Landscape of germline Pathogenic Variants beyond BRCA in Pancreatic Cancer (PC) patients

Background
Pancreatic Cancer (PC) is a lethal cancer with a 5-year survival rate of less than 10% (1). Current evidence suggest that 10 to 20% of PC may be due to germline Pathogenic Variants (PVs) in high-risk genes (2-4). The impact of mutational status on overall survival is still uncertain. Most of the previous studies on PC patients were focused on BRCA1/2 mutations due to the possibility of using PARP inhibitors (5). A recent metaanalysis reported a prevalence of homologous recombination deficiency (HRD) between 14.5%-16.5% (6). However, the precise contribution of additional susceptibility genes other than BRCA is still to be clarified as different panel were used among different studies. Nevertheless, international guidelines recommend multigene germline testing for all PC patients. The purpose of our study was to evaluate the prevalence of PVs focusing on DNA Damage Repair (DDR) and other candidate susceptibility genes, and their impact on patient survival, in a prospective and retrospective series of unselected PC patients.

Methods
PVs in DNA Damage Repair (DDR) and other candidate susceptibility genes were detected through an oncologist-led Multiple Gene Panel (MGP) testing (Tab1). The germline MGP tested 53 genes, selected according to the recent literature. Only PVs and Likely Pathogenic Variants (LPVs) were included in the analyses. We investigated the prevalence and impact of PVs/LPVs on survival on a retrospective series of unselected PC patients.

Results
A total of 185 patients were included in the analyses. Their characteristics are reported in Tab 2. We found either a PV or LPV in 43/185 patients, with PVs in 32 (17.3%) and LPVs in 13 (7%) of the patients. A BRCA1/2 PV or LPV was found in 8/185 (4.3%) patients. The most frequent altered genes other than BRCA were CDKN2A (3.7%), CHEK2 and ATM (2.7%), COL7A1 (4.8%). Median age and stage IV frequency at diagnosis did not differ in Wild-Type (WT) and PV+LPV patients. Median overall survival (mOS) was 11 months. A trend towards better survival was observed for PV+LPV (12.9 mOS) than among WT cases (9.4 mOS), although not statistically significant (p=0.17) (Figure 1).

Among the 17 patients who survived for longer than 20 months, there were one COL7A1 PV, 2 CDKN2A and 2 ATM PV carriers, one of whom is still alive at 57 months from diagnosis and the start of neoadjuvant treatment. Few data available about chemotherapy regimens do not allow further analyses.

Conclusions
A high PV and LPV overall frequency was found in our unselected prospective and retrospective series of PC patients (23%), with a 4.3% of BRCA PV rate, in line with the literature. Interestingly, we found a 3.5 month longer mOS in PV+LPV as compared to WT patients, although not statistically significant. Encouraging good prognosis was observed for some ‘outliers’ with PVs and LPVs in COL7A1, CDKN2A and ATM. Increasing knowledge in tumor biology is a critical step to develop personalized treatment and, consequently, improve therapeutic benefit.

Table 1. mutational panel

Table 2. Patients Characteristics (N=185)

Figure 1. PC Patient survival according to PVs/LPVs

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References
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