Updates in Multiple Myeloma

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Disclosure of Conflicts of Interests

Hana Safah, MD has the following financial relationships to disclose:

Speaker – Astellas, BMS, GSK, Incyte,Jazz, Sanofi

Updated Results from CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel,a BCMA–Directed CAR-T Cell Therapy, in RR/MM

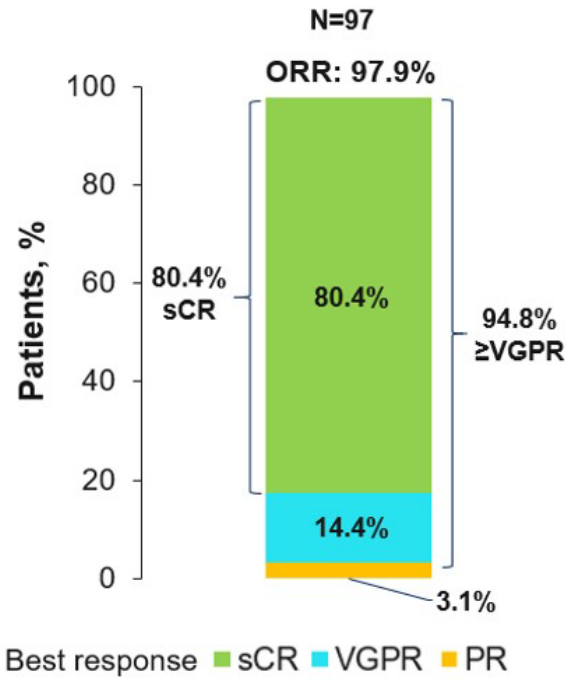
Ciltacabtagene autoleucel (cilta-cel), (CAR-T) cell expressing anti-BCMA CAR (consisting of 2 BCMA-binding domains, a CD3-ζ signalling domain, and a 4-1BB costimulatory domain), followed by T-cell expansion.

Methods

- 113 patients , 14% did not receive Cita-cell infusion because of progression, death or withdrawal, no manufacture failure
  - Median age 61, median # of lines of therapy 6, all underwent apheresis
- Patients underwent lymphodepletion with 300 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine both given intravenously daily for 3 days.
- A single infusion of cilta-cel at a target dose of $0{\cdot}75 \times 10^6$ CAR-T cellskg (range $0{\cdot}5 \times 10^6$–$1{\cdot}0 \times 10^6$) was administered 5–7 days after the start of lymphodepletion

Efficacy

Figure: Overall response rate (N=97)



ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

MRD-negative at 10-5 in complete response or stringent complete response: 33/34; 94%
Achieved in 1 month

Median PFS was not reached, 12-months
PFS was 77%, OS 85%

Berdeja, Lancet 2021.

Safety

- 14 Deaths: 0 within the first 30 days, 2 within 100 days, 12 more than 100 days post infusion.
  - TRM: 2 to sepsis or septic shock , 1 CRS and HLH, 1 lung abscess, 1 respiratory failure , 1 neurotoxicit
  - Other: 2 due to progressive disease, 3 AEs considered unrelated to treatment ,2 acute myelogenous leukemia
- All 97 patients had adverse events, including grade 3–4 events
  - Haematological adverse events were the most common; grade 3–4 anaemia [68%]), leukopenia [61%]), thrombocytopenia [60%]), and lymphopenia [50%], recovered to grade 2 or less by day 30
  - CRS in 95%, (51%) patients had grade 1, 39% grade 2, 3% grade 3, (1%) each had grade 4 and 5
    - Median time to onset from cilta-cel infusion was 7·0 days (IQR 5·0–8·0); (89%) after day 3
    - Median duration was 4·0 days (IQR 3·0–6·0; excluding one patient with 97-day duration).
    - 91% of patients received treatment, tocilizumab 69%; corticosteroids 22%, and anakinra 19%, 1 patient with grade 5 CRS and HLH died
  - Neurotoxocity 12% all had CRS and 8% had ICANs
    - Median time to onset 8.0 days, median duration 4.0 days median time to recovery was 74·5 days (IQR 28·0–159·0)
    - Resolved in all patients

Berdeja, Lancet 2021.

