AACR Virtual Meeting, June 22-24, 2020 Poster # 6478

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Circulating stromal cells in resectable pancreatic cancer is associated with high pathological stage and poor clinical outcomes

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ABSTRACT

Pancreatic cancer (PC) is a difficult malignancy to diagnosis and properly stage, with extremely poor outcomes even for patients (pts) with operable disease. Cancer Associated Macrophage-Like cells (CAMLs) are a recently described circulating stromal cell common to the blood of cancer pts, whose presence and size (≥50μm) is a prognostic indicator of poor progression free survival (PFS), and overall survival (OS). However, the clinical value of CAMLs in PC has not been evaluated. We recruited treatment naïve PC pts referred for surgical resection before therapy induction to study CAML association to PFS/OS. We investigate whether a simple blood test can better identify pts with metastatic disease and act as a predictor for PFS and OS.

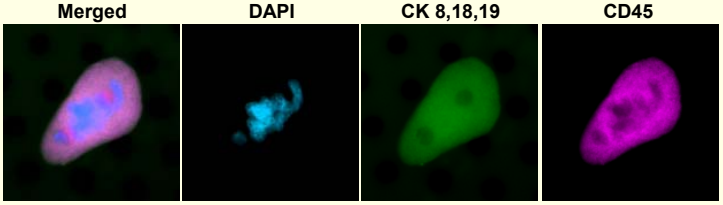


Figure 1. Example of CAML from a pancreatic cancer patient. CAMLs are CD45/CD14 positive (purple) and positive for Cytokeratin (green).

MATERIALS & METHODS

63 whole peripheral blood samples were drawn from untreated newly diagnosed PC pts referred for surgical resection prior to induction of therapy. Pts were recruited for a 2 year single blind prospective pilot study testing CAMLs, CAML size, CA19-9, & CEA to pathological stage (PS), and resectability(R). Pts were referred based on resectability of resectable (RS) (n=20), borderline resectable (BR) (n=27), locally advanced (LA) (n=6), or metastatic (M) (n=10). Blood samples (7.5mL) were taken prior to any neoadjuvant therapy. Blood samples were filtered by CellSieve™ filtration and CAMLs quantified. Analysis of CAMLs, protein markers, and resectability were used to evaluate PFS and OS significance by log-rank testing. 13 pts received multiple blood draws to track success of treatment of disease.

Age (Median)	**66.6(range 45-90)**
Gender (Male/Female)	**37 / 26**
Resectability (R) / Pathological Stage (PS)	**R / PS**
RS / I	**20 / 19**
BR / II	**27 / 13**
LA / III	**6 / 6**
M / IV	**10 / 18**
Unknown	**0 / 7**
CAMLs Present at Baseline	**58 (92%)**
CA19-9 (≥40 U/mL)/ (<40 U/mL)/Unknown	**27 / 31 / 5**
CEA (≥5 ng/mL)/ (<5ng/mL)/Unknown	**10 / 44 / 9**
Neoadj Chemo +/-	**54 / 9**
Adj Chemo +/-	**40 / 23**
Radiation Therapy + / -	**41 / 22**
Surgical Resection + / -	**37 / 26**
Resection Margin +/-	**3 / 38**

INTRODUCTION

High mortality of PC is a result of low accuracy in clinical assessment, with ~60% of Stage I PCs being upstaged prior to, or during, tumor resection[1]. More accurate alternatives to standard scans, such as PC biomarkers, are needed to better predict cancer spread at initial clinical assesement[2]. CAML cells are a recently identified blood based biomarker found in cancer patients which appear to provide clinical utility in a variety of solid tumor types[3,4]. CAML number and increases in size, from phagocytic engorgement, have both been shown to predict disease aggressiveness and its ability to spread[3,4]

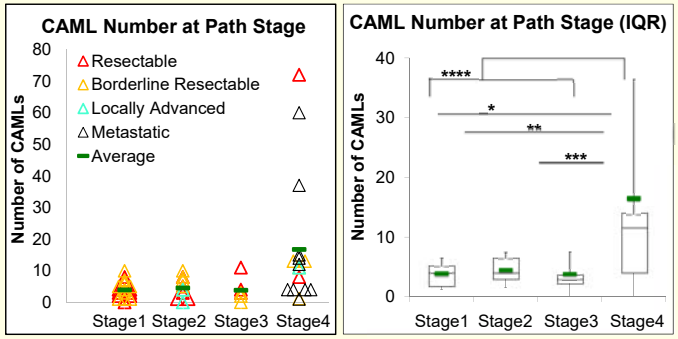


Figure 2: Number of CAMLs Based on Clinical or Pathological Staging. T-Test *(p=0.020), **(p=0.027), ***(p=0.023), ****(p=0.022). Error Bar=Standard Dev. Green Bar=Average.

