DRAGON Trial: Durable remission rate with the latent TGFβ1 inhibitor linavonkibart (SRK-181) and pembrolizumab in patients with immune checkpoint inhibitor resistant advanced cancers

Authors

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Background

Transforming growth factor-beta 1 isoform (TGFβ1) drives tumor immune escape by promoting an immunosuppressive pro-tumor microenvironment. Linavonkibart is a first-in-class fully human IgG4 context-independent anti-latent TGFβ1 monoclonal antibody.

Methods

Linavonkibart+pembrolizumab showed antitumor activity with no dose-limiting toxicity during dose escalation. In expansion cohorts, linavonkibart (1500mg q3w)+Pembrolizumab were administered in melanoma (MEL), urothelial carcinoma (UC), and non-small cell lung cancer (NSCLC) patients, who were non-responders to prior anti-PD1; and in clear cell renal cell carcinoma (ccRCC) and head and neck squamous cell carcinoma (HNSCC) patients, with disease progression on the most recent prior anti-PD1. Biomarker analyses include immunohistochemistry and flow cytometry.

Results

As of 11 Jun 2024, 78 patients (28.2% females, median age 65 years) were enrolled. Patients had received a median of 3 prior lines of therapies (range 1-9). All patients had a best response of SD or PD on prior anti-PD1 (except 1 HNSCC patient, who had PR). All patients had progressed on their most recent anti-PD1 (except 2 MEL patients). Treatment-related AEs (TRAE, ≥10%) of any grade were rash (33.3%), pruritus (26.9%), fatigue (21.8%) and diarrhea (15.4%). Rash (12.8%) was the only grade 3 TRAE (≥5%); only one grade 4 TRAE (dermatitis exfoliative generalized) occurred. There was no grade 5 TRAE. Treatment-related SAE (≥2% [2 pt]) was pemphigoid (2.6%). Efficacy results are presented in the table below. Tumor

assessments were based on RECIST 1.1 criteria by PI. PFS rate (95% CI) for ccRCC patients at 6 months and 9 months were 44% (25.6, 61) and 28.6% (12.1, 47.5), respectively.

Intent-to-Treat patients (n)	ccRCC (N=30)	HNSCC (N=11)	MEL (N=11)	UC (N=11)
ORR	23.3%	18.2%	27.3%	9.1%
CR (n)	1	0	1	0
PR (n)	6	2	2	1
Duration of Response Median (range, months)	9.7^{+} (2.5^{+}-22.9^{+})	3.3^{+} (0.1-6.4^{+})	4.9 (1.8-7.1)	12.9 (12.9-12.9)

$^{+}$: patients are ongoing, data may potentially increase.

In ccRCC patients, baseline CD8+ T-cell infiltration status and baseline Treg levels correlated with positive clinical outcome: ORR increased to 33% (4/12) and 57.1% (4/7) for CD8+ infiltrated patients and elevated Treg patients, respectively. Across all cohorts, treatment with linavonkibart+Pembrolizumab shifted the microenvironment to more proinflammatory in responding patients.

Conclusions

Linavonkibart+Pembrolizumab treatment demonstrated promising efficacy in anti-PD1 resistant patients across multiple tumor types with a manageable safety profile. Baseline biomarker data from ccRCC patients showed clinical outcomes correlated with CD8+ infiltration and elevated Treg Levels, suggesting a potential patient selection strategy. These data support further investigation of linavonkibart.