Paving the Road to Personalized Medicine in Cervical Cancer: Theranostic Biomarker Evaluation in a 592-Specimen Library

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Abstract (#3911)

Background: The results from Gynecologic Oncology Group protocol 240, that blockade and non-platinum chemotherapy, predictive biomarkers are requichemotherapy plus bevacizumab significantly improves overall survival over chemotherapy alone among women with advanced cervical cancer, represents a *proof of concept* of the potential for anti-angiogenesis therapy and the value of systemic therapy in this disease. To identify patients likely to derive the greatest benefit from angiogenesis red and predicated on *theranostics*, the emerging field through which developing technologies and capabilities in the diagnostic sector can be applied to pharmacogenomics and personalized medicine.
Methods: We interrogated a database of theranostic biomarkers from the CARIS repository. 592 specimens in the cervical cancer library were evaluated by a combination of sequencing (NGS), gene amplification (ISH), and protein expression (IHC).
Results: NGS sequencing in 224 specimens identified mutational hotspots corresponding to PI3KCA (26%), BRCA2 (21%), BRCA1 (10%), KRAS (10%), TP53 (10%), and FBXW7 (10%). Gene amplification of EGFR (11%, 20/174) and HER2 (8%, 32/395) was also observed. IHC studies were noteworthy for the following protein signatures: anti-programmed death receptor 1 (PD1) tumor infiltrating lymphocytes (65%, 53/82); over-expression of cMET (22%, 82/376); over-expression of estrogen receptor (20%, 118/590), progesterone receptor (8%, 48/589), and androgen receptor (4%, 22/578); gemcitabine-specific low RRM1 (44%, 256/538), topotecan-specific high TOPO1 (56%, 294/528), paclitaxel-related high TLE3 (27%, 256/537) and low TUBB3 (74%, 202/273), and pemetrexed-related low TS (48%, 256/537).
Conclusion: The August 14, 2014 U.S. FDA approval of bevacizumab for advanced cervical cancer constitutes a regulatory milestone that fulfills a high unmet clinical need. Our data support the inclusion of theranostic biomarkers to help guide therapy in clinical trials for patients who have progressed on anti-angiogenesis therapy or who are considered otherwise incurable. Poly-ADP-ribose polymerase inhibition, MEK, cell cycle checkpoint, and PI3K/AKT/mTOR pathway inhibitors, EGFR- and HER2-directed therapy, immunotherapy, hormonal therapy, and non-platinum chemotherapy may be suitable for study.

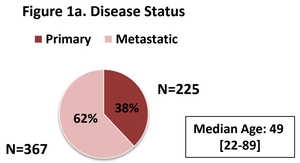
Methods

Five hundred ninety two cervical cases referred to Caris Life Sciences from 2009 through 2014 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (next-generation sequencing [NGS]), protein expression (immunohistochemistry) and gene amplification (FISH or CISH).

Results

Table 1. Reported Histology of Cervical Cancer Cases

Histology	Frequency
squamous cell carcinoma	51%
adenocarcinoma	32%
poorly-differentiated carcinoma	7%
adenosquamous	4%
metastatic carcinoma	2%
Carcinoma, mixed mullerian, tumor, papillary serous carcinoma, carcinosarcoma, invasive carcinoma	1%
non small cell carcinoma, endocervical carcinoma, infiltrating serous carcinoma, serous carcinoma	0.2-0.3%



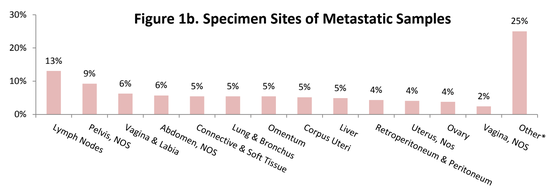


Table 1 and Figures 1a-1b. Tumor and Patient Characteristics. Table 1. Histology distribution according to submitted pathology reports, Figure 1a. Disease status and Figure 1b. Sites of metastasis based on submitted specimens used for profiling.

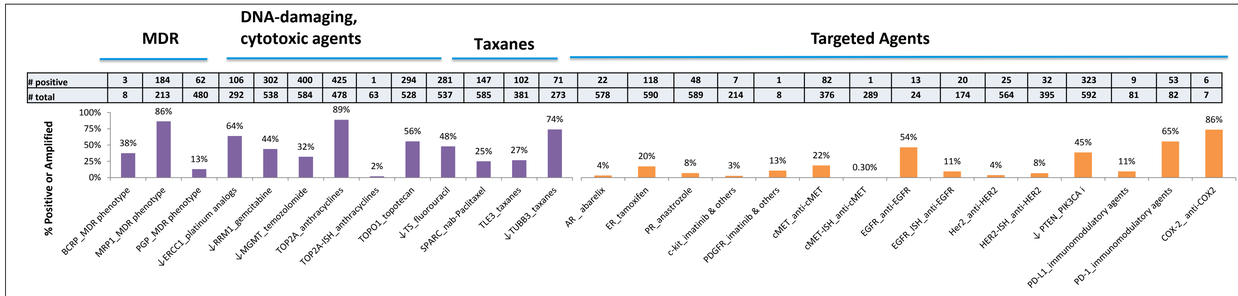


Figure 2. Protein and Gene Copy Number Results and associated Therapies. Percentages represent % positivity for IHC and % amplified for ISH. Purple bars represent biomarkers associated with Cytotoxic Therapies, and Orange bars represent biomarkers associated with Targeted Therapies. N for each biomarker given in blue table above.