Updated of Results from the Phase I CRB-402 Study in RRMM

BACKGROUND

- Idecabtagene vicleucel (ide-cel, bb2121) is the first (CAR) T cell therapy approved for the treatment of RRMM after four or more prior lines of therapy.
- bb21217 is a (BCMA) directed CAR T cell therapy which uses the same CAR molecule as ide-cel bb2121, with the addition of a PI3K inhibitor (bb007) to enrich the drug product (DP) for memory-like T cells and decrease the proportion of highly differentiated or senescent T cells to improve DOR

PURPOSE test whether DPs enriched for memory like CAR T cells will persist and function longer than non-enriched DPs and this increased persistence will positively influence duration of response (DOR).

Noopur S. Raje, Blood 2021

Updated of Results from the Phase I CRB-402 Study in RRMM

Efficacy FU at 9.0 months

CAR+ T cells	150x10^6	300x10^6	450x10^6	Total
N	12	14	46	72
ORR, n (%)	10 (83)	6 (43)	34 (74)	50 (69)
sCR/CR, n (%)	5 (42)	2 (14)	13 (28)	20 (28)
≥VGPR, n (%)	10 (83)	5 (36)	27 (59)	42 (58)
Median Time to CR (min, max), M	6 (1,24)	10 (3,18)	1 (1,13)	3 (1,24)
Median DOR (95% CI), M	11.5 (3-18)	NE (6-NE)	17 (9-NE)	17 (11-35)

CAR+ T cells remained detectable in 30/37 (81%) patients and 9/15 (60%) patients at 6 and 12 M respectively, post bb21217 infusion

MRD –ve in 93% in pts> CR by NGS

Analysis of peripheral blood samples collected 15 days post bb21217 infusion demonstrated patients with higher than the median number of CD8+ CAR+ T cells expressing CD27 and CD28 had significantly longer DOR (p=0.0024), compared to patients with lower than the median values.

Noopur S. Raje, Blood 2021

Updated of Results from the Phase I CRB-402 Study in RRMM

Safety

- Cytokine release syndrome (CRS) developed in 54/72 (75%) patients and was predominately G1/2 (51 pts), with 1 G3 event and 2 deaths (previously reported).
  - Median time to first onset of CRS was 2 days (1-20); tocilizumab (38 pts) + corticosteroids (12 pts) was used to manage CRS.
  - Eleven (15%) patients developed neurotoxicity [8 G1/G2, 2 G3, 1 G4] with median time to first onset of 7 (2-24) days.

CONCLUSIONS

higher levels of proliferative, less differentiated memory like CAR+ T cells at peak expansion are more likely to lead to prolonged DOR, continuing to support the hypothesis that the memory like T cell phenotype associated with bb21217 results in prolonged DOR.

Noopur S. Raje, Blood 2021

Phase 1/2 Trial Results Underscore Teclistamab's Efficacy in RRMM

- Teclistamab T-cell–redirecting, bispecific IgG Ab targeting BCMA and CD3 receptors to induce T-cell–mediated cytotoxicity of BCMA-expressing myeloma cells

Efficacy

- 150 pts, SQ phase 2 of 1.5 mg/Kg, all participants have received at least 3 lines of therapy and triple–class exposed
- median time to first response was 1.2 months (range, 0.2-5.5), ORR was consistent independent of cytogenetic risk or extent of prior therapy refractoriness
- median DOR and OS was not reached at the clinical cutoff;
- Depth of response
  - 58% >/= VGPR
  - 29 % (CR) or better
  - 21% sCR
  - By ITT, 25% (MRD) negativity at a threshold of 10–5 (95% CI, 18.0%-32.4%)
  - In patients who achieved a CR or better, the MRD negativity rate was 42%
  - PFS at 9 months was 59% (95% CI, 48.8%-67.0%)
- (AEs): (CRS; 72%, grade I except for 1 grade 3 all recovered), injection-site erythema (26%), fatigue (25%). Neutropenia, anemia, and thrombocytopenia were the most common hematologic AEs reported, while 5 patients developed immune effector cell–associated neurotoxicity syndrome.
- A phase 3 study is currently underway, in part to evaluate the treatment in earlier-line settings and in combination with other agents. Additional data regarding patients with prior BCMA will also be reported.

Moreau P, Presented at: 63rd American Society of Hematology Annual Meeting & Exposition; December 13, 2021; Abstract 896.

