies
- Median PFS 22.4 vs 11.5 months (HR 0.63)
- Specific activity in t(11;14) RRMM patients
- Median PFS not reached vs 9.5 months (HR 0.11) in t(11;14) patients
- Median PFS not reached vs 9.9 months (HR 0.21) in patients with t(11;14) and/or high BCL2 expression
- But higher mortality overall with venetoclax+Vd (6% vs 1% grade 5 AEs)

Phase 2 study: Venetoclax + Kd (n=49)[2]

- 1–3 prior therapies
- ORR 80% (92% in t(11;14) patients)
- ≥CR 41% (54% in t(11;14) patients)
- Median DOR 19.7 months
- Median PFS 22.8 months (24.8 months in t(11;14) patients)
- Grade ≥3 AEs 92%; SAEs 53%

Venetoclax + Dara-dex vs Dara-Vd (n=81)[3]

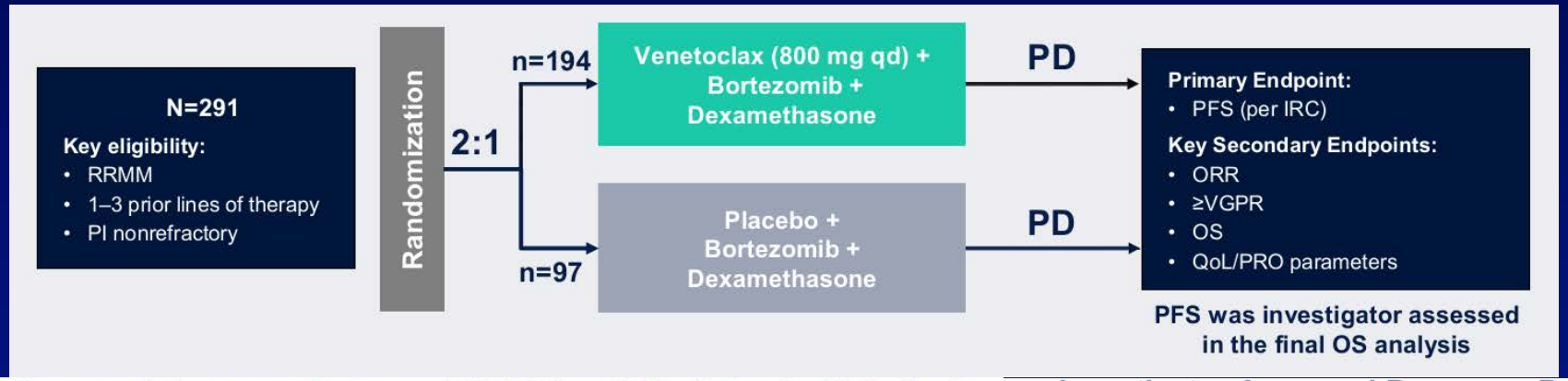
- ≥1 prior therapy
- t(11;14)-positive RRMM
- 3 arms: venetoclax 400 mg + Dara-dex, venetoclax 800 mg + Dara-dex, Dara-Vd
- 55 received Ven-Dara-dex, 26 received Dara-Vd
- ORR 96% vs 65%
- ≥VGPR 93% vs 39%
- ≥CR 67% vs 19%
- Median PFS not reached vs 15.5 months after median follow-up of 28.2 vs 16.9 months

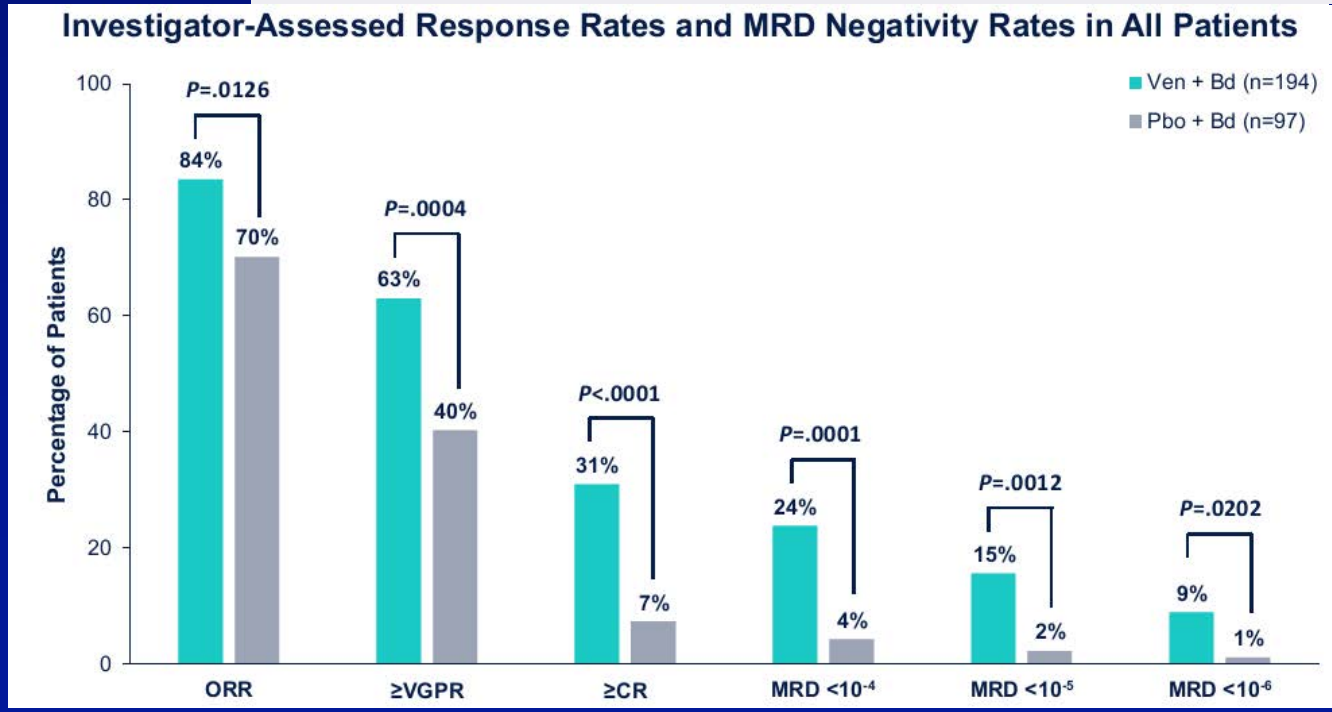
CANOVA phase 3 trial: Venetoclax + dex vs Pom-dex in t(11;14)-positive RRMM[4]

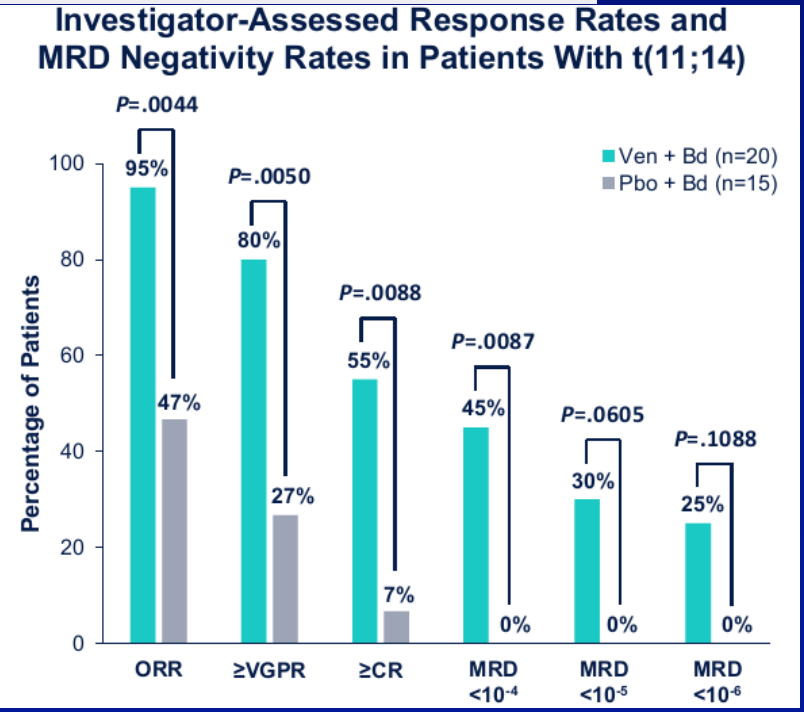
- 133 vs 130 patients with ≥2 prior therapies
- Median PFS 9.9 vs 5.8 months (HR 0.823) – primary endpoint not met
- Post-hoc sensitivity analysis of PFS (with starting a new MM therapy counted as an event): median PFS 9.4 vs 4.0 months (HR 0.651, p=0.003)
- Median TTNT 21.2 vs 8.3 months (HR 0.546)
- ORR 62% vs 35%; ≥VGPR 39% vs 14%
- Median OS 32.4 vs 24.5 months (HR 0.697)
- Grade 3/4 AEs 67% vs 83%
- AEs leading to discontinuation 15% vs 16%
- 7 vs 0 infections leading to death

1. Kumar SK, et al. Lancet Oncol 2020;21(12):1630–42. 2. Costa LJ, et al. Blood Adv 2021;5(19):3748–59. 3. Bahlis NJ, et al. Blood 2023;142(suppl 1):abstract 338.
4. Mateos MV, et al. IMS 2023; abstract OA-52. Figure adapted from Sgherza N, et al. Front Oncol 2021;11:716751.

BELLINI: Venetoclax + Vd (n=194) vs placebo-Vd (n=97)[1,2]

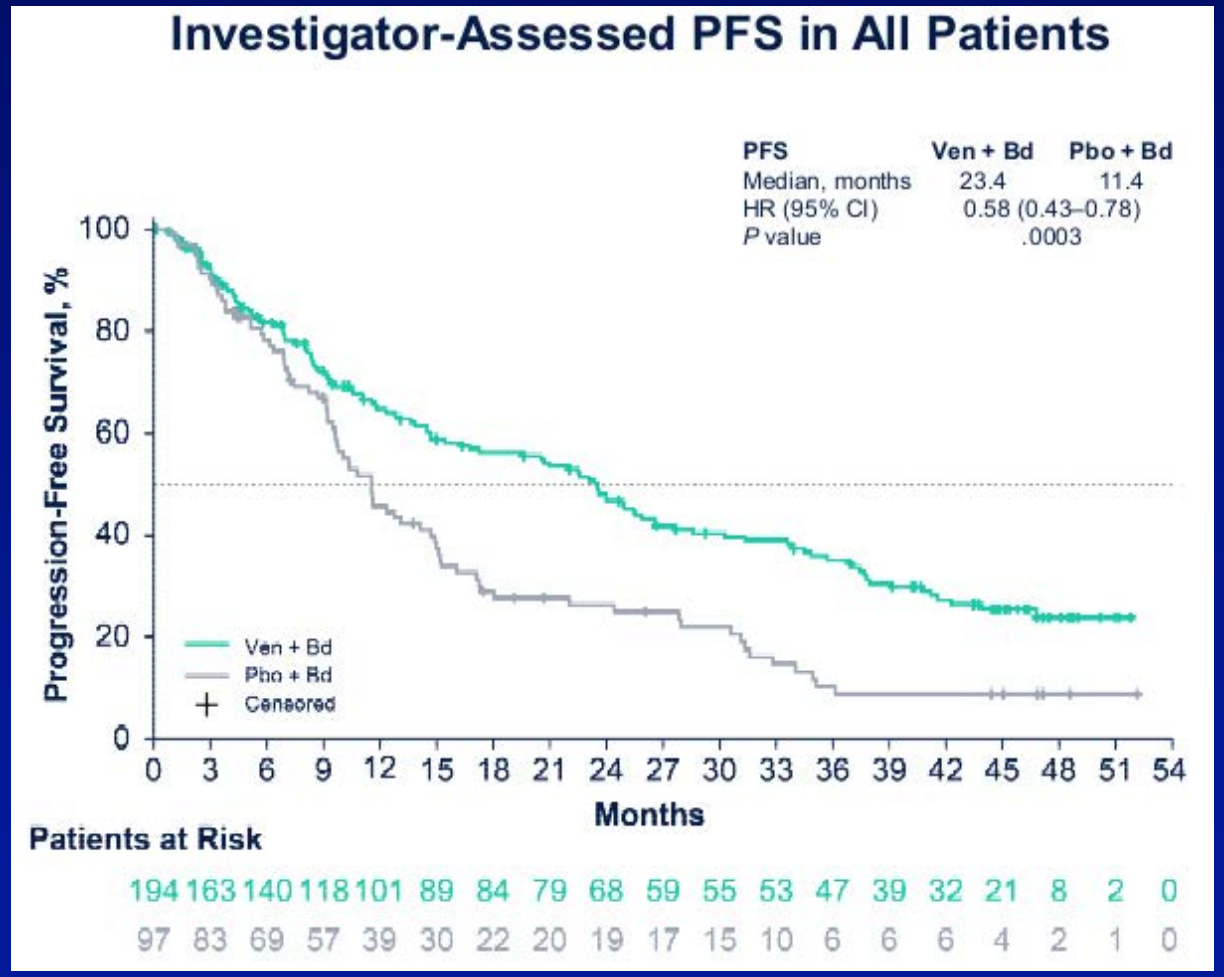


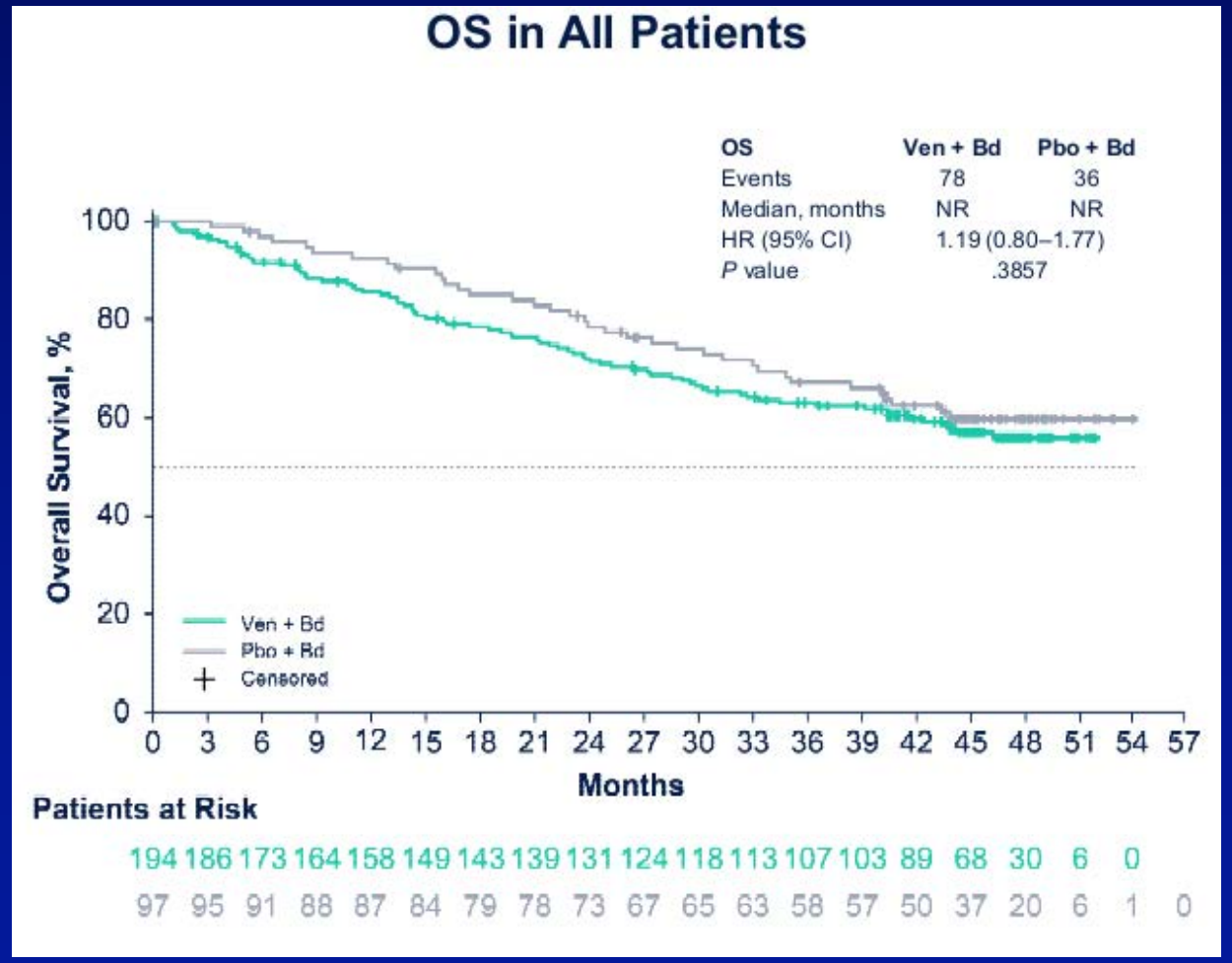




1. Kumar SK, et al. Lancet Oncol 2020;21(12):1630–42.
2. Kumar S, et al. Blood 2021;138(Supplement 1):abstract 84.

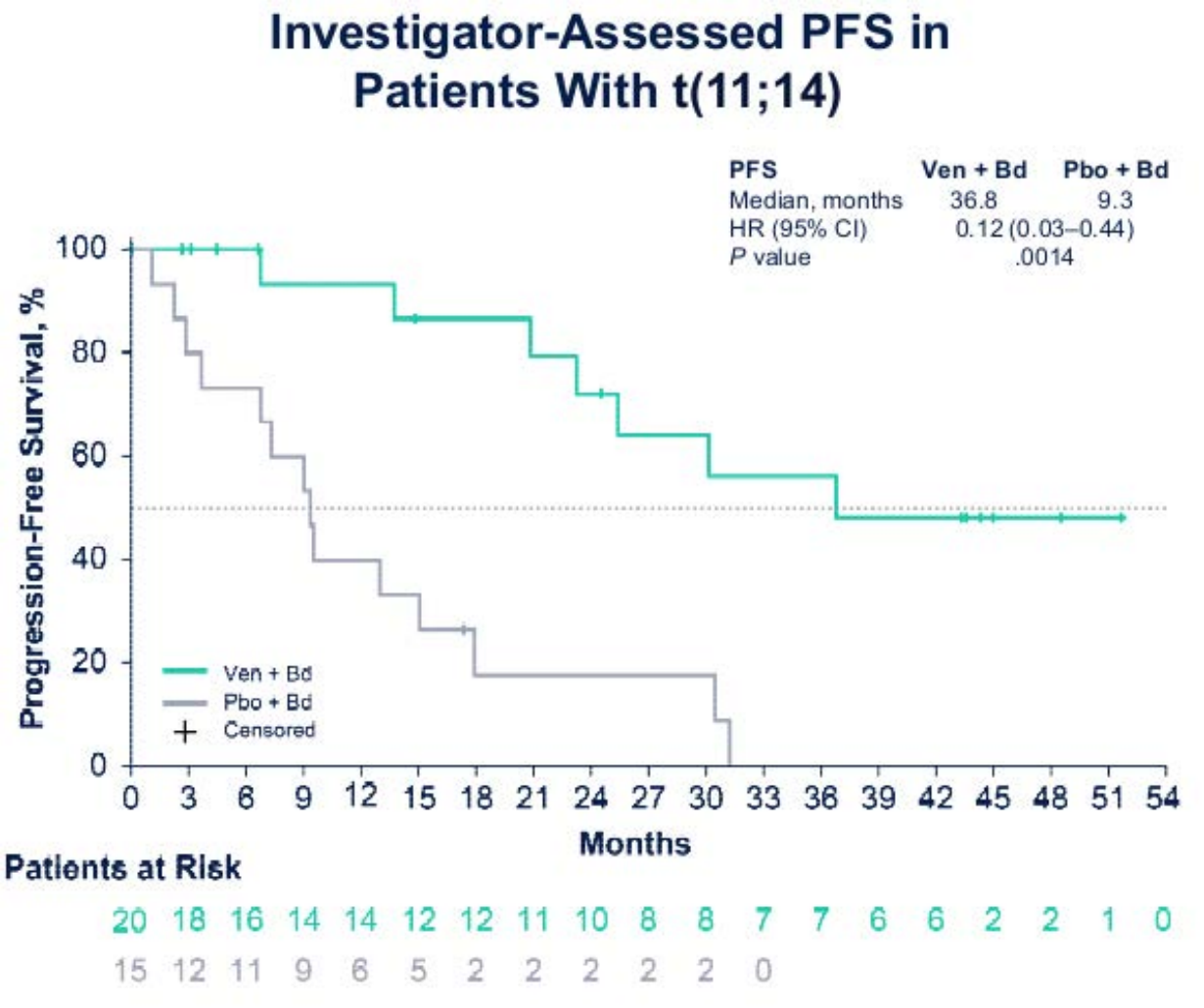
BELLINI: Venetoclax + Vd vs placebo-Vd (n=97) Final PFS and OS analysis[1]

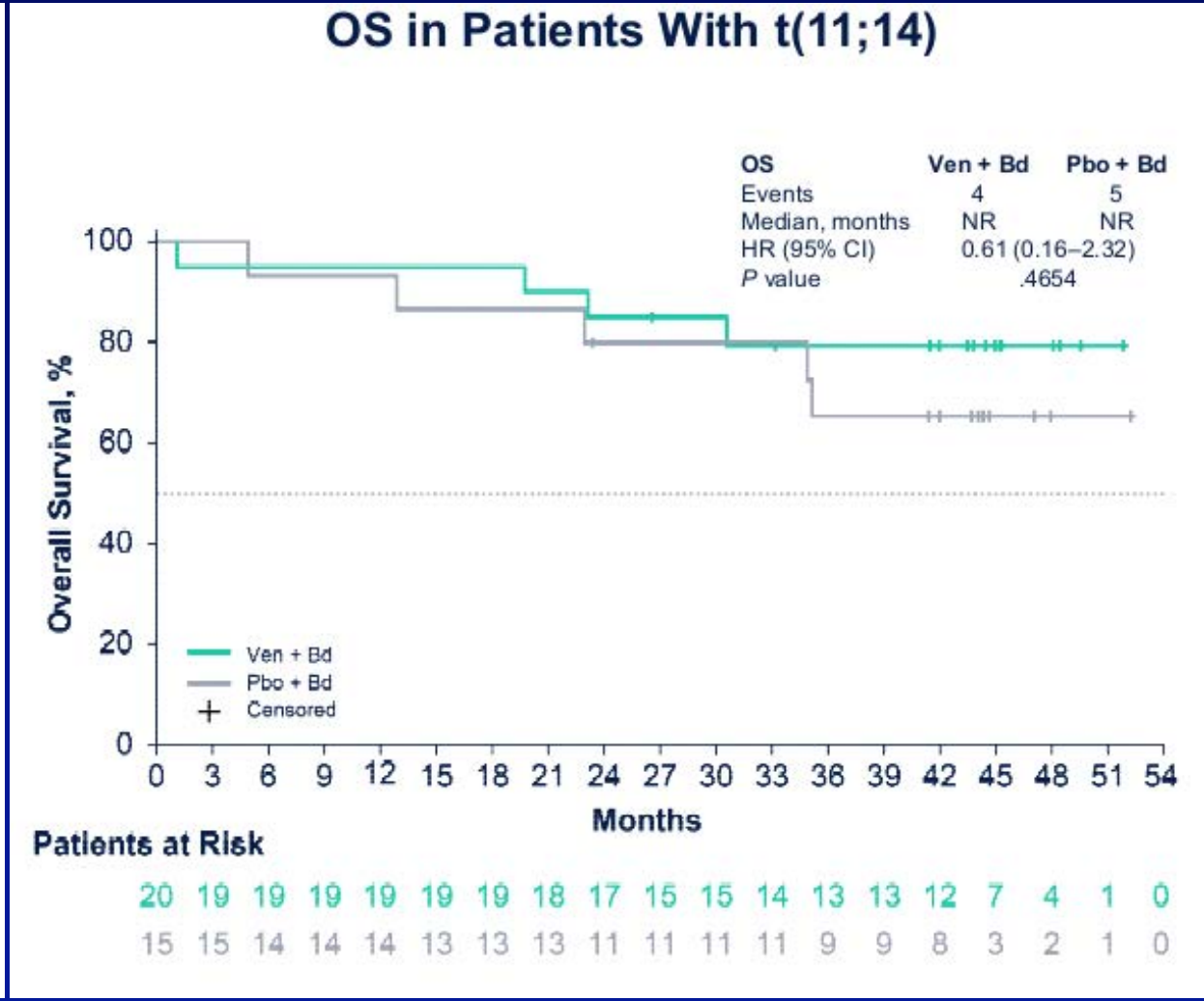




1. Kumar S, et al. Blood 2021;138(Supplement 1):abstract 84.

BELLINI: Venetoclax + Vd vs placebo-Vd (n=97) Final PFS and OS analysis in patients with t(11;14)[1]