RESULTS

- CAMLs were found in 92% of BL samples averaging 8 CAMLs/7.5mL
- Metastasis was identified in all patients with >12 CAMLs at BL (**Fig 2**)
- Changes in CAML number during treatment correlated with treatment response **(Fig 3)**
- CAML number and size at BL were prognostic for PFS (p=0.002 and p<0.001) (**Fig 4**)
- CAML size, but not number, was prognostic for OS (p=0.019 and p=0.248) (**Fig 4**)

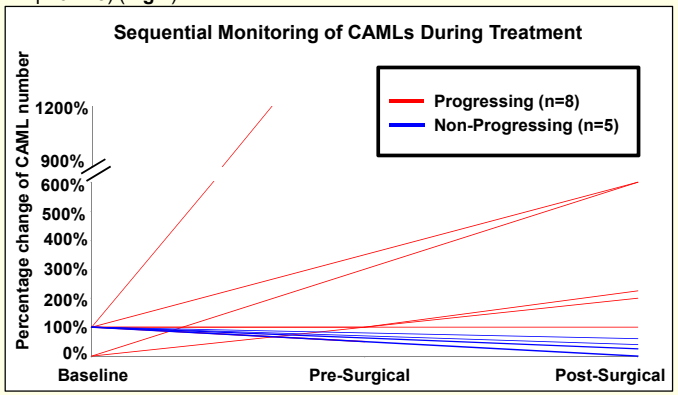
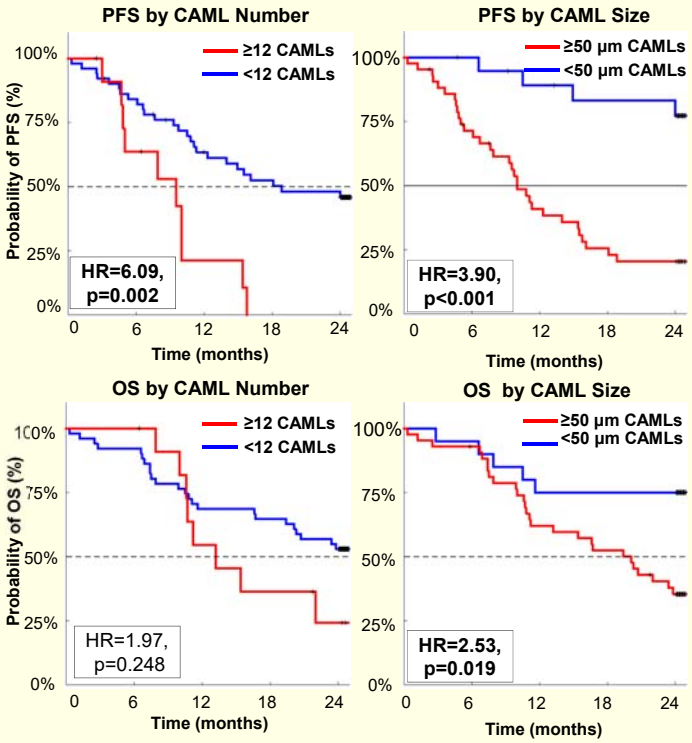


Figure 3. Tracking Changes in number of CAMLs during course of treatment correlates with treatment response

Figure 4. Kaplan-Meier Analysis of PFS and OS as a function of CAML Number and CAML Size



CONCLUSIONS

- Number of CAMLs and CAML size more accurately predicts for metastatic disease than standard clinical scans.
- CAML number and size predicted for more aggressive disease likely to progress using standard of care treatment.
- Monitoring CAMLs pre- and post-surgical resection appeared to indicate response to treatment and predicted patients likely to recur.
- These data suggest that CAMLs could aid in more accurate predicting of disease stage in PC disease, limiting unnecessary surgical procedures and allow for more appropriate treatment modalities.

References

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