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Poster 4087

T cell receptor pharmacodynamics associated with survival and response to tremelimumab (T) in combination with durvalumab (D) in patients (pts) with unresectable hepatocellular carcinoma (uHCC)

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Objective

- We present an exploratory molecular analysis of peripheral blood T cell receptors following treatment with two tremelimumab (T) plus durvalumab (D) combinations, including a novel combination regimen containing a single, priming dose of T (T300+D), and T and D as monotherapies, and the potential association with objective response rate (ORR) and overall survival (OS), in patients with unresectable hepatocellular carcinoma

Conclusions

- A greater number of expanded T cell clones at Day 29 was associated with longer survival and a greater likelihood of a clinical response
- The number of expanded T cell clones increased with higher doses of tremelimumab, and a greater proportion of patients had above-the-median number of expanded T cell clones in the T300+D and T arms versus the T75+D arm
- These results, taken together with the clinical safety data,[1] support the clinical benefit of the T300+D regimen
- Further work is needed to understand the relative contributions of CD4 and CD8 T cell clonal expansion on the improved ORR and OS observed with T300+D and T monotherapy
- T300+D and D are being evaluated in the Phase 3 HIMALAYA study (NCT03298451) in unresectable hepatocellular carcinoma versus sorafenib[2]

Plain language summary

Why did we perform this research?

Immunotherapy helps the body's own immune system to recognize and kill cancer cells. Tremelimumab and durvalumab are immunotherapies that are being developed for the treatment of hepatocellular carcinoma, a type of liver cancer. In Study 22, a single, priming dose of tremelimumab in combination with durvalumab (T300+D) appeared to help patients live longer and help their tumors shrink in size, compared with using multiple lower doses of tremelimumab, or using either treatment on its own[1]

How did we perform this research?

Blood samples were taken from patients before and after treatment to determine whether changes in an aspect of the immune response correlated with improved outcomes for the patient

What were the findings of this research and what are the implications?

We found that this feature of the immune response measured in this research appeared to be dependent on the dose of tremelimumab, with the largest immune response seen in patients who received the higher doses of tremelimumab. Patients with an increased immune response tended to have better outcomes; patients lived longer and their tumors decreased in size. The novel T300+D combination is now being investigated, versus sorafenib, in more patients in a larger clinical study called HIMALAYA

Where can I access more information?

Clinical trial registry: https://clinicaltrials.gov/ct2/show/NCT02519348

QR code materials: https://bit.ly/2RsoTIU

Funding statement: This study was funded by AstraZeneca

References: 1. Kelley RK, et al. J Clin Oncol 2020;38(15_suppl). Abs 4508

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Poster

Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below.
https://bit.ly/2RsoTIU

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Introduction

- Tremelimumab (T), an anti–CTLA-4 antibody, and durvalumab (D), an anti–PD-L1 antibody, are under investigation as monotherapies and in combination for the treatment of multiple tumor types, including hepatocellular carcinoma (HCC)[1,3–6]
- In this Phase 2 study in unresectable HCC (uHCC; Study 22, NCT02519348), a novel, single, priming dose of tremelimumab plus durvalumab (T300+D) combination regimen has shown favorable clinical activity and safety versus D or T monotherapy or another combination (T75+D)[1]
- Additionally, an expansion of proliferative CD8+ lymphocytes at Day 15 was associated with improved response and was most profound for the T300+D-treated patients[1]
- Changes in peripheral blood T cell receptor (TCR) clonality have been associated with clinical benefit from anti–CTLA-4 therapy in other indications[7]
- Here, we present an exploratory molecular analysis of peripheral blood TCRs, evaluating changes in TCR clonality in patients receiving different doses of T and D

Methods

Study design

- Immune checkpoint therapy-naïve patients with uHCC who had progressed on, were intolerant to, or refused, sorafenib were randomized to receive one of the following dose regimens (Figure 1):
  - T300+D: 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

