PREDICTIVE VALUE OF PLASMA ATM IN THE CCTG PA.7 TRIAL: GEMCITABINE (GEM) AND NAB-PAACLITAXEL (NAB-P) VS. GEM, NAB-P, DURVALUMAB (D) AND TREMELIMUMAB (T) AS FIRST LINE THERAPY IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC)


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CCTG PA.7 Study Schema:

Patients with treatment naïve metastatic PDAC

Stratify:
- ECOG
- Prior Adjuvant Therapy

Randomize 2:1

GEM (1000mg/m2 D1,8, 15) 
Nab-P (125mg/m2 D1, 8, 15)
Durvalumab 
1500 mg IV q 28 days
Tremelimumab: 
75 mg IV q 28 days, cycles 1-4

DNA repair pathway aberrations beyond MMR have been associated with potential immune sensitivity

Sample Size: 180

Primary endpoint:
- OS
Secondary endpoints:
- PFS
- Safety and toxicity
- ORR
Tertiary endpoints:
- QoL
- Correlative studies

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Results: Overall Survival

Stratified Hazard Ratio = 0.94; 90% CI (0.71-1.25); p=0.72
Adjusted Cox Model HR = 0.90; 90% CI (0.67-1.20); p=0.54
Median Gem+Nab-P = 8.8 months; 90% CI (8.3-12.2)
Median Gem+Nab-P+Durva+Treme = 9.8 months; 90% CI (7.2-11.2)
Correlative Analysis

• cfDNA analysis performed on pre-treatment plasma samples
  
  • Sequenced with PredicineATLAS™ NGS Assay
    • 600-gene, 2.4 Mb panel
  
• Plasma DNA repair analysis was performed on 174/180 patients with available samples
  
• Tumor derived variants detected in 173/174 patients (99.4%)
  
• 172 patients were MSS and 1 was MSI-H
Results: ATM mutations appeared predictive of benefit in the immunotherapy arm

Overall Survival in Patients with germline ATM Wild Type (158/174 (90.8 %))

ATM Wild Type - Overall Survival

Hazard Ratio = 0.99; 90% CI (0.73-1.33) P = 0.94

Median OS
9.79 mo
10.2 mo

Overall Survival in Patients with germline ATM mutations (16/174 (9.2%))

ATM Mutated - Overall Survival

Hazard Ratio = 0.10; 90% CI (0.03-0.37) P = 0.004

Median OS
13.9 mo
4.9 mo

P-interaction = 0.014 (significant at pre-specified p=0.1)

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Conclusions:

- The addition of durvalumab and tremelimumab to gemcitabine and nab-paclitaxel did not result in a significant improvement in OS, PFS or ORR.

- Plasma cfDNA analysis was successful in over 99% of patients with available samples.

- Plasma germline \( ATM \) mutations may predict benefit from the addition of dual immune checkpoint inhibitors (D and T) to Gem and Nab-P.

- This data supports that there may be groups beyond dMMR that should be investigated further for benefit of immunotherapy in PDAC.