The impact of tumor molecular profile-directed treatment on survival in ovarian cancer

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Updated abstract

Background

We sought to determine whether tumor molecular profile-directed treatment in ovarian, primary peritoneal and fallopian tube carcinomas influenced survival.

Methods

With IRB approval, Caris Life Sciences® maintains the Caris Registry™, a database of clinicopathologic and outcome variables from consenting patients whose tumors underwent molecular profiling. Molecular profiling was performed using a multiplatform approach to stratify agents by degree of potential therapeutic benefit. The Caris Registry™ was queried for all patients with a diagnosis of ovarian, primary peritoneal and fallopian tube carcinomas enrolled between 2010 and 2014. Patients were stratified based on chemotherapeutic agents received during their disease course: the "Benefit" cohort received at least one agent designated to be of potential benefit and no agents with potential lack of benefit while the "Lack of Benefit" cohort received at least one agent with potential lack of benefit. Survival was calculated from the date of profiling and from the date of diagnosis to the date of death/censoring using the Kaplan-Meier method.

Results

Of 450 patients identified in the registry, 102 were excluded due to non-invasive pathology, non-epithelial histology, and missing or ambiguous treatment information. Of the remaining 348 eligible and evaluable patients, 170 formed the Benefit cohort and the remaining 178 were assigned to the Lack of Benefit cohort. There were no significant differences in baseline clinicopathologic characteristics between the two groups. Patients in the Benefit cohort experienced significantly longer post-profiling survival when compared with patients in the Lack of Benefit cohort (HR 0.54, 95% CI 0.37-0.80; p = 0.0018). Additionally, there was a trend toward longer overall survival in the Benefit cohort.

Conclusions

Tumor molecular profile-directed treatment significantly improves post-profiling survival in patients with ovarian, primary peritoneal and fallopian tube carcinomas. Despite limited follow-up, trends toward improved overall survival were also demonstrated.

Background

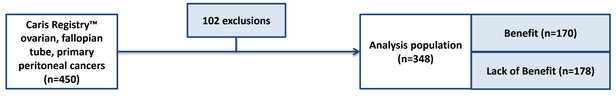
- A pilot study showed that comprehensive molecular profiling identified molecular targets in patients with refractory metastatic cancer. In 18 of 66 patients treated with a molecularly-guided therapy, the approach resulted in a longer progression-free survival (PFS) compared to the PFS interval of the patient's most recent regimen. 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]
- To evaluate the effectiveness of Caris Life Sciences® Molecular Intelligence™ (CMI™) directed therapy, the Caris Registry™ was established as a post-marketing registry to offer an ongoing oncology molecular profiling-based clinical outcomes database.

Methods

- Patients referred to Caris Life Sciences® between 2009 and March 2014 were enrolled in the Caris Registry™.
- This IRB-approved registry includes baseline clinical information at the time of CMI™ testing, CMI™ results, treatments received and clinical outcomes including progression-free and overall survival updated at nine-month intervals after enrollment.
- Tumor biopsy samples were analyzed with a combination of Sanger sequencing, next generation sequencing, pyrosequencing, immunohistochemistry (IHC), gene amplification with fluorescent/chromogenic in-situ hybridization (F/C-ISH), and ribonucleic acid fragment analysis depending on physician request.
- IHC analysis was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (Benchmark X, Ventana, AutostainerLink 48, Dako), and commercially available antibodies.
- FISH was used for evaluation of 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 CISH (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 the 450 patients with ovarian, fallopian tube, or primary peritoneal cancers included in the Caris Registry™, 102 were excluded due to non-invasive pathology, non-epithelial histology, and missing or ambiguous treatment or follow-up information.
- The analysis population (n=348) was divided into two cohorts based on matching of treatments to CMI™ report recommendations.
- **Group 1 (n=170) – BENEFIT – Patient cohort defined as having received at least one treatment associated with potential benefit and no treatments associated with lack of benefit at any time following diagnosis.**
- **Group 2 (n=178) – LACK OF BENEFIT – Patient cohort defined as having received at least one treatment associated with potential lack of benefit at any time following diagnosis.**



Demographics

- Patient characteristics (age, race, stage at diagnosis, and site of biopsy analyzed) were well-balanced across Benefit and Lack of Benefit cohorts.
- Of the 348 eligible and evaluable patients, 303 were diagnosed with epithelial ovarian carcinoma, 26 with primary peritoneal carcinoma and 19 patients with fallopian tube carcinoma. The distribution of primary site of disease was similar between the two cohorts.