Figure 1. Study 22 design

D, durvalumab; T, tremelimumab

Objectives and assessments

- Primary endpoint: safety
- Key secondary endpoints:
  - Overall survival (OS)
  - Objective response rate (ORR)
  - Duration of response

T cell receptor analysis

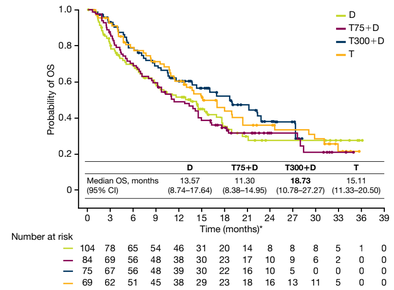
- DNA was isolated from PAXgene®-preserved whole blood collected at baseline and on Day 29, corresponding to 4 weeks after the single, initial dose of D and/or T from evaluable samples. Paired samples were available from a subset of clinically-evaluable patients
- CDR3 sequences of TCR β-chain were sequenced using the immunoSEQ® Assay (Adaptive Biotechnologies, Seattle, WA)
- Associations with ORR and OS were evaluated. Statistical measures of biomarker data are descriptive only and considered exploratory

Results

Overall survival

- The longest median OS was observed with T300+D (Figure 2)[1]

Figure 2. OS



*Time from randomization (Part 2A, 3) or first dose (Part 2B)
CI, confidence interval; D, durvalumab; OS, overall survival; T, tremelimumab

T cell receptor analysis

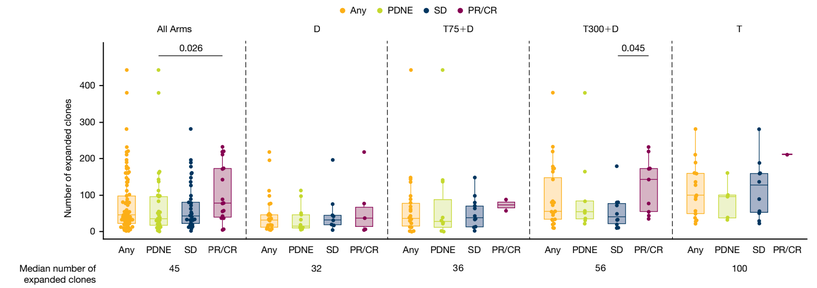
- ImmunoSEQ-evaluable paired samples were available from a subset of patients (Table 1 and Supplementary Figure 1)
- A T dose-dependent increase in the median and upper CI limit of expanded T cell clones was observed in T-containing arms at Day 29
- There were no significant differences in baseline richness or Simpson clonality of T cells across treatment arms (Table 1 and Supplementary Figure 2)
- A greater number of expanded T cell clones was associated with response and appears to be driven by higher doses of tremelimumab (Figure 3)
  - Across all treatment arms, responders had a larger median number of expanded T cell clones on Day 29 versus non-responders (77.5 vs 40)
  - The median number of expanded T cell clones is greatest for T300+D and T monotherapy responders, although small sample size in individual arms prevents robust, firm conclusions
- A greater number of expanded T cell clones is associated with longer OS (Figure 4)
  - The median number of expanded T cell clones in D monotherapy was 32, so this cut-off point was used across all treatment arms to evaluate the impact of adding tremelimumab
  - The fraction of patients with expanded T cell clones increased at higher tremelimumab doses, and these patients also have longer OS with the addition of tremelimumab to durvalumab therapy

Table 1. Response and clonality for clinically-evaluable and immunoSEQ-evaluable patients

