Multi-platform molecular profiling of 1,180 patients increases median overall survival and influences treatment decision in 53% of cases

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Amended Abstract

Background: A prospective, observational study was initiated in 2009 with IRB approval to track outcomes and determine the clinical utility of multi-platform molecular profiling (MMP) across a variety of solid tumors. A secondary objective was to assess the impact of MMP on physicians' treatment decisions.
Materials and Methods: This study included all 1180 patients (465 deaths) enrolled where treatment, follow-up, and MMP data was available spanning more than 40 lineages. Patients that received one or more drugs predicted to be of benefit and no drugs predicted to be of lack of benefit were placed into the "Matched" (M) arm. Patients that received at least one drug predicted to be of lack of benefit were placed into the "Unmatched" (U) group. Classification of patients into each arm was made for drugs administered after MMP (n=1027) as well as before (n=1180; 153 patients received no therapies after profiling).
Results: Survival analysis of M (n=534) vs U (n=493) showed there was a significant increase in overall survival (p=.0001, HR = .68), median increase in survival of 422 days (1068 vs 646). The patients in the B group received 3.2 therapies compared to 4.2 in the L group. When the groups were expanded to include treatments given prior to MMP there was an increase in overall survival (p = 0.0003, HR = 0.714), with an increase in median survival of 1.1 years (978 vs 580). There was no detectable bias from age, gender, race, or stage. Upon post profiling follow-up, physicians indicated that the molecular profile influenced their decision on 629 of the 1180 (53%) patients. Of the 629 patients, 97% (611) received a drug recommended in the benefit category and 46% (292) did not receive any lack of benefit category drugs.
Conclusion: This study shows that MMP has a significant ability to detect a better prognostic group for overall survival for refractory, metastatic, or rare cancers for which there is no standard of care. MMP was demonstrated to have clinical impact on physician treatment selection in a majority of cases. Moreover, when patients receive effective drugs, they are exposed to fewer overall agents, reducing the toxicity, potentially decreasing costs, and improving survival.

Background

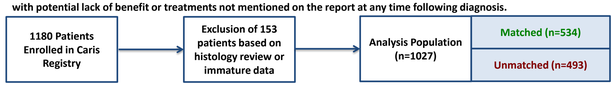
- A pilot study has shown that comprehensive molecular profiling can be used to find molecular targets in patients with refractory metastatic cancer. In 18 of 66 patients treated with a molecularly guided therapy, the approach resulted in a longer PFS on an MP-suggested regimen than on the prior regimen on which the patient had just experienced progression. Exploratory analysis demonstrated that this PFS ratio correlated with the clinical parameter of overall survival. [1]
- A recent study in patients with refractory breast cancer showed that tumor profiling resulted in a revision of the original treatment decision for all patients and tumor profiling-based therapy resulted in a clinical benefit in 52% of heavily pretreated patients. [2]
- A review of all patients treated in a single center in Australia resulted in clinical and survival benefits in over half of the patients and confirmed the role of molecular profiling in a clinical practice setting. [3]
- Though preliminary evidence supports clinical utility, the degree to which CMI improves patient outcomes has not yet been demonstrated conclusively.
- To provide further proof of the effectiveness of including guidance from molecular profiling in clinical decision-making, Caris Life Sciences has established a post marketing Registry with the aim to complete a series of multicentre prospective observational studies and developing an ongoing oncology molecular profiling-based clinical outcomes database as well as exploring and validating existing and novel biomarkers.
- An initial report from the CMI registry demonstrates that the overall survival of ovarian cancer patients treated with drugs associated with potential benefit according to a predictive biomarker panel was longer than in those who received drugs associated with potential lack of benefit. [4]

