

Early results of the PASS-01 trial: Pancreatic adenocarcinoma signature stratification for treatment-01.

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Background: Over 60% of patients with pancreatic ductal adenocarcinoma (PDAC) present with metastatic disease. Both modified FOLFIRINOX (mFFX) and gemcitabine/nab-paclitaxel (GnP) are first-line options in advanced PDAC, however have not been compared prospectively in North American patients. Moreover, biomarkers to guide selection are lacking. Basal-like and Classical subtypes are prognostic, but their predictive impact is unknown. Patient-derived organoids (PDOs) are now feasible to study for drug pharmacotyping. Expedient molecular profiling with additional PDO drug sensitivities could enable better precision choices in PDAC.

Methods: PASS-01 is a multi-center randomized phase II trial evaluating the benefit of 1st line mFFX vs GnP in de novo metastatic PDAC patients with ECOG PS 0-1, (germline BRCA1/2, PALB2 excluded) who have baseline tumor biopsies (bx) for whole genome/transcriptional sequencing (WGTS) and PDO generation/pharmacotyping with standard and novel drugs. The primary endpoint is the PFS of mFFX vs GnP (received at least 1 dose of assigned chemo, per protocol (PP)), 136 patients needed to reach 80% power to detect a difference in median PFS of 7 vs 5 months between mFFX and GnP at significance level of 0.3 in a 2-sided test. Secondary endpoints include: ORR, SAEs, OS, impact of RNA signatures and GATA6 expression on outcomes. Each patient is discussed at a molecular tumor board immediately following their 1st 8-week CT with the goal of recommending precision 2nd-line treatment options on progression.

Results: This trial accrued 160 pts between 09/20 and 01/24, 45% in Canada, 55% in US with 140 eligible for 1st line PFS, data lock Mar 1/24 (see table). Median PFS (PP) was 5.1 mo for GnP and 4.0 mo for mFFX (p=0.14). Best response PR/SD for GnP: 29/45% and 24/35% for mFFX. SAEs attributed to the study were 3% GnP, 13% mFFX and 0.7% bx. Median OS (ITT) was 9.7 mo with GnP and 8.4 mo with mFFX, p=0.04. Of 113 patients in the PP analysis with progression, 64 (57%) received 2nd-line treatment (GnP, n= 30, mFFX n=34) Of these, a correlate-guided approach was delivered in 32 (50%), including 21 (66%) receiving chemo and 11 (34%) receiving a targeted or immunotherapy regimen. Correlative studies are underway. Preliminary analysis shows >80% successful whole genomes and >72% RNA signatures. PP patients include 9 % KRAS wild-type and 21% Basal-like PDAC. PDO-drug models have been established in 50%.

Conclusions: Upfront multi-omic profiling of PDAC can be successfully incorporated into a multicenter randomized trial. While we have observed PP improved PFS and ITT longer OS favouring GnP in this cohort without gBRCA 1/2 or PALB2m, the benefit of chemo for advanced PDAC patients remains poor, with 43% unable to receive 2nd line, arguing strongly for the development of 1st-line biomarker selected strategies. Clinical trial information: NCT04469556. Research Sponsor: Stand Up To Cancer; CV6197; Lustgarten Foundation; Pancreatic Cancer Canada; Ontario Institute for Cancer Research.

N=140 (PP)	GnP n= 69	mFFX n= 71
Med age	64	62
ECOG PS 0/1	59/41	46/54
% liver mets	81	86
BL Ca-19-9 U/ml	1295	1677