Real-world clinical outcomes and molecular features of lung-specific and liver-specific metastases in pancreatic ductal adenocarcinoma (PDAC)

John Davelaar [1], Arsen Osipov [1], Edik M Blais [2], Natalie Moshayedi [1], Nima Nikravesh [1], Gillian Gresham [1], Lei Zheng [3], Autumn McRee [4], Jennifer Chuy [5], Rachna Shroff [6], Raymond Wadlow [7], Gary L Gregory [2], Patricia DeArbeloa [2], Lynn M Matrisian [8], Emanuel F Petricoin III [2], Michael J Pishvaian [3], Shant Thomassian [1], Jun Gong [1], Andrew E Hendifar [1]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Perthera, Inc, Holliston, MA; [3]Johns Hopkins University, Baltimore, MD; [4]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [5]Montefiore Medical Center, Bronx, NY; [6]University of Arizona Cancer Center, Tucson, AZ; [7]Inova Schar Cancer Institute, Fairfax, VA; [8]The Pancreatic Cancer Action Network, Manhattan Beach, CA

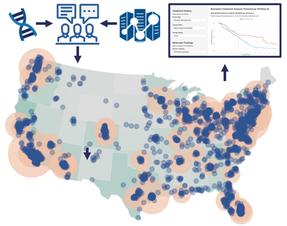
Background

Pancreatic cancer (PDAC) remains one of the most lethal malignancies following metastatic presentation, most commonly occurring in the lung and liver. Approximately 15-20% of patients have upfront resectable disease[1,2]; however, 80% percent of these patients develop disease recurrence[2]. Additionally, over 40% present with metastatic disease[1]. Previous studies have observed variable survival outcomes in PDAC patients depending on site of metastases. Molecular phenotypes of varying sites of metastasis which may drive disease biology based on site of metastasis have not been fully elucidated. Here, we aim to understand survival outcomes and molecular features for PDAC based on involvement of lung versus liver metastases.

Methodology

We retrospectively analyzed longitudinal clinical outcomes across 852 patients with PDAC with next generation sequencing (NGS) from Perthera's Real-World Evidence database (Figure 1) whose tumors first metastasized to either the lung or the liver. Median overall survival (mOS) was measured from either the date of initial diagnosis (resectable cases only, stage I-III) or advanced diagnosis (stage IV) until death. Differences in survival (Figure 2) and frequencies of mutations (Figure 3) were evaluated between patients with lung-specific and liver-specific metastases using Cox regression and Fisher's exact test, respectively.

Pancreatic Cancer Cohort



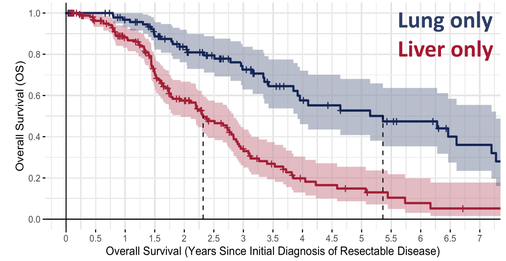
This CSMC-led GIPOCS group queried Perthera's Real-World Evidence database to explore differences in molecular features and outcomes based on the initial site of distant metastasis in PDAC.

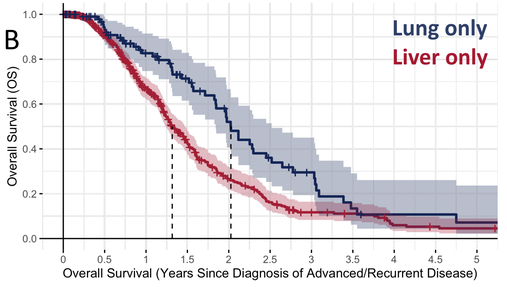
Patients with metastatic (site-specific) PDAC & NGS Testing Results (n = 852)

- Resectable (n=265)
  - Liver only metastases (n=170)
  - Lung only metastases (n=95)
- Advanced (n=587)
  - Liver only metastases (n=485)
  - Lung only metastases (n=102)

Figure 1: Cohort of patients with resectable or advanced PDAC used in OS/PFS analyses. Subjects with evidence of both liver and lung lesions within 6 months of metastatic presentation were excluded.

Prognostic Impact of Lung- vs Liver-Metastasizing PDAC on OS





Resectable PDAC Cohort

Group	# of Patients	mOS [95% CI]
Liver only metastases	170	2.3y [1.9-2.8]
Lung only metastases	95	5.1y [3.9-7.3]
Liver vs Lung	P-Value	HR [95% CI]
	2.036e-08	**3.06** [2.07-4.51]

Advanced PDAC Cohort

Group	# of Patients	mOS [95% CI]
Liver only metastases	485	1.3y [1.2-1.5]
Lung only metastases	102	2.0y [1.8-2.5]
Liver vs Lung	P-Value	HR [95% CI]
	0.001246	**1.63** [1.21-2.19]

Figure 2: OS analyses comparing lung-only metastases and liver-only metastases in resectable (A) and advanced (B) PDAC cohorts.

