Title: Tiragolumab plus atezolizumab and bevacizumab in targeted therapy-refractory, immune checkpoint blockade-naive, advanced *EGFR*-mutated NSCLC

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Background:

Treatment of advanced epidermal growth factor receptor-mutated (*EGFRm)* non-small cell lung cancer (NSCLC) has evolved with EGFR targeted therapy (TT)-based treatment emerging as the frontline standard. Despite this, most patients experience disease progression and have limited subsequent options. Immune checkpoint blockade (ICB) has improved outcomes in driver-mutation negative NSCLC but remains ineffective as monotherapy and unsafe in combination with EGFR-TT in ICB-naïve *EGFRm* NSCLC.

Activated EGFR signaling upregulates vascular endothelial growth factor (VEGF), promoting angiogenesis and immune suppression through impaired cytotoxic T-cell infiltration and expansion of regulatory T cells. Clinically, PD-1 blockade plus anti-VEGF and chemotherapy has shown activity in TT-refractory *EGFRm* NSCLC. Whether VEGF inhibition combined with dual ICB is efficacious in the absence of chemotherapy remains unknown. To address this, we designed a phase II trial evaluating tiragolumab (anti-TIGIT), atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) in EGFR TT-refractory, ICB-naïve, advanced *EGFRm* NSCLC (NCT04958811).

Methods:

Patients with advanced *EGFRm* NSCLC with progression on appropriate EGFR TT were enrolled and treated with tiragolumab 600mg IV, atezolizumab 1200mg IV, and bevacizumab 15mg/kg IV every 3 weeks (q3w). Key exclusion criteria included prior ICB and untreated or symptomatic brain metastases. A Simon two-stage design was utilized, with 12 patients enrolled to stage 1 and, if ≥1 response observed, an additional 9 patients enrolled to stage 2. The primary endpoint was objective response rate (ORR) by RECIST v1.1. Secondary endpoints included safety, progression free survival (PFS), and overall survival (OS). Pre- and on-treatment tumor and blood collections were obtained for correlative analyses.

Results:

Nine of 21 patients were enrolled before trial was halted due to discontinuation of tiragolumab development by sponsor. Median age was 67 years (interquartile range (IQR): 57-70) with median of two prior therapies (IQR 1-4). EGFR subtypes comprised exon 19 deletion (44%), L858R (22%), C719S (11%), G819X (11%), and exon 20 insertion (11%). At a median follow up of 28.1 months, no responses were achieved (ORR 0%, 95% CI, 0-30), with five patients achieving stable disease (disease control rate [DCR] 56%, 95% CI, 27-81). Median PFS was 1.55 months (95% CI, 1.25-NA) and median OS was 7.89 months (95% CI, 5.1-NA). Two patients had durable stable disease exceeding 6 months. Grade ≥3 treatment-related adverse events occurred in 4 patients (44%), including proteinura (22%), stroke (11%), cough (11%), and hyponatremia (11%). One patient was started on osimertinib monotherapy following disease progression on docetaxel plus ramucirumab after progression on trial therapy and developed hepatic failure resulting in death (grade 5).

Conclusions:

Accrual was halted early following termination of tiragolumab development. Interim analysis demonstrated minimal clinical efficacy of dual ICB with VEGF inhibition in TT-refractory, ICB-naïve *EGFRm* NSCLC. These findings suggest this combination is unlikely to represent an effective therapeutic strategy in this population. Additional blood and tissue correlative analyses will be conducted to assess for potential signals of benefit among patients who achieved prolonged stable disease.