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PHASE 1A TRIAL OF PLN-101095, AN INTEGRIN α V β 8 AND α V β 1 INHIBITOR, AS MONOTHERAPY AND IN COMBINATION WITH PEMBROLIZUMAB, IN TREATMENT-RESISTANT PATIENTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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Background Analyses of transforming growth factor- β (TGF- β) expression in tumors treated with immune checkpoint inhibitors (ICIs) suggest that in the tumor microenvironment may play a role in poor response to ICIs. PLN-101095 is a novel, orally bioavailable small molecule that inhibits integrin α V β 8 and α V β 1 binding to the latency-associated peptide of TGF- β , prevents its activation, and enhances the of ICIs including CD8+ T-cell infiltration in preclinical models.

Methods A Phase 1a, first in human, dose-escalation, consecutive-cohort, open-label study was designed to evaluate the safety, tolerability and pharmacokinetics of PLN-101095 as monotherapy and in combination with pembrolizumab in patients with advanced or metastatic solid tumors progressing on treatment with pembrolizumab. Eligible patients must be \geq 18 years, have received at least 3 doses (200 mg Q3W) of , have evidence of disease progression at least 3 months after initiation of , and no other available effective treatment options. PLN-101095 will be administered as a lead-in monotherapy for 14 days, followed by PLN-101095 in combination with pembrolizumab starting on Day 15.

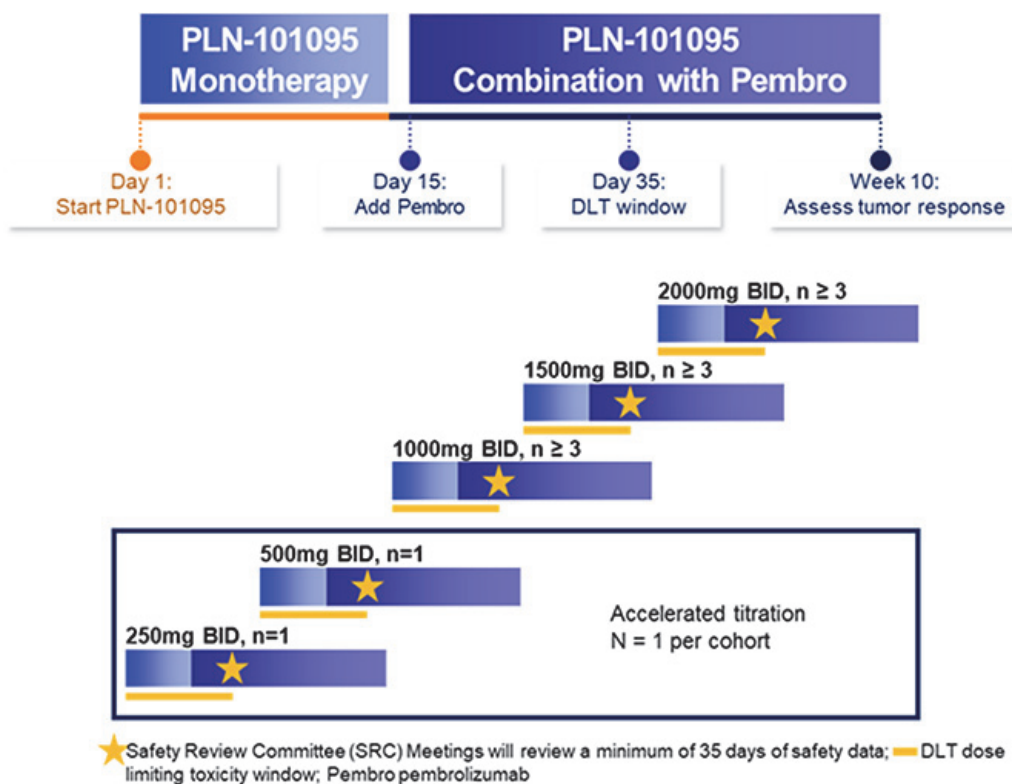
Dose-escalation will be determined by a Bayesian optimal interval dose escalation design with accelerated titration (n = 1) permitted for dose levels 1 and 2 (figure 1). A minimum

of 3 participants will be accrued to dose levels 3 to 5. Following the dose-escalation cohorts, dose-expansion cohorts using a Simon's 2-stage design are planned.

Conclusions This first-in-human trial will evaluate the safety and tolerability of PLN-101095, administered first as monotherapy to re-sensitize participants' tumors to pembrolizumab, and subsequently in combination with pembrolizumab. Enrolled patients will have demonstrated primary or acquired resistance to pembrolizumab and for assessing anti-tumor activity and pharmacodynamic effects. This trial design enables the efficient conduct of dose escalation trials involving ICI-sensitizing drugs in patients with resistance to ICIs.

Ethics Approval The protocol and all amendments are approved by the appropriate institutional review board or independent ethics committee at each participating study site. The study is being conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

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Abstract 714 Figure 1 Study design.