A Phase 1/2 Study of a Novel Fully Human BCMA-Specific CAR T Cells (CT103A) in RRMM

BACKGROUND

CT103A was designed with a fully human single-chain variable fragments (scFvs) so it could bypass the potential host anti-CAR immunogenicity and retain antitumor activity.

Reporting on safety and efficacy data from the CT103A

Methods

71 RRMM , median 4 lines of prior therapy (3-13), infused with 1.0×10^6 CAR+ T cells/kg. Notably, it was the first time that prior BCMA CAR-T exposed patients were eligible to participate in an anti-BCMA CAR-T cell trial (18%).

A Phase 1/2 Study of a Novel Fully Human BCMA-Specific CAR T Cells (CT103A) in RRMM

RESULTS

- median time to first response was 15 days (range 11-124)
- ORR 94.4%, with 50.7% ≥ CR, 28% VGPR, and 14% PR
- 13 pts previously treated with CAR-T, ORR was 76.9%, ≥ CR rate of 38.5%,VGPR of 15.4%, and PR of 23.1%
- MRD- 92% within 17 days, 75% maintained for more than 6 months
- expansion of CT103A reached the peak at a median of 12 days (range 5 to 29).
  - CT103A was still detectable in 88.5% (23/26) patients at 6 months and 87.5% (14/16) patients at 12 months after infusion
- In addition, only 2 of 71 patients were positive for anti-drug antibody, which was reported to be a high-risk factor for disease relapse/progression after CAR-T therapy.

Safety

- ≥ grade 3 treatment-related AEs were hematological toxicities
- 93.0% of the patients experienced CRS 96 days), among which only 2.8% were grade 3, 2 ICANs

Daratumumab (DARA)-(VTd) in Transplant-Eligible Patients (Pts) with (NDMM): Analysis of Minimal Residual Disease (MRD) Negativity in Cassiopeia Part 1 and Part 2

BACKGROUND

- The 2-part phase 3 CASSIOPEIA study (NCT02541383) investigated the combination of DARA with VTd (D-VTd) in transplant-eligible NDMM
- In Part 1, D-VTd induction/consolidation (ind/cons) led to increased rates of MRD negativity and prolonged progression-free survival (PFS) compared with VTd.
- In Part 2 Dara Q 8 wks for 2 years vs obs in maintenance, DARA post-ASCTmaintenance significantly improved PFS in pts who received VTd ind/cons.

PURPOSE reports the results of the MRD negativity outcomes of the the 2-part phase 3 CASSIOPEIA study.

Loiseau, Blood 2021

1- PFS: At median follow-up of 35.4 mo, median PFS was not reached (NR) with DARA maintenance and 46.7 mo with OBS (HR 0.53; 95% CI 0.42–0.68; *P* <0.0001)

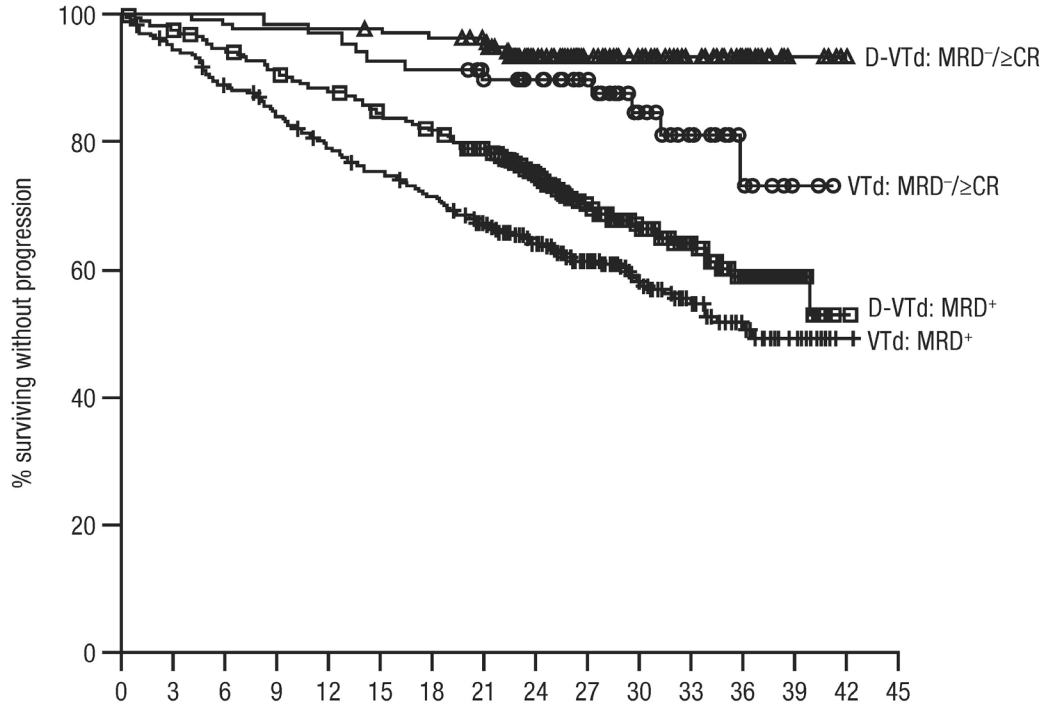
2- Dara vs OBS maintenance, CR 72.9% vs 60.8%

