Identification of signal transduction pathway activity with a potential clinical implication in high-grade serous ovarian carcinoma

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Introduction:

High-grade serous carcinoma (HGSC) is the most common subtype of ovarian cancer, with a high mortality rate, even after successful first-line treatment (debulking surgery and chemotherapy). Although therapeutic options for targeted therapy are rapidly expanding, identification of patients who respond to these therapies remains a challenge. In this study, we used a new technology that measures functional signal transduction pathway (STP) activity to identify HGSCs with a potential clinical target by comparing STP activity in HGSC and in normal Fallopian tube epithelium (FTE); the tissue of origin of most HGSCs.

Methods:

Samples:

50 primary tissue samples from postmenopausal patients with advanced stage HGSC, **PRIOR** to start of chemotherapy and 9 postmenopausal morphologically normal FTE samples (by laser capture microdissection).

Pathway analysis:

STP activity was measured using the G7 (qPCR) OncoSIGNal test (InnoSIGN BV, The Netherlands). Measured pathways: androgen receptor (AR), estrogen receptor (ER), PI3K, MAPK, Hedgehog (HH), TGFβ and Notch.

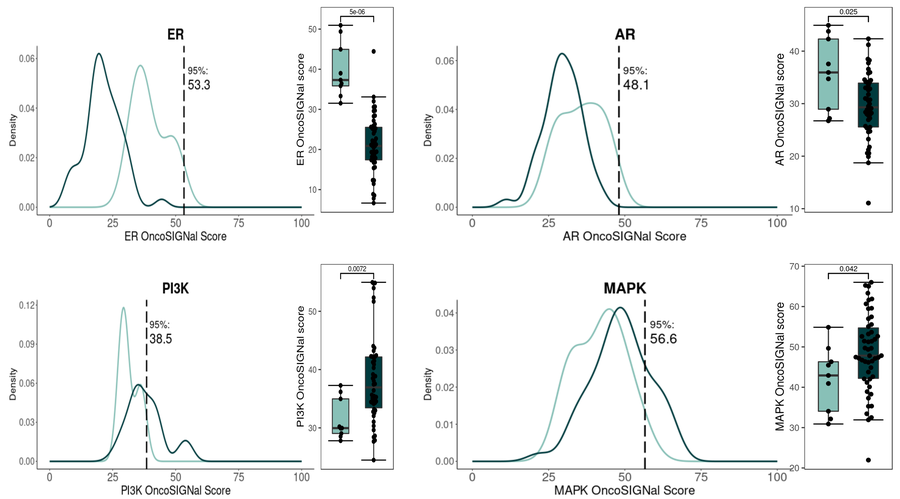
Statistics:

Differences in STP activity between groups were compared with Mann-Whitney U tests. Cut-off value for aberrant STP activity was defined as the 95th percentile of STP activity measured in FTE.

Results:

HGSC group (n=50) as compared to FTE (n=9):

Lower median ER ($p < 0.001$) pathway activity.
Higher median PI3K ($p < 0.01$), HH ($p < 0.001$) and TGFβ pathway activity ($p = 0.01$).



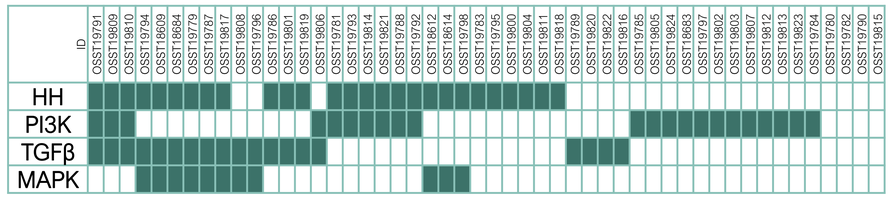
postmenopausal HGSC (n=50)
postmenopausal FTE (n=9)

Pathway	High Aberrant in HGSC
ER (n=0)	0%
AR (n=0)	0%
Notch (n=0)	0%
MAPK (n=11)	22%
TGFβ (n=19)	38%
PI3K (n=22)	44%
HH (n=27)	54%
Combined aberrant pathways	
HH + PI3K (n=9)	18%
HH + TGFβ (n=12)	24%

Results:

Individual HGSC samples:

Aberrant increased activity was identified for the MAPK (n = 11), PI3K (n = 22), HH (n = 27) and TGFβ (n = 19) pathways.
Frequently observed combinations of aberrant STP activity were HH/TGFβ (n = 15) and HH/PI3K (n = 9).



Aberrant increased STP activity indicated per HGSC patient by color-coding.
Distinct aberrant STP profiles among the HGSC cohort.

Conclusion

- In 92% of analyzed HGSC samples a clinical target could be identified using STP analysis.
- Differentiation between normal and aberrant STP activity could have clinical utility in the selection of HGSC patients for targeted therapy.

Next step:

A prospective study in ovarian cancer patients (STAPOVER) has been designed to demonstrate clinical utility (NCT03458221).
Additional FTE samples will be measured to increase sample size.

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