Phase 1 expansion of IMC-C103C, a MAGE-A4×CD3 ImmTAC bispecific protein, in ovarian carcinoma

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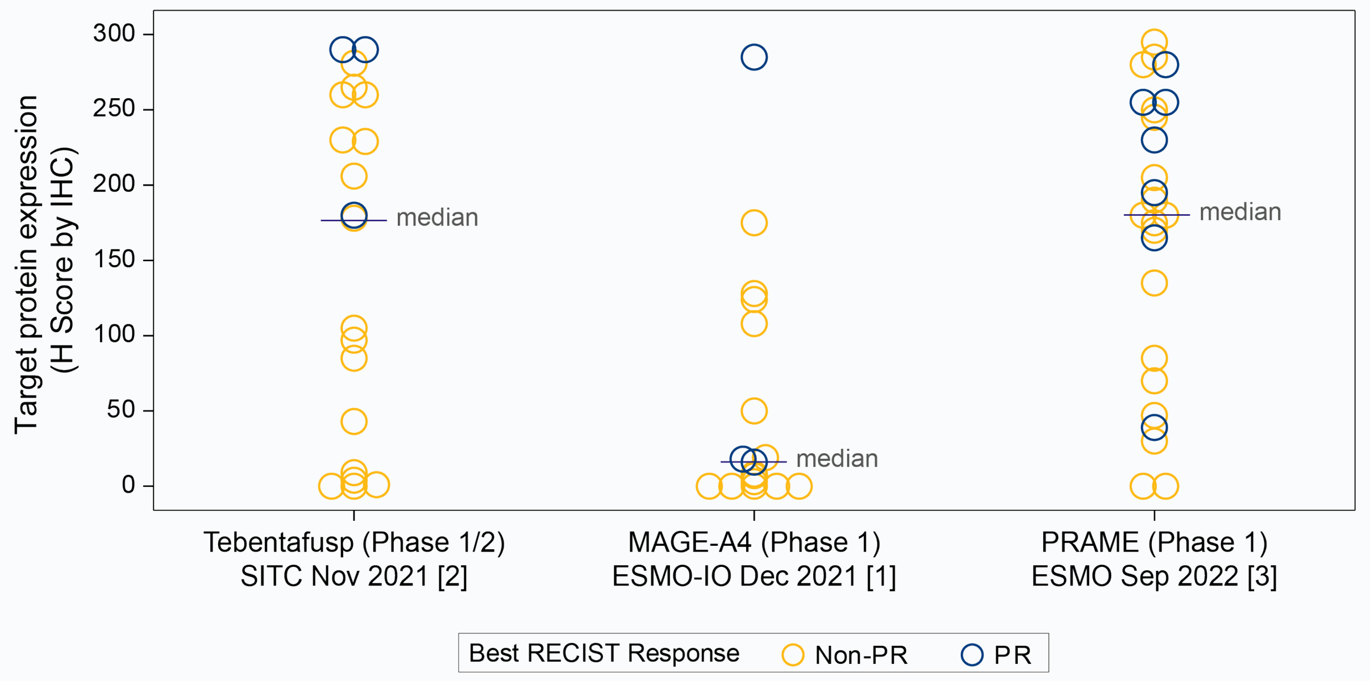
Background

- ImmTAC molecules are TCR bispecific fusion proteins that redirect polyclonal T cells to target intra- or extra-cellular cancer proteins (> 90% of proteome)
- IMC-C103C (MAGE-A4 × CD3) is an investigational ImmTAC targeting an HLA-A2-presented peptide derived from the intra-cellular cancer testis antigen MAGE-A4
- MAGE-A4 is expressed in several tumors, including lung, ovarian, head and neck, and GEJ, but has limited normal tissue expression
- This analysis provides an update to data presented at ESMO-IO 2021 [1], focusing specifically on patients with ovarian cancer (OC) who received doses of IMC-C103C at ≥ 90 mcg intravenously (IV)

Figure 1. RECIST PRs enriched at higher target protein expression (H score)



- Across the ImmTAC platform, RECIST PRs are enriched at higher protein expression (Figure 1)
- However, ctDNA reduction and OS benefit with tebentafusp were observed at both high and low protein expression and were not always associated with radiographic response [2]

