SWOG S2433: A RANDOMIZED PHASE III STUDY OF SECOND-LINE CHEMOTHERAPY WITH OR WITHOUT PANITUMUMAB FOR KRAS WILD TYPE, LOCALLY ADVANCED OR METASTATIC PANCREATIC ADENOCARCINOMA

5.0 ELIGIBILITY CRITERIA

5.1. Disease Related Criteria

a. Participants must have a histologically or cytologically confirmed diagnosis of ductal adenocarcinoma of the pancreas.

b. Participants must have previously documented KRAS wild type (i.e., absence of any KRAS mutation) and BRAF V600E wild type (i.e., absence of a BRAF V600E mutation) status determined by tumor tissue-based NGS assay. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification status. Sites must confirm eligibility criterion 5.1.b. with at least one of the study chairs via email to S2433SC@swog.org prior to registration. See Section 18.7 for the study chair approval process.
NOTE: Blood-based NGS assays, such as circulating tumor DNA (ctDNA) or liquid biopsies, will not be accepted for meeting eligibility criteria.

c. Participants must have documented unresectable and/or metastatic disease on CT or MRI imaging completed prior to randomization. Imaging must have been completed within 28 days prior to randomization for participants with measurable disease. CT scans or MRIs used to assess non-measurable disease must have been completed within 42 days prior to randomization. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

d. Participants must not have known mutations in PTEN, NRAS, EGFR extracellular domain exons 1-16, no amplifications of HER2 and MET, and no gene fusions of RET, NTRK1, and ALK by tumor tissue-based NGS analysis.
NOTE: Participants who are not tested for these mutations are eligible if they have previously documented KRAS wild type (i.e. absence of any KRAS mutation) and BRAF V600E wild type (i.e. absence of a BRAF V600E mutation) status. If results are available, sites must also confirm eligibility criterion 5.1.d. with at least one of the study chairs via email to S2433SC@swog.org prior to registration. See Section 18.7 for the study chair approval process.

e. Participants must not have known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 28 days before randomization.
NOTE: Participants must be neurologically asymptomatic and without corticosteroid treatment at the time of enrollment.

5.2. Prior/Concurrent Therapy Criteria

a. Participants must have received only one line of prior systemic cytotoxic chemotherapy for locally advanced or metastatic PDA, and have radiographically progressed, refractory, or intolerant to this therapy.
   - Prior neoadjuvant or adjuvant therapy with 5-FU or gemcitabine-based chemotherapy counts as a line of therapy if the participant's disease progressed to locally advanced or metastatic disease within 6 months of completing treatment.
   - Participants with cancers harboring molecular alterations including microsatellite instability (MSI-high), elevated tumor mutational burden (TMB ≥10 mut/Mb), and FGFR1-3, NRG1, and ROS fusions are allowed to have received an additional line of targeted therapy applicable to the respective molecular alterations at the treating investigator discretion.
   - Prior maintenance therapy with Olaparib or Rucaparib for germline or somatic BRCA1/2 or PALB2 mutations does not count as a line of therapy.

b. Participants must not have prior treatment with an anti-EGFR antibody (e.g., cetuximab or panitumumab).

c. Participants must not have prior treatment with an EGFR tyrosine kinase inhibitor (e.g., erlotinib).

d. Participants must not have received any pancreatic anticancer therapy (e.g., standard of care or investigational chemotherapy, molecularly targeted therapy, or radiation) within 14 days prior to randomization.

e. Participants must not have a known contraindication to receiving chosen chemotherapy backbone at the planned doses in accordance with the local approved label.

5.3. Clinical/Laboratory Criteria

a. Participants must be ≥ 18 years old at the time of randomization.

b. Participants must have Zubrod Performance Status of 0-2 (see Section 10.5).

.

c. Participants must have a complete medical history and physical exam within 28 days prior to randomization.

d. Participants must have an adequate organ and marrow function as defined below within 28 days prior to randomization:
   - absolute neutrophil count ≥1.0 x 10^3/uL
   - hemoglobin ≥8 g/dL
   - platelets ≥75 x 10^3/uL
   - total bilirubin ≤1.5 x institutional upper limit of normal (IULN)
   - AST ≤ 10 x ULN

   NOTE: Use of growth factor support (e.g., G-CSF or romiplostim [Nplate]) is permitted, and prior use does not constitute an exclusion criterion. Recent blood transfusions are also allowed.

e. Participants must have a creatinine ≤ the IULN OR measured OR calculated creatinine clearance ≥ 30 mL/min using the following Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to registration. For creatinine clearance formula see the tools on the CRA Workbench https://txwb.crab.org/TXWB/Tools.aspx.

f. Participants with known history of human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at registration and have undetectable viral load test on the most recent test results obtained within 6 months prior to randomization.

g. Participants with a known history of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load while on suppressive therapy on the most recent test results obtained within 6 months prior to randomization, if indicated.

h. Participants with a known history of hepatitis C virus (HCV) infection must have been treated and cured. Participants currently being treated for HCV infection must have undetectable HCV viral load test on the most recent test results obtained within 6 months prior to randomization, if indicated.

i. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

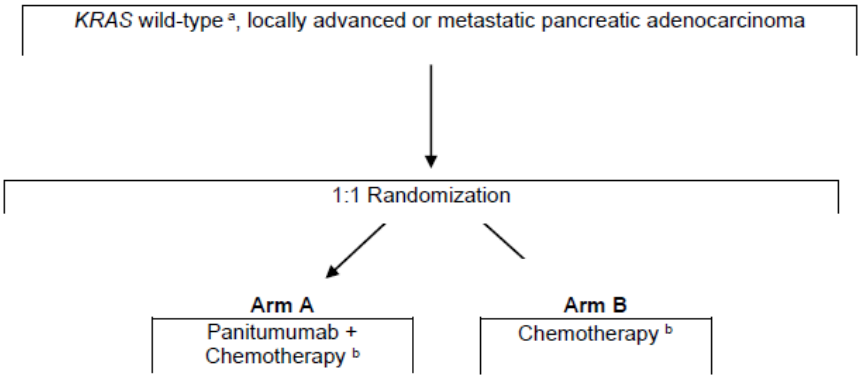
j. Participants must not be pregnant or nursing (nursing includes breast milk fed to an infant by any means, including from the breast, milk expressed by hand, or pumped). Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

5.4. Additional Criteria

a. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.2.b.

b. Participants who can complete patient reported outcomes (FACT-G and PRO- CTCAE) questionnaires in English or Spanish must be offered the opportunity to participate in the quality-of-life studies as outlined in Section 15.5.

SCHEMA



[a] Participants must have previously documented *KRAS* wild type (i.e., absence of any *KRAS* mutation) and *BRAF* V600E wild type (i.e., absence of a BRAF V600E mutation) status by tumor tissue-based NGS analysis confirmed by the **S2433** Study Chairs. See Section 5.1 and 18.6.

[b] The treating investigator and participant will select the appropriate standard-of-care therapy — Nanoliposomal Irinotecan (Nal-IRI) with Fluorouracil and Leucovorin (5FU/LV), FOLFIRI (Fluorouracil, Leucovorin, and Irinotecan), or Gemcitabine with Nab-Paclitaxel (GA) — based on the participant's prior therapy and disease characteristics. See Section 7.1.