Methods

- 1180 cases of solid cancers referred to Caris Life Sciences between 2009 and March 2015 were enrolled in the Caris registry.
- Research subject enrollment in this IRB-approved Registry included baseline clinical information at the time of Caris Life Sciences® Molecular Intelligence™ Services (CMI) molecular profiling, CMI results, treatment received and clinical outcomes including progression-free and overall survival.
- Registry data is collected at nine-month intervals post-enrollment.
- Specific testing was performed on tumor biopsy samples from all patients per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis.
- IHC analysis was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (Benchmark XT, Ventana, and AutostainerLink 48, Dako), and commercially available antibodies.
- Fluorescent in-situ hybridization (FISH) was used for evaluation of the HER-2/neu [HER-2/CEP17 probe], EGFR [EGFR/CEP7 probe], and cMET [cMET/CEP7 probe] (Abbott Molecular/Vysis). HER-2/neu and cMET status were evaluated by chromogenic in-situ hybridization (INFORM HER-2 Dual ISH DNA Probe Cocktail; commercially available cMET and chromosome 7 DIG probe; Ventana). The same scoring system was applied as for FISH.
- Direct sequence analysis was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the Illumina MiSeq platform. Specific regions of 45 genes of the genome were amplified using the Illumina TruSeq Amplicon Cancer Hotspot panel.
- Mutation analysis by Sanger sequencing included selected regions of BRAF, KRAS, c-KIT, EGFR, and PIK3CA genes and was performed by using M13-linked PCR primers designed to amplify targeted sequences.

Statistical Considerations and Patient Cohort Selection

- Of 1180 patients with solid cancers included in the Caris registry, 153 were excluded as no follow-up information has yet been captured and a further 21 were excluded based on reported histology.
- The analysis population (n=1027) was divided into two cohorts based on matching of treatments to CMI report recommendations.
- **Group 1 (n=534) – MATCHED – Patient cohort defined as having received at least one treatment associated with potential benefit and no treatment associated with lack of benefit at any time following diagnosis.**
- **Group 2 (n=493) – UNMATCHED – All patients not included in the benefit cohort (treated with at least one treatment associated with potential lack of benefit or treatments not mentioned on the report at any time following diagnosis.**



Demographics

- Race, gender, age and tumor grade were well balanced across matched and unmatched cohorts.

		Matched (N=534)	Unmatched (n=493)
Race	American Indian	2 *(0.4%)*	2 *(0.4%)*
	Asian	29 *(5.4%)*	15 *(3.0%)*
	Black	38 *(7.1%)*	43 *(8.7%)*
	Other/unknown	12 *(2.2%)*	13 *(2.6%)*
	White	453 *(84.8%)*	420 *(85.2%)*
Age	0-40	37 *(6.9%)*	37 *(7.5%)*
	40-50	78 *(14.6%)*	75 *(15.2%)*
	50-60	145 *(27.2%)*	136 *(27.6%)*
	60-70	155 *(29.0%)*	137 *(27.8%)*
	70-100	119 *(22.3%)*	108 *(21.9%)*

		Matched (N=534)	Unmatched (n=493)
Sex	Female	412 *(77.2%)*	366 *(74.2%)*
	Male	122 *(22.8%)*	127 *(25.7%)*
Grade	Grade1 *Well Differentiated*	30 *(5.6%)*	21 *(4.3%)*
	Grade2 *Moderately Differentiated*	156 *(29.2%)*	126 *(25.6%)*
	Grade 3 *Poorly differentiated*	254 *(47.6%)*	256 *(51.9%)*
	Grade 4 *Undifferentiated*	22 *(4.2%)*	21 *(4.3%)*
	High Grade	2 *(0.4%)*	4 *(0.8%)*
	Low Grade	1 *(0.2%)*	0 *(0%)*
	Unknown	69 *(12.9%)*	65 *(13.2%)*

- Tumor type was well balanced across matched and unmatched cohorts.

