MultipleMyelomaHub

EHA 2019 | Updated analysis of the HORIZON phase II trial: Melflufen + dexamethasone for RRMM

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On Sunday 16 June at the 24th Congress of the European Hematology Association (EHA), Paul Richardson presented Abstract S1605, showcasing updated results of the phase II HORIZON (OP-106) trial (NCT02963493). This study investigated the efficacy and safety of melflufen and dexamethasone in patients with relapsed or refractory multiple myeloma (RRMM).[1]

Melflufen is a peptide-conjugated alkylator that exerts its cytotoxic effects once cleaved by peptidases. It is a unique, first-in-class anticancer drug as it selectively kills myeloma cells, which tend to overexpress aminopeptidases.[2] In the previous analysis, melflufen and low-dose dexamethasone led to an overall response rate (ORR) of 33% and had a manageable safety profile.[3]

The primary endpoint of this trial was investigator-assessed ORR according to International Myeloma Working Group (IMWG) criteria. Secondary endpoints, included safety, progression-free survival (PFS), overall survival (OS), duration of response (DoR), and clinical benefit rate (CBR).

Study design & baseline characteristics

- N=121 treated patients as of 06/05/2019. Patients had RRMM with ≥2 prior lines (with immunomodulatory drugs [IMiD] or proteasome inhibitors [PI]) and were refractory to pomalidomide and/or daratumumab
- Dosing (28-day cycles):
  - Melflufen: 40mg intravenously on Day 1 of each cycle
  - Dexamethasone: 40mg weekly on Days 1, 8, 15, and 22
  - Treatment continued until disease progression (PD) or unacceptable toxicity
- Patient prior therapy status:
  - Double class refractory (IMiD+PI): 91%
  - Refractory to anti-CD38: 79%
  - Triple class refractory (IMiD+PI+anti-CD38): 74%
  - Refractory to alkylators: 59%
  - ≥1 prior autologous stem cell transplantation (ASCT): 69%
  - ≥2 ASCTs: 11%
  - Relapsed ≤1 year after ASCT: 20%
- **Table 1.** Key baseline characteristics:

Baseline characteristic	**Patient cohort (N=121)**
Median age (range)	64 (35–86)
Male patients	55%
Median time since diagnosis (range)	6.2 (0.7–25) years
Median number of prior lines (range)	5 (2–12)
International Staging System (ISS):	
Stage 1	38%
Stage 2	30%
Stage 3	29%
Unknown	4%
High-risk cytogenetics:	62%
≥2 high-risk abnormalities	19%
del(17p)	17%
Extramedullary disease	60%
Refractory to last line of therapy	98%
Patients used ≥3 regimens in last 12 months prior enrolment	36%

Key findings

- **Table 2.** Response outcomes:

	Intention-to-treat population **(ITT; n=113)**	**Double class refractory (n=22)**	**Anti-CD3 refractory (n=89)**	**Triple class refractory (n=83)**
ORR	28%	55%	22%	20%
CBR	40%	64%	33%	32%
Stringent complete response (sCR)	1%	5%	-	-
Very good partial response (VGPR)	9%	14%	8%	8%
Partial response (PR)	19%	36%	15%	12%
Metabolic response (MR)	12%	9%	10%	11%
Stable disease (SD)	46%	36%	49%	49%

- Median PFS (ITT): 4.0 months (95% CI, 3.7–4.6)
- Median PFS by response subgroup:
  - ≥PR: 6.4 months
  - MR: 4.9 months
  - SD: 3.6 months
  - PD: 1.1 months
- Similar PFS was observed across the different refractory groups (double class, triple class, anti-CD3)
- Median OS:
  - ITT population: 11.2 months (95% CI, 8.1–13.9)
  - Triple class refractory subgroup: 8.5 months (95% CI, 6.4–11.8)
- Median DoR by response subgroups:
  - All responders (n=32): 4.4 months (95% CI, 3.6–8.3)
  - Triple class refractory (n=17): 3.6 months

Safety

- Most common Grade 3 adverse events (AEs) were:
  - Any AE: 24%
  - Thrombocytopenia: 21%
  - Neutropenia: 26%
  - Anemia: 26%
- Most common Grade 4 AEs were:
  - Any AE: 49%
  - Thrombocytopenia: 36%
  - Neutropenia: 31%
  - Anemia: 1%
- Six patients experienced treatment-related bleeding:
  - Grade 1: n=4 patients
  - Grade 3: n=2 patients
- Overall the incidence rate of non-hematological malignancies was low
- No treatment-related deaths were reported
- The following dose modifications of melflufen occurred due to treatment-emergent AEs (46%):
  - Dose reduced: 22%
  - Dose delayed: 36%
  - Drug discontinued: 24%

Conclusions

Melflufen in combination with dexamethasone resulted in an ORR of 28% in the ITT population, 55% in the double class refractory subgroup (PI+IMiD), and 20% in the triple class refractory group (PI+IMiD+anti-CD3). The combination seemed to have promising activity in this very vulnerable RRMM population refractory to pomalidomide and/or daratumumab treatment, as well as to lenalidomide and PI-based therapies (majority of patients triple class refractory). The safety profile of the treatment was generally tolerable and manageable. Melflufen plus dexamethasone is being compared to pomalidomide plus dexamethasone in RRMM patients in the ongoing phase III trial OCEAN (NCT03151811).

References

1. Richardson G.P. Horizon (OP-106): updated efficacy and safety of melflufen in relapsed/refractory multiple myeloma (RRMM) refractory to daratumumab (Dara) and/or pomalidomide (POM). Abstract S1605. 24th European Hematology Association Meeting, 2019, Amsterdam, NL
2. Melflufen – Oncopeptides, https://www.oncopeptides.se/en/about-ygalo/ (Accessed 20.06.19)
3. Richardson G.P. *et al.* 2018. OP-106 Horizon — Melflufen Therapy for RRMM Patients Refractory to Daratumumab and/or Pomalidomide; Updated Results and First Report on PFS. *Blood* 132, 600–600. DOI:10.1182/BLOOD-2018-99-113095