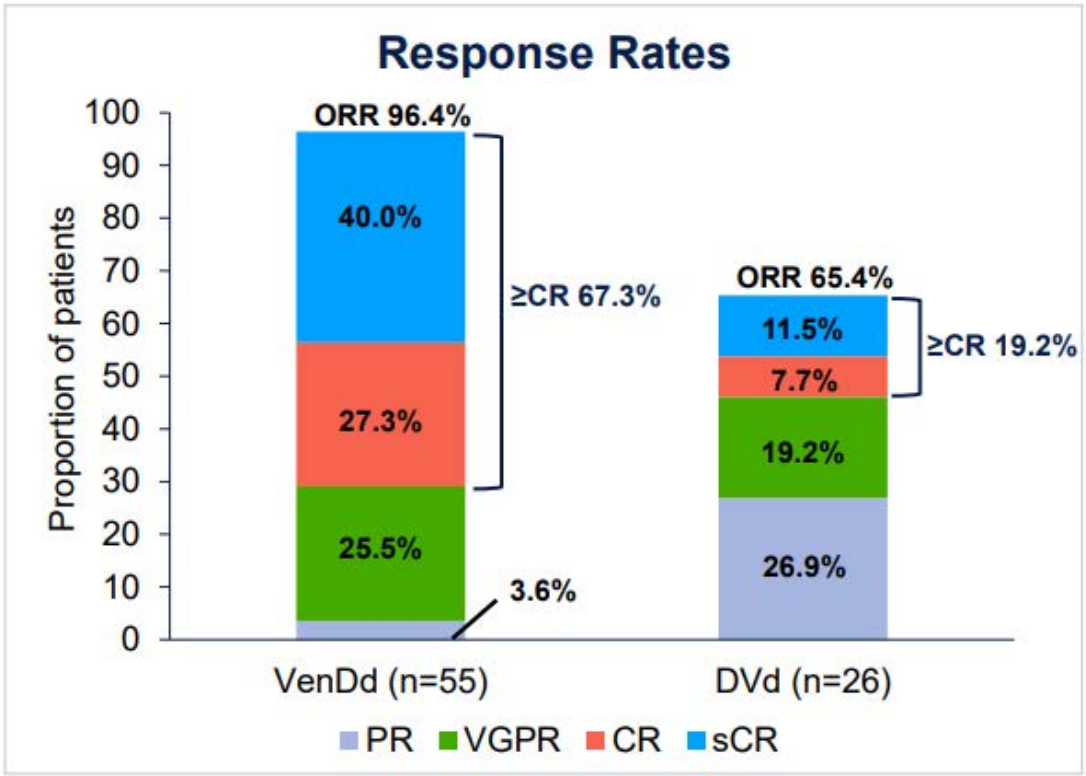


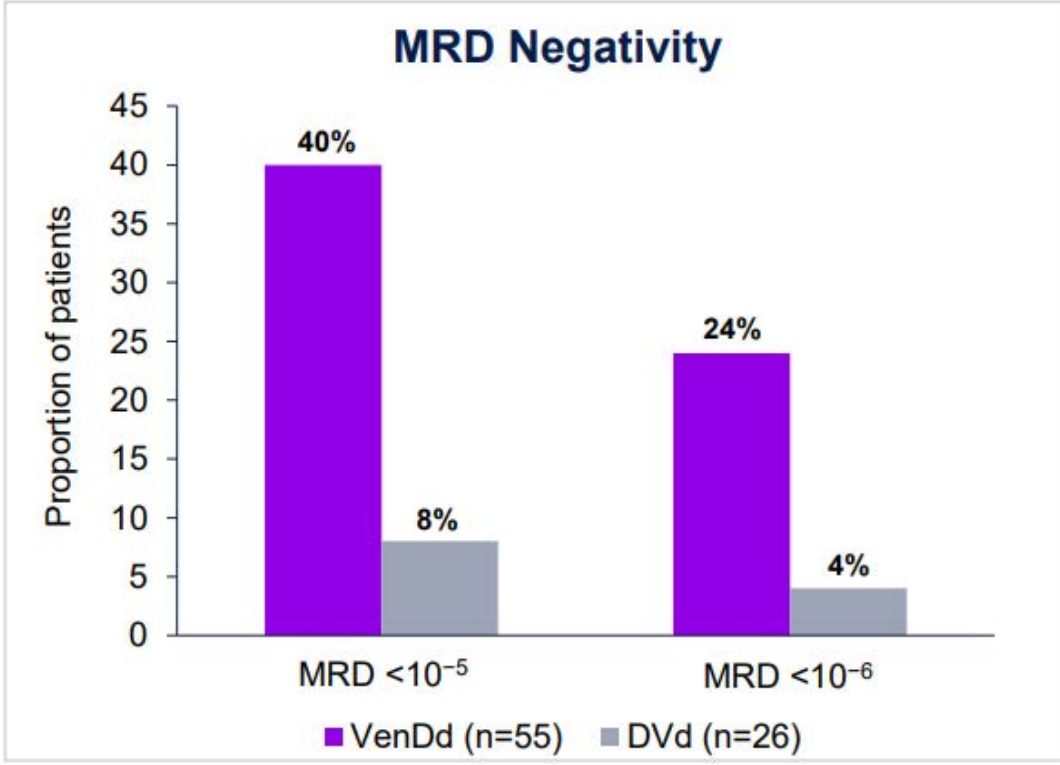


1. Kumar S, et al. Blood 2021;138(Supplement 1):abstract 84.

Venetoclax + Dara-dex vs Dara-Vd in patients with t(11;14) RRMM

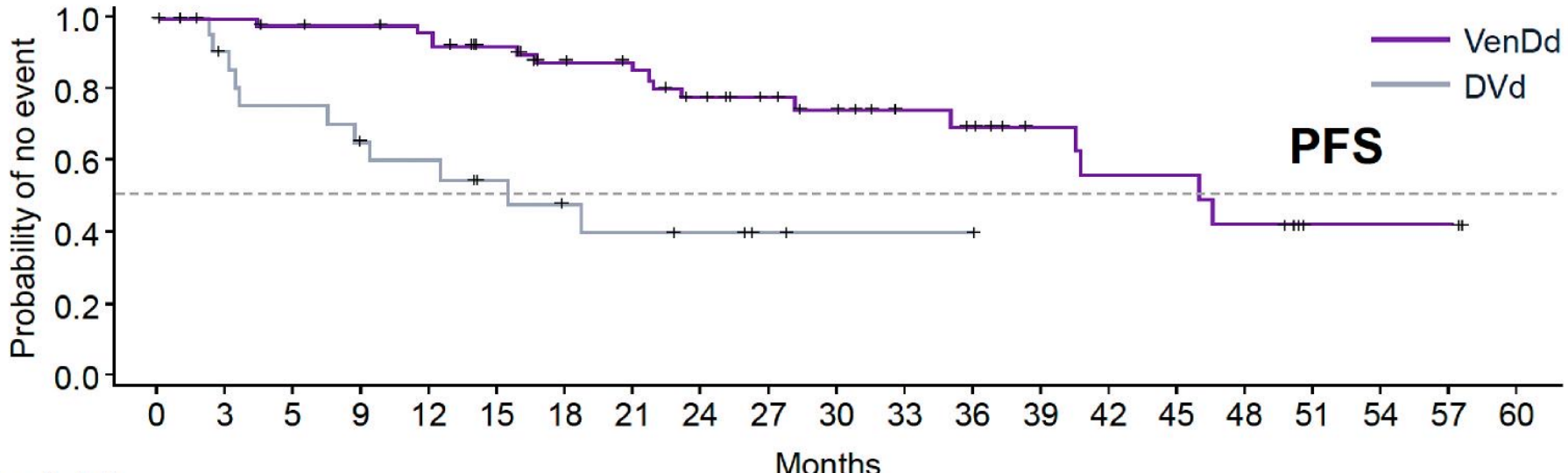
Patients (≥1 prior therapy)	Efficacy	Safety
•3 arms: venetoclax 400 mg + Dara-dex, venetoclax 800 mg + Dara-dex, Dara-Vd •55 received Ven-Dara-dex, 26 received Dara-Vd	•ORR 96% vs 65%, ≥VGPR 93% vs 39%, ≥CR 67% vs 19% •Median PFS NR vs 15.5 months (median follow-up 28.2 vs 16.9 months)	•No new safety signals observed





Bahlis NJ, et al. Blood 2023;142(suppl 1):abstract 338.

Venetoclax + Dara-dex vs Dara-Vd in patients with t(11;14) RRMM



Patients at risk

VenDd	55	54	52	51	48	43	36	34	28	24	21	17	14	10	8	8	6	2	2	2	0
DVd	26	18	15	12	11	8	6	5	4	2	1	1	1	0	0	0	0	0	0	0	0

Survival estimate (%) (95% CI)

	Events	Month 12	Month 18	Month 24	Month 33	Median (Months) [95% CI]
VenDd (N=55)	16	94.2 (83.1, 98.1)	87.9 (74.4, 94.4)	77.7 (62.1, 87.4)	74.3 (57.8, 85.1)	46.1 (40.6, NE)
DVd (N=26)	11	59.9 (35.5, 77.6)	47.6 (24.1, 68.0)	39.7 (17.0, 61.8)	39.7 (17.0, 61.8)	15.5 (7.5, NE)

Bahlis NJ, et al. Blood 2023;142(suppl 1):abstract 338.

Activity and safety of CELMoDs in heavily pretreated patients with RRMM

Iberdomide + dex, Dara-dex, Vd, or Kd

CC-220-MM-001: Iberdomide-dex expansion cohorts[1–3]

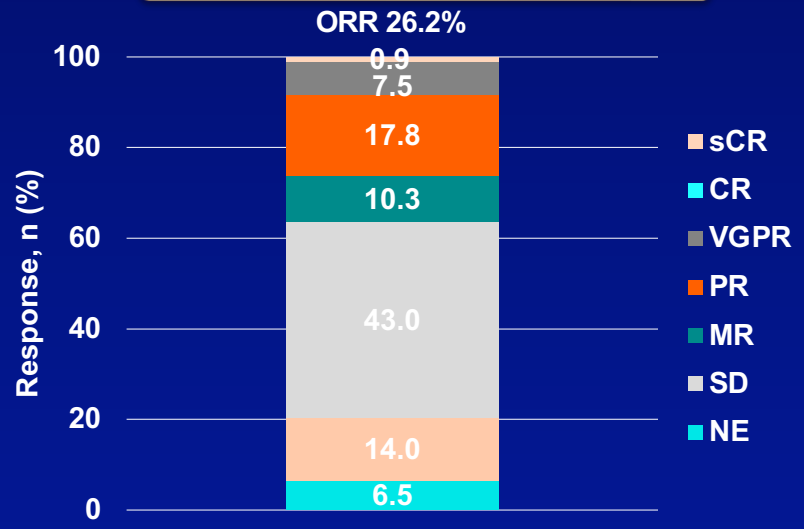
Cohort D (N=107)[1,2]

- 29.9% high-risk cytogenetics
- Median 6 prior therapies
- 100% IMiD-refractory
- 97.2% PI-refractory
- 100% CD38 mAb-refractory
- 97.2% triple-class refractory
- Median duration of treatment: 4 cycles

Cohort I (N=38, BCMA-exposed)[3]

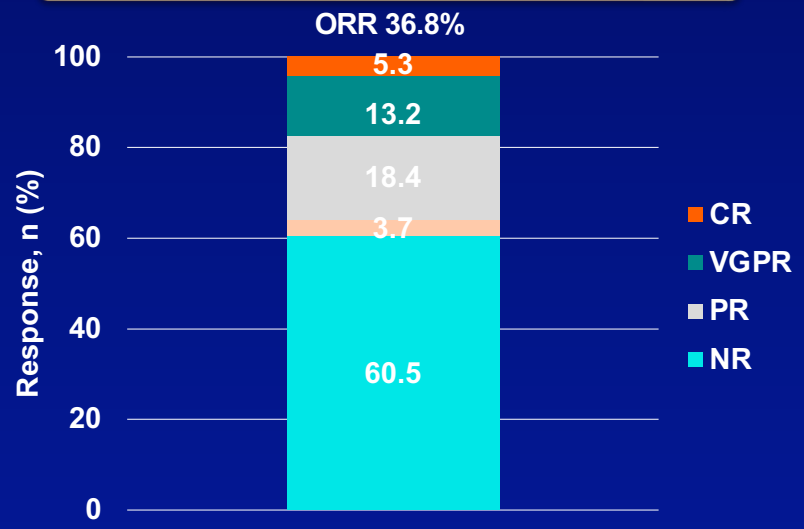
- 31.6% high-risk cytogenetics
- Median 7 prior therapies
- 100% triple-class exposed
- 100% exposed to BCMA-targeted therapy: 36.8% prior CAR T-cell therapy, 34.2% prior ADC, 23.7% prior T-cell engager
- Median duration of treatment: 3.5 cycles

Cohort D, Iberdomide-dex (N=107)[1,2]



- Median DoR 7.0 months
- Median PFS 3.0 months
- Median OS 10.4 months
- Grade 3/4 neutropenia 25.2/19.6%, anemia 28.0/0%, thrombocytopenia 6.5/15.0%, infections 24.3/2.8% (COVID-19 4.7/1.9%)

Cohort I, Iberdomide-dex (N=38)[3]



- Median DoR 7.5 months
- Median PFS 2.4 months
- Grade 3/4 AEs in 78/9%, including neutropenia 50.0%, anemia 28.9%, leukopenia 23.7%, thrombocytopenia 21.1%, infections 23.7% (pneumonia 21.1%)
- No patients discontinued iberdomide due to AEs

1. Lonial S, et al. Blood 2021;138(suppl 1):abstract 162. 2. Lonial S, et al. Lancet Haematol 2022;9(11):e822–32. 3. Lonial S, et al. Blood 2022;140(suppl 1):abstract 1918.

Activity and safety of CELMoDs in heavily pretreated patients with RRMM

Iberdomide + dex, Dara-dex, Vd, or Kd

CC-220-MM-001: Iberdomide + Dara-dex, Vd, or Kd[1]

Iberdomide-Dara-dex (N=43)

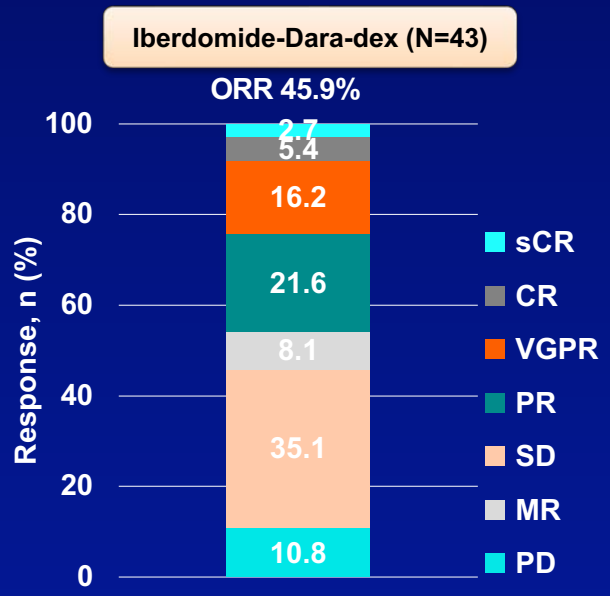
- 16.3% EMD
- Median 4 prior therapies
- 95.3% IMiD-refractory
- 86.0% PI-refractory
- 37.2% CD38 mAb-refractory
- 32.6% triple-class refractory
- Median duration of treatment: 4 cycles

Iberdomide-Vd (N=25)

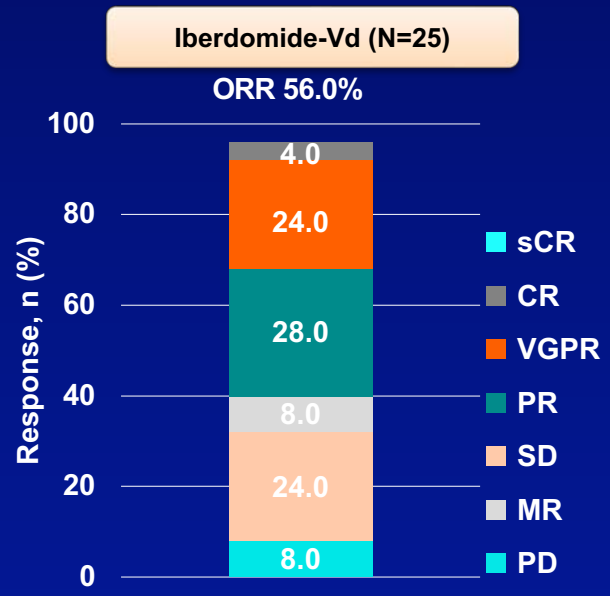
- 16.0% EMD
- Median 5 prior therapies
- 80.0% IMiD-refractory
- 68.0% PI-refractory
- 80.0% CD38 mAb-refractory
- 48.0% triple-class refractory
- Median duration of treatment: 6 cycles

Iberdomide-Kd (N=9)

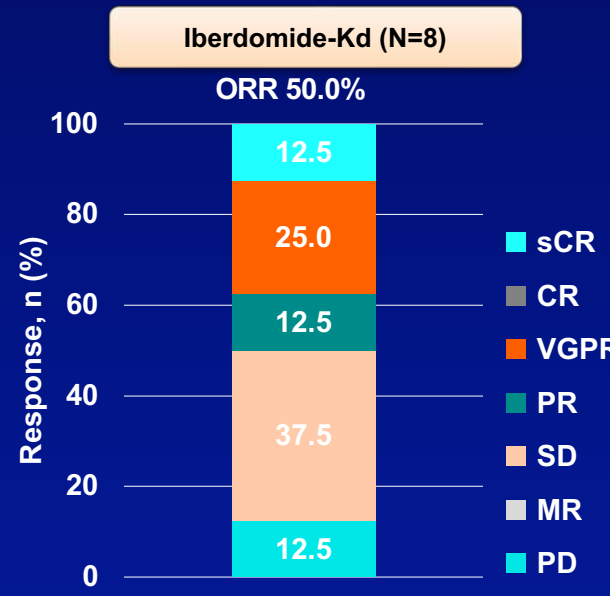
- 22.2% EMD
- Median 6 prior therapies
- 88.9% IMiD-refractory
- 66.7% PI-refractory
- 77.8% CD38 mAb-refractory
- 55.6% triple-class refractory
- Median duration of treatment: 5 cycles



- Median DoR not reached
- Grade 3/4 hematologic AEs: neutropenia 12.8/53.8%, anemia 20.5/0%, thrombocytopenia 7.7/5.1%
- Grade 3 nonhematologic AEs: fatigue 2.6%, diarrhea 2.6%
- Infections 59.0% (grade 3/4: 10.3/5.1%)



- Median DoR 35.7 weeks
- Grade 3/4 hematologic AEs: neutropenia 20/8%, anemia 12/0%, thrombocytopenia 4/20%
- Grade 3 nonhematologic AEs: diarrhea 4%, rash 4%
- Infections 68% (grade 3/4: 16/4%)



- Median DoR not reached
- Grade 3/4 hematologic AEs (N=9): neutropenia 22.2/11.1%, anemia 0%, thrombocytopenia 0/11.1%
- Grade 3 nonhematologic AEs: fatigue 11.1%
- Infections 77.8% (grade 3/4: 22.2/11.1%)

1. Lonial S, et al. HemaSphere 2021;5(S2):49–50, abstract S187.

Activity and safety of CELMoDs in heavily pretreated patients with RRMM

Mezigdomide + dex: Phase 1/2 study, N=178

First-in-human phase 1 trial: Mezigdomide + Dex

Dose escalation

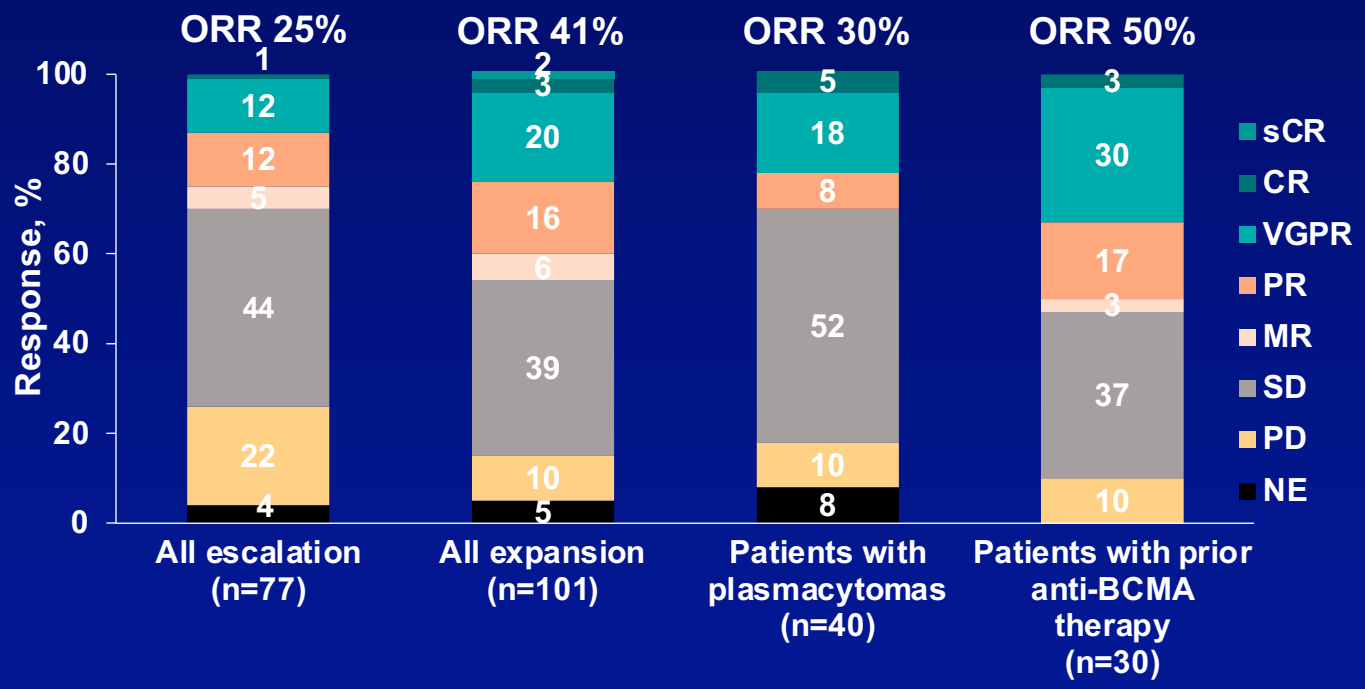
- 77 heavily pretreated RRMM patients
- 30% high-risk cytogenetics, 35% EMD
- Median 6 prior therapies
- 56% triple-class-refractory

Dose expansion at RP2D

- 101 heavily pretreated RRMM patients
- 37% high-risk cytogenetics, 40% EMD
- Median 6 prior therapies
- 100% triple-class-refractory

Efficacy in dose expansion cohort

- Median DOR 7.6 months
- Median PFS 4.4 months
- In patients with prior anti-BCMA therapy, median DOR 6.9 months and median PFS 5.4 months



Safety in dose escalation/expansion cohorts

- Grade 3/4 neutropenia 71%/76%, anemia 38%/36%, thrombocytopenia 24%/28%, febrile neutropenia 9%/15%
- Infections 74%/65% (Grade 3/4 40%/35%)
- Treatment discontinuation due to AEs NR/6%

Richardson PG, et al. N Engl J Med 2023;389(11):1009–22.