3- The rate of MRD negativity was higher with D-VTd ind/cons than with VTd (9.2% vs 5.4%; odds ratio [OR], 1.79; *P*=0.0150) and consolidation (33.7% vs 19.9%; OR, 2.06; *P*<0.0001).

4-MRD negativity (in ≥CR pts at 10^{-5}) was 58.6% with DARA vs 47.1% with OBS (OR 1.80; 95% CI 1.33–2.43; *P*= 0.0001)

5- OS not reached in either arm

Figure: Landmark PFS analysis of pts progression-free at 1 year post-induction for pts who achieved 1 year sustained MRD negativity and pts who did not by treatment group



No. at risk																
VTd: MRD⁺	380	359	336	315	294	279	264	239	185	137	99	64	43	19	1	0
VTd: MRD⁻/≥CR	70	70	70	69	68	65	64	60	53	45	27	18	9	2	0	0
D-VTd: MRD⁺	337	329	316	305	293	277	269	251	194	148	101	68	42	15	1	0
D-VTd: MRD⁻/≥CR	147	147	145	144	144	143	141	135	107	79	60	42	26	5	1	0

PFS, progression-free survival; pts, patients; MRD, minimal residual disease; D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ≥CR, complete response or better.

Loiseau, Blood 2021

Daratumumab (DARA)-(VTd) in Transplant-Eligible Patients (Pts) with (NDMM): Analysis of Minimal Residual Disease (MRD) Negativity in Cassiopeia Part 1 and Part 2

CONCLUSION

- In CASSIOPEIA, the highest and most durable rates of MRD negativity were achieved after D-VTd ind/ASCT/cons and DARA maintenance.
- Reduced intensity (Q8W) DARA maintenance did not significantly improve MRD negativity compared to OBS in patients treated with D-VTd.
- In patients treated with VTd, DARA maintenance did improve MRD negativity, but this effect was not long lasting.

Loiseau, Blood 2021

D-(RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma : Updated Analysis of Griffin after 24 Months of Maintenance

BACKGROUND

In the primary analysis of the phase 2 GRIFFIN trial (NCT02874742) in (ASCT)-eligible NDMM pts (median FU, 13.5 mo), (D-RVd) improved the rate of stringent complete response (sCR) by the end of post-ASCT consolidation versus RVd (42.4% vs 32.0%, 1-sided *P*=0.068)

