Background INCB086550 is an orally administered small-molecule inhibitor of programmed cell death ligand 1 (PD-L1). This is an ongoing phase 1, open-label, multicenter study.

Methods Eligible patients are aged ≥18 years with advanced solid tumors and Eastern Cooperative Oncology Group performance status of 0–1. Patients had disease progression after treatment with available therapies or were ineligible for or without access to standard treatment. Part 1 uses a modified 3+3 dose-escalation design to identify a maximum tolerated dose (MTD) of INCB086550. Multiple doses are expanded in additional cohorts: part 2 cohort A (tumors that progressed on previous PD-1 treatment), part 2 cohort B (immunotherapy-naive), part 3 (high microsatellite instability [MSI-H] or deficient mismatch repair), and part 4 (human papilloma virus-positive tumors). The primary endpoints were safety and tolerability measured by monitoring frequency and severity of adverse events (AEs) and to determine a pharmacologically active dose and/or MTD. Tumor response was evaluated per RECIST v1.1 or RANO.

Results As of April 1, 2022, 138 patients received INCB086550 treatment at doses ranging from 100 mg once daily to 800 mg twice daily (bid); median age was 65 years (range, 31–86), 60.9% were women, 80.4% were white. 78 patients (56.5%) had ≥2 lines of prior therapy. The most common tumor types were colorectal (13.8%), cervical (10.9%), and anal (10.9%). 121 patients (87.7%) discontinued treatment, 90 of whom discontinued for disease progression. Treatment-emergent AEs (TEAEs) occurring in >20% of patients were fatigue, nausea, decreased appetite, constipation, vomiting, and diarrhea. Serious TEAEs (SAEs) occurred in 50 patients (36.2%); SAEs occurring in >2 patients were small intestinal obstruction, abdominal pain, intestinal pain, pulmonary fibrosis, and pneumonia. No dose-limiting toxicities (DLTs) occurred. Grade ≥3 treatment-related AEs occurred in 18 patients (13.0%), with aspartate aminotransferase increased, fatigue, immune-mediated neuropathy, and rash reported in >1 patient (n=2 each). Sponsor-defined immune-related TEAEs occurred in 41 patients (29.7%), 22 (15.9%) of which were peripheral neuropathies. Stepdown/intermittent dose regimens did not mitigate events of immune-mediated peripheral neuropathy. 16 patients (11.6%) had TEAEs that led to discontinuation of INCB086550. Two patients (1.4%) achieved a complete response (squamous cell anal cancer, 400 mg bid; MSI-H colorectal cancer, 400 mg bid); 10 patients overall (7.2%) achieved partial response.

Conclusions No DLTs occurred. Encouraging antitumor activity has been observed. INCB086550 has a safety profile consistent with monoclonal antibody immune checkpoint inhibitors, except for an observed increased rate of immune-mediated peripheral neuropathy.

Trial Registration NCT04629339

Ethics Approval This study was reviewed and approved by the institutional review boards of the participating institutions. Approval numbers are: EC/FAHMP (Belgium), P/2020-149; ARS/RHA (Regional Health Authority) (France), 2018-2610; AIFA (Italy), 133700; IRAS (UK), 282291; REC (UK), 20/LO/1001; (USA), RM 598, 1254008, 2018-0765, MOD00971017, 20182238, 1291221. All patients provided written informed consent.