Methods

- 33 patients with OC (16 new and an update for 17 previously reported at ESMO-IO 2021 [1]) were enrolled in dose escalation (n=22) and expansion (n=11) cohorts following step up dosing regimen outlined in Figure 2
- Key eligibility criteria:
  - HLA-A*02:01+ (central testing)
  - Relapsed/refractory/intolerant of platinum chemotherapy and PARP inhibitors (if BRCA1 or BRAC2 mutation)
  - All OC histologies allowed for escalation; only high-grade serous OC for expansion
- Patients were enrolled regardless of MAGE-A4 tumor expression, which was evaluated retrospectively for an H score by immunohistochemistry (IHC)
- Tumor assessments were every 9 weeks following the first dose
- Median follow-up time (range): 7.4 (0.5 – 20.5) months. (Data cut-off on 20 Oct 2022)

Dosing timepoint	Dose administered (intravenous)	
Week 1: C1D1	15 mcg (all patients)	
Week 2: C1D8	45 mcg (all patients)	
Week 3: C1D15 onwards	**Dose escalation** 90 mcg (n=6) 140 mcg (n=7) 180 mcg (n=3) 240 mcg (n=6)	**Expansion** 140 mcg (n=11)

Results

Table 1. Baseline demographics

Characteristics	Total (N=33)
Age, yrs – median (range)	59 (44 – 78)
ECOG PS [n (%)]	
0	21 (64%)
1	12 (36%)
Ovarian cancer histopathology [n (%)]	
High-grade serous	30 (91%)
Low-grade serous	1 (3%)
Clear cell	1 (3%)
Serous papillary	1 (3%)
Number of prior lines of therapy	
Mean ± SD	5.2 ± 2.5
Median	5.0
Range	(2 – 12)
Prior platinum [n (%)]	33 (100%)
Prior bevacizumab [n (%)]	26 (79%)
Prior PARP inhibitor [n (%)]	23 (70%)
BRCA mutation status [n (%)]	
Positive	7 (21%)
Negative	24 (73%)
Not done/Unknown	2 (6%)

- Patients were heavily pre-treated with a median of 5 prior lines of therapy

Results

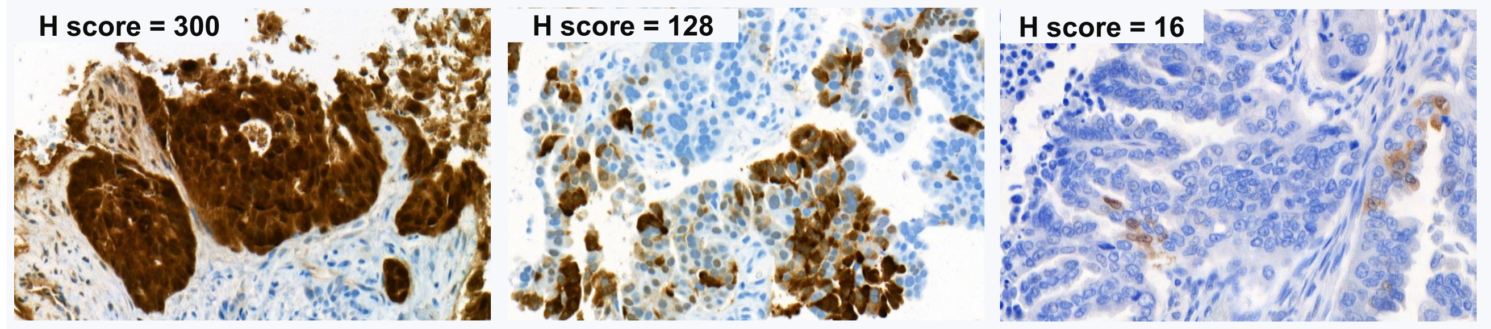
Table 2. Safety profile consistent with mechanism of T cell activation

