Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in previously untreated patients with metastatic uveal melanoma

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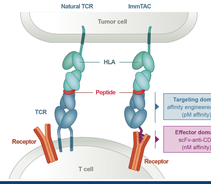
Abstract 4020

Background

- ImmTAC® (Immune-mobilizing monoclonal T cell receptor [TCR] Against Cancer) molecules are bispecific fusion proteins consisting of an affinity-enhanced TCR, which targets intracellular antigens presented as peptide–human leukocyte antigen (HLA) complexes, and an anti-CD3 single-chain variable fragment (scFv) effector end (Figure 1).
- Tebentafusp is designed to be a first-in-class investigational ImmTAC molecule capable of engaging, redirecting, and activating polyclonal CD3+ T cells against the melanocyte-associated antigen, gp100, resulting in lysis of gp100+ target cells.
- Tebentafusp has shown an overall survival benefit for patients with previously untreated metastatic uveal melanoma (mUM) in a Phase 3 trial (NCT03070392) [1].
- Cytokine-mediated adverse events (AEs) are commonly reported in patients treated with T cell engaging therapies.
- Cytokine release syndrome (CRS) recognition and management is based on non-specific clinical signs including fever, hypotension, and hypoxia.
- Due to the low rate of severe CRS in the Phase 1 & 2 trials [2, 3], prophylactic corticosteroids, antihistamines or acetaminophen were not mandated.

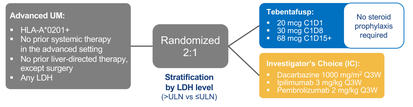
Figure 1. ImmTAC molecules mimic the immune synapse formed by a natural T cell-tumor cell interaction



Methods

- IMCgp100-202 [NCT02570308] was an open-label, multi-center, randomized controlled study of the safety and efficacy of tebentafusp versus investigator's choice in patients with previously untreated mUM.
- 245 HLA-A*02:01+ 1L mUM patients were treated with tebentafusp at 68 mcg (Dose 3+) following intra-patient dose escalation of 20 mcg (Dose 1) and 30 mcg (Dose 2) (Figure 2).
- Patients were monitored overnight after the first 3 doses during dose escalation to allow management of hypotension and other cytokine-related AEs.
- Per protocol, patients did not receive corticosteroids as primary prophylaxis for CRS.
- AEs, SAEs, vital signs, and concomitant medications reported by investigators were programmatically evaluated by Immunocore (Sponsor) post-hoc to comprehensively identify all potential episodes of CRS based on ASTCT consensus criteria [4].

Figure 2. IMCgp100-202 Study design



Primary Endpoint: Overall Survival

Results

Table 1. Baseline demographics

Characteristic	Tebentafusp (n=252*)
Age – median year (range)	64 (23-92)
Gender, male – n (%)	128 (51)
Time since primary diagnosis – median year (range)	3.0 (0.1-25)
ECOG status† – n (%)	
0	192 (76)
1	49 (19)
Elevated LDH level (>ULN) – n (%)	90 (36)
Largest metastatic lesion – n (%)	
M1a (≤3.0 cm)	139 (55)
M1b (3.1-8.0 cm)	92 (37)
M1c (≥8.1 cm)	21 (8)
Metastasis location‡ – n (%)	
Hepatic only	131 (52)
Extrahepatic only	9 (4)
Hepatic & extrahepatic	111 (44)

* 245 patients were treated with tebentafusp; 7 did not receive treatment (4 patient decision, 2 adverse events, 1 withdrawal of consent for follow-up);
† 11 patients had missing ECOG status;
‡ Three patients had missing metastasis location (1 tebentafusp; 2 IC).

Table 2. ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopression	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Recreated from Lee et al. 2019 [4].
Organ toxicities associated with CRS may be graded to CTCAE v5.0 but they do not influence CRS grading.
* Fever is defined as temperature ≥38°C not attributable to any other cause.
† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.
‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table 3. Most common cytokine-mediated treatment-related AEs

Treatment-related AE*	All grades n (%)	Grade ≥3 n (%)
Pyrexia	185 (76)	9 (4)
Chills	114 (47)	1 (0.4)
Nausea	105 (43)	2 (0.8)
Hypotension	93 (38)	8 (3)
Hypoxia	2 (0.8)	1 (0.4)

*TRAEs per investigator that are also cytokine-mediated per Lee et al. criteria [5].

- Treatment-related AEs (any grade) per investigator that were cytokine-mediated were mostly mild to moderate (Table 3)
- 76% of patients had fever, the hallmark of CRS.
- Investigators separately reported 51 patients with at least one CRS AE.

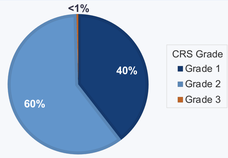
Table 4. Highest CRS grade by patient*

(N=245)	n (%)	Most common AE
No CRS	28 (11)	N/A
Grade 1	29 (12)	Pyrexia, Chills
Grade 2	186 (76)	Pyrexia, Chills, Nausea, Hypotension
Grade 3	2 (1)	CRS, Hypotension, Chills
Grade 4	0	

*Based on sponsor post-hoc adjudication per ASTCT consensus grading criteria [4].

