

**412PD Clinical activity, safety, and PK/PD from a phase I study of RO6874281, a fibroblast activation protein (FAP) targeted interleukin-2 variant (IL-2v)**

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**Background:** High-dose IL-2 is approved for patients with metastatic melanoma and renal cell carcinoma but is associated with significant toxicity, frequently requiring intensive care. RO6874281 carries an engineered IL2v moiety with abolished binding to IL-2Ra. Affinity to IL-2Rβγ is retained, resulting in activation of immune effector CD8 T and NK lymphocytes, but reduced activity on regulatory T cells (Tregs). The antibody part of RO6874281 binds with high affinity to FAP, which is strongly expressed on tumor-associated fibroblasts, and mediates retention and accumulation in malignant lesions.

**Methods:** Study BP29842 investigates safety, PK/PD and anti-tumor activity of RO6874281, administered i.v. once per week in an outpatient setting to patients with metastatic solid tumors. The dose escalation part enrolled 28 patients with metastatic solid tumors and identified a recommended dose (RD) of 20mg, using one-step intra-patient escalation (15mg followed by 20mg). Patients with treatment refractory melanoma and squamous cell carcinomas are enrolled to an extension cohort to confirm safety and further explore PK/PD and activity of the RD. So far, 16 patients were enrolled to this cohort including 6 with melanoma.

**Results:** To date, most frequent adverse events (>30%) were pyrexia, infusion related reactions, fatigue/asthenia, nausea, diarrhea, decreased appetite and elevated aspartate and/or alanine transaminase. The majority of events were mild or moderate (Grade 1/2). At RD, RO6874281 rapidly expands CD8 and NK cells but not Tregs, both in peripheral blood and sequential tumor biopsies. Objective long-lasting (> 6 months) responses were observed in one patient each with head and neck cancer, penile squamous cell carcinoma and checkpoint inhibitor resistant malignant melanoma across

the escalation dose range. Further, tumor shrinkage was observed in 4 melanoma patients, including 1 uveal and 1 mucosal.

**Conclusions:** RO6874281 is the first targeted IL-2 variant with acceptable outpatient safety to display monotherapy activity, including in tumor types not previously reported to respond to IL-2. Ph1b/Ph2 studies in combination with atezolizumab and other agents are currently underway.

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