Prognostic Value of Plasma Circulating Tumor (ct) DNA KRAS Mutations and Serum CA19-9 in Unresectable Pancreatic Cancer (PC) Patients

Julia S. Johansen[1], Cecile Rose T. Vibat[2], Saege Hancock[2], Inna Chen[1], Latifa Hassaine[2], Errin Samuelsz[2], Eric A.Collisson[3], Benny Vittrup Jensen[1], Timothy Lu[2], Vlada Melnikova[2], Mark G. Erlander[2]

[1]Department of Oncology, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark; [2]Trovagene, San Diego, CA; [3]Department of Oncology, University of California, San Francisco, CA

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precision cancer monitoring

Background

The overall survival (OS) time of patients with unresectable pancreatic cancer (PC) varies widely. Diagnostic tools are presently lacking to predict patient outcome.

The vast majority of pancreatic tumors harbor *KRAS* mutations, which can be detected in circulating tumor (ct)DNA.

Study Aim

The aim of this prospective study with retrospectively analyzed samples was to evaluate the utility of baseline and serial measurements of *KRAS* mutation load in ctDNA, alone or in combination with CA-19-9, as an outcome predictive marker in locally advanced and metastatic PC patients undergoing palliative chemotherapy.

Clinical Study Design

Prospective study of archived samples from 182 patients with non-resectable, locally advanced or metastatic PC undergoing treatment with chemotherapy (Danish BIOPAC study)

ctDNA *KRAS* detection at baseline for association with OS

- 176 of 182 patients with evaluable plasma at baseline

ctDNA *KRAS* monitoring for response to chemotherapyand association with OS

- 617 evaluable plasma samples
- Timepoints: baseline, before cycle 2 of chemotherapy, every 2-3 months at time of CT scans

- Patient demographics: 84 females and 92 males, median age 68, range 45-89 years
- Locally advanced (n=50) or metastatic (n=132) pancreatic cancer
- Palliative treatment with gemcitabine or FOLFIRINOX

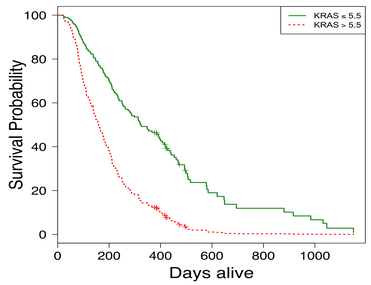
Methodology

- Highly sensitive, quantitative mutation enrichment PCR-NGS (MiSeq) assay for the detection of *KRAS* codon 12/13 mutations in highly fragmented plasma ctDNA.
- The Lower Limit of Detection (LLoD) of ctDNA *KRAS* G12/13 assay is 0.002% mutant alleles in a background of wild-type DNA.

Results

Association between Baseline ctDNA *KRAS* G12/13 and OS

- Statistically negative association between baseline ctDNA *KRAS* G12/13 copies and OS was observed in a multivariate COX proportional hazards analysis, indicating that patients with lower systemic *KRAS* burden survive longer (p<0.0001).
- The hazard ratio (HR) of death for patients with ≥ 5.5 *KRAS* copies/10^5 genome equivalents (GE) is ***2.4*** times as high (95% CI: 2.0 to 4.9) as those with *KRAS* G12/13 copies <5.5/10^5 GE.

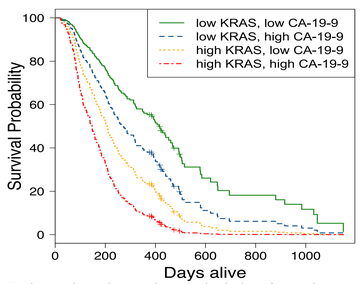


Estimated Kaplan-Meier survival plots for males, age < 65, receiving gemcitabine. Similar results obtained for female and older patients.

