TPS9605 **Poster Session**

A phase II study of binimetinib plus imatinib in patients with unresectable KIT-mutant melanoma.

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Background: Patients (pts) with melanoma refractory to immune checkpoint inhibition (ICI) remain in need of rational therapeutic options. Pts with rare melanoma subtypes (acral, mucosal) are in particular need given lower objective response rates (ORR) to ICI, and lower incidence of BRAF V600-mutant disease. Such BRAF mutations are found in only 5-10% of acral/mucosal melanomas, while KIT mutations/amplifications are found in 10-20%. Even when present, a KIT alteration does not guarantee response to KIT inhibition, with only one-third responding as shown in previous phase II studies. A significant number of KIT-mutant melanomas have been shown to demonstrate NF1 or SPRED1 loss, with recent preclinical work showing these alterations to be associated with loss of negative suppression of RAS, resulting in RAS activation and MEK dependence. We hypothesize that NF1 or SPRED1 loss cooperates with KIT mutations to drive melanomagenesis and resistance to KIT inhibition, and propose to target this vulnerability with a combination targeted therapy approach. This phase II study will be the first to evaluate the efficacy and safety of binimetinib plus imatinib in pts with KIT-mutant melanoma. **Methods:** This is a multicenter, investigator-initiated phase II study of binimetinib in combination with imatinib in pts with KIT-mutant unresectable melanoma who have progressed on or who are ineligible for ICI. Pts will be ≥18 yo with performance status ECOG 0-2, and have unresectable Stage IIIB/C/D or Stage IV melanoma that is KIT-mutant by CLIA-certified testing platform. Pts will have progressed on prior ICI or other standard-of-care (SOC) therapies, or be ineligible for/unable to tolerate SOC therapies. Pts with brain metastasis will be eligible if clinically stable with no need for CNS-specific treatment required prior to study start. Pts previously treated with a MEK inhibitor will be excluded. A Simon 2-stage Minimax design will be used; the null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. 15 pts will be accrued in the Stage 1. If there are <1 responses, the study will be stopped. Otherwise, 10 additional pts will be accrued in Stage 2 for a total of 25. The null hypothesis that the true response rate is 0.1 will be rejected if ≥6 responses are observed. This yields a type I error rate of 0.05 and power of 0.8017 when the true response rate is 0.3. Primary endpoint: ORR (RECIST). Secondary endpoints: duration of response, progression-free survival, overall survival, clinical benefit rate (CR, PR, or SD ≥16 weeks), safety profile (CTCAE). Exploratory objectives include investigation of association between clinical response and baseline NF1 and SPRED1 status, and pathologic correlates of acquired resistance. 11 pts have been screened; 8 of planned 15 pts in Stage 1 have been enrolled. Enrollment is ongoing at UCSF and UCSD. Clinical trial information: NCT04598009. Research Sponsor: None.