Activity and safety of CELMoDs in heavily pretreated patients with RRMM

Mezigdomide + Vd or Kd

CC-92480-MM-002 Phase 1/2 Study: Mezigdomide + Vd / Kd[1]

Mezigdomide + Vd (N=28)

- 42.9% high-risk cytogenetics
- Median 3 prior therapies
- 82.1% R-refractory
- 50.0% PI-refractory
- 50.0% CD38 mAb-refractory
- Median duration of treatment: 12.5 cycles

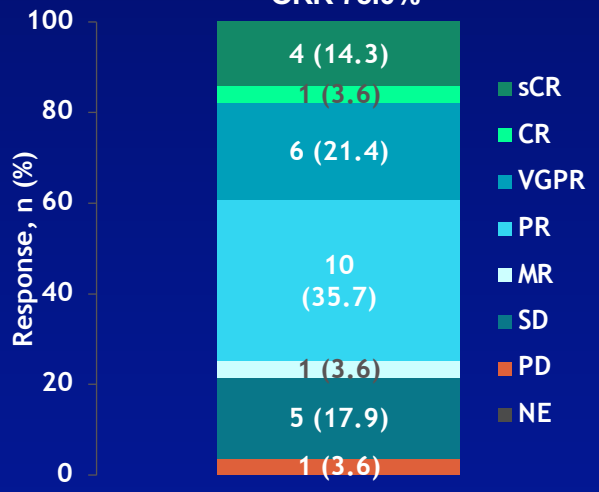
Mezigdomide + Vd 1.0 mg (N=38) / 0.6 mg (N=11)

- 55.1% high-risk cytogenetics
- Median 1 prior therapy
- 63.3% R-refractory
- 16.4% PI-refractory
- 34.7% CD38 mAb-refractory
- Median duration of treatment: 15 cycles

Mezigdomide + Kd (N=27)

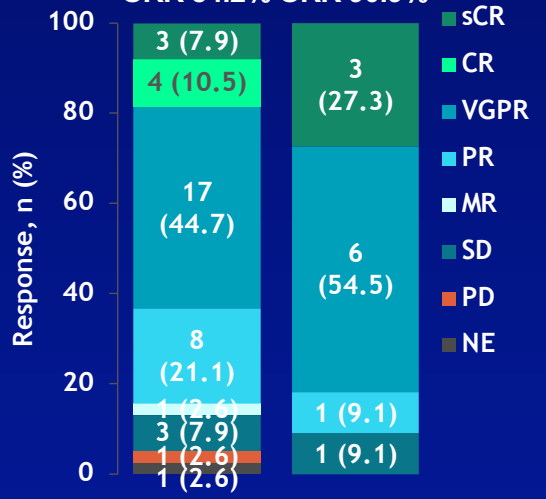
- 59.3% high-risk cytogenetics
- Median 2 prior therapies
- 77.8% R-refractory
- 51.9% PI-refractory
- 74.1% CD38 mAb-refractory
- Median duration of treatment: 12 cycles

Mezigdomide + Vd (N=28, dose escalation)



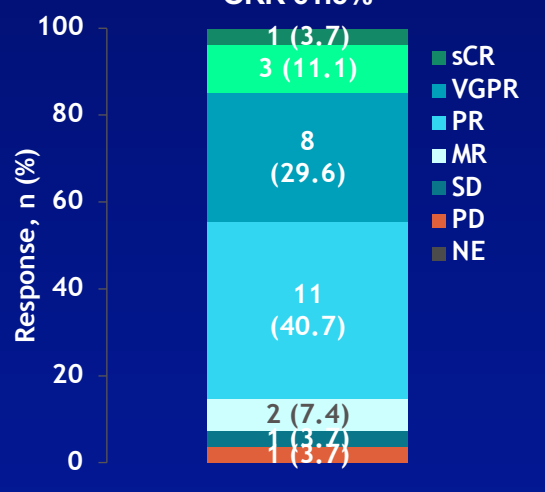
- Median DOR 10.9 months
- Grade 3/4 neutropenia 35.7%
- Grade 3/4 thrombocytopenia 21.4%
- Grade 3 anemia 14.3%
- Grade 3 diarrhea, insomnia 10.7%
- Infections 71.4% (Grade 3/4 17.9%)

Mezigdomide + Vd (1.0 mg, N=38 / 0.6 mg, N=11)



- Median DOR not reached
- Grade 3/4 neutropenia 59.2%
- Grade 3/4 thrombocytopenia 26.5%
- Grade 3 anemia 6.1%
- Grade 3 diarrhea 8.2%
- Infections 79.6% (Grade 3/4 32.7%)

Mezigdomide + Kd (N=27)



- Median DOR 12.3 months
- Grade 3/4 neutropenia 40.7%
- Grade 3/4 thrombocytopenia 18.5%
- Grade 3 anemia 17.6%
- Grade 3 diarrhea 11.1%
- Infections 70.4% (Grade 3/4 29.6%)

1. Oriol A, et al. Clin Lymphoma Myeloma Leukemia 2023;23(Suppl 2):S31.

Activity and safety of CELMoDs in heavily pretreated patients with RRMM

Mezigdomide + Dara-dex or Elo-dex

CC-92480-MM-002 Phase 1/2 Study: Mezigdomide + Dara-dex / Elo-dex[1]

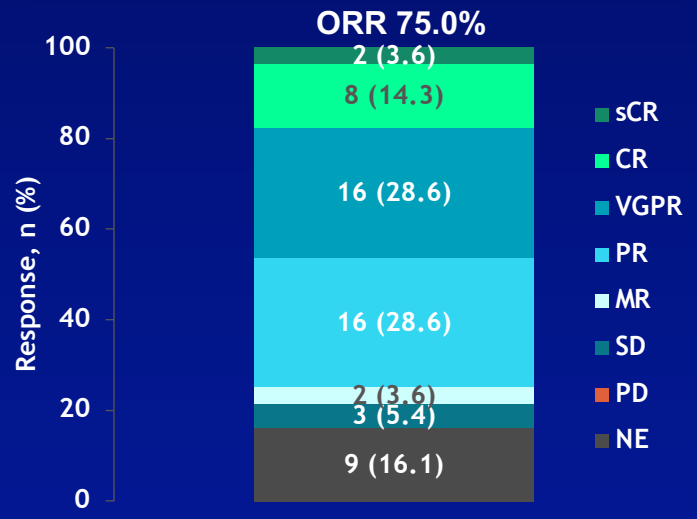
Mezigdomide + Dara-dex (N=56)

- Median age 67 years
- Median time since diagnosis 8.2 years
- Median 2 prior therapies
- 82.5% IMiD-refractory
- 61.4% PI-refractory
- 15.8% prior ASCT
- 8.8% prior CD38 mAb

Mezigdomide + Elo-dex (N=20)

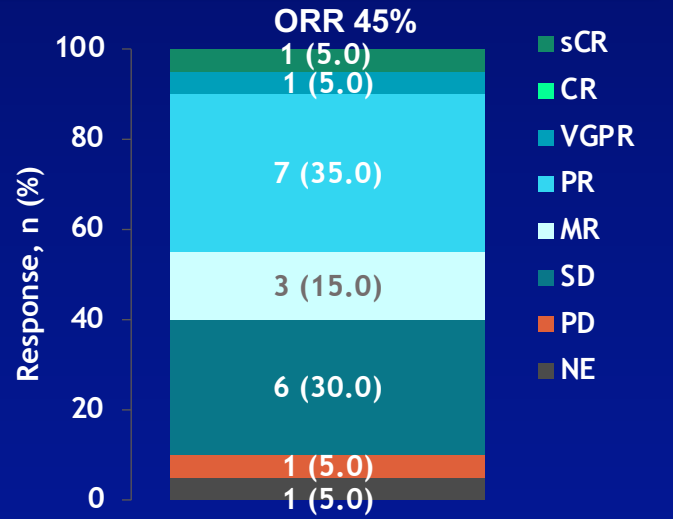
- Median 3 prior therapies
- 85% prior CD38 mAb

Mezigdomide + Dara-dex (N=56)



- DOR / PFS not yet mature (with lower boundary for median DOR currently 24 mos.)
- Grade 3/4 neutropenia 53.6%
- Grade 3/4 thrombocytopenia 7.1%
- Grade 3/4 anemia 10.7%
- Grade 3/4 infections 19.6%

Mezigdomide + Elo-dex (N=20)



- DOR / PFS not yet mature (with lead pt. @ 24 mos. DOR)
- Grade 3/4 neutropenia 40%
- Grade 3/4 thrombocytopenia 10%
- Grade 3/4 anemia 20%
- Grade 3/4 infections 35%

1. Richardson PG, et al. Blood 2023;142(Suppl 1):abstract 1013.

Conclusions and next steps/future directions

CD38 mAb-based regimens consistently producing significant improvements in outcomes in NDMM	• Dara-based quadruplets are emerging standards of care in NDMM – e.g. GRIFFIN, PERSEUS in transplant setting, GEM2017FIT in non-transplant setting • Isa-based quadruplets also emerging treatment options in NDMM – e.g. IsKia, GMMG-HD7/SKylaRk • Dara/Isa-based quadruplets in studies of MRD-adapted therapy for NDMM
CD38 mAb-based triplets consistently demonstrating significant improvements in outcomes in RRMM	• Isa-based triplets are among the standards of care in early RRMM – e.g. ICARIA-MM, IKEMA – alongside existing Dara-based triplets • Isa is a distinct CD38 mAb from Dara – potentially valuable as complementary / alternative therapies
XPO1 inhibitor-based therapy a valuable treatment option for patients with RRMM	• Selinexor-Vd approved based on BOSTON phase 3 trial • Selinexor-based quadruplet regimens under investigation, e.g. Selinexor-Dara-Vd • Additional selinexor combination strategies to improve therapeutic index under investigation, including selinexor-pomalidomide combinations and clinical trials exploring selinexor-mezigdomide
Next-generation BCL-2 inhibitors under investigation	• Venetoclax-based combinations demonstrated substantial activity in t(11;14) or BCL-2-high RRMM • Illustrates pitfalls of MoA vs MoA phase 3 trials (CANOVA) compared with benefits of additive triplet vs doublet phase 3 trials (BELLINI) • Next-generation agents lisaftoclax and sonrotoclax in early-phase clinical investigation in RRMM
Notable activity and safety of CELMoDs in heavily pretreated patients with RRMM	• Early-phase dose-escalation and expansion studies demonstrating feasibility and activity of iberdomide- and mezigdomide-based combination regimens in RRMM • Combination strategies in Phase 3 trials (SUCCESSOR-1: Mezi+Vd; SUCCESSOR-2: Mezi+Kd; EXCALIBER: Iber-Dara-dex) in RRMM

Overview

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Third Annual National General Medical Oncology Summit

Agenda

Module 1: Current and Potential Role of Immune Checkpoint Inhibitors — Dr Klempner

Module 2: Other Available and Emerging Therapeutic Approaches — Dr Janjigian

Agenda

Module 1: Current and Potential Role of Immune Checkpoint Inhibitors — Dr Klempner

Module 2: Other Available and Emerging Therapeutic Approaches — Dr Janjigian

Current and Potential Roles for Immune Checkpoint Inhibitors

Samuel J. Klempner, MD

MGH Cancer Center

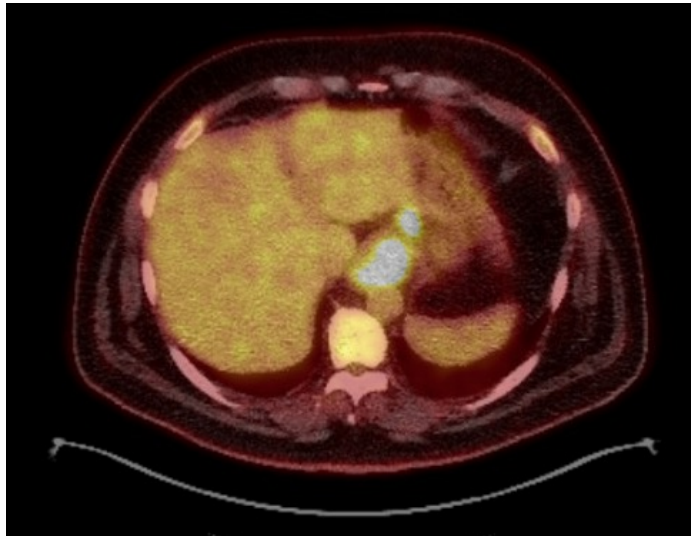
Boston, MA

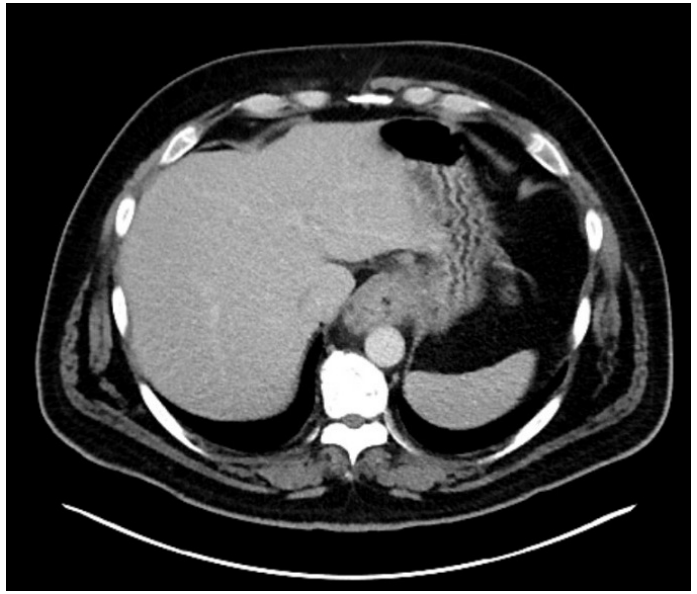
Disclosures

Advisory Committees	Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Coherus BioSciences, Daiichi Sankyo Inc, Merck, Mersana Therapeutics Inc, Natera Inc, Pfizer Inc, Sanofi, Servier Pharmaceuticals LLC
Consulting Agreements	Astellas, Novartis
Medical Advisory Boards (No Compensation)	Debbie's Dream Foundation, Hope for Stomach Cancer
Stock Options/Ownership — Public Companies	Nuvalent (ended 11/2022), Turning Point Therapeutics Inc (ended 6/2022)
Nonrelevant Financial Relationships	American Gastroenterological Association, Degregorio Family Foundation, National Cancer Institute/National Institutes of Health, Stand Up 2 Cancer/AACR

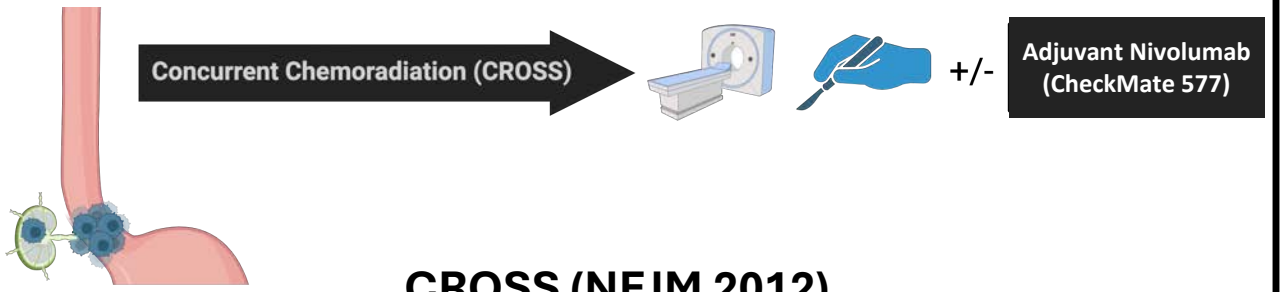
Starting in the Clinic

- 49M with h/o GERD presents with slowly progressive dysphagia and 20lb weight loss.
- EGD/EUS: Fungating, partially obstructive GEJ mass extending to cardia, uT3N1
- PET-CT: FDG-avid primary and enlarged FDG-avid 2cm gastrohepatic LN
- PATHOLOGY: Mod-diff adenocarcinoma, pMMR
- STAGING LAP: bulky GEJ tumor, no gross peritoneal disease, cytology negative.
- CLINICAL STAGING: cT3N1M0, resectable



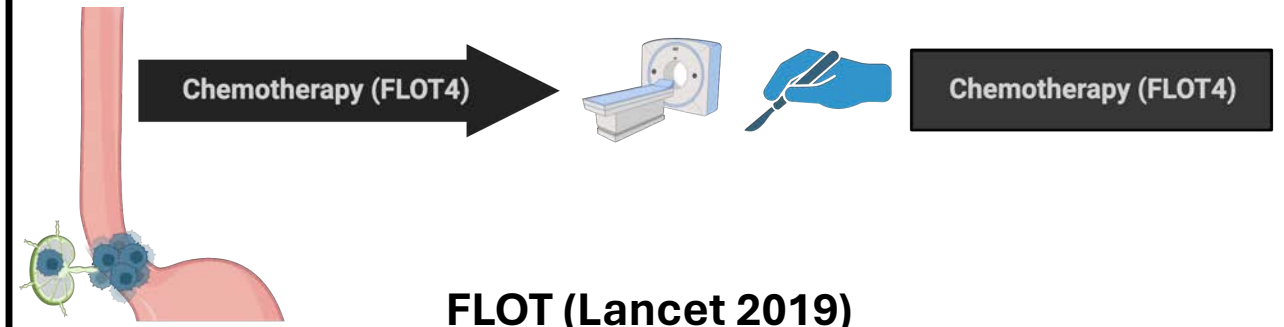


Management Strategies for Resectable GEJ Cancers



CROSS (NEJM 2012)

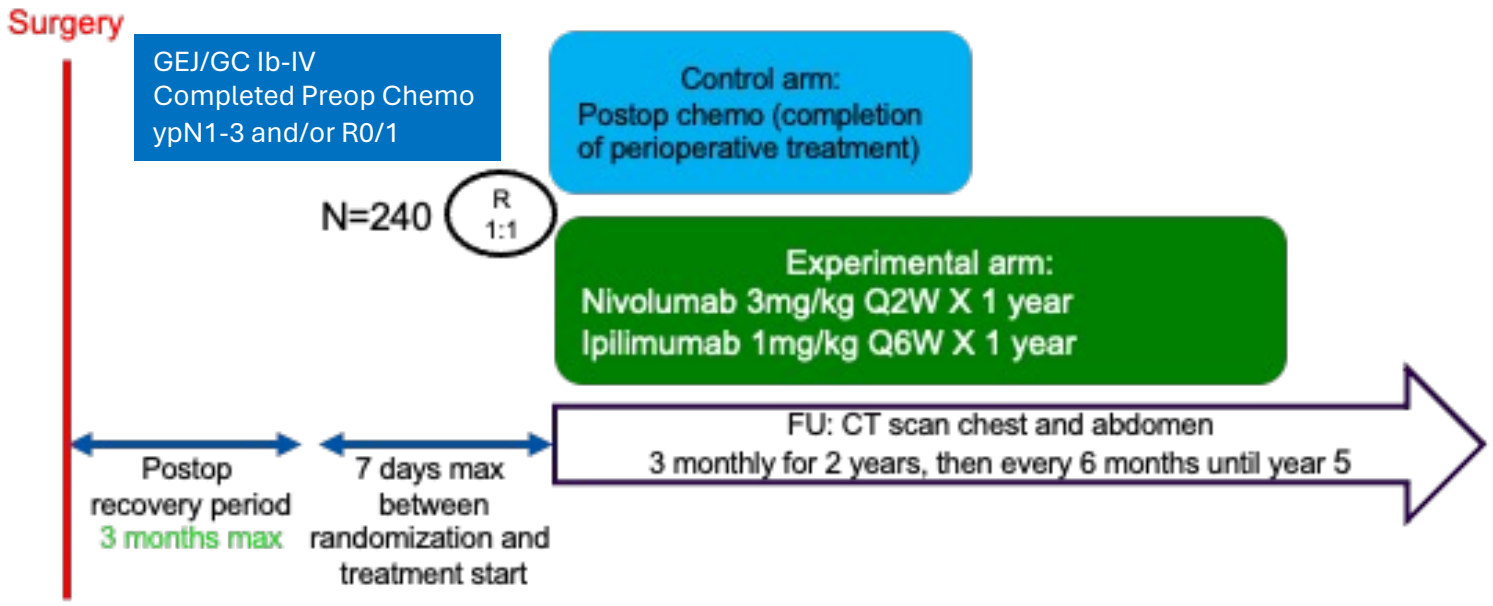
Feature	Result
Adenocarcinoma	75%
GEJ	22%
T3	84%
N+	65%
R0 Resection	92%
pCR (adenocarcinoma)	23%
mOS (adenocarcinoma)	43 months (HR = 0.73)
mPFS (adenocarcinoma)	30 months (HR = 0.69)
3yr OS Rate (Overall)	58%
5yr OS Rate (Overall)	47%



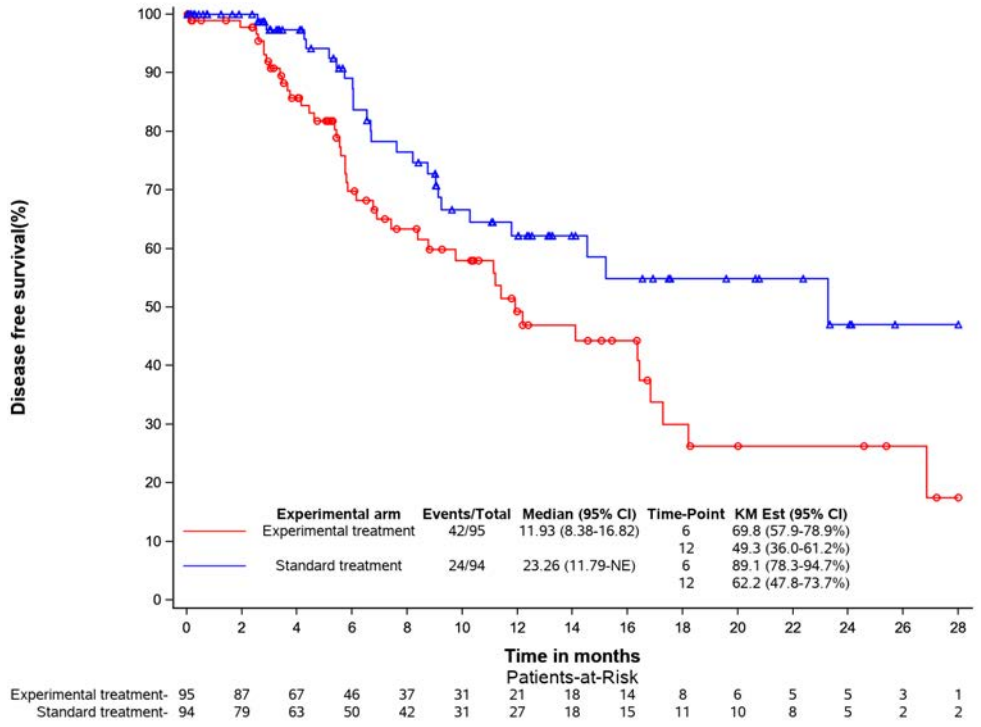
FLOT (Lancet 2019)

Feature	Result
Siewert 1	23%
Siewert 2/3	33%
Gastric	44%
T3	75%
N+	78%
R0 Resection	85%
pCR	16%
ypN0	49%
mOS	50 months (HR = 0.77)
mDFS	30 months (HR = 0.75)
3yr OS Rate	48%
5yr OS Rate	36%

You Gave FLOT But The Path is ypT2N1-- Give IO?