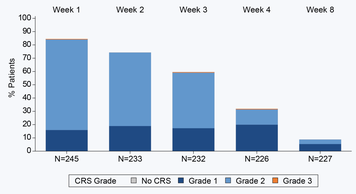
- 217 of 245 patients (89%) experienced any grade CRS, as determined by the Sponsor in a post-hoc review (**Table 4**).
- 45% (83/186) of patients who experienced Grade 2 CRS as their maximum grade only experienced a Grade 2 event (no Grade 1).
- All patients who experienced Grade 3 CRS as their maximum grade also experienced a lower grade CRS episode at some point.

Figure 3. All CRS episodes (all grades)



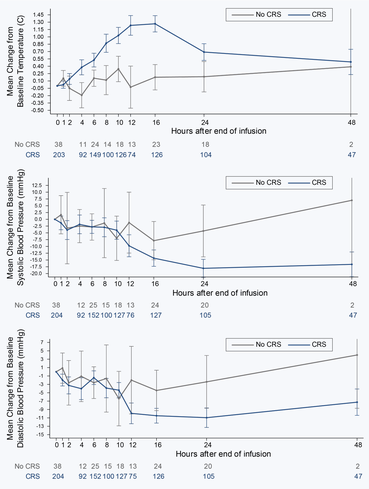
- 805 distinct CRS episodes occurred in 217 of 245 tebentafusp-treated patients: 321 Grade 1; 481 Grade 2; 3 Grade 3.
- CRS episodes were mostly mild to moderate in grade (99.6% Grade 1-2; **Figure 3**).
- 2 patients permanently discontinued treatment due to CRS; 1 Grade 2 and 1 Grade 3. There were no treatment-related deaths.

Figure 4. Frequency and severity of new CRS episodes by dose



- CRS episodes most commonly occurred after the first dose, with decreased frequency and severity after subsequent doses (**Figure 4**).
- Patients could experience a distinct CRS episode after more than 1 dose.
- Only 3 Grade 3 CRS episodes in 2 patients:1 at week, 1 at week 3, and 1 at week 4.

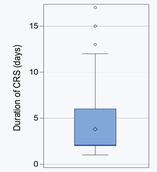
Figure 5. Mean change from baseline in body temperature and blood pressure following dose 1



In patients identified as experiencing any grade CRS following dose 1:

- An increase in body temperature was observed as early as 4-6 hours after tebentafusp administration.
- Trend for decreased blood pressure detected within 12-16 hours after tebentafusp administration.

Figure 6. Time to improvement of Grade ≥2 CRS to Grade 1 or less



- Median time for Grade ≥2 CRS to improve to Grade 1 or less was 2 days.
- Time to improvement > 2 days may be artifactually prolonged due to vital signs typically collected only during observation (through day 2 after first 3 doses) and not in the intervening days between next dose.

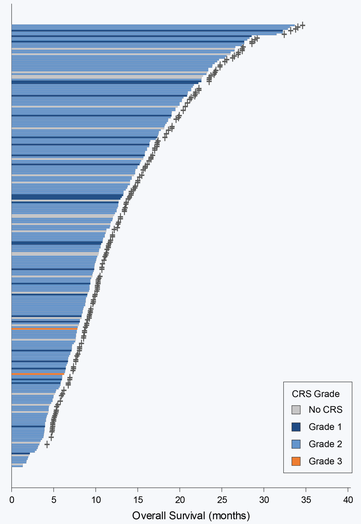
Solid line denotes median; diamond denotes mean

Table 5. Medications

Treatment of CRS	Any grade (N=217) n (%)	Grade ≥2 (N=188) n (%)
Antipyretic	192 (88)	158 (84)
IV fluids	93 (43)	93 (49)
IV steroids	57 (26)	46 (24)
Oxygen	20 (9)	20 (11)
Vasopressor	2 (1)	2 (1)
Tocilizumab	2 (1)	2 (1)

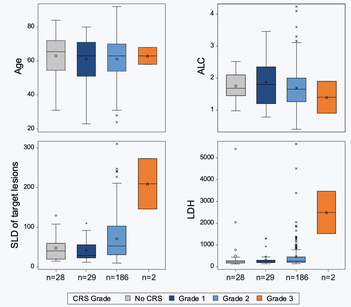
- Most CRS episodes conservatively managed.
- Grade 2 and 3 CRS episodes treated with intravenous fluid (IVF), corticosteroids, and supplemental oxygen as needed (**Table 5**).
- 2 patients received vasopressor (1 G2 and 1 G3) and 2 separate patients received tocilizumab (1 G2 and 1 G3).

Figure 7. Overall survival by CRS grade



- No apparent association between CRS and overall survival.

Figure 8. No major association* between grade of CRS with age, absolute lymphocyte count or disease burden (SLD of target lesions) and LDH at baseline



Patients grouped by overall (highest) grade of CRS, in terms of baseline age, absolute lymphocyte count, SLD of target tumors, and LDH. Box plots represents first and third quartile with median indicated by horizontal line; whiskers represent upper and lower adjacent values.

* Only 2 patients with Grade 3 CRS limit interpretation of association for severe CRS.

ALC: absolute lymphocyte count; LDH: lactate dehydrogenase; SLD, sum of longest diameters.

Conclusions

- Tebentafusp protocols did not mandate prophylactic corticosteroids.
- Most CRS events were mild to moderate in severity.
- Incidence of severe CRS (per ASTCT grading criteria) was very low and limited to first 4 doses.
- CRS events were generally reversible within 2 days using standard management strategies, decreased in frequency and severity with subsequent doses, and rarely led to treatment discontinuation.
- There was no apparent association between CRS and overall survival.

References

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