A propensity score weighted comparison of tebentafusp or pembrolizumab versus combination ipilimumab and nivolumab in untreated metastatic uveal melanoma

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Background

Tebentafusp (tebe) demonstrated an overall survival (OS) benefit, HR 0.51, compared to investigator choice (IC) in a Phase III trial (NCT0100-202; NCT03793292) in untreated metastatic uveal melanoma (MUM). 82% of the IC arm received pembrolizumab plus nivolumab (ipi+niv): ipi+niv (ipi+niv) was not studied [1].

The GEM-1402 trial, conducted by the Spanish Multidisciplinary Melanoma Group (GEM), was a multicenter, open-label, single-arm, phase 2 study to assess the efficacy of tebentafusp (tebe) in patients with MUM [2].

Comparisons of treatments across different studies can be biased by differences in patient characteristics; therefore, two statistical methods were employed to adjust the treatment effect for imbalances in important variables across the two studies.

We compared OS between (MUM)103 and GEM-1402 using summary and patient-level data.

Methods

1. Two analyses were conducted:
   a. a matched-adjusted indirect comparison of tebe or pemb (MUM103) with ipi+niv (GEM-1402) [3]
   b. a propensity score analysis of tebe or pemb (MUM103) with ipi+niv (GEM-1402) [4]

2. To adjust for differences in patient characteristics in the propensity score analysis, propensity scores from a logistic regression model were used to generate inverse probability of treatment weights (IPTW). The key difference being that this analysis used published summary level data from GEM and the propensity score analysis used individual patient data.

3. OS was compared using weighted Cox models and Kaplan-Meier curves.

4. The primary propensity score analysis was complete case with ATT (average treatment effect of the treated) weights.

5. Sensitivity analyses used alternative missing data methods (multiple imputations) and weights (stabilized IPTW): A*02:01 positive by central assay.

6. Data cut-offs of 9 July 2019 for GEM1402 and 20 October 2020 for MUM103 were used.

Results

- Figure 1. IPTW weighting balances key baseline characteristics (tebe vs ipi+niv propensity score analysis)
- Figure 2. OS favored tebe vs ipi+niv in propensity score analysis
- Figure 3. Sensitivity analyses showed consistent superior OS for tebe
- Figure 4. IPTW balances key baseline characteristics (pemb vs ipi+niv PS analysis)
- Figure 5. No significant difference in survival for pemb vs ipi+niv in propensity score analysis
- Figure 6. No significant difference in overall survival between pemb and ipi+niv in all sensitivity analyses

Conclusions

- Tebentafusp is the only therapy to demonstrate an OS benefit in previously untreated MUM patients against an IC arm that was mainly pemb.
- In a cross-trial comparison, patient-level propensity score analysis also demonstrated a strong OS benefit for tebentafusp vs ipi+niv.
- Fewer patients discontinued tebentafusp in MUM103-202 compared with pemb in GEM1402 due to treatment related toxicity (2% vs 23%, respectively).
- Two additional propensity score analyses showed no evidence that the combination of anti-PD1+anti-CTLA4 improves OS compared with anti-CD191 alone in previously untreated MUM patients.
- These results further support initial use of tebentafusp in previously untreated MUM patients as a first line of standard care instead of anti-CD191 or anti-CTLA4 therapy.

References


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