PFS on 1st/2nd Line SOC in Lung- vs Liver-Metastasizing Pancreatic Cancer

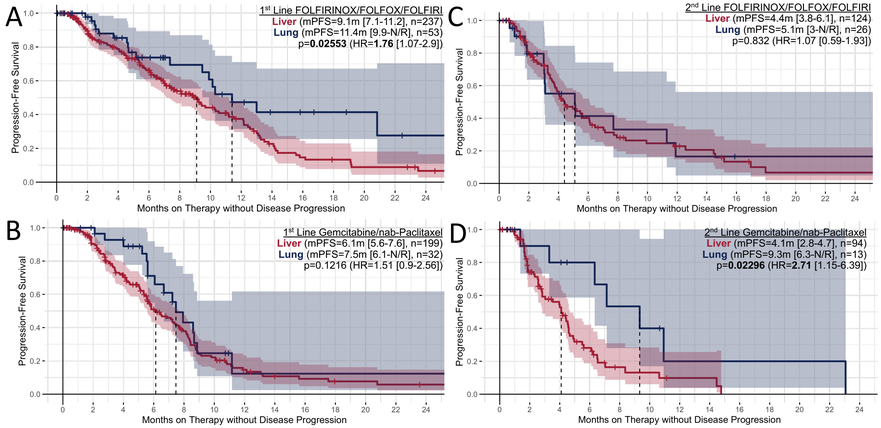


Figure 4: PFS for patients with lung-only vs. liver-only metastasizing pancreatic cancer on 1st and 2nd line SOC. Differences between PFS for lung-only and liver-only pts were noted but do not necessarily suggest treatment-specific predictive associations given a general trend towards favorable outcomes in the lung group.

Conclusion

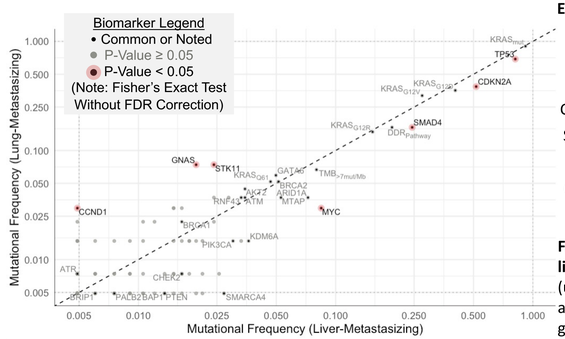
Novel Insight: Are molecular markers predictive of better OS in lung- vs liver-only metastasizing PDAC?

- Moderately enriched mutational frequencies in liver-only cohort were SMAD4, TP53, MYC, CDK2NA with the lung-only cohort exhibiting moderate enrichment in STK11, CCND1, and GNAS (Figure 3).
- Lung only metastasis in both resectable and advanced PDAC confers a significant survival advantage compared to liver only metastasis (Figure 2). This is not likely attributed to differences in actionable markers[4].
- More research is needed to better understand the molecular drivers behind the enrichments identified above. These differences were more prominent than previous analyses of primary vs metastatic lesions[3].

Results

Among resectable patients, mOS from initial diagnosis was significantly shorter in patients that developed liver only metastasis compared to those with lung only metastasis (2.3 vs 5.1 years, p=2.036e-08, Figure 2A). In the advanced PDAC cohort, mOS from diagnosis of advanced disease was also significantly shorter in liver only versus lung only metastasis (1.3 vs 2.0 years, p=0.001246, Figure 2B). PDAC tumors presenting to the liver first were modestly enriched (unadjusted p<0.05) for TP53 mutations (81.4% in liver vs 69.2% in lung), MYC amplifications (8.6% vs 3.0%), and inactivating CDK2NA alterations (51.5% vs 39.1%) whereas lung-specific mutation frequencies were higher for STK11 mutations (2.4% in liver vs 7.5% in lung), CCND1 amplifications (0.5% vs 3.0%) , GNAS alterations (2.0% vs 8.5%) (Figure 3). Differences in treatment-specific outcomes were not significant supporting a potential prognostic role for lung only metastases (Figure 4). No differences in KRAS mutations nor specific isoforms were noted between lung vs liver only metastasis.

Genomic Alteration Frequencies in Lung- vs Liver-Metastases



Enriched gene	Enrichment trend	Liver frequency		Lung frequency
TP53	Mutations	**81.4%**	>	69.2%
MYC	Amplifications	**8.6%**	>	3.0%
CDK2NA	Mutations/Loss	**51.5%**	>	39.1%
SMAD4	Mutations/Loss	**24.4%**	>	16.3%
STK11	Mutations	2.4%	<	**7.5%**
CCND1	Amplifications	0.5%	<	**3.0%**
GNAS	Alterations	2.0%	<	**8.5%**

Figure 3: Enrichment analyses comparing mutational frequency of liver-only to lung-only metastases. Significant differences (unadjusted p<0.05) are highlighted by **red circles**. Commonly altered or otherwise noteworthy genes are also annotated with gray text to provide context but were not significantly different.

Acknowledgements

We wish to thank the patients, families, and caregivers involved in this study

This work was supported by donations to the Pancreatic Cancer Action Network (PanCAN)

Conflicts of Interest

Perthera is a privately-held precision oncology company (not a lab) that facilitates molecular testing and captures real-world outcomes to support investigators, sponsors, and health systems[3,4].

References

1. Rebelo, et al, *Journal of Pancreatology*. 2019
2. Moletta, et al, *Cancers*. 2003; PMID: 31315222
3. Brar et al. *Br J Cancer*. 2019; PMID: 31292535
4. Pishvaian et al. *The Lancet Oncology*. Mar 2020; PMID: 32135080

Questions? @Perthera or hope@perthera.com