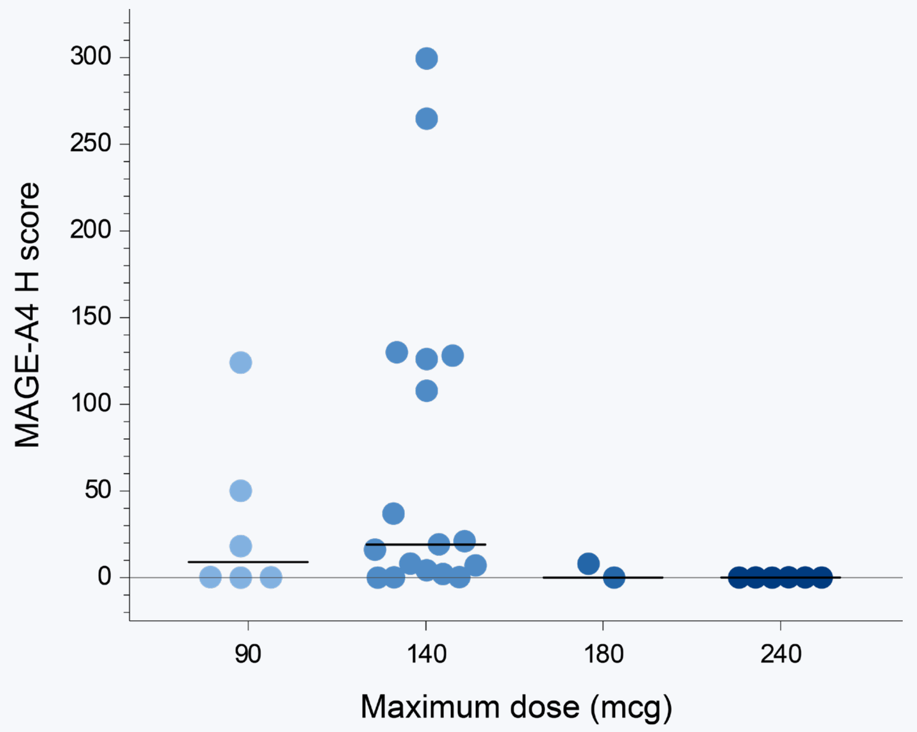
Preferred term[A]	# of patients (%) (N=33)
All grades (treatment-related events in ≥30% of total patients)	
Pyrexia	22 (67%)
Chills	18 (55%)
Cytokine release syndrome (CRS)	16 (49%)
Headache	14 (42%)
Vomiting	14 (42%)
Neutropenia[B]	12 (36%)
Hypotension	11 (33%)
Nausea	11 (33%)
Grade 3-4 (treatment-related events in ≥5% of total patients)	
Neutropenia[B]	10 (30%)
Lymphopenia[C]	8 (24%)
ALT increased	3 (9%)
AST increased	3 (9%)
Anemia[D]	3 (9%)
White blood cell decreased	2 (6%)

- Most common related AEs were consistent with CRS, generally dose dependent, typically Grade 1 or 2, occurring in first 3 weeks, and resolving within a day by supportive care
- Most common related Grade 3 or 4 AE was neutropenia but was reversible with treatment interruption or G-CSF, and decreased with corticosteroid premedication
- 1 patient had a DLT of AST increase at 240 mcg dose but continued on treatment
- No related AE led to treatment discontinuation or death

[A] Includes events reported as a sign/symptom of CRS; [B] Neutropenia is a composite term consisting of neutropenia and neutrophil count decreased; [C] Lymphopenia is a composite term consisting of lymphopenia and lymphocyte count decreased; [D] Anemia is a composite term consisting of anemia and hemoglobin decreased. CRS was graded by the Investigators using ASTCT criteria (Lee et al. 2019) [4]. All other events were graded using NCI CTCAE v5.0. ALT, alanine transaminase; AST, aspartate transaminase.