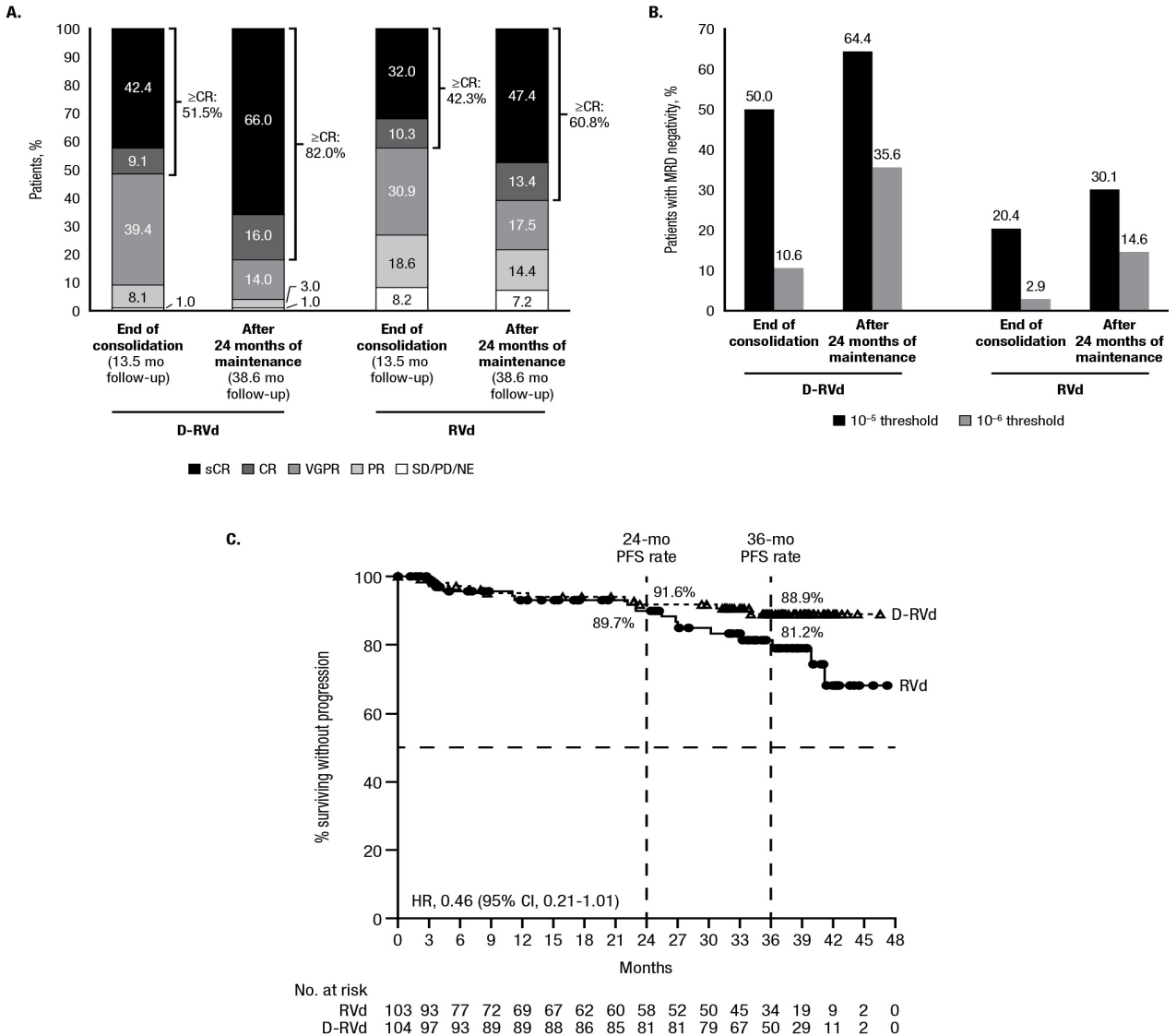
PURPOSE

present updated efficacy and safety results after 24 months of maintenance therapy or treatment discontinuation (median follow-up, 38.6 mo).

Laubach, Blood 2021

D-(RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma : Updated Analysis of Griffin after 24 Months of Maintenance

Figure: Summary of updated response rates[a] (A) and MRD-negativity rates[b] (B) over time, and PFS[c] after 24 months of maintenance (C) in GRIFFIN.



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MRD, minimal residual disease; PFS, progression-free survival; ITT, intent-to-treat population; D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; ≥CR, complete response or better; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable; HR, hazard ratio; CI, condence interval.

[a]Response-evaluable population; D-RVd, n = 100; RVd, n = 97.

[b]ITT population; D-RVd, n = 104; RVd, n = 103; median follow-up for MRD negativity data for all time points is 38.6 months.

[c]ITT population; D-RVd, n = 104; RVd, n = 103; HR and 95% CI calculated via Cox proportional hazards model with treatment as the sole explanatory variable and stratified by ISS disease staging (I, II, or III) and baseline creatinine clearance (30-50 or >50 mL/min) at randomization.

D-(RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma : Updated Analysis of Griffin after 24 Months of Maintenance

CONCLUSION

- After 24 months of maintenance therapy, the addition of DARA to RVd induction and consolidation in conjunction with ASCT, followed by DARA plus R maintenance, continued to demonstrate deep and durable responses in pts with transplant-eligible NDMM, including sCR and MRD-negativity (10^{-5} and 10^{-6}) rates.
- While this study was not powered for PFS, there is a positive trend towards improved PFS in the D-RVd group.
- These results support the use of D-RVd induction/consolidation and D-R maintenance in transplant-eligible NDMM pts.

