

First-In-Human Phase I Study of Aprutumab Ixadotin, a Fibroblast Growth Factor Receptor 2 Antibody–Drug Conjugate (BAY 1187982) in Patients with Advanced Cancer

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Appendices

Appendix 1. Full listing of patient inclusion and exclusion criteria.

Inclusion criteria (dose-escalation phase):

Patients were eligible for inclusion in the dose escalation phase of the trial if all of the following criteria were met:

- Ability to understand and the willingness to sign a written informed consent. A signed informed consent must have been obtained prior to any trial-specific procedures
- A tumor tissue sample (formalin-fixed paraffin-embedded blocks/slides) from archival tissue or fresh biopsy needed to be available for planned retrospective fibroblast growth factor receptor 2 (FGFR2) RNAscope analyses
- All patients must be ≥ 18 years at the first screening examination/visit
- Eastern Cooperative Oncology Group performance status of 0 to 1
- Life expectancy of ≥ 12 weeks
- Patients with advanced, histologically or cytologically confirmed solid tumors described to express FGFR2 that are refractory to any standard therapy, or have no standard therapy available, or for which patients actively refused prior to discussion of the study any treatment that would have been regarded as standard, and in whom, in the opinion of the investigator, experimental therapy with BAY 1187982 may have been beneficial. For the dose-escalation phase, the trial population was limited to solid tumor types with a described expression of FGFR2 (e.g., gastric cancer, esophageal cancer, gastrointestinal stromal tumors, cervical cancer, head & neck cancer, lung

cancer, ovarian cancer, triple-negative breast cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, cholangiocarcinoma)

- Radiographically or clinically evaluable tumor
- Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements which were conducted within 14 days prior to start of first dose:
 - Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophil count $\geq 1500/\text{mm}^3$
 - Absolute lymphocyte count $\geq 500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
 - Alanine aminotransferase and aspartate aminotransferase ≤ 3.0 x ULN (independent of liver involvement)
 - Prothrombin time/international normalized ratio (INR) and activated partial thromboplastin time ≤ 1.5 x ULN for patients not undergoing anticoagulative treatment
 - Serum creatinine (SCr) ≤ 1.5 x ULN and estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m², according to the abbreviated Modification of Diet in Renal Disease equation:
 - $\text{GFR} = 186 \times (\text{SCr}^{-1.154}) \times (\text{age}^{-0.203})$
 - (SCr, serum creatinine level, expressed in mg/dL; multiply by 0.742, if female; multiply by 1.212, if African-American)
- Troponin I and brain natriuretic peptide (BNP) or N-terminal of the prohormone BNP were within normal range

- Women of child-bearing potential must have had a negative pregnancy test performed within 7 days prior to the start of treatment
- Women and men of reproductive potential must have agreed to use adequate contraception when sexually active. This applied for the period between signing of the informed consent form and 3 months after the last administration of study drug. The definition of adequate contraception was based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include but are not limited to: (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception. Patients must have agreed to utilize two reliable and acceptable methods of contraception simultaneously

Exclusion criteria (dose-escalation phase):

Patients were excluded from the trial if they displayed or met any of the following criteria:

- Prior exposure to the investigational drug
- History of allergic reactions to monoclonal antibody therapy (or excipients in the formulation) as well as known or suspected allergy or intolerance to any agent that was given in the course of this trial
- Anticancer chemotherapy, experimental cancer therapy including clinical trial, or cancer immunotherapy within 3 weeks prior to the first dose of the investigational drug. Anticancer therapy was defined as any agent or combination of agents with clinically proven antitumor activity administered by

any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints

- Toxic effects of previous anticancer chemotherapy, experimental cancer therapy, or cancer immunotherapy had to be normalized. Toxic effects of prior anticancer therapy considered as chronic, including but not limited to chemotherapy-induced fatigue, alopecia, or anorexia of Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 2 and neuropathy of CTCAE grade ≤ 1 , where anymore resolution was not expected, did not prevent the patient from participating in this trial
- Prior local radiotherapy was allowed if it was completed at least 3 weeks prior to the first dose of the investigational drug and the patient had evaluable lesions not previously irradiated (palliative radiotherapy was allowed)
- Significant liver dysfunction determined as Child-Pugh score B or C
- Known (prior and current) central nervous system (CNS) metastatic disease. Patients who had received definitive treatment for CNS metastases and who had been disease/symptom free with no evidence of progression for at least 3 months may have been considered for enrollment after discussion and approval with the sponsor. Patients with CNS symptoms must have undergone a magnetic resonance imaging or computed tomography scan to exclude new or progressive CNS metastases
- Patients with spinal cord compression were excluded
- History of clinically significant cardiac disease including:
 - Myocardial infarction or onset of unstable angina
 - Impaired cardiac function or clinically significant cardiac disease
 - Cardiac arrhythmias which were not manageable by standard therapy

- Congestive heart failure New York Heart Association \geq II
- Clinically relevant findings in the echocardiogram such as a second- or third-degree atrioventricular block, prolongation of the QRS complex >120 msec, or a confirmed QT interval corrected according to Fridericia correction interval >480 msec
- Left ventricular ejection fraction $<50\%$ (as measured at screening by echocardiography or multi-gated acquisition scan)
- Uncontrolled hypertension defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >90 mmHg, despite optimal medical management
- Congenital coagulation abnormalities including, but not limited to: thrombophilia, anti-thrombin deficiency, protein C deficiency, protein S deficiency, von Willebrand disease, and hemophilia
- Patients undergoing anti-coagulative treatment for prophylactic use of warfarin, clopidogrel, ticlopidine, rivaroxaban, dabigatran, or heparin (except low molecular weight heparin) due to a previous history of thrombotic event, stroke, infarction, or atrial fibrillation. Warfarin use for prevention of catheter embolization to the patient who did not have a history of thrombotic events was permitted and INR was to be stably controlled within the target range determined at the site
- Patients with arterial or venous thrombotic or embolic events, such as cerebrovascular accident (including transient ischemic attack), deep vein thrombosis, or clinically relevant pulmonary embolism within 3 months prior to the first dose of the investigational drug

- Hemorrhage/bleeding event CTCAE grade ≥ 2 within 4 weeks prior to the first dose of the investigational drug
- Patients with renal impairment on dialysis
- History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of the investigational drug
- Evidence or history of uncured (i.e., any absolute risk of latent infection) hepatitis B or C, any active hepatitis, or human immunodeficiency virus infection
- Active infections CTCAE grade >2
- Previous or concurrent cancer that was distinct in primary site or histology from actual disease and which was measurable or needed anticancer treatment within the last 5 years prior to screening. Patients with a history of gastric or colorectal cancer confined to mucosal layer, cervical cancer *in situ*, treated basal cell carcinoma, or superficial bladder tumors (Ta and Tis) were eligible
- Major surgery or significant trauma within 2 weeks prior to the first dose of the investigational drug
- Biological response modifiers, such as granulocyte-colony stimulating factor, within 3 weeks prior to administration of the investigational drug
- Substance abuse, medical, psychological, or social conditions that may have interfered with the patient's participation in the trial or evaluation of the trial result
- Patients who were pregnant or were breast-feeding

- Any condition that was unstable or could jeopardize the safety of the patient and his/her compliance with the trial procedures