	Arm (Clinically-evaluable patients)	D (n = 104)	T75+D (n = 84)	T300+D (n = 75)	T (n = 69)
Data for clinically-evaluable patients	ORR, %	10.6	9.5	24.0	7.2
	Median OS, months (95% CI)	13.6 (8.7–17.6)	11.3 (8.4–15.0)	18.7 (10.8–27.3)	15.1 (11.3–20.5)
Data for ImmunoSEQ-evaluable patients	Patients with samples, n	30	26	28	17
	ORR, %	23.0	7.7	32.0	5.9
	Median OS, months (95% CI)	NA (10–NA)	16 (9–NA)	19 (11–NA)	21 (10–NA)
	Median number of expanded T cell clones at Day 29 (95% CI)	32 (13–46)	36 (22–70)	56 (36–84)	100 (50–160)
	Median baseline Simpson clonality (95% CI)	0.079 (0.046–0.890)	0.054 (0.040–0.090)	0.079 (0.046–0.110)	0.076 (0.036–0.880)
	Median baseline richness, 10^3 clones (95% CI)	59 (47–88)	62 (42–79)	51 (47–66)	60 (41–67)

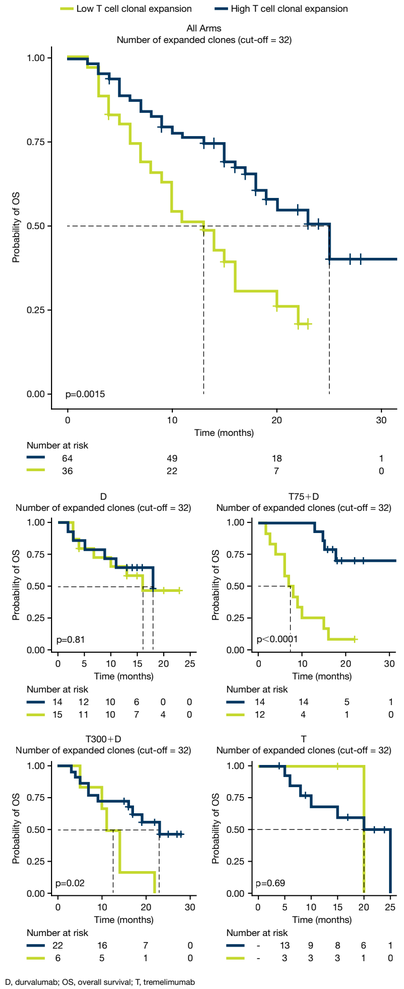
CI, confidence interval; D, durvalumab; NA, not available; ORR, objective response rate; OS, overall survival; T, tremelimumab

Figure 3. T cell clonal expansion by best overall response



CR, complete response; D, durvalumab; PDNE, progressive disease and non-evaluable data plotted together; PR, partial response; SD, stable disease; T, tremelimumab

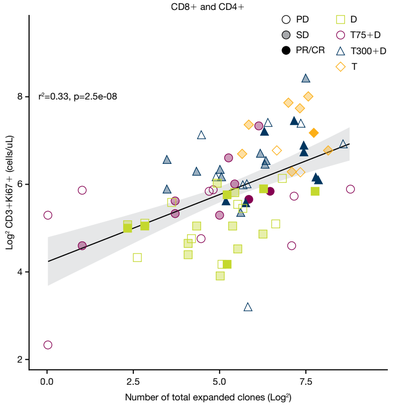
Figure 4. OS by T cell clonal expansion status



D, durvalumab; OS, overall survival; T, tremelimumab

- The increased number of expanded T cell clones correlates with increased proliferating T cells on treatment (Figure 5 and Supplementary Figure 3)
  - Previously, we presented an association of response to T300+D with greater CD8+ T cell proliferation
  - Here, we see a correlation between proliferating T cells and the number of expanded T cell clones
  - Taken together, these data suggest that both expanding the number of unique T cell clones and increasing T cell proliferation are needed to optimize the chances for clinical response

Figure 5. T cell clonal expansion and proliferation



T cell proliferation was measured by flow cytometry on whole blood samples collected on Day 15
CD, cluster of differentiation; CR, complete response; D, durvalumab; PD, progressive disease; PR, partial response; SD, stable disease; T, tremelimumab

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Disclosures

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