Laubach, Blood 2021

Final OS Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

BACKGROUND

- The Phase 3 BELLINI study primary analysis showed significantly improved response rates and progression-free survival (PFS) in pts with RRMM treated with Ven added to Bor/D versus placebo; however, increased mortality was observed in the Ven group.
- Pts with t(11;14) translocation or high *BCL2* expression showed improved responses and PFS without increased mortality.

PURPOSE

present updated safety and efficacy data from the prespecified final OS analysis.

Kumar, Blood 2021

Final OS Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

Table. Progression-Free Survival and Overall Survival in All Patients and Key Biomarker Subgroups.

	N	Ven + Bd	Pbo + Bd	HR (95% CI)
Median PFS, mo				
All pts	291	23.4	11.4	0.58 (0.43–0.78)
Pts with t(11;14)	35	36.8	9.3	0.12 (0.03–0.44)
Pts with *BCL2*^{high}	98	30.1	9.9	0.37 (0.21–0.64)
Pts with t(11;14), *BCL2*^{high}	114	34.3	9.9	0.32 (0.20–0.53)
Pts with non-t(11;14), *BCL2*^{low}	164	15.3	12.2	0.76 (0.51–1.13)
Median OS, mo				
All pts	291	NR	NR	1.19 (0.80–1.77)
Pts with t(11;14)	35	NR	NR	0.61 (0.16–2.32)
Pts with *BCL2*^{high}	98	NR	NR	0.70 (0.32–1.51)
Pts with t(11;14), *BCL2*^{high}	114	NR	NR	0.82 (0.40–1.70)
Pts with non-t(11;14), *BCL2*^{low}	164	46.4	NR	1.34 (0.81–2.20)

B, bortezomib; d, dexamethasone; HR, hazard ratio; NR, not reached; OS, overall survival; Pbo, placebo; PFS, progression-free survival; pts, patients; Ven, venetoclax.

Safety

- discontinuation 26% in the Ven arm and 11% of pts in the Pbo arm.
- 16 (6%) treatment-emergent deaths occurred (14 [7%] with Ven and 2 [2%] with Pbo), with 3 of these deaths due to disease progression (2 [1%] with Ven and 1 [1%] with Pbo).

Kumar, Blood 2021

Final OS Results from BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma

CONCLUSIONS

- final OS analysis, the addition of Ven to bortezomib and dexamethasone showed significantly improved PFS but resulted in increased mortality versus Pbo in the total population.
- Ven added to bortezomib and dexamethasone showed the greatest PFS improvement in pts with t(11;14) or high *BCL2*, with a favorable benefit-risk profile.

Kumar, Blood 2021

Ixazomib, Daratumumab and Low Dose Dexamethasone in Intermediate-Fit Patients with Newly Diagnosed Multiple Myeloma (NDMM); Results of Induction Treatment of the Phase II HOVON 143 Study

BACKGROUND

Accordingly, intermediate-fit patients, according to the IMWG frailty index, have an inferior survival and higher rates of treatment discontinuation as compared to fit NTE-NDMM patients.

PURPOSE prospectively investigate the efficacy and tolerability of the novel regimen ixazomib-daratumumab-low dose dexamethasone in intermediate-fit NTE-NDMM patients

Ixazomib, Daratumumab and Low Dose Dexamethasone in Intermediate-Fit Patients with Newly Diagnosed Multiple Myeloma (NDMM);

Table 1 Demographics at registration of eligible intermediate-fit patients

Ixa-Dara-dex	N=65
Male (%)	35 (54)
Median age (years) [range]	76 [65-80]
=75	28 (43)
76-80	37 (57)
WHO performance (%)	
0	25 (38)
1	28 (43)
2	6 (9)
3	3 (5)
unknown	3 (5)
Charlson Comorbidity Index (CCI) =2 (%)	19 (29)
Activities of Daily Living (ADL) =4 (%)	-
Instrumental ADL (iADL) =5 (%)	9 (14)
ISS disease stage (%)	
I	16 (25)
II	37 (57)
III	12 (18)
Elevated LDH (%)	3/64 (5)
High risk cytogenetic disease*	8/56 (14)