Variable	HR (95% CI)	p-value
Baseline KRAS ≥ 5.5 v. < 5.5	2.4 (1.6 – 3.4)	<0.0001
CA 19-9 ≥ 315 v. <315	1.6 (1.2 – 2.3)	0.005
Gender (male v. female)	1.6 (1.2 – 2.2)	0.004
Chemotherapy (gemcitabine v. FOLFIRINOX)	1.6 (0.96 – 2.5)	0.075
Age (65-75 v. ≤ 65)	1.2 (0.8 – 1.7)	0.40
Age (>75 v. ≤ 65)	1.8 (1.1 – 2.8)	0.02

Combination of Baseline ctDNA *KRAS* G12/13 and CA-19-9 is a More Powerful Predictor of OS

- A combination of pre-treatment levels of ctDNA *KRAS* G12/13 and CA 19-9 allows for a better fit of the model and a stronger association with OS. R^2 = 23.9%, as compared 19.7% for the model with *KRAS* alone.
- The HR of death for patients with ≥ 5.5 *KRAS* copies/10^5 GE and ≥ 315 U/mL CA 19-9 is ***4.1*** times as high as those with low *KRAS* and CA 19-9.



Estimated Kaplan-Meier survival plots for males, age < 65, receiving gemcitabine. Similar results obtained for female and older patients.

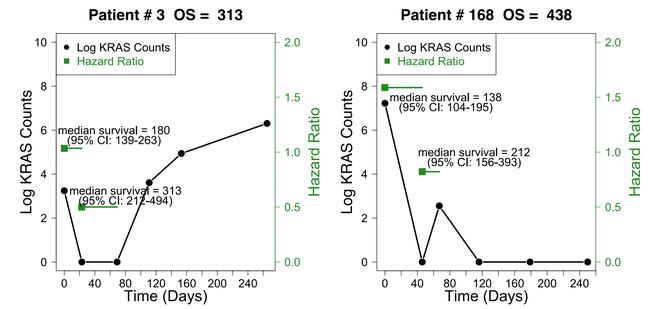
KRAS copies/ 10^5 GE	CA 19-9 U/mL	N	HR (95% CI)
≤ 5.5	< 315	29	1.0
≤ 5.5	≥ 315	30	1.6 (0.94 to 2.8) p = 0.08
> 5.5	< 315	29	2.5 (1.4 to 2.8) p = 0.002
> 5.5	≥ 315	85	4.1 (2.5-6.8) p < 0.0001

Combination of ctDNA KRAS and CA-19-9 identifies a group of patients (17%) with significantly greater overall survival

Results

Monitoring ctDNA *KRAS* Burden on Chemotherapy

- Monitoring ctDNA *KRAS* levels on therapy may reflect tumor dynamics and better correlate with patient outcomes.
- In order to account for the effect of therapy, we built a time-dependent model that allows adjustment of estimated patient survival based on the combination of pre-treatment ctDNA *KRAS* levels and *KRAS* levels after 2 weeks on first line chemotherapy.



- When taking into account ctDNA *KRAS* levels after 2 weeks on treatment, an estimated median survival more accurately reflects actual survival of individual patients (as compared to the median survival estimated based on pre-treatment ctDNA *KRAS* levels only).

Conclusions

- In a study of 182 patients with locally advanced or metastatic pancreatic cancer, a statistically significant negative association was found between baseline ctDNA *KRAS* counts and OS (p < 0.0001). A combination of ctDNA *KRAS* and CA 19-9 was a more powerful predictor of OS than either marker alone and allowed identification of a group of patients (17%) with significantly greater overall survival.
- Use of the time-dependent model for monitoring patients beyond baseline allows more accurate assessment of responsiveness to therapy and associated increase or decrease of predicted survival.

For more information, please contact:

Julia S Johansen, MD
Herlev Hospital
Copenhagen University Hospital
julia.johansen@post3.tele.dk

Mark Erlander, PhD
11055 Flintkote Avenue
San Diego, CA 92121
merlander@trovagene.com