		Treatment arm (ITT population)	
		CT (N=94)	Nivo/Ipi (N=95)
ypN stage, N (%)			
	ypN0	4 (4.3)	2 (2.1)
	ypN1	30 (31.9)	24 (25.3)
	ypN2	24 (25.5)	20 (21.1)
	ypN3	36 (38.3)	49 (51.6)
Pre-operative chemotherapy regimen, N (%)			
	non-FLOT	7 (7.4)	8 (8.4)
	FLOT	87 (92.6)	87 (91.6)
Neoadjuvant chemotherapy duration (weeks), Median (Range)		7.5 (5.0 – 12.0)	8.0 (5.0 - 10.0)



	CT am	Nivo/Ipi arm
Median DFS(m) (95% CI)	23.26 (11.79 – NE)	11.93 (8.36- 16.82)
12m DFS % (95% CI)	62.2 (47.8-73.7)	49.3 36.0- 61.2)

ESMO GI 2023

What if You Had Given NACRT? CheckMate 577

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4–16 weeks prior to randomization)
- Residual pathologic disease – ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])

N = 794
R 2:1

n = 532 → **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W

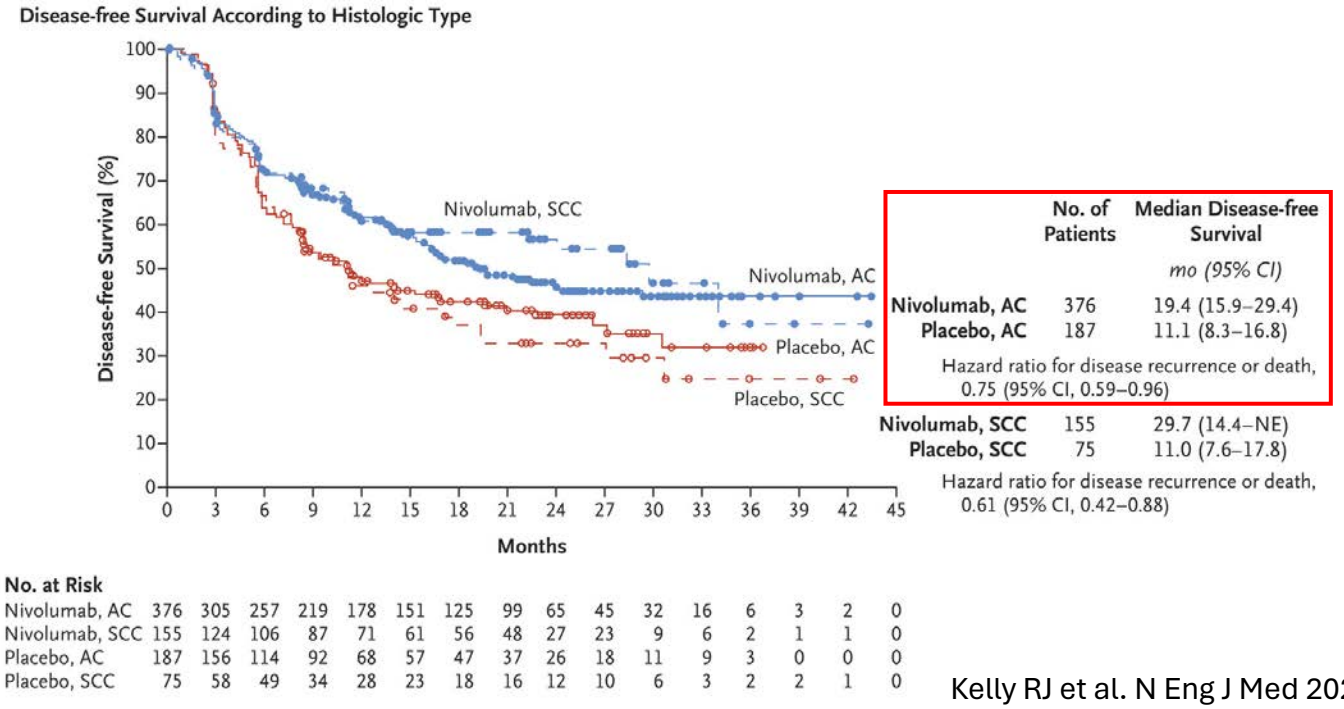
n = 262 → **Placebo** Q2W × 16 weeks then Q4W

Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[a]

Secondary endpoints:
- OS
- OS rate at 1, 2, and 3 years

Exploratory endpoints:
- Safety
- Biomarkers



	No. of Patients	Median Disease-free Survival (mo (95% CI))
Nivolumab, AC	376	19.4 (15.9–29.4)
Placebo, AC	187	11.1 (8.3–16.8)

Hazard ratio for disease recurrence or death, 0.75 (95% CI, 0.59–0.96)

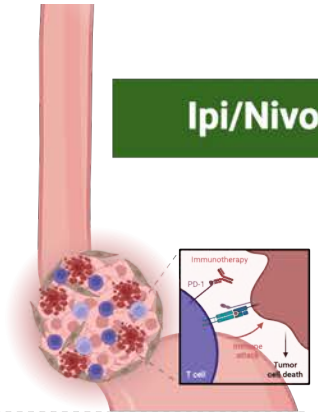
Nivolumab, SCC	155	29.7 (14.4–NE)
Placebo, SCC	75	11.0 (7.6–17.8)

Hazard ratio for disease recurrence or death, 0.61 (95% CI, 0.42–0.88)

Geographic region — no. (%)		
Europe	202 (38)	101 (39)
United States or Canada	167 (31)	88 (34)
Asia	77 (14)	29 (11)
Rest of the world‡	86 (16)	44 (17)
ECOG performance-status score — no. (%)§		
0	308 (58)	156 (60)
1	224 (42)	106 (40)
Disease stage at initial diagnosis — no. (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Not reported	2 (<1)	0
Tumor location at trial entry — no. (%)		
Esophagus	311 (58)	151 (58)
Gastroesophageal junction	221 (42)	111 (42)
Histologic type — no. (%)¶		
Adenocarcinoma	376 (71)	187 (71)
Squamous-cell carcinoma	155 (29)	75 (29)
Other	1 (<1)	0
Tumor-cell PD-L1 expression at trial entry — no. (%)‖		
<1%	374 (70)	196 (75)
≥1%	89 (17)	40 (15)
Indeterminate or could not be evaluated	69 (13)	26 (10)
Pathological lymph-node status at trial entry — no. (%)**		
≥ypN1	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Not known	0	1 (<1)
Pathological tumor status at trial entry — no. (%)**		
ypT0	31 (6)	16 (6)
ypT1 or ypT2	202 (38)	106 (40)
ypT3 or ypT4	296 (56)	140 (53)
Not known	3 (<1)	0

Kelly RJ et al. N Eng J Med 2021

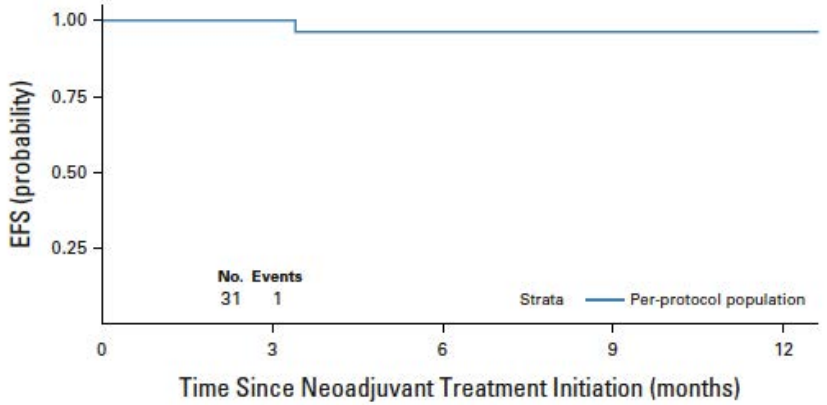
What if Your Patient was dMMR?

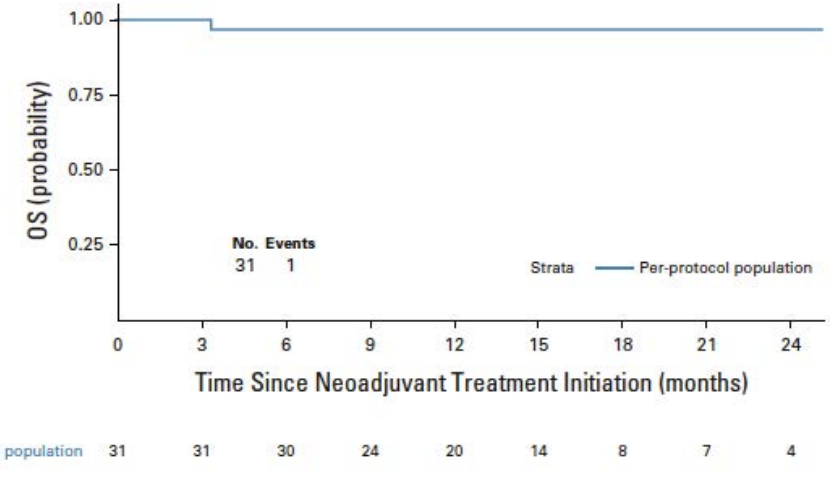


Ipi/Nivo x 3months

Nivo x 9months

Primary Endpoint = Path CR rate
29/32 (91%) Underwent surgery
pCR rate = 59%, MPR rate = 79%





Neoadjuvant or perioperative ICI if tumor is MSI-H/ dMMR[p,r,s]

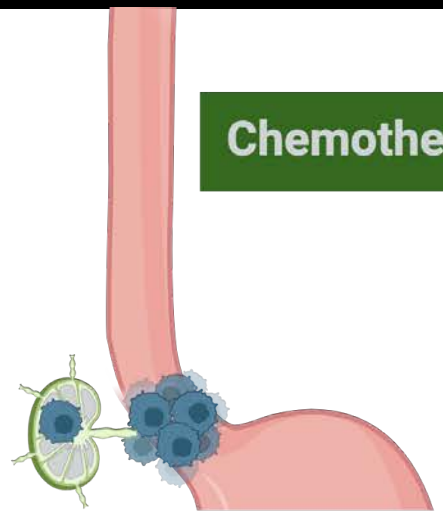
- **FDG-PET/CT as clinically indicated[t]**
- **Chest/abdomen CT with oral and IV contrast (not required if FDG-PET/ CT is done)[u]**
- **Upper GI endoscopy and biopsy[v]**

No evidence of disease[v]	**Observation[w]**
Persistent local disease	**Surgery (preferred)[d,f,x] or Palliative Management (GAST-9)**
New metastatic disease	**Palliative Management**

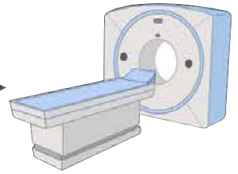
- **MMR/MSI testing is recommended for all gastroesophageal cancers, regardless of stage**
- **Neoadjuvant or perioperative ICI is on the NCCN guidelines dMMR or MSI gastroesophageal cancers**

Phase II NEONIPIGA, JCO 2022

What About Perioperative ICI For Everyone?



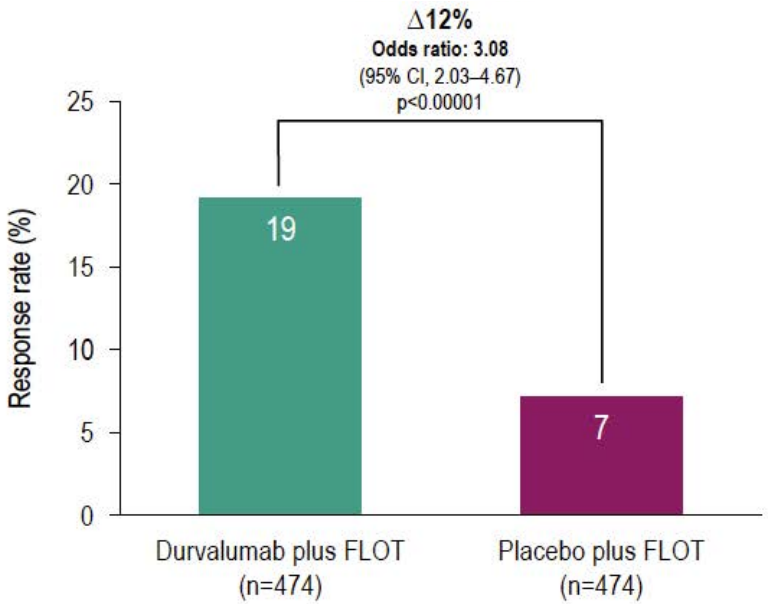
Chemotherapy + PD-1/L1



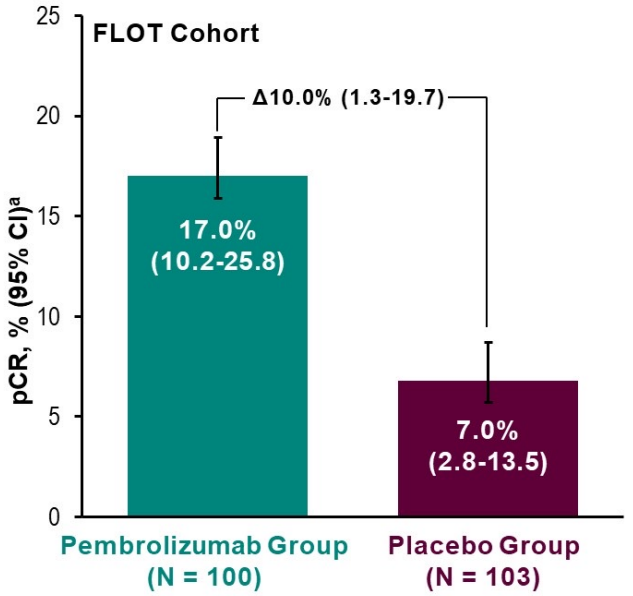
Chemotherapy + PD-1/L1

PD-1/L1

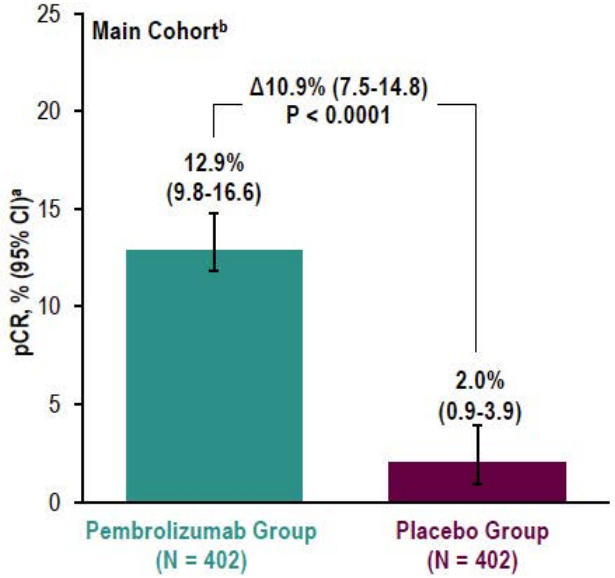
MATTERHORN



KEYNOTE-585

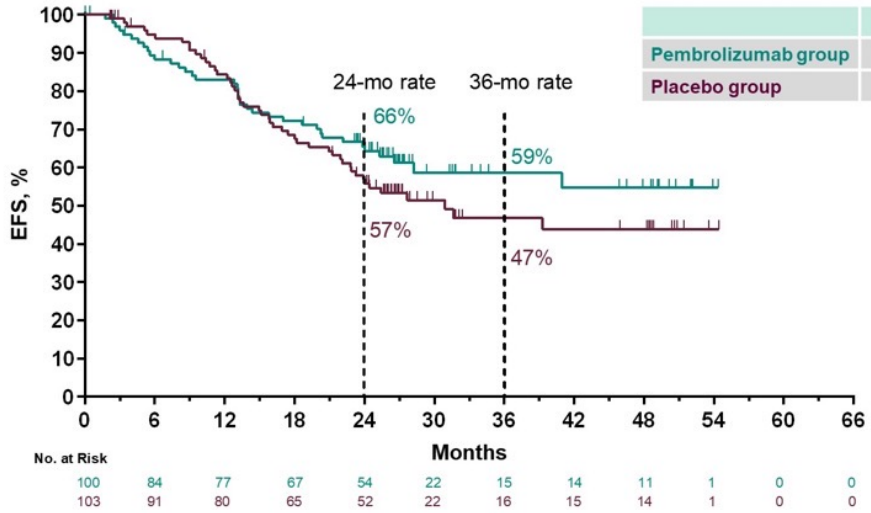


KEYNOTE-585 Main (Cis/5FU)



What About Perioperative ICI For Everyone?

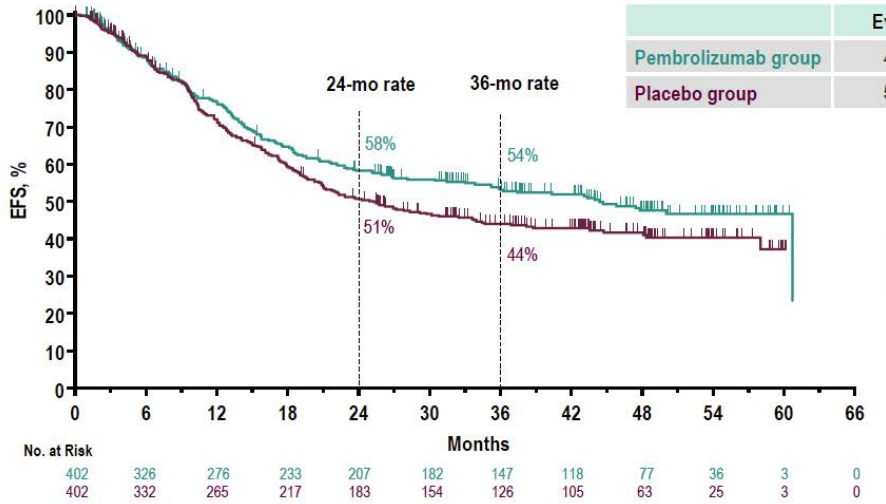
Event-Free Survival: FLOT Cohort



	Events	Median (95% CI), mo
Pembrolizumab group	37%	NR (28.2-NR)
Placebo group	47%	30.9 (22.8-NR)

HR 0.79 (95% CI, 0.52-1.22)

Event-Free Survival: Main Cohort

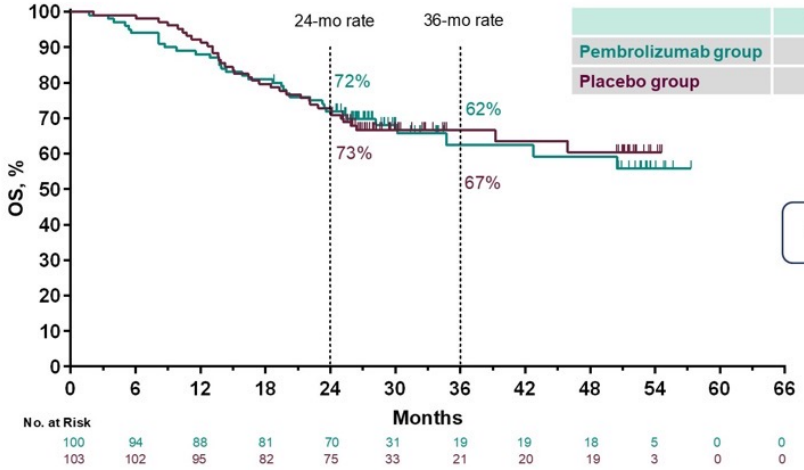


	Events	Median (95% CI), mo
Pembrolizumab group	46%	44.4 (33.0-NR)
Placebo group	53%	25.3 (20.6-33.9)

HR 0.81 (95% CI, 0.67-0.99)
P = 0.0198[a]

Negative Trial

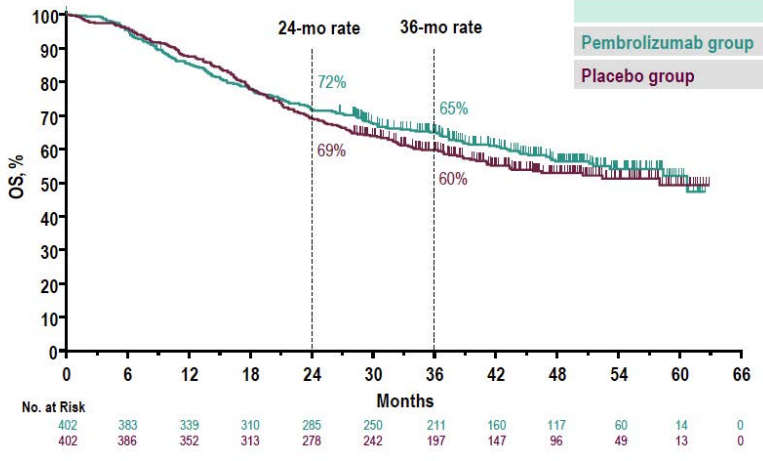
Overall Survival: FLOT Cohort



	Events	Median (95% CI), mo
Pembrolizumab group	35%	NR (34.7-NR)
Placebo group	35%	NR (45.9-NR)

HR 1.04 (95% CI, 0.66-1.66)

Overall Survival: Main Cohort



	Events	Median (95% CI), mo
Pembrolizumab group	41%	60.7 (51.5-NR)
Placebo group	45%	58.0 (41.5-NR)

