Low Immunogenicity and Favorable Safety Seen With Novel Regimen of Tremelimumab (T) Plus Durvalumab (D) in Patients With Unresectable Hepatocellular Carcinoma (uHCC)

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Introduction

- Recent immune checkpoint therapy data suggest the occurrence of anti-drug antibodies (ADA) can reduce drug efficacy by several mechanisms, including blockade of target binding or increased drug clearance.[1-4]
- Additionally, the complex of ADA and drug has the potential to induce immune-mediated adverse effects, possibly resulting in safety concerns for the patient.[5]
- Durvalumab and tremelimumab are human monoclonal antibodies that block programmed cell death ligand 1 and cytotoxic T-lymphocyte-associated antigen 4 immune checkpoint proteins, respectively, and are under investigation for the treatment of HCC.
- We evaluated immunogenicity and safety of durvalumab and tremelimumab regimens in patients with uHCC from a Phase 1/2 study (Study 22, NCT02519348).

Methods

- Immune checkpoint therapy-naïve patients with uHCC who progressed on, were intolerant to, or refused sorafenib were randomized to receive 1 of the following dose regimens (**Figure 1**):
  - T300 + D: a novel regimen consisting of a single priming dose of T 300 mg + D 1500 mg, then D 1500 mg Q4W
  - D monotherapy: D 1500 mg Q4W
  - T monotherapy: T 750 mg Q4W for a total of 7 doses, then Q12W
  - T75 + D: T 75 mg + D 1500 mg Q4W for a total of 4 doses, then D 1500 mg Q4W.
- Safety and tolerability were the primary endpoints of Study 22.
- Blood samples for ADA testing were collected at baseline and on the first day of treatment weeks 1, 5, 13, and 25.
- ADA evaluable patients were those who received any study drug and had a baseline and ≥1 post-baseline ADA test result.
- The presence of ADAs to durvalumab or tremelimumab was assessed by an electrochemiluminescent bridging assay (Meso Scale Discovery, Rockville, MD) (**Figure 2**).
- ADA titers are reported as the reciprocal of the highest sample dilution that gave a positive result.

Figure 1: Study 22 design

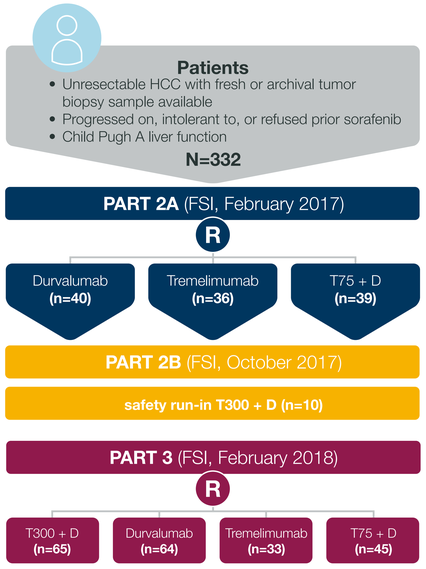
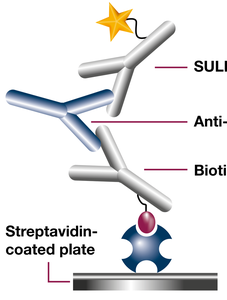


Figure 2: ADA assay



Only complexes of ADA with the 2 forms of tagged drug emit a signal. Signal intensity is directly related to the amount of ADA captured from the patient sample.[1]

Figure adapted from *Immunogenicity Assays* from *MESO SCALE DISCOVERIES®*.

ADA evaluation in patients with uHCC

Durvalumab ADA results

	T300 + D (n=74)	D mono (n=101)	T75 + D (n=82)
Durvalumab ADA evaluable patients, n (%)	55 (74)	56 (55)	43 (52)
ADA+ any visit, n/n	0	0	1/43
Treatment-emergent ADA+	0	0	1/43
Treatment-boosted[a]	0	0	0
Treatment-induced[b]	0	0	1/43
ADA+ baseline only	0	0	0
Persistently positive[c]	0	0	1/43
Transiently positive[d]	0	0	0

[a]Baseline positive ADA titer that was boosted to ≥4-fold during the study. [b]ADA+ postbaseline only. [c]≥2 postbaseline ADA+ measurements with ≥16 weeks between first and last positive measurements or ADA+ at last measurement. [d]ADA+ at baseline and ≥1 postbaseline ADA+ measurement and not meeting persistence requirement.

- Only 1 patient was ADA+ for durvalumab (T75 + D arm).
- The durvalumab ADA+ patient tested positive at a single time point (Week 4) with a low ADA titer of 8.

