Supplementary Methods

Eligibility criteria

General inclusion criteria:

- Signed informed consent
- Age ≥18 years
- Radiologically measurable and clinically evaluable disease
- Life expectancy of ≥12 weeks
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites requiring urgent alternative medical intervention (e.g., central nervous system [CNS] metastases, respiratory/organ failure due to tumor compression, spinal cord compression, tumor infiltration into great thoracic vessels and/or mediastinal structures, pulmonary cavitations with risks of rupture towards the pleura or bronchial system)
- Confirmed at least one tumor lesion with location accessible to safely biopsy per clinical judgment of the treating physician and the participant's consented willingness to undergo baseline and on-treatment tumor biopsies for pharmacodynamic (PD) biomarker analysis (special requirements apply to Part C; for these participants, approval by the Medical Monitor is mandatory)
- Eastern Cooperative Oncology Group Performance Status 0–1
- Participants with unilateral pleural effusion should fulfill the following criteria for pulmonary and cardiac functions:
    - Forced expiratory volume 1 (FEV1) >70% and forced vital capacity (FVC) >70% of predicted value; participants with lung metastases should present with diffusing capacity of the lungs for carbon monoxide DLCO >60% of predicted value
    - See exclusion criteria for participants with bilateral pleural effusion
- Adequate cardiovascular function:
    - New York Health Heart Association (NYHA) classification functional class 1 or better left ventricular systolic function (LVEF)
    - 50%, as determined preferentially by transthoracic echocardiogram (TTE) or else by multiple-gated acquisition (MUGA) scan
    - Baseline corrected QT interval ≤470 ms
    - Resting blood pressure systolic ≤150 mmHg and diastolic ≤100 mmHg (average of three or more readings on two or more sessions)
    - Baseline resting bradycardia ≥45 beats per minute or baseline resting tachycardia ≤100 beats per minute

- All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to grade ≤1, except alopecia (any grade) and grade 2 peripheral neuropathy
- Adequate hematological function: neutrophil count of ≥1.5 x 10^9 cells/L, platelet count of ≥100,000/µL, hemoglobin ≥9 g/dL (5.6 mmol/L), lymphocytes ≥0.5 x 10^9 cells/L (borderline lymphocyte values that are right below the limit with the machine count, lymphocytes can also be confirmed with manual counts if machine count is below limit)
- Adequate liver function: total bilirubin ≤1.5 x upper limit of normal (ULN); direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 ULN, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤2.5 x ULN. In case of liver metastases AST and ALT: ≤ 5 x ULN. Eligibility of patients with liver metastases should be discussed and agreed with the Sponsor if AST and ALT are between 2.5 x and 5 x ULN
- Adequate renal function: serum creatinine ≤ 1.5 x ULN or creatinine clearance (CRCL) by Cockcroft-Gault formula ≥ 50 mL/min for participants in whom, in the investigator‘s judgment, serum creatinine levels do not adequately reflect renal function
- Negative serum pregnancy test within 7 days prior to study treatment in premenopausal women and women <12 months after menopause (menopause is defined as amenorrhea for ≥12 months)
- For women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea, with no identified cause other than menopause) and have not undergone surgical sterilization (removal of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate non-hormonal methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 4 months after the last dose of study drug for RO6874281, and for at least 7 months after the last dose of trastuzumab. For cetuximab, please refer to local prescribing information for cetuximab
    - Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or

post-ovulation methods) and withdrawal are not acceptable methods of contraception

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 2 months after the last dose of study treatment. Men must refrain from donating sperm during this same period
    - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 2 months after the last dose of study treatment to avoid exposing the embryo to RO6874281
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception

Inclusion criteria exclusively for part A (FAP-IL2v monotherapy):

- For Part A exclusively (RO6874281 monotherapy), confirmed advanced and/or metastatic solid tumor, with at least one tumor lesion of location accessible to biopsy per clinical judgment of the treating physician, and confirmed progression at baseline; for whom no standard therapy that would confer clinical benefit to the participant exists

General exclusion criteria:

- Symptomatic or untreated CNS metastases
- History of treated asymptomatic CNS metastases with any of the following criteria:
    - Metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
    - History of intracranial hemorrhage or spinal cord hemorrhage
    - Lacking radiographic demonstration of improvement upon the completion of CNS directed therapy and evidence of interim progression between the completion of CNS directed therapy and the baseline radiographic study
    - Ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dosage are allowed