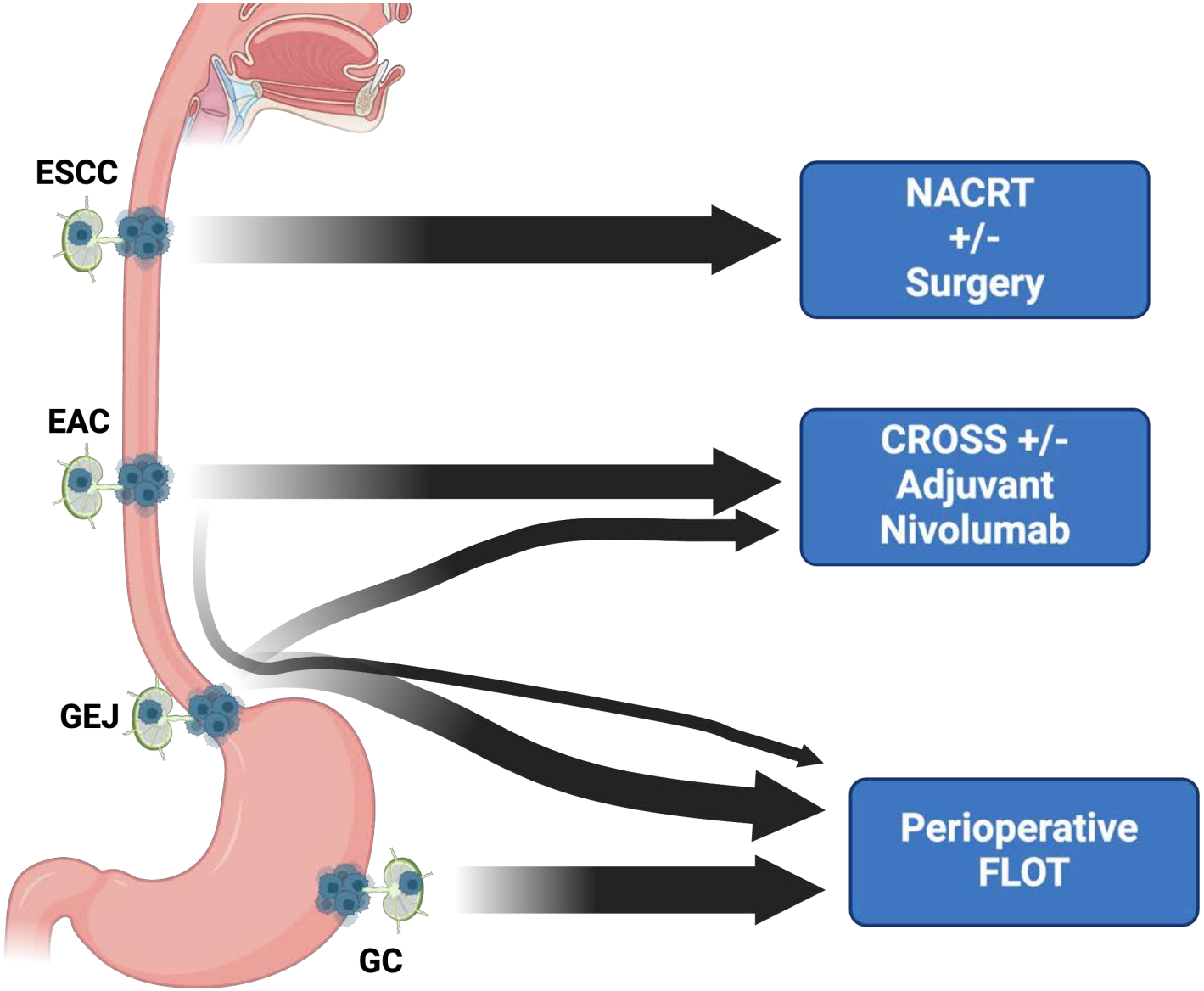
HR 0.90 (95% CI, 0.73-1.12)

Lancet Onc 2023

What About Perioperative ICI For Everyone?

Feature	MATTERHORN Exp (n=474)	MATTERHORN Control (n=474)	KEYNOTE-585 Main Exp (n=402)	KEYNOTE-585 Main Control (n=402)	KEYNOTE-585 FLOT Exp (n=100)	KEYNOTE-585 FLOT Control (n=103)
Asia	19%	19%	47%	48%	3%	3%
Non-Asia	81%	81%	53%	52%	97%	97%
GC	68%	67%	79%	80%	60%	62%
GEJ	32%	33%	21%	20%	40%	38%
Clinical N-	31%	30%	18%	17%	31%	31%
Clinical N+	69%	70%	81%	82%	69%	69%
PD-L1 <1	10%	10%	18%	17%	19%	21%
PD-L1 >1	90%	90%	73%	76%	73%	75%
MSI	8%	7%	9%	9%	7%	2%
R0 Resection	86%	86%	80%	75%	79%	80%
pCR	19%	7%	13%	2%	17%	7%
ypN0 rate	52%	37%	N/A	N/A	N/A	N/A
EFS (median)	N/A	N/A	44.4m	25.3m	NR (28.2-NR)	30.9m
OS (median)	N/A	N/A	60.7m	58.0m	NR (34.7-NR)	NR (45.9-NR)

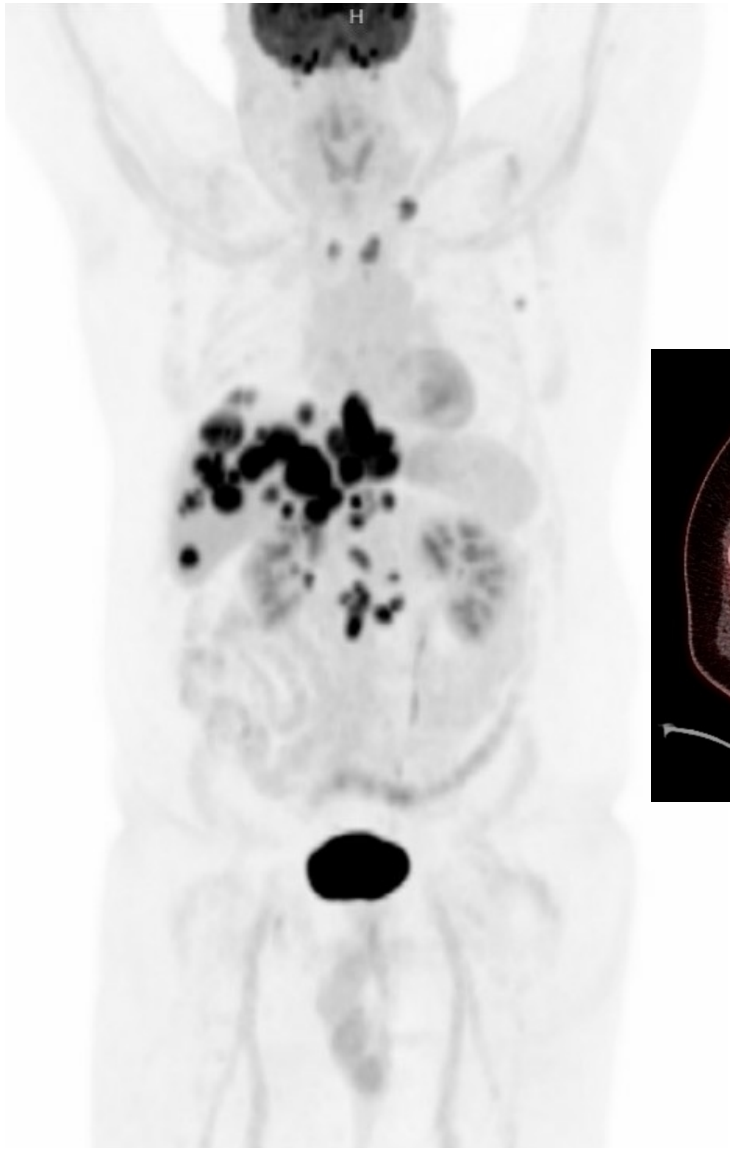
SUMMARY #1: NON-METASTATIC DISEASE

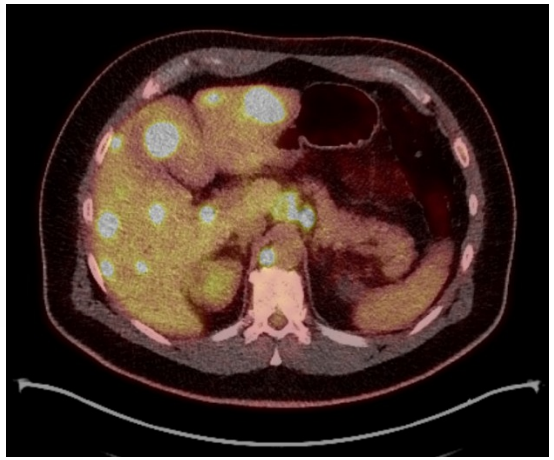


- Do you need a staging lap?
- MMR/MSI testing for everyone
- There is increasing harmonization around FLOT in GEJ/GC (we are getting better)
- Surgery really needs to be done by high volume expert
- No role for neoadjuvant or periop ICI outside of dMMR/MSI

Back to the Clinic

- HPI: Your prior GEJ patient treated with perioperative FLOT has metastatic recurrence at 3 yrs.
- PET-CT: Diffuse bilobar hepatic mets, widespread lymphadenopathy
- PATHOLOGY: Liver biopsy with mod-diff adenocarcinoma, pMMR, HER2 IHC 1+, PD-L1+ (CPS = 4)





Adding RATIONALE to PD-1 in Frontline Therapy

Inclusion criteria:
- Age ≥18 years
- Locally advanced unresectable or metastatic adenocarcinoma of stomach- / gastro-oesophageal junction
- No HER2-positive disease
- No prior systemic therapy for advanced disease
- At least one measurable or non-measurable lesion (RECIST v1.1)
- ECOG PS 0 or 1

R 1:1 (n=997)

	Initial up to 6 treatment cycles	Cycle 7 and beyond
TIS[a] + Chemo[b] (n=501)	→	TIS[a] + optional capecitabine[c]
PBO[a] + Chemo[b] (n=496)	→	PBO[a] + optional capecitabine[c]

Treatment until unacceptable toxicity or disease progression

Endpoints
- ***Primary endpoint:*** OS in PD-L1 score ≥5%[d] and ITT populations
- ***Secondary endpoints:*** PFS, ORR, DoR, DCR, CBR, HRQoL, and safety

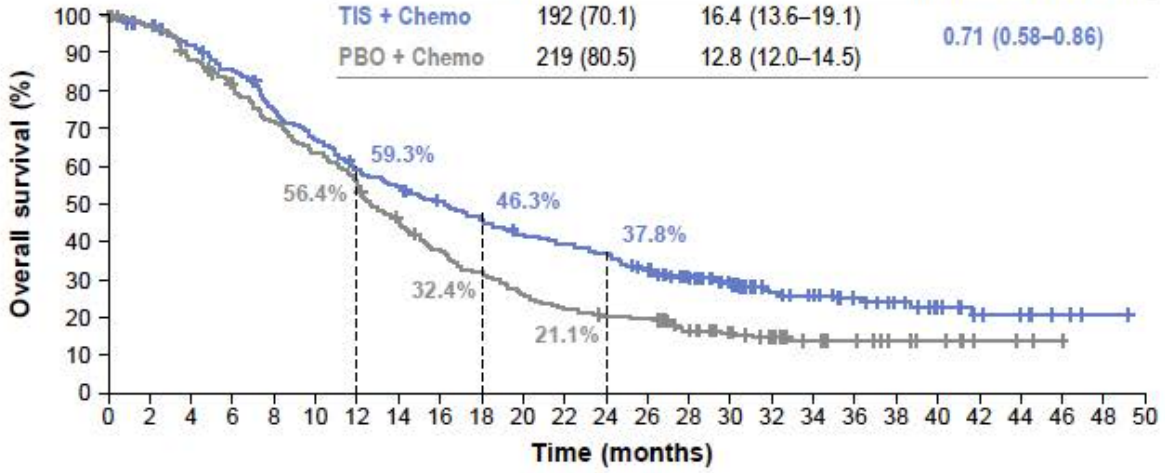
Stratification
- Regions of enrolment
- Peritoneal metastasis
- PD-L1 expression score (≥5% vs <5%)[d]
- Investigator-chosen chemotherapy (XELOX or FP)

Statistical considerations
- Analysis of OS in the ITT population was to be performed after OS in the PD-L1 score ≥5% population had been demonstrated to be statistically significant favouring TIS + chemo
- Planned to enrol 980 patients: 87% power to detect HR 0.80 with 768 OS events in the ITT population (all randomised patients) at a one-sided alpha of 0.025
- Final analysis (cutoff date: 28 February 2023) based on 776 OS events (ITT)

ESMO 2023

PD-L1 Score ≥5% Population

	Events, n (%)	Median OS (95% CI), Months	Stratified[a] HR (95% CI)
TIS + Chemo	192 (70.1)	16.4 (13.6–19.1)	0.71 (0.58–0.86)
PBO + Chemo	219 (80.5)	12.8 (12.0–14.5)	

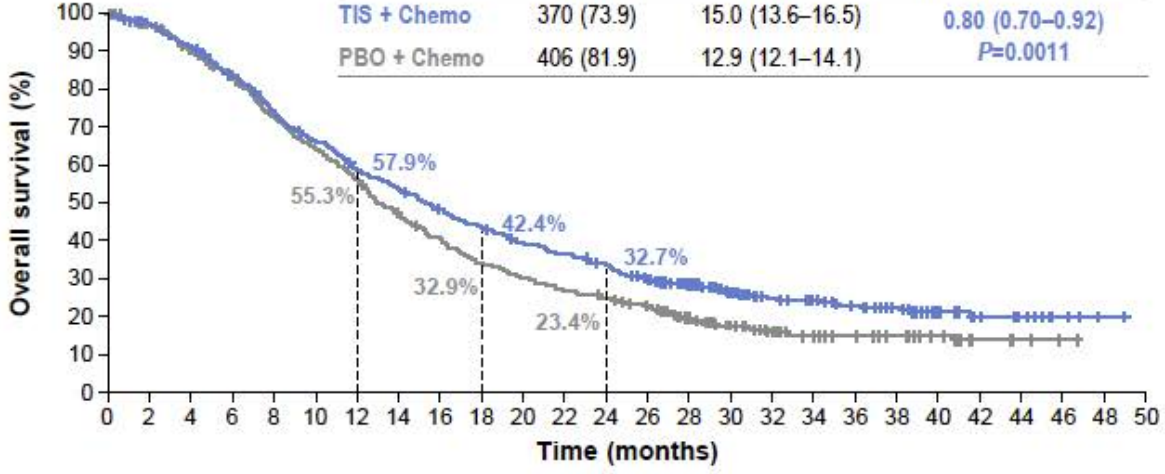


Number of patients at risk

TIS + Chemo	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
PBO + Chemo	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

ITT Population

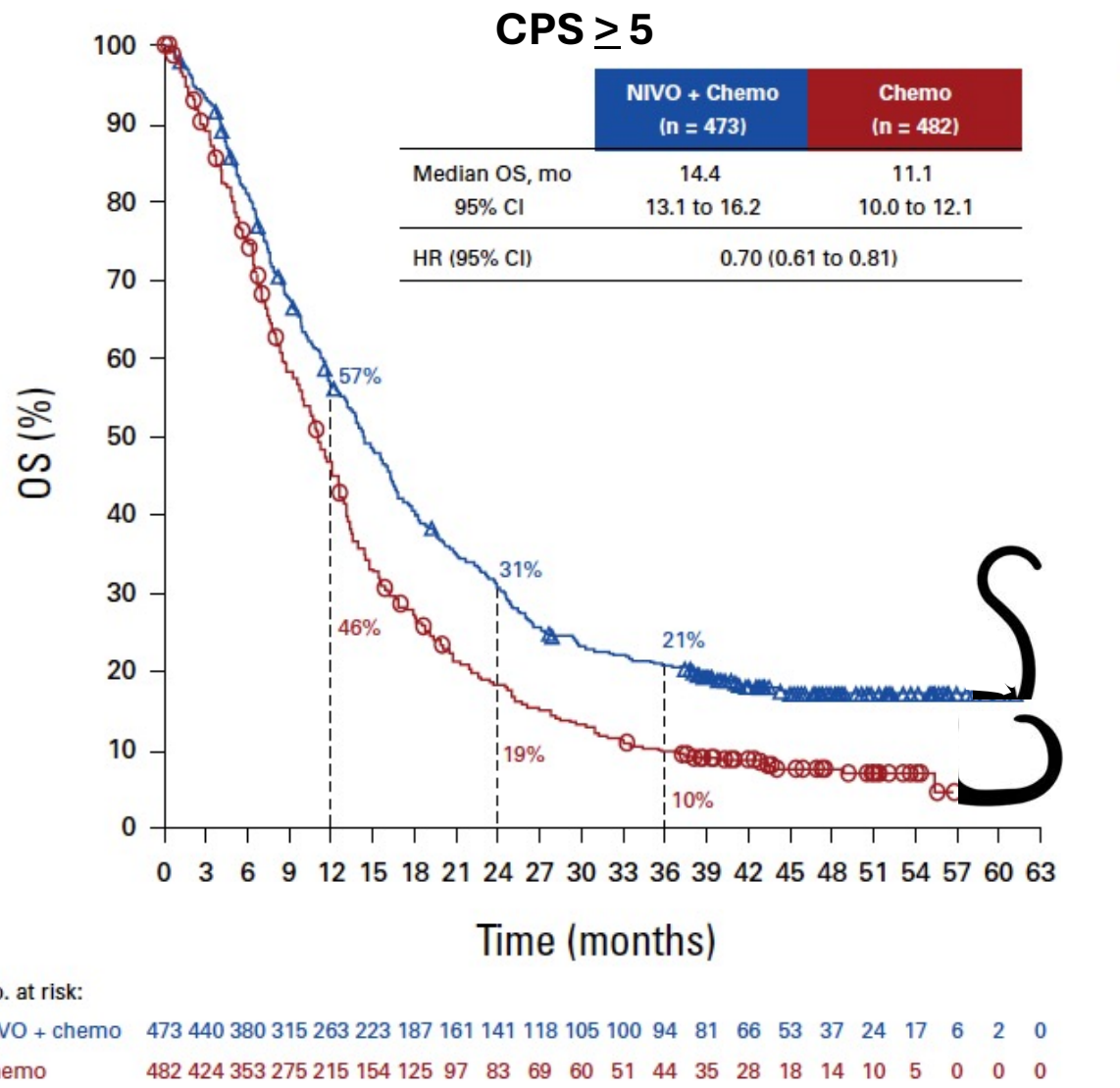
	Events, n (%)	Median OS (95% CI), Months	Stratified[a] HR (95% CI) Log-Rank Test *P*-value
TIS + Chemo	370 (73.9)	15.0 (13.6–16.5)	0.80 (0.70–0.92) *P*=0.0011
PBO + Chemo	406 (81.9)	12.9 (12.1–14.1)	

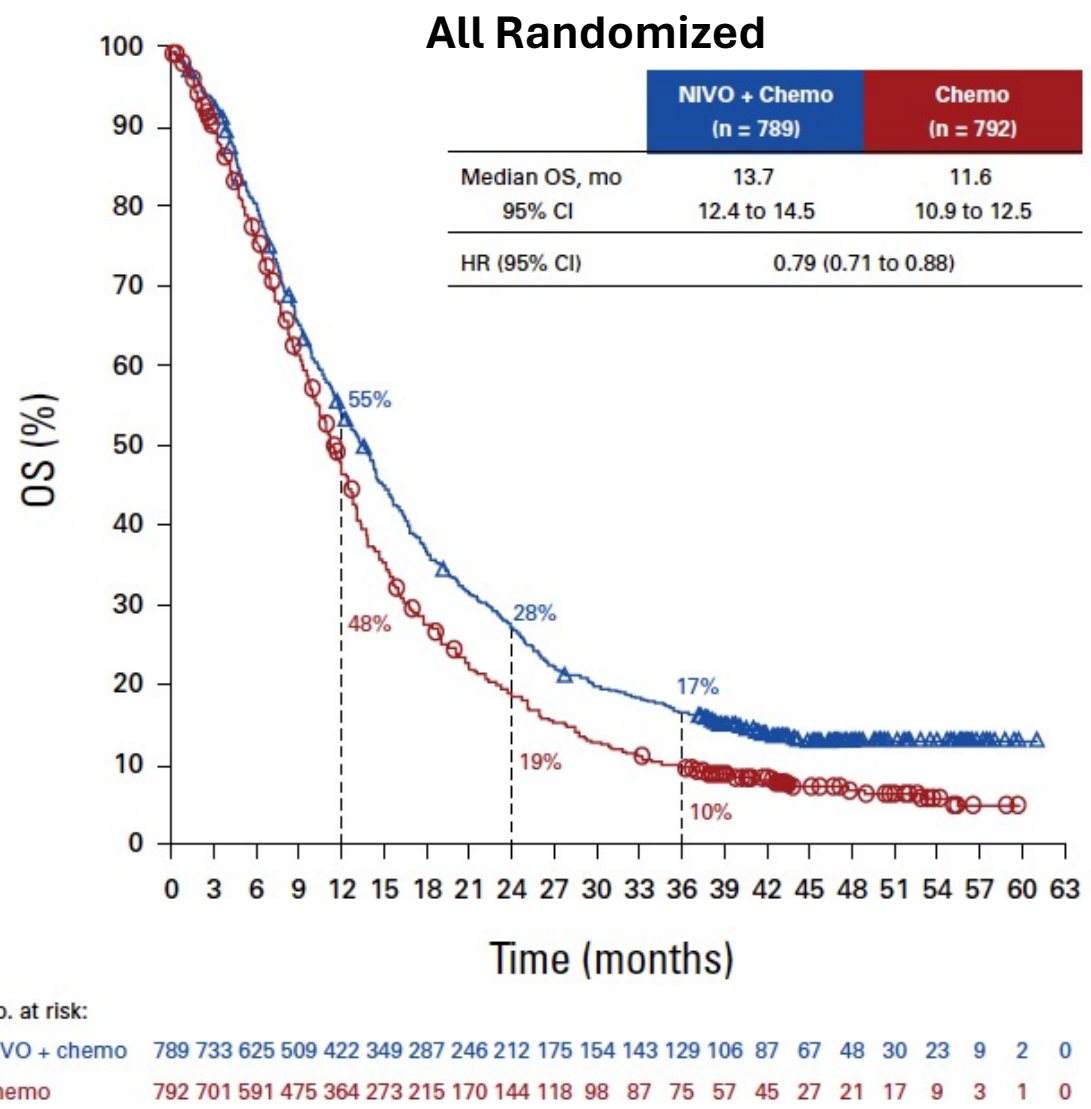


Number of patients at risk

TIS + Chemo	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO + Chemo	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