Tumor Type	Matched (N=534)	Unmatched (n=493)	Tumor Type	Matched (N=534)	Unmatched (n=493)
Ovary	168 *(31.5%)*	140 *(28.4%)*	Liver Hepatocellular Carcinoma	3 *(0.6%)*	1 *(0.2%)*
Breast	80 *(15.0%)*	69 *(14.0%)*	Melanoma	3 *(0.6%)*	4 *(0.8%)*
Female Genital Tract Malignancy	67 *(12.5%)*	56 *(11.4%)*	Anal Cancer	2 *(0.4%)*	3 *(0.6%)*
Colorectal	58 *(10.9%)*	62 *(13.4%)*	Lymphoma	2 *(0.4%)*	0 *(0%)*
Non-Small Cell Lung Cancer (NSCLC)	46 *(8.6%)*	59 *(12.6%)*	Major & Minor Salivary Glands	2 *(0.4%)*	0 *(0%)*
Urinary Tract	18 *(3.4%)*	12 *(2.4%)*	Non-Epithelial Ovarian Cancer	2 *(0.4%)*	2 *(0.4%)*
Neuroendocrine Tumors	14 *(2.6%)*	11 *(2.2%)*	Cancer of Unknown Primary	1 *(0.2%)*	8 *(1.4%)*
Leiomyosarcoma	10 *(1.9%)*	7 *(1.4%)*	Epithelial Skin Cancer	1 *(0.2%)*	1 *(0.2%)*
Pancreatic Adenocarcinoma	10 *(1.9%)*	12 *(2.4%)*	Paragangliomas	1 *(0.2%)*	0 *(0%)*
Gastroesophageal cancer	9 *(1.7%)*	15 *(3.0%)*	Uveal Melanoma	1 *(0.2%)*	0 *(0%)*
Soft Tissue Tumors	9 *(1.7%)*	13 *(2.6%)*	Adrenal cortical carcinoma	0 *(0.%)*	1 *(0.2%)*
Unknown	8 *(1.5%)*	1 *(0.2%)*	Lung Bronchiolalveolar carcinoma	0 *(0.%)*	1 *(0.2%)*
Head and Neck Squamous Carcinoma	6 *(1.1%)*	8 *(1.4%)*	Mesothelioma	0 *(0.%)*	1 *(0.2%)*
Cholangiocarcinoma	5 *(0.9%)*	1 *(0.2%)*	Neuroblastoma	0 *(0.%)*	1 *(0.2%)*
Glioblastoma	4 *(0.7%)*	1 *(0.2%)*	Small Intestinal Malignancies	0 *(0.%)*	1 *(0.2%)*
Prostatic Adenocarcinoma	4 *(0.7%)*	1 *(0.2%)*	Thyroid Carcinoma	0 *(0.%)*	1 *(0.2%)*

Decision Impact on Treatment Selection

- The CMI report influenced the treatment decision in over half of cases overall.
- 97% of these changed treatment decisions resulted in a treatment associated with potential benefit being administered.
- Treatments associated with potential lack of benefit were avoided in almost half of cases.

	Response	n	%
Total number of patients included		1180	
Did the Caris Reported Drug/Biomarker Results influence the physician's decision to treat the subject?	YES	629	53
	NO/MISSING	551	47
If Yes, did the MI Report results cause a change in treatment choice for this subject? *(agent listed as potential clinical benefit was selected to treat subject)*	YES	611	97
	NO/MISSING	18	3
If Yes, did the MI Report results cause the physician not to treat a subject with an agent? *(agent listed as potential lack of benefit was avoided in a subject)*	YES	292	46
	NO/MISSING	337	54

Selected Biomarker Expression across cohorts

- According to comprehensive profiling, the matched cohort have significantly more potential sensitivity to platinum agents (ERCC1 loss 83% vs 53% p<0.001), gemcitabine (RRM1 loss 74% vs 62% p=0.0004), 5-FU based antimetabolites (TS loss 85% vs 75%p=0.0007), taxanes (TUBB3 loss 62% vs 45%; p=0.0006) androgen deprivation therapy (AR 27% vs 19% p=0.0153), and hormone therapy (ER 35% vs 25% p=0.0023; PR 24% vs 20% p=0.001).
- The matched cohort had significantly less BCRP expression compared to the unmatched cohort (56 vs 71%, p=0.0347).
- The unmatched cohort had significantly more actionable mutations (KRAS 23% vs 39% p=0.0393; BRAF 3% vs 19% p=0.0163; PIK3CA 32% vs 70% p=0.0412).

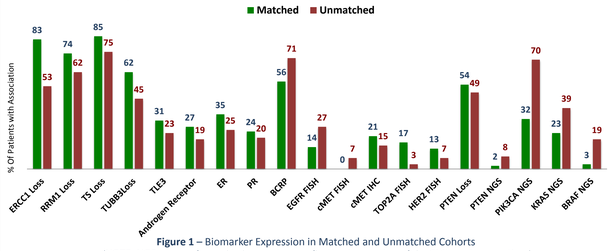


Figure 1 – Biomarker Expression in Matched and Unmatched Cohorts
(NOTE: NGS was performed in less patients reflecting innovation of the CMI service over time)

Overall Survival from Time of Tumor Profiling Grouped by All Treatments Received

- Patients who were received only treatments associated with potential benefit according to the CMI report (n=534) had a significant increase in median overall survival (OS) from the time of profiling compared to those in the unmatched cohort (n=493) (median OS 1068 vs 646 days, HR = 0.68, p=0.001).
- Patients in the matched cohort were treated with less treatments overall after profiling compared to those in the unmatched cohort (median 3.2 vs 4.2 therapies).