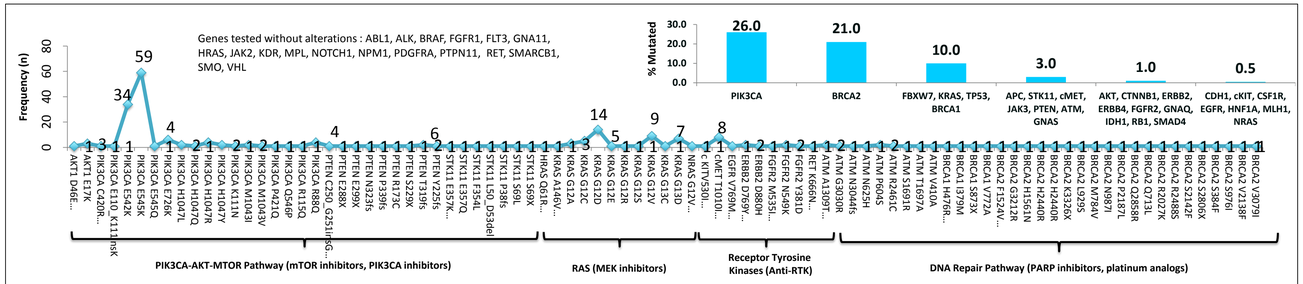
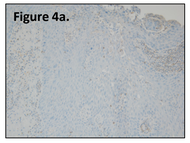


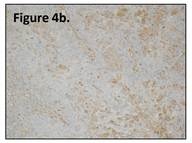
Figure 3. (Inset) Percent Mutated by NGS (n= 224; exception BRCA1/2 n=) and Frequency of Targetable Variants (protein changes) found. Variants are grouped based on targeted therapy options available. PIK3CA variants E545K and E542K (both exon 9) are the most frequent, followed by KRAS G12D, G12V (both exon 2).

Results

Table 2. Most Promising Targets for Cervical Cancer based on Frequency and Availability of Targeted Agents in Clinical Trials

Target	Frequency	Targeted Agent
BRCA1 mutation	10%	PARP inhibitors
BRCA2 mutation	21%	
PIK3CA mutation	26%	PIK3CA inhibitors; mTOR inhibitors
PTEN mutation, expression loss	3%; 45%	
AKT mutation, STK11 mutation	3%; 1%	
EGFR overexpression	54%	cetuximab
HER2 overexpression, amplification	4%; 8%	trastuzumab
PD1 positive TILs, PDL1 tumor expression	65%; 11%	immunomodulatory agents
COX2 overexpression	86%	COX2 inhibitors
KRAS mutations	10%	MEK inhibitors





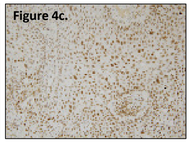


Figure 4. Representative tumor staining by IHC. (a) PD-1 positive (TIL count/HPF > 5) (b) PDL1 positive tumor expression (2+ 10%) and (c) TOPO1 positive expression (2+ 35%) in representative cervical cancer patient.

Conclusions

- Multiplatform profiling of cervical cancers reveals multiple targets for traditional cytotoxic therapies, as well as targeted therapies.
- IHC and ISH reveals high frequency targets for cytotoxic agents such as low ERCC1 (64%), low TUBB3 (74%) and high TOPO1 (56%) and biomarkers for targeted agents such as high EGFR (54%), HER2 amplification (8%) and PD1/PDL1 expression.
- Mutational analysis revealed targetable alterations: highest mutation rates in PIK3CA (exon 9) and BRCA2, followed by KRAS (exon 2).
- Poly-ADP-ribose polymerase inhibition, MEK, cell cycle checkpoint, and PI3K/AKT/mTOR pathway inhibitors, EGFR- and HER2-directed therapy, immunotherapy, hormonal therapy, and non-platinum chemotherapy may be suitable for study based on these analyses.

References

1. Duenas-Gonzalez, A. et al. (2014). "New molecular targets against cervical cancer." Intl J Women's Health 6: 1023-1031.
2. Husseinzadeh, N., et al. (2014). "mTOR inhibitors and their clinical application in cervical, endometrial and ovarian cancers: a critical review." Gynecol Oncol 133(2): 375-381.

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