The Tail is the Tail: 3-yr CheckMate 649 Follow Up

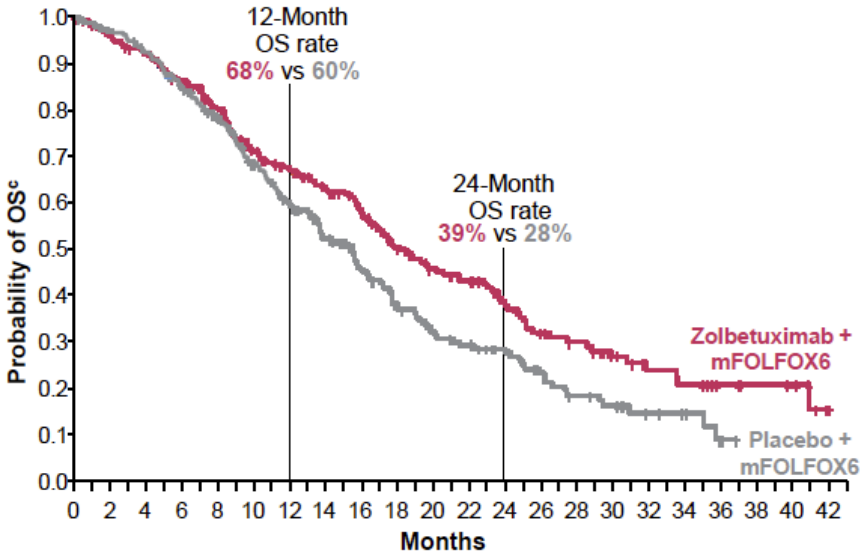




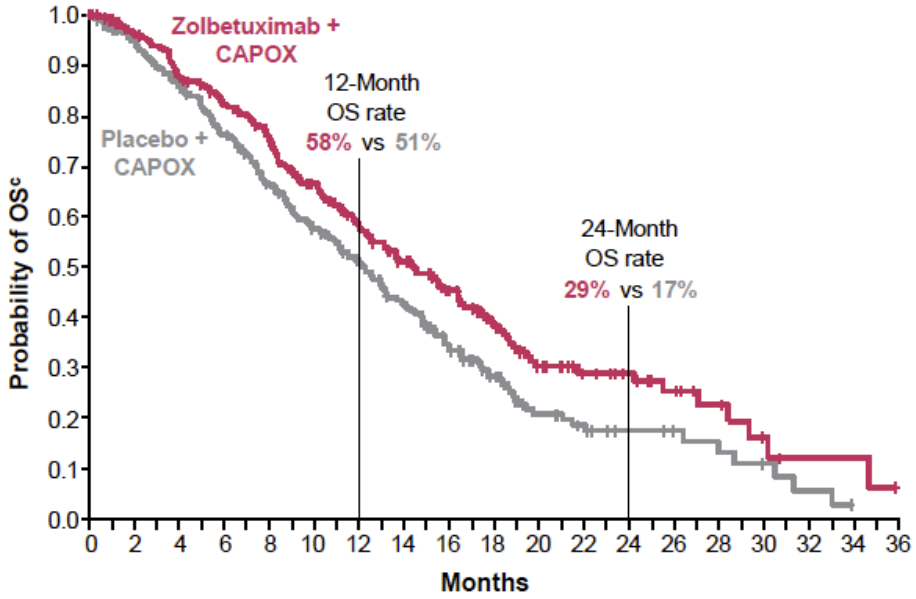
CM-649 3yr, JCO 2024

Other Animals Have Tails Too

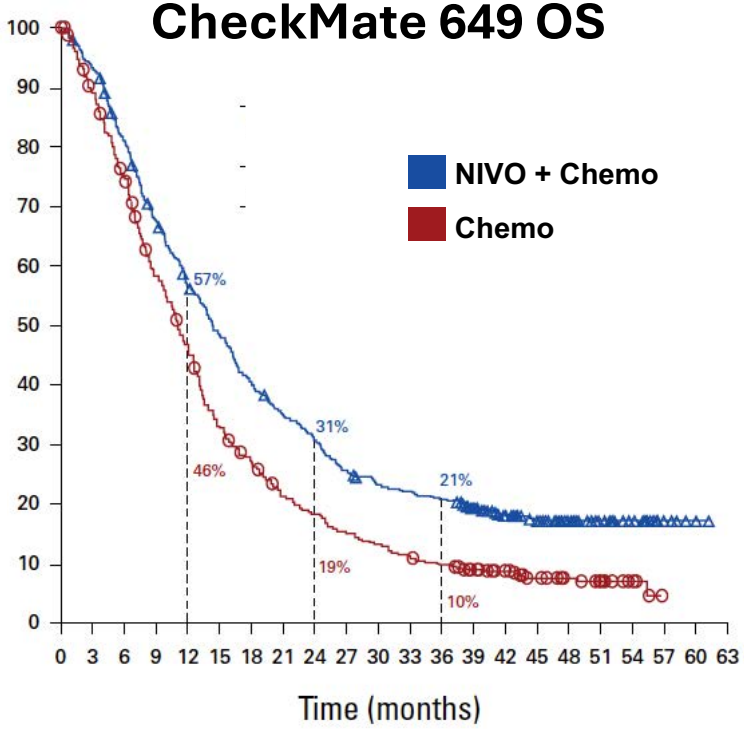
SPOTLIGHT OS



GLOW OS



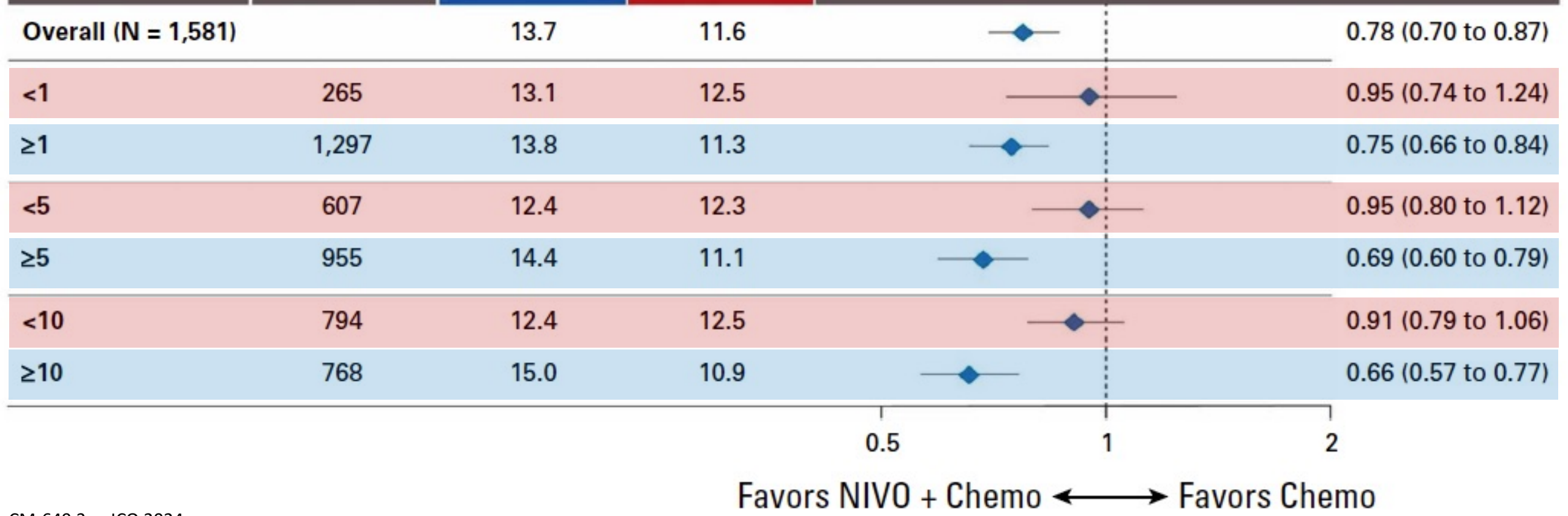
CheckMate 649 OS



SPOTLIGHT and GLOW, ESMO 2023, CM-649 3yr, JCO 2024

The Tail is the Tail: 3-yr CheckMate 649 Follow Up

PD-L1 CPS[a]	No. of Patients	Median OS, Months		Unstratified HR for Death (95% CI)
		NIVO + Chemo	Chemo	
Overall (N = 1,581)		13.7	11.6	0.78 (0.70 to 0.87)
<1	265	13.1	12.5	0.95 (0.74 to 1.24)
≥1	1,297	13.8	11.3	0.75 (0.66 to 0.84)
<5	607	12.4	12.3	0.95 (0.80 to 1.12)
≥5	955	14.4	11.1	0.69 (0.60 to 0.79)
<10	794	12.4	12.5	0.91 (0.79 to 1.06)
≥10	768	15.0	10.9	0.66 (0.57 to 0.77)



CM-649 3yr, JCO 2024

KEYNOTE-859

Key Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma of the stomach or GEJ
- Locally advanced unresectable or metastatic disease
- No prior treatment
- Known PD-L1 status (assessed centrally using PD-L1 IHC 22C3)
- HER2-negative status (assessed locally)
- ECOG PS 0 or 1

R 1:1

- Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)
- Placebo IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Stratification Factors

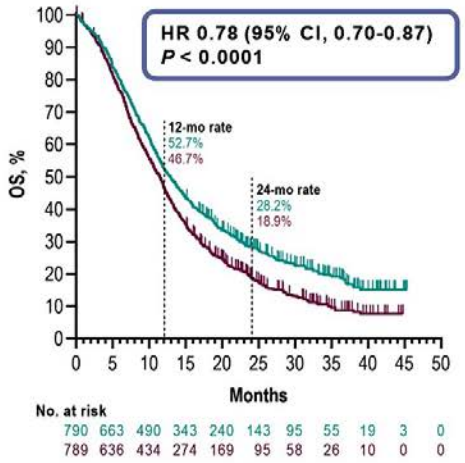
- Geographic region (Europe/Israel/North America/Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

- **Alpha-controlled analyses:** OS, PFS, and ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations

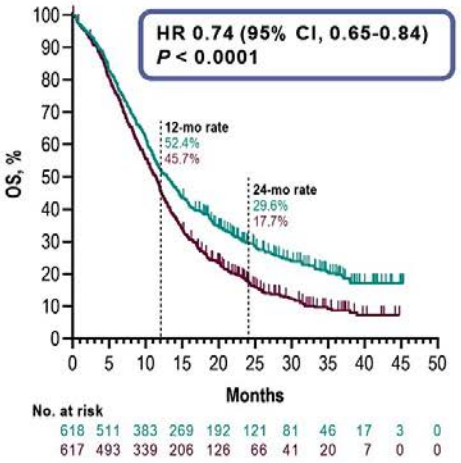
Overall[1]

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



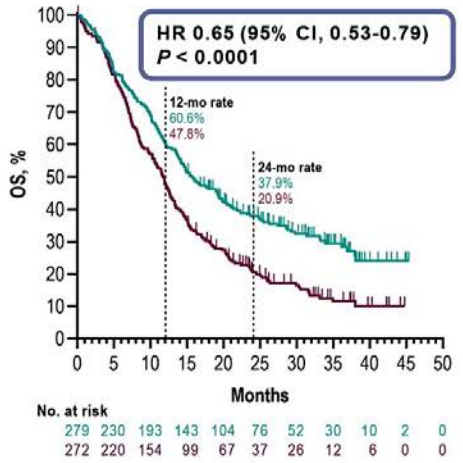
PD-L1 CPS ≥1

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	75.1%	13.0 (11.6-14.2)
Placebo + chemo	85.3%	11.4 (10.5-12.0)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)

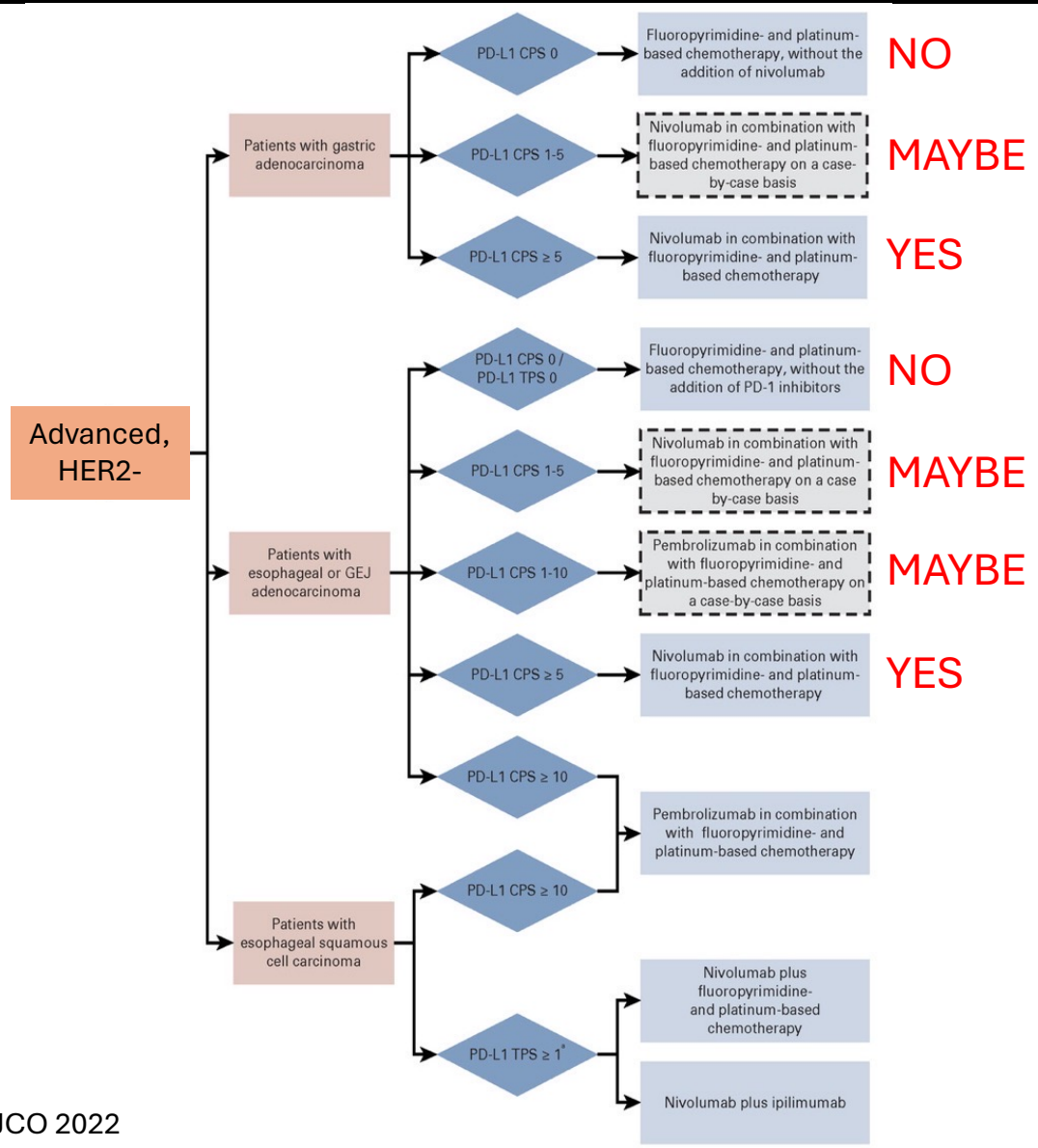


1. Rha SY et al. *Ann Oncol* 2023;34:319-320.
Data cutoff date: October 3, 2022.

Rha SY et al. ASCO 2023;Abstract 4014.

RTP RESEARCH TO PRACTICE

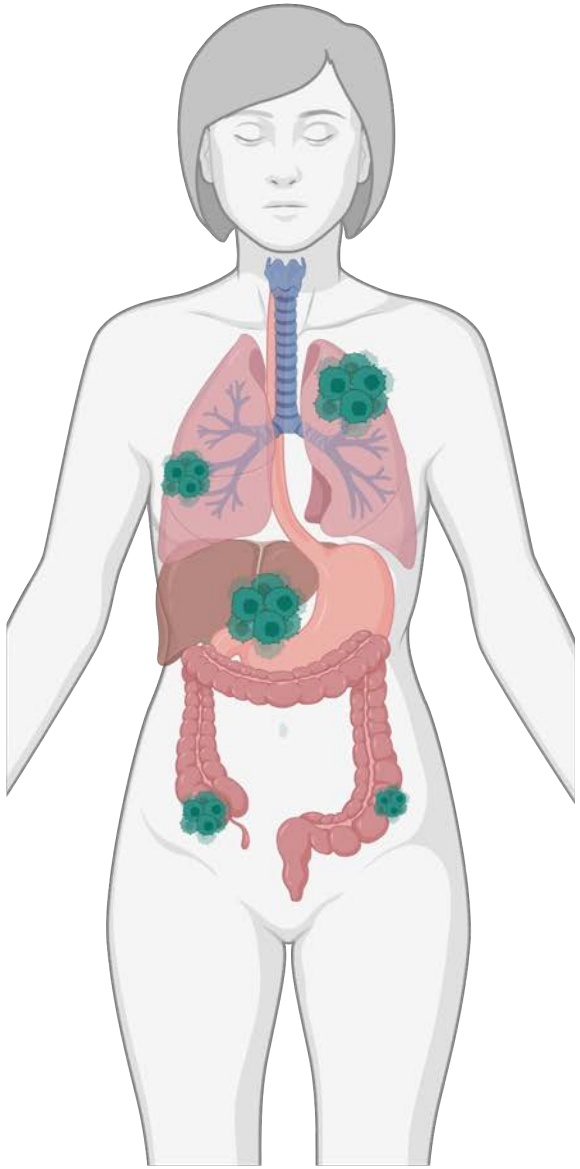
What Does ASCO Say?



- PD-L1 **CPS** testing helps to inform role for IO in 1L for EAC, GEJ, GC
- PD-L1 **TPS** may be better predictor in ESCC
- Approach to CPS consideration similar in GEJ adeno and GC
- ASCO guidance is somewhat divergent from FDA labels in GEJ/GC
- Shared decision making remains important

JCO 2022

SUMMARY #2: ADVANCED DISEASE



- 5FU/Oxaliplatin is the preferred frontline backbone
- NEED to test everyone for biomarkers
- The addition of anti-PD-1 improves OS, benefit largely restricted to PD-L1+ patients
- Trials are the pathway to advance our standards
- Oligometastatic strategies and peritoneal-directed approaches should be done in context of a trial

Agenda

Module 1: Current and Potential Role of Immune Checkpoint Inhibitors — Dr Klempner

Module 2: Other Available and Emerging Therapeutic Approaches — Dr Janjigian

Memorial Sloan Kettering Cancer Center

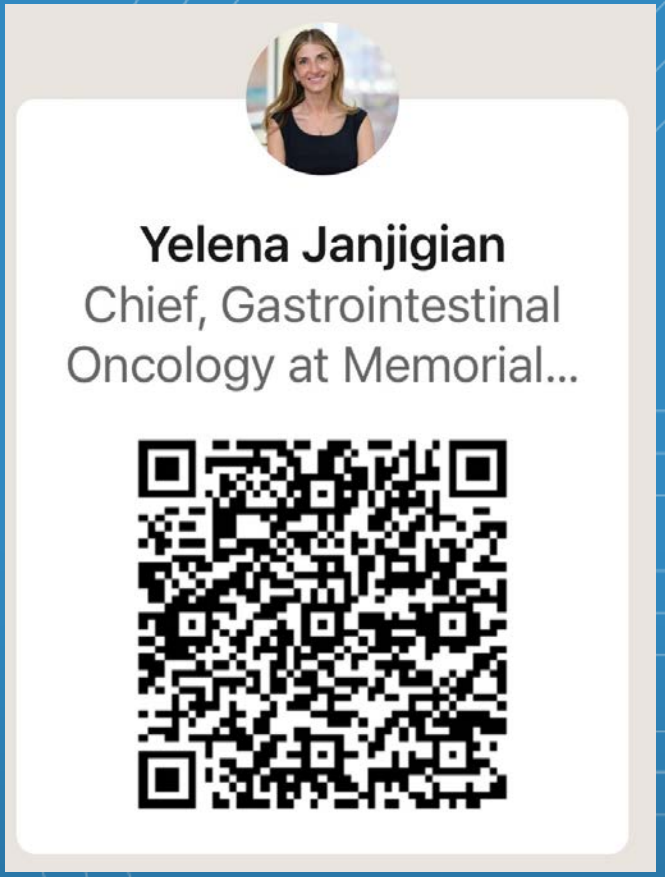
Available and Emerging Therapeutic Approaches

Yelena Y. Janjigian, MD
Chief Attending Physician

Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Email: janjigiy@mskcc.org

Sunday, March 24th | 8 minutes



Disclosures

Advisory Committees and Consulting Agreements	AbbVie Inc, Amerisource Bergen, Arcus Biosciences, AskGene Pharma, Astellas, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo Inc, Geneos Therapeutics, GSK, Guardant Health, Imugene, Inspirna, Lilly, Lynx Health LLC, Merck, Merck Serono, Mersana Therapeutics Inc, Pfizer Inc, Seagen Inc, Silverback Therapeutics, Zymeworks Inc
Contracted Research	Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Genentech, a member of the Roche Group, Inspirna, Lilly, Merck, Transcenta
Data and Safety Monitoring Boards/Committees	Arcus Biosciences, Daiichi Sankyo Inc, Transcenta
Stock Options — Private Company	Inspirna
Nonrelevant Financial Relationships	Clinical Care Options, Cycle for Survival, Fred's Team, HMP Education, Imedex, MJH Life Sciences, National Cancer Institute, Paradigm Medical Communications, PeerView Institute, US Department of Defense

53-year-old woman with Stage IV gastric adenocarcinoma

GERD, PPI

↑ gas, bloating, early satiety, wt loss (25 lbs/11 kg)

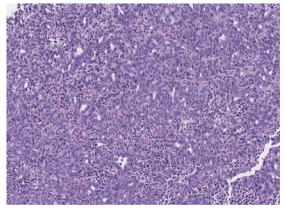
EGD: ulcer
CT CAP: 2.5cm lesion lesser curvature, peritoneal carcinomatosis

FOLFOX + nivolumab x 11 cycles

5FU/Nivolumab maintenance

EGD: benign on bx
CT CAP: Resolution of radiographic disease

Months: - 4 | - 2 | 0 | 5 | 9 | 36



Infiltrating adenocarcinoma moderately to poorly differentiated

IHC for **HER2** (4B5, Ventana): **Negative** (Score 0)
IHC for **PD-L1** expression (clone E1L3N): **Combined Positive Score (CPS) 20 (of 100)**
Mismatch repair proteins: MLH1, MSH2, MSH6, PMS2 present
ACLDN18.1&2 (clone 43-14A) moderate (2) and/or strong
(3) membranous staining in 40% of the tumor cells.