		Benefit (n=170)	Lack of Benefit (n=178)	Total (n=348)
AGE	<61	78	95	173
	>61	92	88	175
RACE	Black	5	9	14
	White	150	162	312
	Other	15	7	22
STAGE AT FIRST DIAGNOSIS	I	20	20	40
	II	20	10	30
	III	102	122	224
	IV	22	17	39
	Unknown	6	9	15
GRADE AT DIAGNOSIS	Grade 1	11	8	19
	Grade 2	25	18	43
	Grade 3	123	127	250
	Unknown	11	25	36

		Benefit (n=170)	Lack of Benefit (n=178)	Total (n=348)
SITE OF BIOPSY ANALYZED	Ovary	61	47	108
	Omentum	34	34	68
	Peritoneum	13	23	36
	Pelvis	12	13	25
	Lymph Nodes	9	15	24
	Connective/Soft Tissue	6	14	20
	Other	35	32	67
INITIAL HISTOLOGY	Adenocarcinoma, NOS	10	7	17
	Clear cell	5	10	15
	Endometroid	17	9	26
	Mixed adenocarcinoma	9	11	20
	Papillary serous	103	121	224
	Other	26	20	46

Other = carcinoma NOS, undifferentiated carcinoma, mucinous

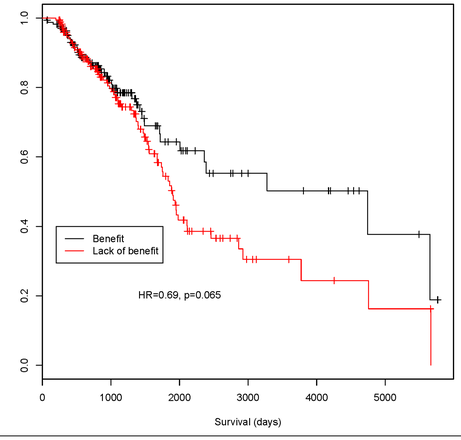
Benefit of some profiling-directed agents by cohort

- The table below shows select treatments associated with benefit and with lack of benefit according to the results of the CMI™ reports.
- More of the patients included in the Benefit cohort were predicted to have platinum and taxane sensitivity and may have received these treatments in an unguided manner in line with standard of care guidelines.

		Total (n=348)		Benefit cohort (n=170)		Lack of Benefit cohort (n=178)	
		Potential Benefit	Potential Lack of Benefit	Potential Benefit	Potential Lack of Benefit	Potential Benefit	Potential Lack of Benefit
Taxanes	paclitaxel	**79.0%** (275)	**18.7%** (62)	**94.7%** (161)	**2.4%** (4)	**59.5%** (106)	**33.7%** (60)
	docetaxel	**62.4%** (217)	**17.2%** (60)	**78.2%** (133)	**1.8%** (3)	**47.2%** (84)	**31.5%** (56)
	nab-paclitaxel	**22.1%** (77)	**19.3%** (67)	**21.8%** (37)	**12.9%** (22)	**21.9%** (39)	**24.7%** (44)
Hormone Receptor Inhibitors	tamoxifen	**62.6%** (218)	**14.1%** (49)	**61.8%** (105)	**10.6%** (18)	**60.1%** (107)	**17.4%** (31)
	megestrol	**59.8%** (208)	**10.9%** (38)	**61.8%** (105)	**8.8%** (15)	**55.6%** (99)	**12.9%** (23)
	anastrozole	**49.4%** (172)	**13.8%** (48)	**50.0%** (85)	**10.6%** (18)	**46.1%** (82)	**16.9%** (30)
	letrozole	**75.6%** (263)	**16.1%** (56)	**77.6%** (132)	**14.1%** (24)	**70.8%** (126)	**18.0%** (32)
	exemestane	**32.2%** (112)	**0.3%** (1)	**40.6%** (69)	**0%** (0)	**22.5%** (40)	**0.6%** (1)
	leuprolide	**20.1%** (70)	**10.9%** (38)	**13.5%** (23)	**8.8%** (15)	**25.8%** (46)	**12.9%** (23)
Anthracyclines	doxorubicin/liposomal-doxorubicin	**64.1%** (223)	**27.9%** (97)	**70.0%** (119)	**19.4%** (33)	**54.5%** (97)	**35.4%** (63)
	epirubicin	**32.2%** (112)	**13.5%** (47)	**25.9%** (44)	**10.0%** (17)	**34.3%** (61)	**16.3%** (29)
Platinums	carboplatin/cisplatin	**58.3%** (203)	**23.6%** (82)	**78.8%** (134)	**0%** (0)	**38.8%** (69)	**44.4%** (79)
	oxaliplatin	**6.0%** (21)	**4.9%** (17)	**8.8%** (35)	**0%** (0)	**3.4%** (6)	**7.9%** (14)
Topoisomerase Inhibitors	irinotecan	**54.0%** (188)	**48.3%** (168)	**51.2%** (87)	**48.8%** (83)	**52.2%** (93)	**47.2%** (84)
	topotecan	**31.9%** (111)	**46.6%** (162)	**32.4%** (55)	**47.1%** (80)	**31.5%** (56)	**45.5%** (81)
Nucleoside analog	gemcitabine	**31.6%** (110)	**32.8%** (114)	**31.8%** (54)	**20.6%** (35)	**29.8%** (53)	**42.7%** (76)
Tyrosine kinase inhibitor	imatinib	**4.9%** (17)	**16.4%** (57)	**4.1%** (7)	**12.9%** (22)	**3.4%** (6)	**19.7%** (35)
Alkylating agents	temozolomide	**13.2%** (46)	**74.7%** (260)	**14.7%** (25)	**71.8%** (122)	**11.8%** (21)	**72.5%** (129)
	dacarbazine	**6.9%** (24)	**17.2%** (60)	**6.9%** (11)	**10.6%** (18)	**7.3%** (13)	**23.0%** (41)
Anti-metabolites	fluorouracil	**19.0%** (66)	**19.5%** (68)	**17.6%** (30)	**15.9%** (27)	**17.4%** (31)	**21.3%** (38)
	pemetrexed	**17.0%** (59)	**54.3%** (189)	**14.7%** (25)	**53.5%** (91)	**18.5%** (33)	**53.9%** (96)
	capecitabine	**12.6%** (44)	**49.4%** (172)	**10.0%** (17)	**48.2%** (82)	**14.6%** (26)	**49.4%** (88)
mTor inhibitors	everolimus/temsirolimus	**8.6%** (30)	**16.7%** (58)	**6.5%** (11)	**10.0%** (17)	**10.7%** (19)	**23.0%** (41)
Androgen receptor inhibitors	flutamide	**4.3%** (15)	**0.3%** (1)	**4.1%** (7)	**0%** (0)	**4.5%** (8)	**0.6%** (1)
Anti-HER2 targeted therapies	trastuzumab	**3.7%** (13)	**95.7%** (333)	**3.5%** (6)	**91.8%** (156)	**3.9%** (7)	**94.4%** (168)