Tremelimumab ADA results

	T300 + D (n=74)	T mono (n=69)	T75 + D (n=82)
Tremelimumab ADA evaluable patients, n (%)	54 (73)	31 (45)	41 (50)
ADA+ any visit, n/n	7/54	5/31	3/41
Treatment-emergent ADA+	4/54	5/31	3/41
Treatment-boosted[a]	0	1/31	0
Treatment-induced[b]	4/54	4/31	3/41
ADA+ baseline only	2/54	0	0
Persistently positive[c]	5/54	5/31	3/41
Transiently positive[d]	0	0	0

[a]Baseline positive ADA titer that was boosted to ≥4-fold during the study. [b]ADA+ postbaseline only. [c]≥2 postbaseline ADA+ measurements with ≥16 weeks between first and last positive measurements or ADA+ at last measurement. [d]ADA+ at baseline and ≥1 postbaseline ADA+ measurement and not meeting persistence requirement.

- Five or fewer patients in each cohort had a TE-ADA+ response to tremelimumab.
- Of the 12 patients TE-ADA+ to tremelimumab, 1 had a persistent ADA response for ≥16 weeks and the other 11 patients were classified as persistent due to the last ADA assessment being positive.
  - Because 16 weeks is ~5 half-lives for a therapeutic monoclonal antibody, 2 positive ADA results ≥16 weeks apart are indicative of a persistent ADA response as opposed to remnants of a transient ADA response.[6]
- Median highest titers to T were 8 for the T300 + D and T arms and 128 for the T75 + D arm.

Safety in ADA+ patients

- The patient who was ADA+ to durvalumab experienced 1 TEAE of serious grade 3 cholangitis, which was considered related to treatment.
- Due to the small number of tremelimumab ADA+ patients, it was not possible to determine an association between ADA+ status and the type and frequency of AEs reported.

AEs in patients ADA+ to tremelimumab

	T300 + D (n=7)	T mono (n=5)	T75 + D (n=3)
Any grade AE, n (%)	7 (100)	5 (100)	3 (100)
TRAE, n (%)	6 (86)	5 (100)	3 (100)
TRAE, grade ≥3, n (%)	2 (29)	5 (100)	2 (67)
SAE, n (%)	2 (29)	4 (80)	1 (33)
Any grade ≥3 AE or SAE, n (%)	5 (71)	5 (100)	3 (100)
ALT increased	0	0	1 (33)
Amylase increased	1 (14)	0	0
Ascites	1 (14)	0	0
AST increased	0	0	1 (33)
Benign prostatic hyperplasia	1 (14)	0	0
Diarrhea	0	1 (20)	0
Epigastric discomfort	1 (14)	0	0
Gastric ulcer	0	1 (20)	0
GGT increased	1 (14)	0	0
Hyperglycemia	1 (14)	1 (20)	0
Hypertension	1 (14)	0	0
Hypokalemia	0	0	1 (33)
Hyponatremia	1 (14)	1 (20)	0
Hypophysitis	0	1 (20)	0
Lipase increased	2 (29)	2 (40)	1 (33)
Myalgia	0	1 (20)	0
Neutrophil count decreased	1 (14)	0	0
Peritonitis bacterial	1 (14)	0	0
Pneumonia	0	1 (20)	1 (33)
Pruritis	0	1 (20)	0
Pulmonary embolism	1 (14)	0	0
Rash	0	1 (20)	0
Transaminases increased	1 (14)	0	0
Vomiting	0	1 (20)	0

Conclusions

- In Study 22, only 1 of 154 evaluable patients was ADA+ to durvalumab, and few patients were positive for TE-ADAs to tremelimumab.
- In this study, both durvalumab and tremelimumab exhibited unremarkable immunogenicity profiles; ADA responses were of short duration (<16 weeks) and had low titers.
- Immunogenicity profiles of durvalumab in patients with uHCC were consistent with those observed in other tumor types, where ~1%–4% of patients developed treatment-emergent ADAs.[7-9]
- T300 + D and D are being evaluated in the Phase 3 HIMALAYA study (NCT03298451) in first-line uHCC versus sorafenib.

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Abbreviations

+, positive; ADA, anti-drug antibodies; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, durvalumab; GGT, gamma-glutamyl transferase; Q4W, every 4 weeks; SAE, serious adverse events; T, Tremelimumab; T300 + D, tremelimumab 300 mg +durvalumab 1500 mg × 1 dose + durvalumab 1500 mg Q4W; T75 + D, tremelimumab 75 mg + durvalumab 1500 mg Q4W × 4 doses, then durvalumab 1500 mg Q4W; TE-ADA+, treatment-emergent ADA+; TRAE, treatment-related adverse event; uHCC, unresectable hepatocellular carcinoma.

For more details on Study 22, please visit **https://clinicaltrials.gov/ct2/show/NCT02519348**

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https://bit.ly/38QqeA1