653.MYELOMA: THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

Efficacy and Safety of Ixazomib-Dexamethasone, Ixazomib-Cyclophosphamide-Dexamethasone, Ixazomib-Thalidomide-Dexamethasone and Ixazomib-Bendamustine-Dexamethasone for Elderly Newly Diagnosed Multiple Myeloma (NDMM) Patients: Analysis of the Phase II Randomized Unito-EMN10 Study

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Ixazomib in combination with dexamethasone, Cyclophosphamide, Thalidomide or Bendamustine, followed by Ixazomib maintenance in ASCT-ineligible NDMM.

METHODS. NDMM patients (pts) ≥65 years old or younger ASCT-ineligible could be enrolled. Treatment consisted of nine 28-day induction cycles of Ixazomib 4 mg on days 1,8,15 and dexamethasone 40 mg on days 1,8,15,22 (Id) or combined with Cyclophosphamide 300 mg/m^2 orally on days 1,8,15 (ICd) or plus Thalidomide 100 mg/day (ITd) or plus Bendamustine 75 mg/m^2 iv on days 1,8 (IBd); followed by maintenance with Ixazomib 4 mg on days 1,8,15 until progression.

Because the study included the novel drug Ixazomib, dual stopping rules combining efficacy (at least very good partial response [VGPR] rate), and safety (predefined toxicity possibly related to Ixazomib) were planned and analyzed in a cohort of 5 patients in each arm during the first 4 cycles. Here we report the results of the cohort analysis during the first 4 cycles and the efficacy and safety analysis during induction treatment.

RESULTS. In February 2017, the protocol was amended due to a low enrolment and the IBd arm, the only one including an iv drug, was closed. After closing this arm, all the other all oral arms continued the enrolment. Overall, 175 pts were enrolled (Id 42, ICd 61, ITd 61, and IBd 11 pts) and 171 pts started treatment.

Median age was 74 years, 20% of pts had high risk cytogenetics, 44% were fit, 30% intermediate and 26% frail, according to the IMWG frailty score. Median follow-up was 13.2 months (IQR 8.9-20.7).

During the first 4 cycles, at least VGPR rate was 24% with Id, 33% with ICd, 31% with ITd and 18% with IBd. In March 2018, after the analysis of the 4th cohort, the Id arm was closed due to high risk of inefficacy.

Overall response rate (ORR) during induction was 73%, VGPR was 39%. ≥VGPR rates were 24% in Id, 48% in ICd, 43% in ITd and 27% in IBd. Median time to first response was 2.4 and to the best response 4 months.

Responses were comparable according to cytogenetics: in high risk pts, ORR was 77%, ≥VGPR 46% and ≥nCR 17% as compared to 71%, 36% and 18% in standard risk pts (p=0.53, p=0.33 and p=1, respectively).

Response rates were also comparable according to frailty status: in frail pts, ORR was 73%, ≥VGPR 36% and ≥nCR 11% as compared to 75%, 40% and 17% in intermediate and 70%, 40% and 22% in fit pts (p=0.78, p=0.90 and p=0.32, respectively).

Median number of induction cycles was 9 (IQR 5-9); 93 (53%) pts completed induction treatment and 14 (8%) pts are still on induction treatment.

During the first 4 cycles, hematologic toxicity was limited, and non-hematologic toxicity manageable. The most frequent G3-4 adverse event (AE) was rash in ITd arm (11%); discontinuation rate due to toxicity was 6%.

During induction, the rate of at least 1 hematologic G≥3 AE was 11% and at least 1 non-hematologic G≥3 AE was 44%. The most frequent G≥3 AEs were neutropenia (8%), gastrointestinal (9%), infections (11%), neurologic (11%) and dermatologic (6%). G3-4 thrombocytopenia (3%) and PN (5%) were limited. Ixazomib dose reduction due to AEs was required in 15% of pts. The rate of non-hematologic AEs was slightly higher in ITd arm (37% in Id, 37% in ICd, 53% in ITd, 55% in IBd). Early death rate (<60 days from start therapy) was 1%.

CONCLUSIONS. ITd and ICd are convenient all-oral induction regimens for ASCT-ineligible NDMM, confirming an improved efficacy of a triplet vs a doublet combination, also in intermediate and frail patients. Id showed lower efficacy, thus suggesting a possible effect of the dose of Ixazomib or the absence of a third drug. Treatment was feasible, with limited toxicity and low discontinuation rate due to AEs, although ITd induced a slightly higher toxicity, but mainly attributable to Thalidomide.

Table.

INDUCTION	All	Id	ICd	ITd	IBd
Efficacy	**N=175**	**N=42**	**N=61**	**N=61**	**N=11**
≥nCR	18%	14%	25%	15%	9%
≥VGPR	39%	24%	48%	43%	27%
≥PR	73%	55%	75%	82%	73%
Safety	**N=171**	**N=41**	**N=59**	**N=60**	**N=11**
Hematologic AEs ≥ Grade 3	11%	5%	12%	13%	18%
Non-Hematologic AEs ≥ Grade3	44%	37%	37%	53%*	55%
Neurologic	11%	7%	7%	18%	9%
Dermatologic	6%	2%	2%	13%	0
Infections	11%	10%	8%	13%	9%
Vascular	7%	5%	7%	10%	0
Gastrointestinal	9%	7%	8%	12%	9%
Discontinuation due to AEs	10%	7%	7%	15%	9%
Ixazomib dose reduction due to AEs	15%	2%	22%	17%	18%

* ITd vs ICd, p=0.10; ITd vs Id p=0.11.

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Disclosures

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OffLabel Disclosure:

The presentation includes discussion of off-label use of a drug or drugs for the treatment of multiple myeloma.

Topics: bendamustine, cyclophosphamide, dexamethasone, ixazomib, multiple myeloma, older adult, thalidomide, brachial plexus neuritis, impedance threshold device, implantable defibrillators

Author notes

* Asterisk with author names denotes non-ASH members.

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