7 Mutations (page 1 of 1)

Samples	Gene	Protein Change	Annotation	Mutation Type
1	PIK3CA	*G106R*		Missense
1	KRAS	*G13D*		Missense
1	CREBBP	*R1446S*		Missense
1	SMARCA4	*R1135W*		Missense
1	BCOR	*L775Vfs*42*		FS ins
1	SETD2	*Y1605N*		Missense
1	NSD1	*S1061N*		Missense

Showing 1-7 of 7 Mutations

HER2+ GEC Combination trastuzumab and pembrolizumab

- 45 yo M with metastatic HER2+ (IHC 3+) GEJ adenocarcinoma involving the lungs
- Started on clinical trial of CAPOX, trastuzumab and pembrolizumab response w/ subsequent progression after 2 years

Samples	Gene	Protein Change	Annotation	Mutation Type	Allele Freq
2	CDK12	*CDK12-intragenic*		Fusion	
1 2 3	TP53	*C176W*		Missense	▪▪
2	SMAD4	*K51**		Nonsense	-
2	RASA1	*L493**		Nonsense	-
1 2	RNF43	*RNF43-intragenic*		Fusion	
2	APC	*S1042R*		Missense	-
2	ATM	*E1530A*		Missense	-
2	DNMT1	*K905N*		Missense	-
2	TRAF2	*TRAF2-MICU1 fusion*		Fusion	
2	CCNQ	*E204G*		Missense	-
2	MICU1	*TRAF2-MICU1 fusion*		Fusion	

Showing 1-11 of 11 Mutations | Show more | Reset

8 Copy Number Alterations (page 1 of 1)

Samples	Gene	CNA	Annotation	Cytoband
1 2	ERBB2	AMP		17q12
1	PRKN	DeepDel		6q26
1 2	CCNE1	AMP		19q12
1 2	AURKA	AMP		20q13.2
1 2	GNAS	AMP		20q13.32
1 2	CEBPA	AMP		19q13.11
1 2	RTEL1	AMP		20q13.33
1 2	KMT2B	AMP		19q13.12

1 = pre-treatment

2 = progression

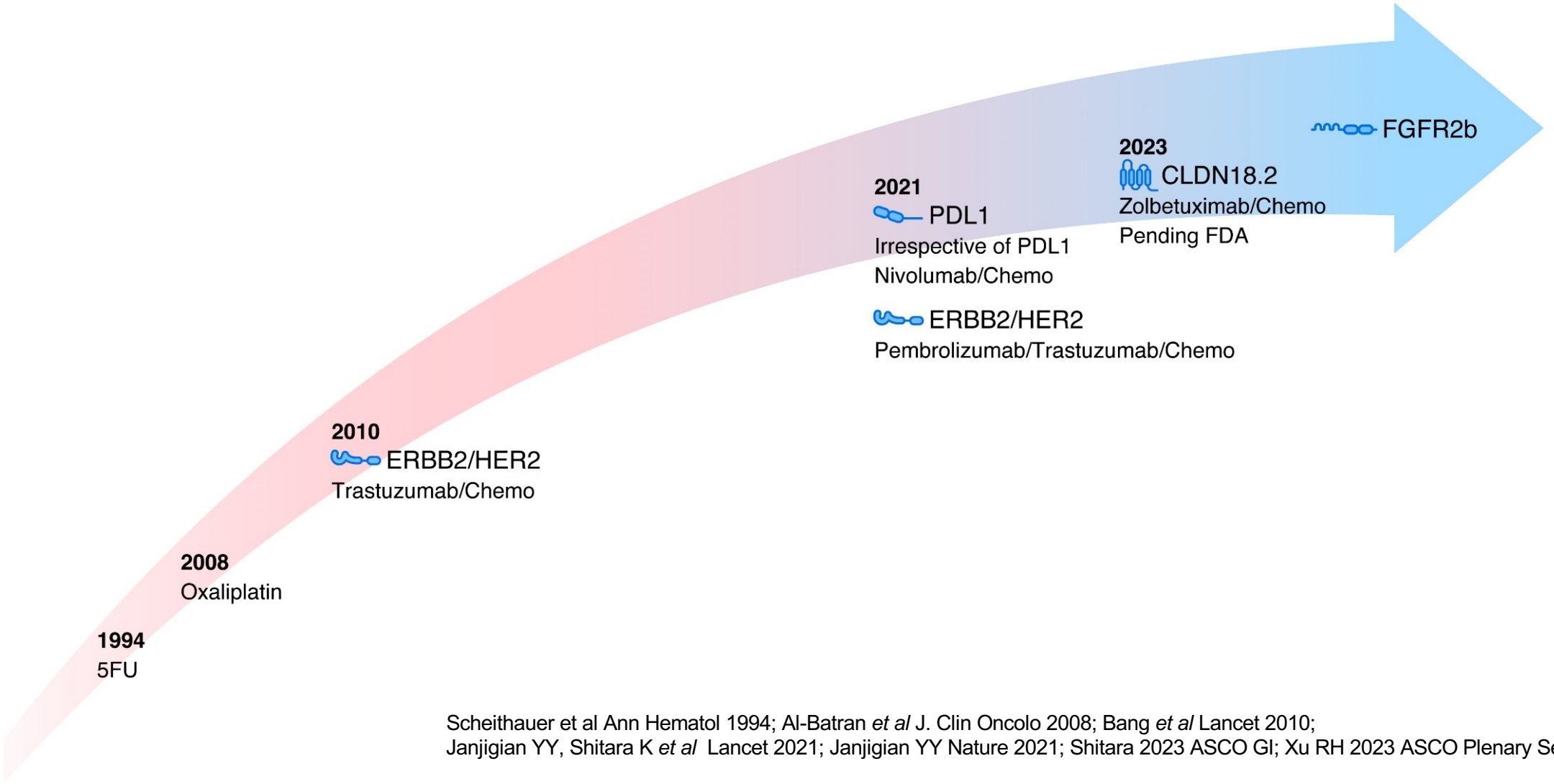
3 = ctDNA (MSK-ACCESS)

Memorial Sloan Kettering Cancer Center

Biomarker selection in gastric adenocarcinoma

Biomarker	Prevalence in metastatic gastric cancer	Therapeutic agent(s)
ERBB2/HER2	**20%**	Trastuzumab and Pembrolizumab
MSI-high	**5%** in Stage IV **20%** in Stage I-III	Pembrolizumab or Nivolumab
EBV-positive	**3%**	Pembrolizumab or Nivolumab
PD-L1 CPSBio	**80%** CPS ≥ 1 **60%** CPS ≥ 5	Pembrolizumab and Nivolumab
FGFR2b overexpression	**30%**	Bemarituzumab
CLDN18.2	**35%**	Zolbetuximab
Tumor sequencing	NTRACK, EGFR, MET, RAS amplification	Larotrectinib, Afatinib, etc.
Plasma DNA	Monitoring for response and resistance	Broad application

Evolution of first-line therapy in gastric cancer



Scheithauer et al Ann Hematol 1994; Al-Batran *et al* J. Clin Oncolo 2008; Bang *et al* Lancet 2010;
Janjigian YY, Shitara K *et al* Lancet 2021; Janjigian YY Nature 2021; Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

Biomarker overlap in gastric cancer

- *Reflex testing of all tumors is critical*
- Overlap between PD-L1 CPS ≥5 and CLD18.2 high in 20% patients

	Kubota Y 2022[1] **CLDN18.2+ 24%**	Pellino A 2021[1] **CLDN18.2+ 33%**	Jia K 2022[2] **CLDN18.2+ 52%**	SPOTLIGHT[1] **CLDN18.2+ 38%**	GLOW[1] **CLDN18.2+ 38%**
HER2+	15%	15%	21%	-	-
dMMR/MSI	5%	13%	14%	-	-
PD-L1[3] CPS < 1	26%	74%	21%		
CPS ≥ 5	42%	18%	--	13%	22%
Diffuse Type	48%	40%	29%	29%	34%
Intestinal Type	52%	46%	38%	25%	14%
Mixed/Other	-	-	-	46%	51%

1. CLDN18.2+ as >= 75% tumor cells with 2+/3+ membrane staining, IHC Ab = clone 43-14A (Kubota and Pellino) RxDx Assay (SPOTLIGHT and GLOW)
2. CLDN18.2+ as >=40% tumor cells with 2+ or higher membrane staining, IHC Ab = ab222512
3. PD-L1 testing antibodies; Kubota SP142 or SP263, Pellino 22C3, Jia E1L3N

Kubota… Shitara ESMO Open., 2022; Pellino JP Medicine. 2021; Jia BMC Med. 2022; Shitara et al Proc ASCO GI 2023, Xu et al ASCO Plenary Series 2023

Therapy prioritization in first-line gastric cancer

- Patient functional status and disease burden
- Therapeutic urgency and timing of biomarker testing
- Adverse event profile
- Strategy to maximize therapeutic options
- **Long term survival**

Immunotherapy in gastric adenocarcinoma

- Nivolumab with chemotherapy approved in the United States for 1st-line treatment irrespective of PD-L1 status[1]
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease[2]
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥ 3rd-line treament[3]
- Pembrolizumab approval for ≥ 3rd-line treatment in the United States to be withdrawn (announced in July 2021)[4]
- Pembrolizumab approved in TMB ≥ 10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,5]

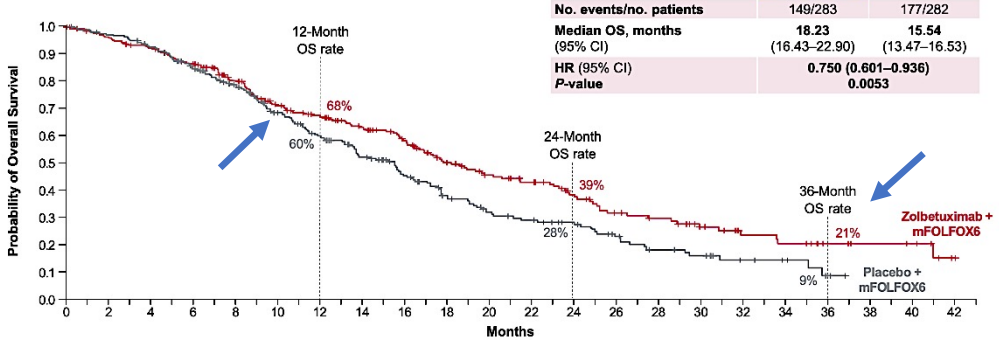
1. Nivolumab [package insert]. Princeton, NJ; 2021. 2. Pembrolizumab [package insert]. Whitehouse Station, NJ; 2021. 3. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel).* 2021;14:151. 4. Press release, July 1, 2021. Accessed July 20, 2021. 5. Press release, August 24, 2020. Accessed July 20, 2021.

OS KM Curves: early & sustained separation are important

CLD18.2 +

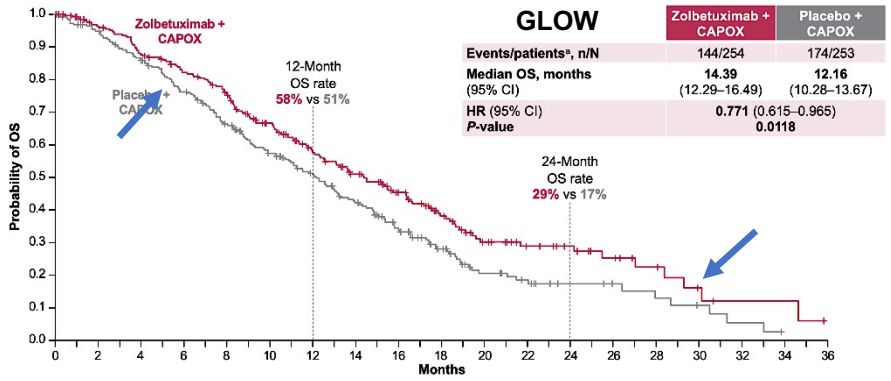
SPOTLIGHT

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	18.23 (16.43–22.90)	15.54 (13.47–16.53)
HR (95% CI)	0.750 (0.601–0.936)	
P-value	0.0053	



GLOW

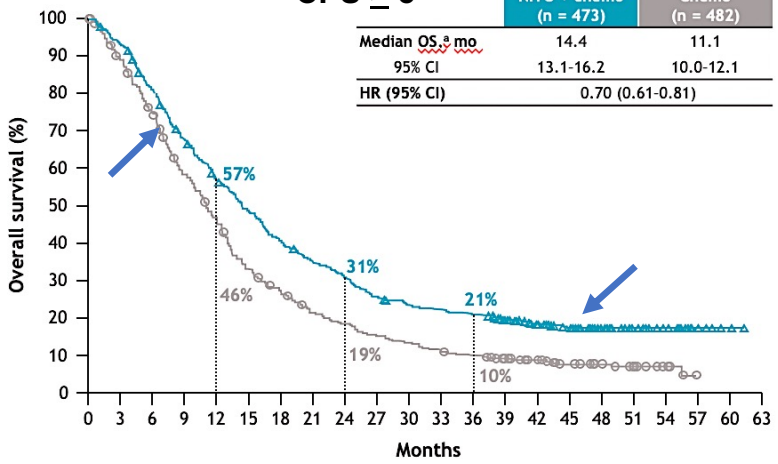
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	14.39 (12.29–16.49)	12.16 (10.28–13.67)
HR (95% CI)	0.771 (0.615–0.965)	
P-value	0.0118	



CheckMate 649 NIVO/CHEMO vs CHEMO

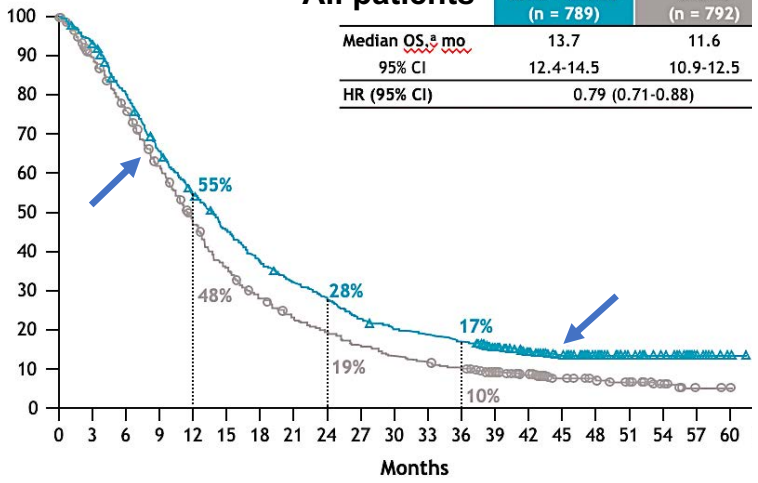
CPS ≥ 5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	14.4	11.1
95% CI	13.1-16.2	10.0-12.1
HR (95% CI)	0.70 (0.61-0.81)	



All patients

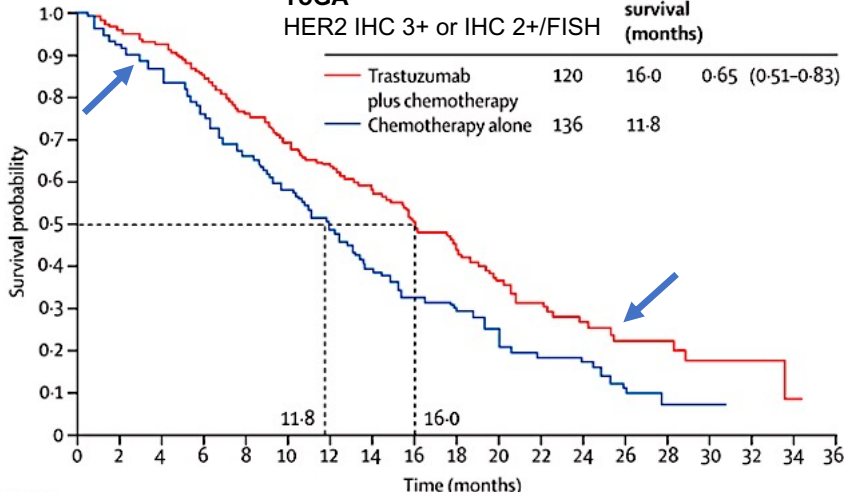
	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.7	11.6
95% CI	12.4-14.5	10.9-12.5
HR (95% CI)	0.79 (0.71-0.88)	



HER2 +

ToGA
HER2 IHC 3+ or IHC 2+/FISH

	Events	Median overall survival (months)	HR (95% CI)
Trastuzumab plus chemotherapy	120	16·0	0·65 (0·51–0·83)
Chemotherapy alone	136	11·8	



Bang *et al* Lancet 2010; Janjigian YY, *et al* *2023 ASCO GI*; Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

OS KM Curves: early & sustained separation are needed

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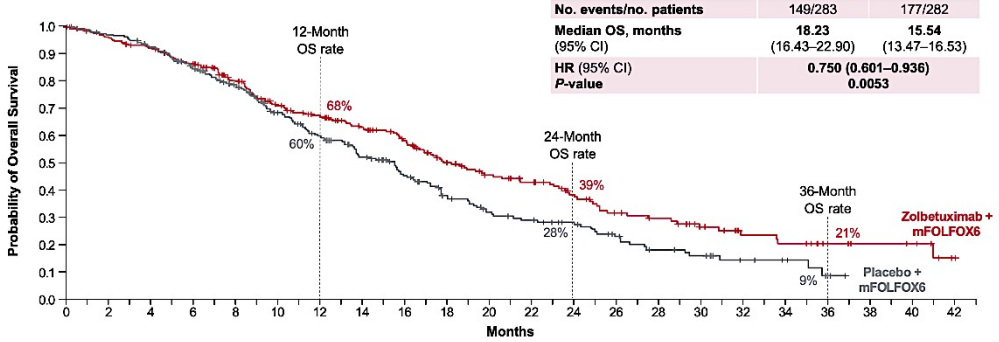

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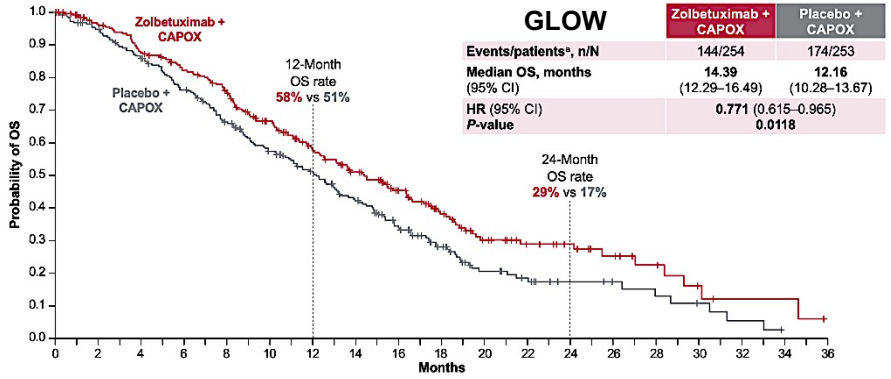
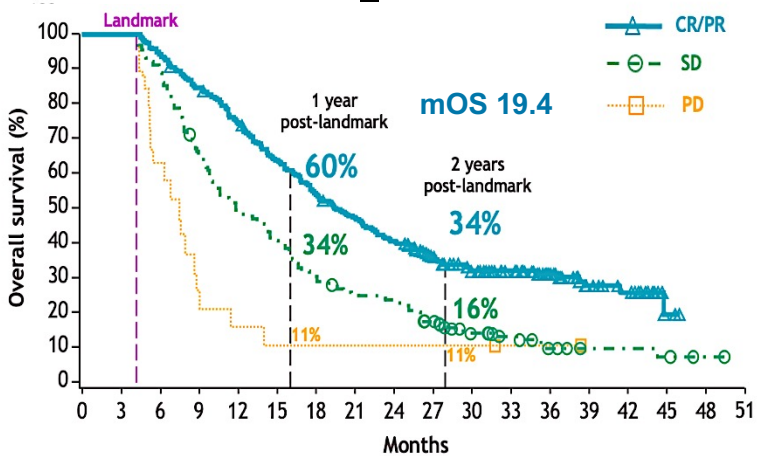
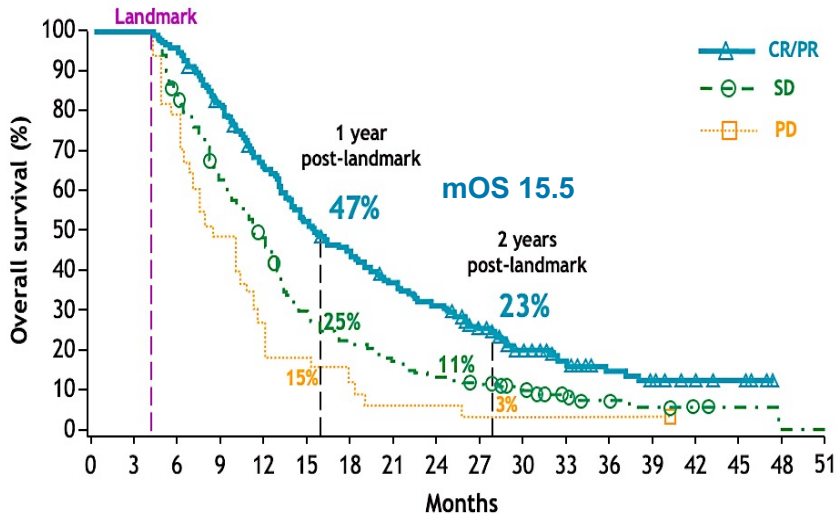


CheckMate 649 NIVO/CHEMO vs CHEMO outcomes by best RECIST response

CPS ≥ 5





HER2 +

ToGA
HER2 IHC 3+ or IHC 2+/FISH

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Trastuzumab plus chemotherapy	120	16·0	0·65 (0·51–0·83)
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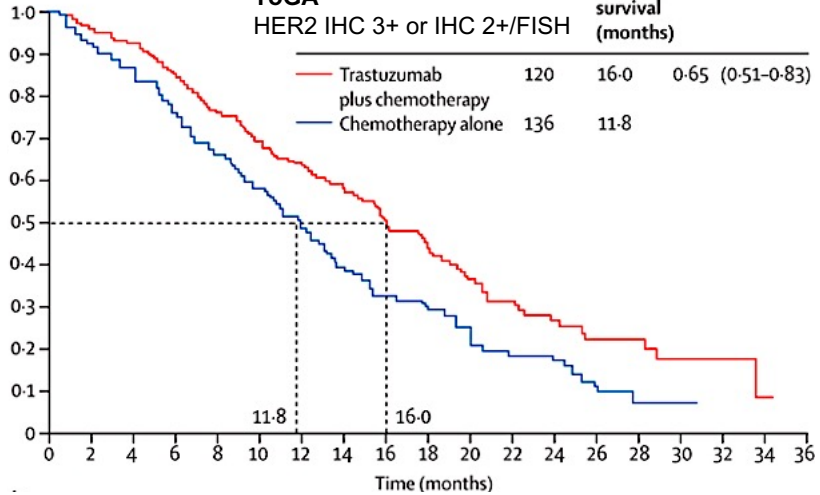
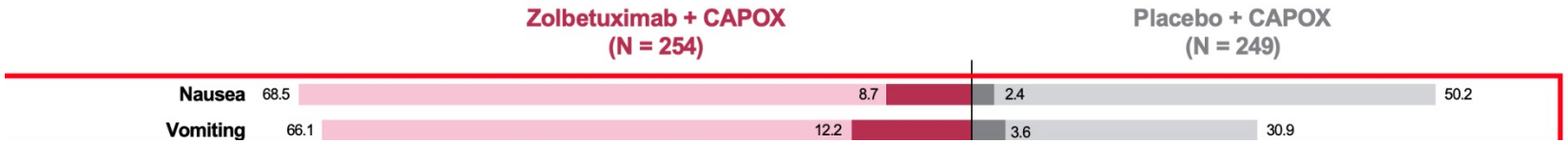


Bang *et al* Lancet 2010; Janjigian YY, *et al* *2023 ASCO GI*; Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