Figure 3. Majority of OC patients had no or low MAGE-A4 expression

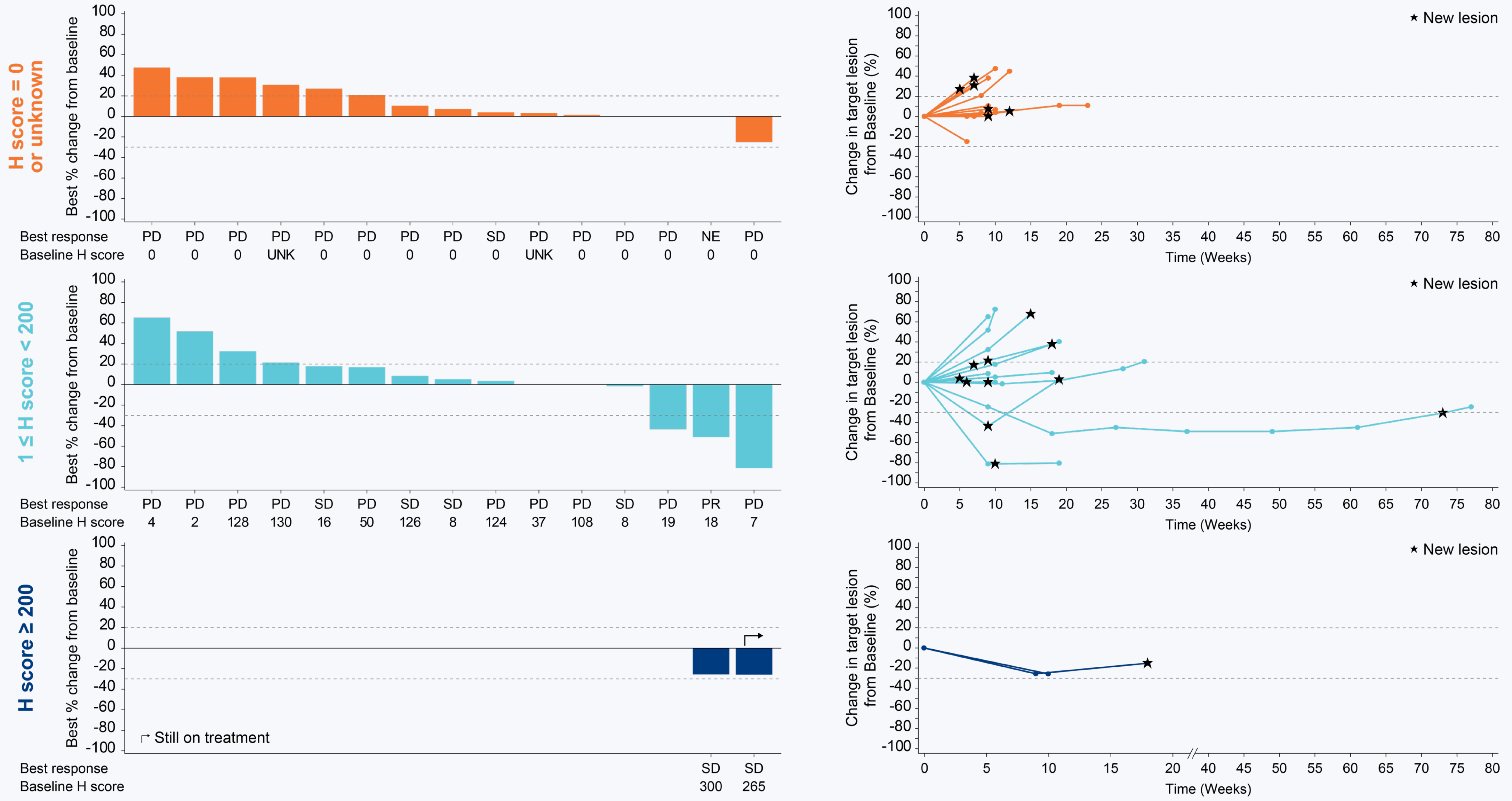




- By IHC, 39% (13/33) of patients were MAGE-A4 negative and 55% (18/33) MAGE-A4 positive*
- Majority of MAGE-A4 positive patients had low expression, median H score 29
- Only 2 patients had H score >200
- At higher doses (≥ 180 mcg), all but one patient (H score 8) were negative for MAGE-A4 expression

* 2/33 patients had unknown H score

Figure 4. Clinical activity by MAGE-A4 expression in 32 response evaluable patients*