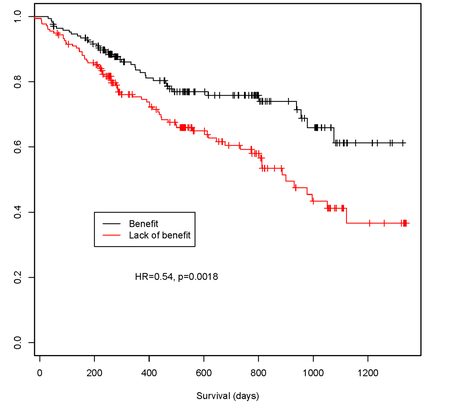
Overall survival from time of diagnosis

- Median overall survival observed for patients included in the Benefit cohort (158.0 months) compared to patients included in the Lack of Benefit cohort (63.4 months) trended towards significance (HR 0.69, 95% CI 0.47-1.02; p=0.065).



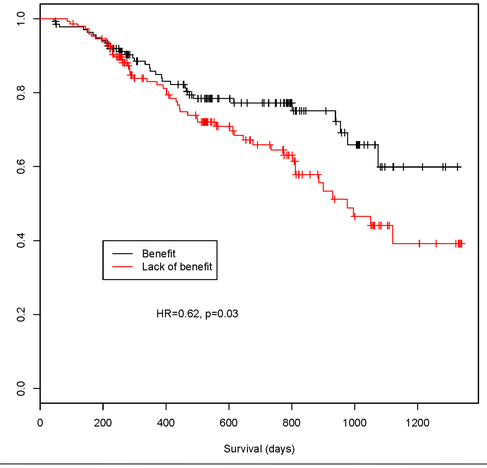
Post-profiling survival

- Median survival from time of tumor profiling for patients included in the Benefit cohort has not yet been reached, but was significantly longer than patients included in the Lack of Benefit cohort who lived for a median of 30.0 months after profiling (HR 0.54, 95% CI 0.37-0.80; p=0.0018).



Post-profiling survival sub-analysis

- A subgroup analysis of the patients who had received at least one post-profiling treatment was performed. This subgroup analysis excluded 60 patients from the Analysis Population of 348, reducing the Benefit cohort to 140 and the Lack of Benefit cohort to 148.
- The median post-profiling survival from the time of profiling observed for patients included in the Benefit cohort has not yet been reached but was significantly longer than patients included in the Lack of Benefit cohort who lived for a median of 32.6 months after profiling (HR 0.62, 95% CI 0.40-0.96; p=0.03).



Conclusions

- This initial report from the Caris Registry™ demonstrates that the post-profiling survival of ovarian, fallopian tube, or primary peritoneal cancer patients treated with agents of potential benefit according to a predictive biomarker panel is significantly longer than in patients who received agents associated with lack of benefit.
- The censoring observed early in the Kaplan-Meier curves for both patient cohorts reflects the nine-month follow-up window and the immature clinical follow-up of this Caris Registry™.
- Molecular profiling revealed that patient tumors in the Lack of Benefit cohort were less likely to benefit from platinum and taxane agents, suggesting that profiling at diagnosis rather than at recurrence could identify patients likely to benefit from experimental regimens in the adjuvant setting.

References

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