*High risk cytogenetic disease: presence of t(4;14) and/or t(14;16) and/or del17p13

Figure 1 PFS, OS, EFS and subdivision EFS

Figure 1a. Progression free survival

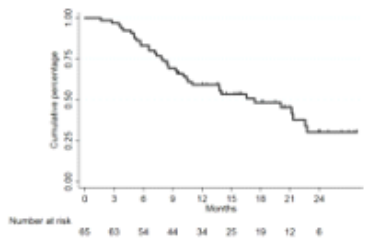


Figure 1b. Overall survival

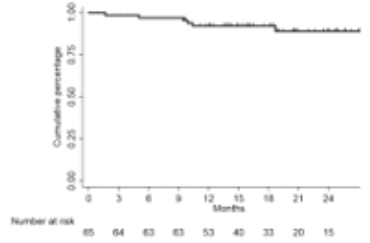


Figure 1c. Event free survival

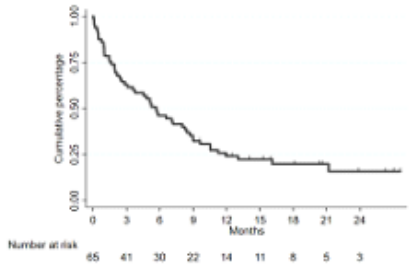
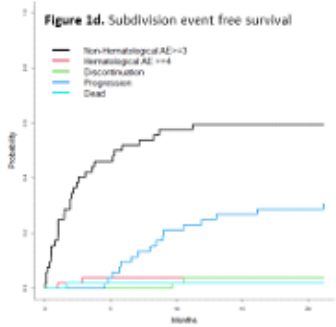


Figure 1d. Subdivision event free survival



Ixazomib, Daratumumab and Low Dose Dexamethasone in Intermediate-Fit Patients with Newly Diagnosed Multiple Myeloma (NDMM); Results of Induction Treatment of the Phase II HOVON 143 Study

CONCLUSIONS In intermediate-fit patients, ixazomib, daratumumab and dexamethasone is an effective and feasible regime, which improves QoL. However, treatment discontinuation due to toxicity (either the whole regimen (6%), but especially ixazomib only (11%)) or incompliance, which negatively affects PFS, remains a concern.

REFERENCE Greon, Blood 2021

Ixazomib and Daratumumab without Dexamethasone (I-Dara) in Elderly Frail RRMM (IFM 2018-02)

BACKGROUND

Frail patients with MM have an inferior outcome, especially in the relapse setting, mainly related to a high discontinuation rate due to treatment related adverse events

PURPOSE

Multicenter Phase 2 Study (IFM 2018-02) of the Intergroupe Francophone Du Myélome (IFM)

Evaluate efficacy and tolerability of Ixazomib-Daratumumab (I-Dara) without Dexamethasone in elderly frail patients with relapsed myeloma

Macro, Blood 2021

Ixazomib and Daratumumab without Dexamethasone (I-Dara) in Elderly Frail RRMM (IFM 2018-02)

- 44 were included between 03/2018 and 05/2021
- first relapse (n=28) or second relapse (n=16). 38 patients (86%) were previously exposed to bortezomib and 8 (18%) refractory to lenalidomide
- Median age was 82 (80-84). All patients had a frailty score ≥2.
- Eleven (32%) patients harbored high-risk cytogenetic, including t(4;14), del17p
- The median duration of Tx among 23 pts with ongoing Tx was 6 months [0-27] at data cutoff (July 19)]. The median duration of Tx among 21 pts who stopped Tx was 7 months [0-21]: 13 had progressive disease.

RESULTS

6 patients died during the study: Daratumumab-related; Ixazomib-related overdose (C2); progressive disease (C2 & C4), sepsis (C1 & C2). Regarding toxicity, 28 ≥grade 3 AE occurred amongst 24 pts (54%).

Macro, Blood 2021

Ixazomib and Daratumumab without Dexamethasone (I-Dara) in Elderly Frail RRMM (IFM 2018-02)

CONCLUSIONS

These preliminary results show a favorable safety profile of ixazomib and daratumumab combination, without dexamethasone, in this specific population of very elderly frail patients with RRMM and high risk cytogenetic for almost one third of them.