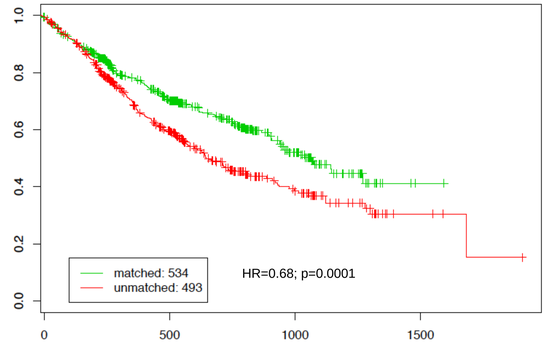


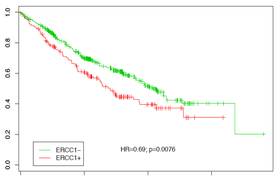
Figure 2 – Kaplan Meier Curve of Overall Survival based on treatments administered after Comprehensive Tumor Profiling (CMI)

- Median overall survival from diagnosis including treatments given prior to comprehensive tumor profiling also demonstrated a survival benefit in the benefit cohort (data not shown) (median overall survival 978 vs 580 days; HR=0.714; p=0.0003).

Study Highlights –Registry Outcomes Confirm Predictive Value of Biomarkers

- ERCC1-negative subjects in the registry cohort had a longer median overall survival than ERCC1-positive subjects if they received a platinum agent(s) at any time after diagnosis (median OS 1038 vs 705 days; HR = 0.69; p=0.0076) or after profiling (median OS 1075 vs 685 days; HR = 0.65; p=0.0025). In patients who did not receive a platinum agent, there was no difference in survival based upon ERCC1 status.
- Similar outcomes have been observed for other biomarkers including RRM1 linked to gemcitabine.

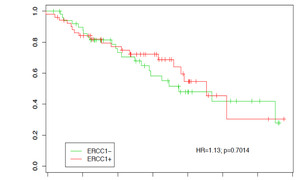
(a) Platinum Agent(s) Received At Any Time After Diagnosis



	n	Deaths	Median OS in days (95% CL)
ERCC1 Negative	421	164	1038 (910-1271)
ERCC1 Positive	146	77	705 (566-1063)

260 observations deleted due to missing data

(b) No Platinum Agents Received At Any Time After Diagnosis



	n	Deaths	Median OS in days (95% CL)
ERCC1 Negative	51	22	748 (580-NA)
ERCC1 Positive	52	19	908 (761-NA)

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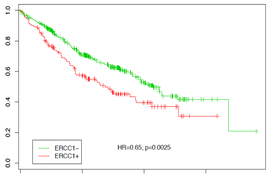
(c) Platinum Agent(s) Received At Any Time After Profiling



	n	Deaths	Median OS in days (95% CL)
ERCC1 Negative	391	148	1075 (955-NA)
ERCC1 Positive	133	40	685 (450-1063)

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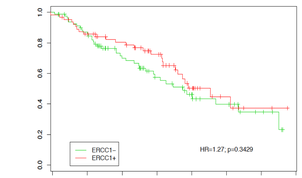
(d) No Platinum Agents Received At Any Time After Profiling



	n	Deaths	Median OS in days (95% CL)
ERCC1 Negative	81	38	748 (580-NA)
ERCC1 Positive	65	26	908 (721-NA)

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Figure 3 – Kaplan Meier Curves of Overall Survival In ERCC1-negative and ERCC1-positive patients with and without platinum intervention

Conclusions

- Comprehensive tumor profiling provided in the Caris Molecular Intelligence® report can influence the physician decision in over 50% of refractory cancer cases in today's routine clinical practice, helping with treatment selection and avoidance of potentially less effective treatments.
- A 32% reduction in the risk of death was observed in patients who received only treatments associated with benefit after profiling.
- Patients in the matched cohort received less treatments after profiling than those in the unmatched cohort.
- Access to targeted therapies if indicated could improve patient outcomes in a restricted number of cases.
- Outcome data in this registry can be used to confirm the predictive value of biomarkers within the CMI multiplatform tumor profiling panel.

References

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4. Oliver K, Xiao N, Spetzler D et al. (2014) The Impact of Tumour Molecular Profile-Directed Treatment on Survival in Ovarian Cancer. J Clin Oncol 32:5s, 2014 (suppl; abstr 5591)