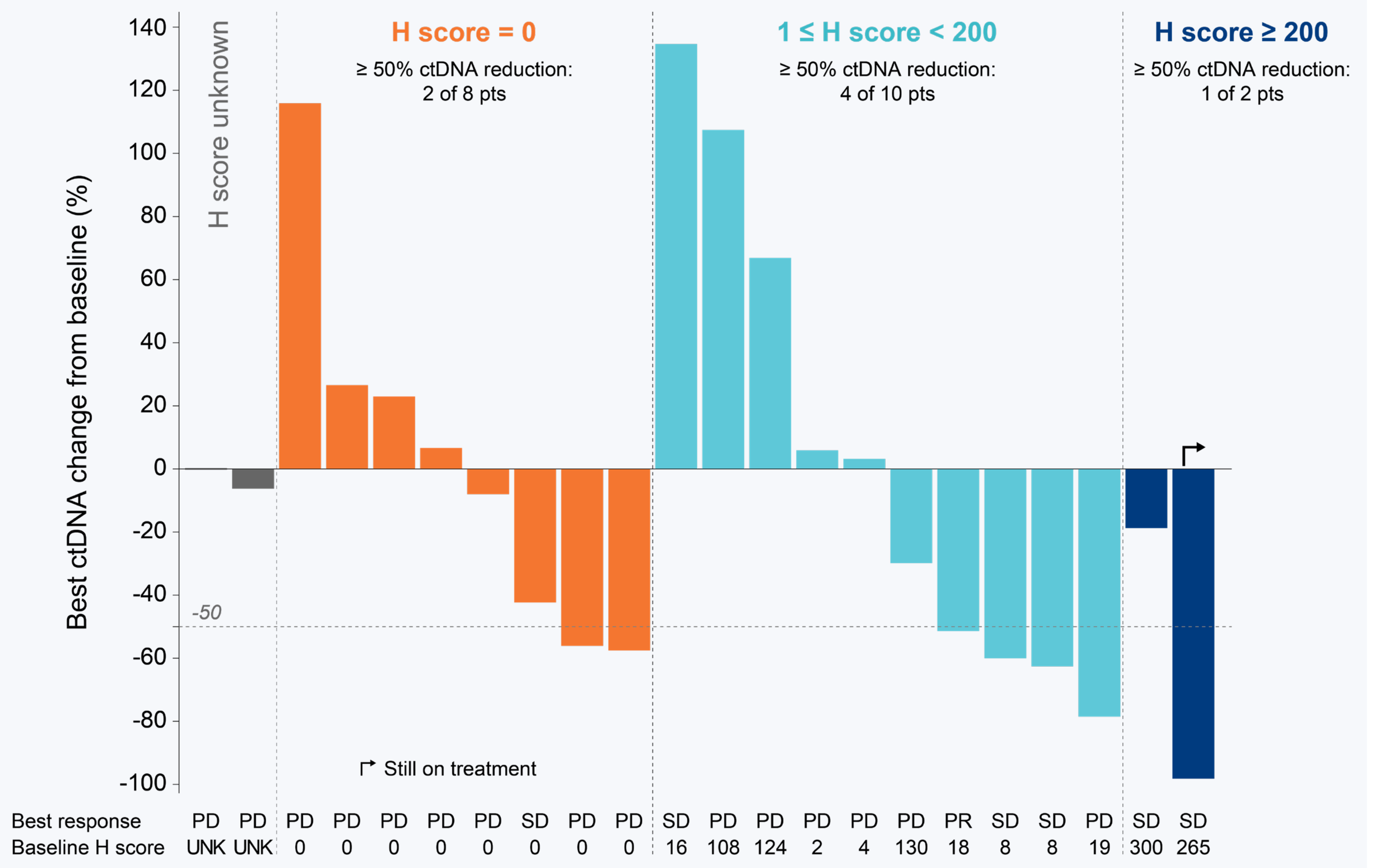
15 MAGE-A4 neg/unk patients
1 had best response of SD

15 patients with H score 1-130
1 had confirmed PR (DOR = 12.7 months) and 4 had best response of SD

2 patients with H score > 200
1 patient had best response of SD and the other has SD at first tumor assessment and still ongoing treatment

* 1 additional patient (H score 21) is still on treatment and has not yet had first tumor assessment

Figure 5: ctDNA reduction mostly observed in patients with MAGE-A4 expression*



* 22 of the 33 OC patients had evaluable baseline and on-treatment ctDNA

- After the first dose, serum IFNγ and TNFα were not induced in MAGE-A4 negative patients and only minimally induced in MAGE-A4 positive patients, consistent with mostly low H scores (data not shown)

Conclusions

- IMC-C103C is clinically active with a manageable safety profile, consistent with the MoA, and no related AEs led to discontinuation or death
- Recent experience with other ImmTAC molecules indicates that RECIST PRs are enriched at higher protein expression but OS benefit and ctDNA reductions are observed at high and low expression
- The vast majority of heavily pre-treated patients with OC had either zero or very low MAGE A4 expression. Few patients had higher MAGE-A4 expression where RECIST responses may be enriched
- However, ctDNA reductions were observed for IMC-C103C at both low and high MAGE-A4 expression and more follow-up would be required for association with OS

References

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