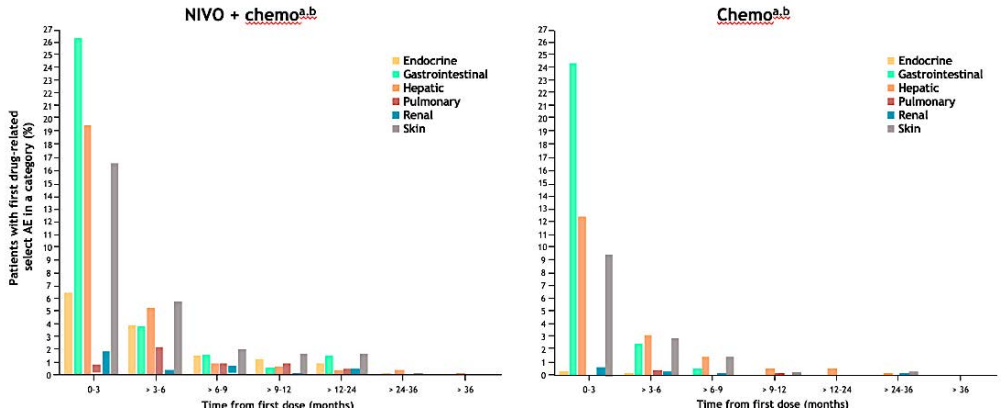
Adverse events on therapy



Event, n (%)	Zolbetuximab + CAPOX (N = 254)	Placebo + CAPOX (N = 249)
All TEAEs	251 (98.8)	244 (98.0)
Grade ≥3 TEAEs	185 (72.8)	174 (69.9)
Serious TEAEs	120 (47.2)	124 (49.8)
TRAEs leading to discontinuation of any study drug	55 (21.7)	39 (15.7)
TRAEs leading to discontinuation of zolbetuximab or placebo	18 (7.1)	11 (4.4)
TRAEs leading to death[a–c]	6 (2.4)	7 (2.8)

All treated,[a] n (%)	NIVO + chemo (n = 782)		Chemo (n = 767)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[b]	739 (95)	473 (60)	682 (89)	346 (45)
Serious TRAEs[b]	176 (23)	134 (17)	95 (12)	78 (10)
TRAEs leading to discontinuation[b,c]	331 (42)	147 (19)	198 (26)	73 (10)
Treatment-related deaths[d]	16[e] (2)		4[f] (< 1)	

Emergence of TRAEs with potential immunologic etiology over time



Bang *et al* Lancet 2010; Yamaguchi *et al* *2022 JSMO*;
Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series Virtual

Prioritization of biomarker-based therapy

Efficacy outcome	CheckMate 649	KEYNOTE-811	SPOTLIGHT	GLOW
	NIVO+CHEMO vs. CHEMO	PEMBRO+TRAS CHEMO vs. TRAS/CHEMO	ZOLBE+CHEMO vs. CHEMO	ZOLBE+CHEMO vs. CHEMO
mOS Δ	ITT HR 0.79; 2.1 mos CPS≥ 5 HR 0.7; 3.3 mos MSI-H HR 0.34; 26.4 mos	-	HR 0.75; 2.7 mos	HR 0.77; 2.2 mos
12 mos OS Δ	11%	-	8%	7%
24 mos OS Δ	12%; 36 mos 11%	-	11%	12%
mPFS Δ	ITT HR 0.79; 0.8 mos CPS≥ 5 HR 0.7; 2.2 mos	-	HR 0.75; 1.9 mos	HR 0.68; 1.4 mos
ORR Δ	ITT 12%; CPS≥ 5 15%;	22.7%	0	0

1. **MSI-H**
2. **HER2**
3. **PDL1 CPS ≥5**
4. **CLD18.2 high**

Janjigian YY, 2023 ASCO GI; Janjigian YY Nature 2021;
Shitara 2023 ASCO GI; Xu RH 2023 ASCO Plenary Series

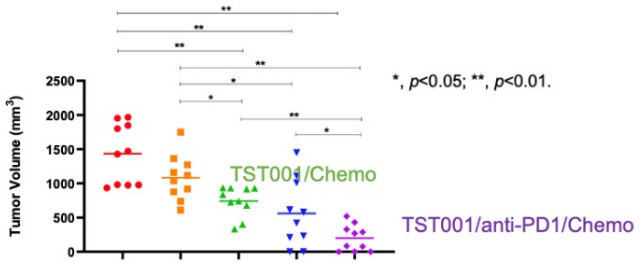
Major Claudin 18.2 strategies in the clinic

TST001: high affinity CLDN18.2 Antibody comparison with zolbetuximab

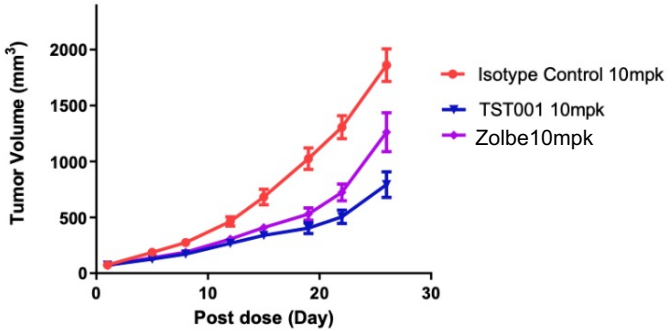
- ✓ **Humanized** vs. chimeric antibody
- ✓ Higher **affinity** (20 pm vs. sub nM)
- ✓ Higher **ADCC activity** (30-100 fold)
- ✓ **More active** at lower dose (6 mg/kg vs. 18 mg/kg)

TST001/anti-PD1/FOLFOX in CLDN18.2 + model

Individual Tumor Volume on Day 22

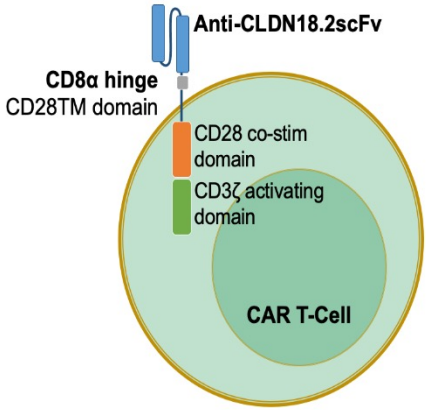


TST001 monotherapy CLDN18.2 low (IHC 1+, 30%) model



CAR T-Cell

CT041[1]

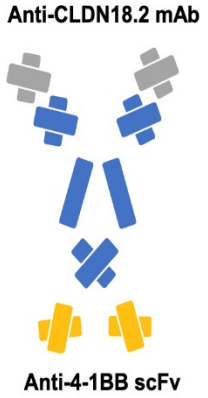


Engineered mAb

ZL-1211[2]
(Humanized IgG1)

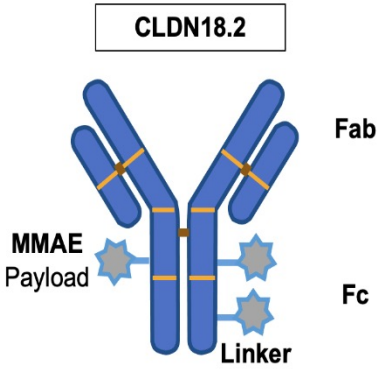
Bispecific Ab

TJ-CD4B[3]



Antibody–Drug Conjugate

CMG901[1]



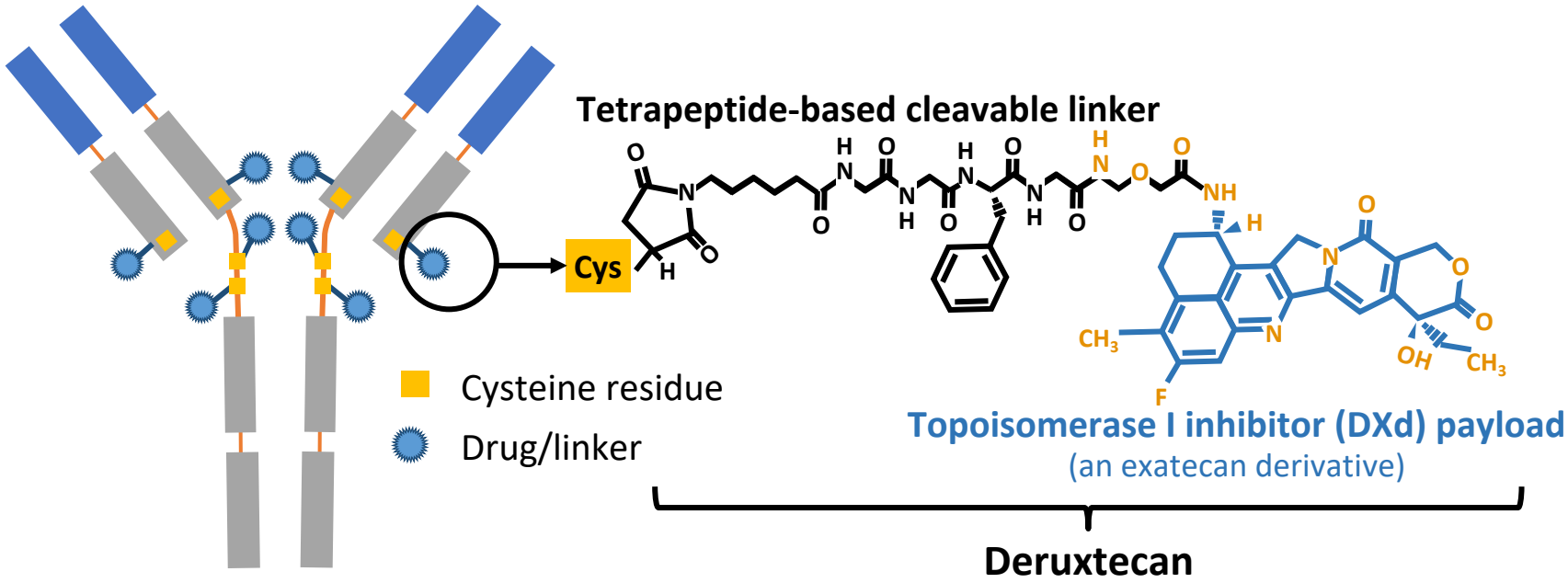
HER2 Inhibition in GE Adenocarcinoma

- Up to 30% HER2+
- First-line trastuzumab/chemotherapy FDA approved mOS 13.8 mos ORR 47%
- 30% of GEJ HER2+ tumors with co-alterations of the RTK/RAS/PI3K pathway–intrinsic resistance
- HER2 inhibition alone in 1st line insufficient to overcome intrinsic resistance-several negative studies (LOGIC, JACOB, HELOISE)
- Pembrolizumab/Trastuzumab/chemotherapy FDA approved in 1st line

Bang Y et al. *Lancet*. 2010;376:687-697 ; Janjigian YY et al. *Cancer Discov*. 2018;8:49-58.*Hecht JR et al. J Clin Oncol, 2016. Tabernero J et al. Lancet Oncol, 2018. Shah MA et al. J Clin Oncol, 2017; Janjigian et al, ASCO 2021; Shitara et al. NEJM 2020*

HER2-Targeted ADC: Trastuzumab Deruxtecan (T-DXd)

Humanized anti-HER2 IgG1 mAb with same AA sequence as trastuzumab



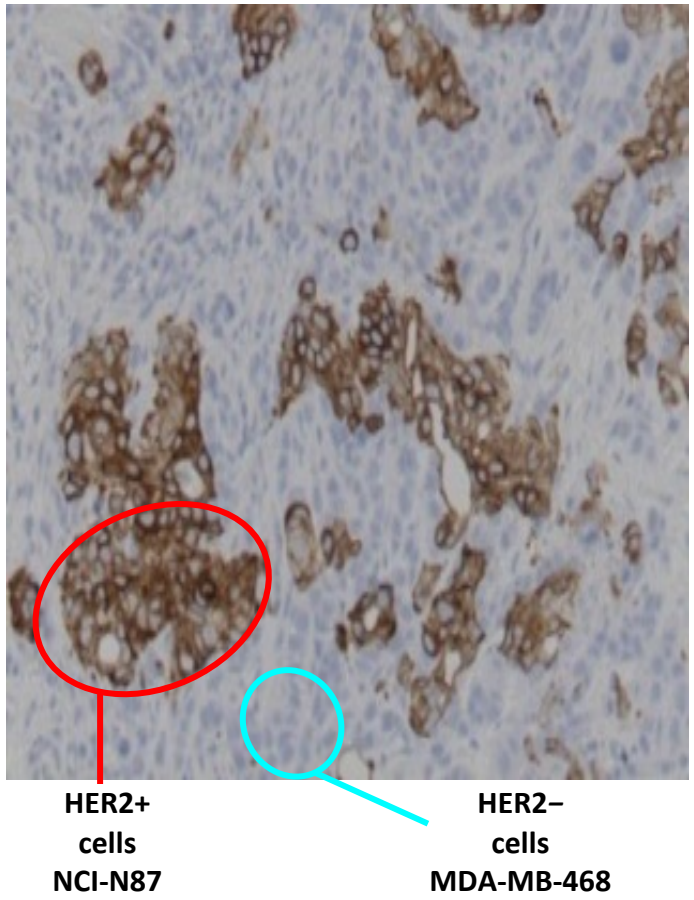
- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039. Ogitani. Clin Cancer Res. 2016;22:5097.

Bystander Effect of ADCs T-DXd to overcome HER2 heterogeneity

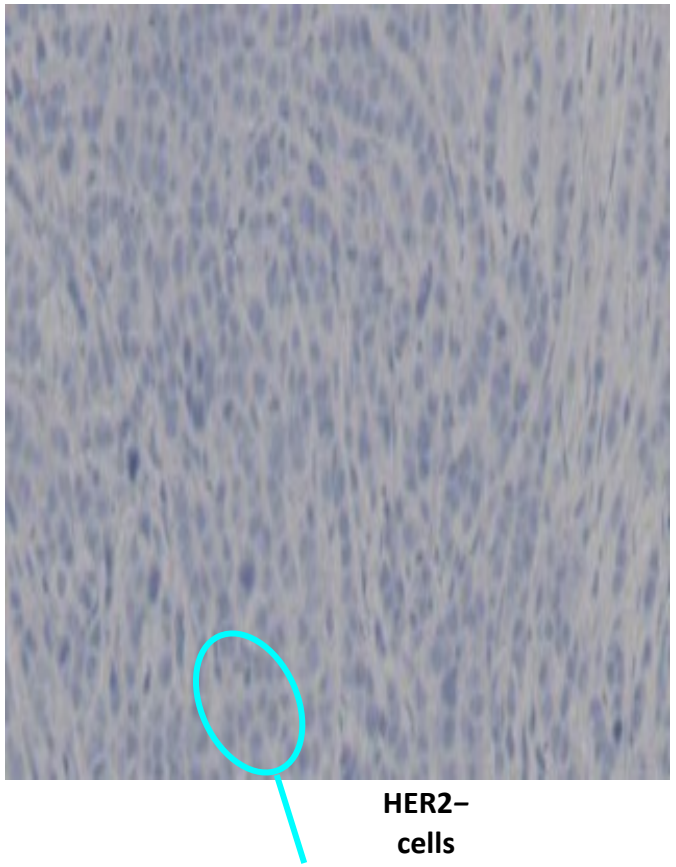
Control

Co-culture of HER2+ and HER2− tumors in vivo



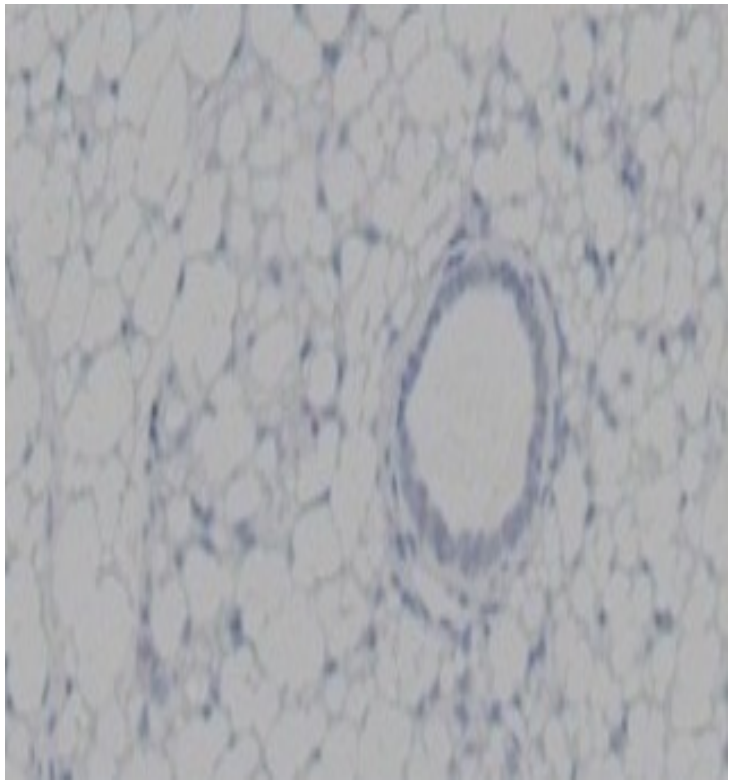
T-DM1, 10 mg/kg

HER2− cells still persist



Trastuzumab Deruxtecan, 3.0 mg/kg

Both HER2+ and HER2− are impacted



Tumor regression

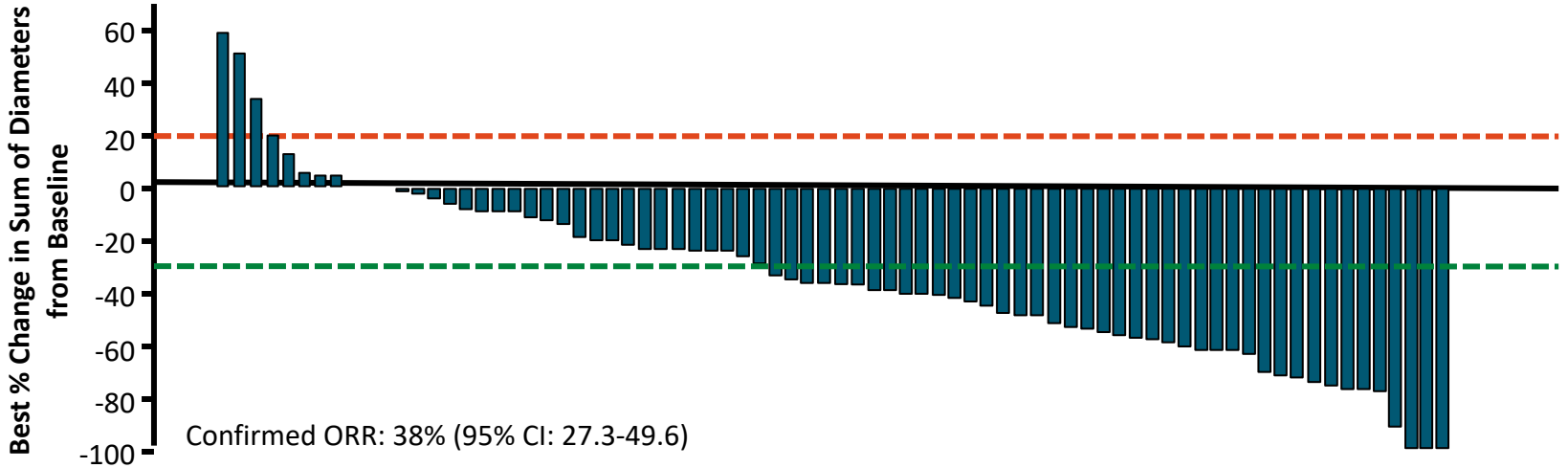
Ogitani. Cancer Sci. 2016;107:1039. Iwata. ASCO 2018. Abstract 2501.

Tumor Size Change with T-DXd in HER2+ Adv Gastric/GEJ Cancer After Trastuzumab (DESTINY-Gastric01 and 02)

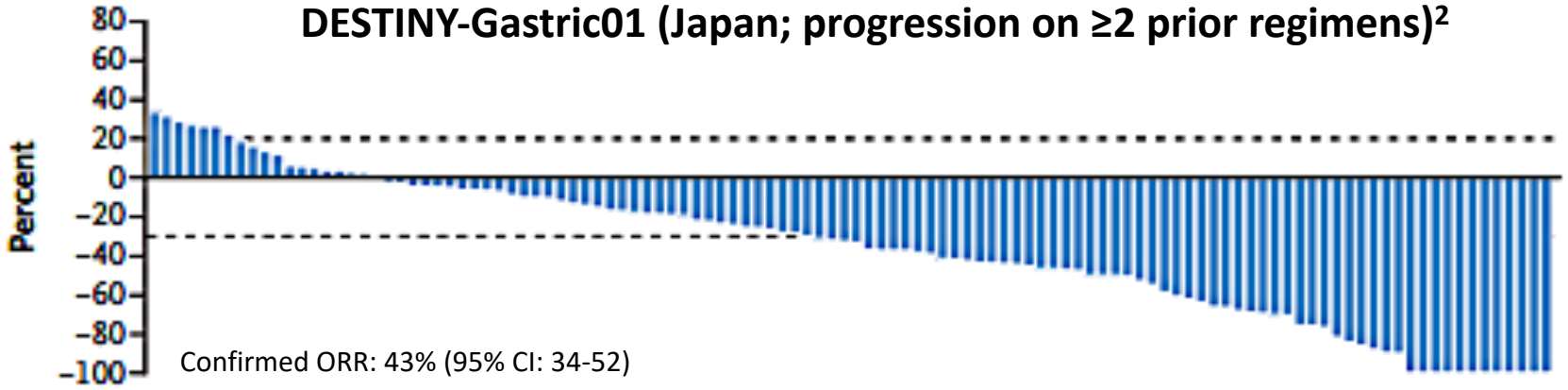
Efficacy[2]	T-DXd (N = 79)
ORR, % (95% CI)	38 (27.3-49.6)
Median DOR, mo	8.1
Median PFS, mo (95% CI)	5.5 (4.2-7.3)

Survival, mo (95% CI)[2]	T-DXd (n = 125)	Chemo (n = 62)
Median OS	12.5 (9.6-14.3)	8.4 (6.9-10.7)
HR for death: 0.59; *P* = .01		
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
HR for PD or death: 0.47		

DESTINY-Gastric02 (US/Europe; progression on 1L trastuzumab)[1]



DESTINY-Gastric01 (Japan; progression on ≥2 prior regimens)[2]



1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Shitara. NEJM. 2020;382:2419.

Future of HER2 therapy

- Anti-PD-1 therapy improves survival & transforms patient lives
- HER2, PDL1 and dynamic nature of CIN will impact long term outcomes
- Greater magnitude of benefit in biomarker enriched populations
- Critical to continue to test for HER2, MSI, PDI-1 and ctDNA
- WES and RNAseq will guide future research strategies
- HER2 ADCs moving to first line with capecitabine & anti-PD-1
- Promise of PD-1/CTLA4 in select patients

The Annual
National General Medical Oncology Summit

Sunday, March 24, 2024

Moderator

Neil Love, MD

Faculty

Ghassan Abou-Alfa, MD, MBA
Natalie S Callander, MD
Kristen K Ciombor, MD, MSCI
Richard S Finn, MD
Yelena Y Janjigian, MD
Samuel J Klempner, MD
Andrew H Ko, MD
Eileen M O'Reilly, MD
Paul G Richardson, MD
John Strickler, MD

We are taking a short break!

The program will resume at 9:30 AM ET

Up Next…

Drs Ghassan Abou-Alfa and Richard Finn
discuss the management of hepatobiliary cancers

RTP
RESEARCH
TO PRACTICE