    - Stereotactic radiation or whole brain radiation within 28 days before study treatment administration
    - Last CNS radiographic study <4 weeks since completion of radiotherapy and <2 weeks since discontinuation of corticosteroids
    - CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days before study treatment administration
- Participants with an active second malignancy (exceptions are non-melanoma skin cancer, cervical carcinoma in situ, or prostate carcinoma that is in remission under androgen deprivation therapy or participants who have a history of malignancy and have been treated with curative intent and the participant is disease free for ≥2 years). Other exceptions may apply and require discussion between the investigator and the Sponsor
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders (e.g., intestinal lung disease), and known autoimmune diseases or other disease with ongoing fibrosis (such as scleroderma, pulmonary fibrosis, and emphysema)
- Participants experience disease with tissue remodeling including wound healing fibrosis/fibrosing reactions, chronic inflammation
- Participants (all indications) with confirmed bilateral pleural effusion are not eligible
- Significant cardiovascular/cerebrovascular vascular disease within 6 months prior to Day 1 of study drug administration, including any of the following: hypertensive crisis/encephalopathy, uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg), unstable angina, transient ischemic attack/stroke, non-compensated congestive heart failure (for NYHA classification, refer to inclusion criteria), serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia), history of thromboembolic events (such as myocardial infarction, or pulmonary embolism)
- Active or uncontrolled infections
- Known HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with intravenous (IV) antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within *2* weeks prior to the start of drug administration
- History of chronic liver disease or evidence of hepatic cirrhosis

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug
- Major surgery or significant traumatic injury <28 days prior to the first RO6874281 infusion (excluding biopsies) or anticipation of the need for major surgery during study treatment
- Dementia or altered mental status that would prohibit informed consent
- Pregnant or breastfeeding women
- Known hypersensitivity to any of the components of RO6874281
- Concurrent therapy with any other investigational drug (defined as a treatment for which there is currently no regulatory authority-approved indication)
- History of, active or suspicion of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

Exceptions:

- Participants with a history of autoimmune hypothyroidism and/or hypopituitarism on a stable dosage of hormone replacement therapy (e.g., thyroxine, hydrocortisone)
- Participants with controlled type 1 diabetes mellitus on a stable insulin regimen
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) may be eligible provided that they meet the following conditions:
    - Rash must cover <10% of the body surface area
    - Disease is well controlled at baseline and only requires low potency topical steroids
    - There are no acute exacerbations of underlying condition ≤12 months (e.g., not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids)
- Adverse events from prior anti-cancer therapy that have not resolved to grade 1, except for alopecia, vitiligo, or endocrinopathies managed with replacement therapy
- Immunomodulating agents:
    - Last dose with any of the following agents, for example, etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents) ≤28 days prior to first dose of study drug
    - Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease)

- Treatment with systemic immunosuppressive medications including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents ≤2 weeks prior to Cycle 1, Day 1. Participants who have received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of ≤10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Sponsor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fluticasone or fludrocortisone) is allowed (see prohibited therapies)
- Radiotherapy within the last 4 weeks before start of study drug treatment, with the exception of limited field palliative radiotherapy
- Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy
- Eligibility of participants who require blood transfusion before and after the start of the study treatment should be discussed by the Sponsor and investigator

Dose-limiting toxicities (DLTs)

A DLT was defined as any of the following events attributed to FAP-IL2v and occurring during the DLT period:

- Hematologic toxicities defined as:
  - Grade 4 neutropenia (absolute neutrophil count <0.5 x 10^9 cells/L) for ≥7 days
  - Grade 3 or 4 febrile neutropenia (ANC <1.0 × 10^9 cells/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for >1 hour)
  - Grade 4 thrombocytopenia
  - Grade 3 thrombocytopenia associated with bleeding episodes
- Grade ≥3 non-hematologic toxicity, excluding the following:
  - Fever >40°C occurring within 48 hours of fibroblast activation protein-α targeted interleukin-2 variant (FAP-IL2v) infusion and resolving within 48 hours to grade ≤2 and fully resolved within 1 week
  - Alopecia (any grade)
  - Grade 3 nausea and vomiting, with appropriate treatment, lasting <48 hours
  - Fatigue and malaise that resolve to grade ≤2 within 1 week
  - Grade 3 hypophosphatemia resolving to grade ≤2 within 1 week
  - Grade 3 diarrhea lasting for ≤2 days with no fever or dehydration
  - Laboratory values of grade ≥3 that are judged not clinically significant by the investigators
  - Grade 3 hyperbilirubinemia lasting ≤48 hours that resolves to grade 1 in <1 week
  - Grade 3 AST and/or ALT elevations that resolve to grade 1 in 1 week
- Failure to recover from any toxicity that results in a dose delay of the next scheduled administration of >14 days
- Elevated ALT or AST (> 3 x ULN) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia as described in the protocol.