Translational analysis of Esophageal Adenocarcinoma (EAC) patients treated with oxaliplatin and capecitabine (Xelox) +/- the dual Erb B inhibitor AZD8931 in the DEBIOC study

ASCO Annual Meeting 2020

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Abstract #301033
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BACKGROUND

- AZD8931 is a small-molecule inhibitor with equipotent activity against erbB1 (EGFR), erbB2 (Her2), and erbB3.
- The Dual Erb B Inhibition in Oesophago-gastric Cancer (DEBIOC) trial reported an acceptable safety profile for neoadjuvant Xelox +/- AZD8931 but limited efficacy.
- We utilized EAC patient samples from the dose expansion phase of DEBIOC to evaluate the impact of neoadjuvant Xelox +/-AZD8931 on biological pathways using a unique software-driven solution.

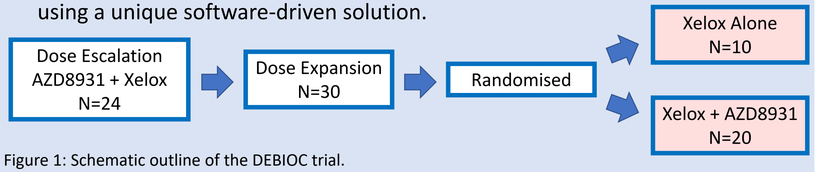

Figure 1: Schematic outline of the DEBIOC trial.

CLARA^T Total mRNA Report

clara^T provides a comprehensive overview of tumor profiles according to the Hallmarks of Cancer incorporating:

- 10 key biologies
- 92 gene expression signatures
- 7337 single genes

Figure 2: clara^T utilizes the Hallmarks of Cancer. Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell* 2011;144:646–74. With permission from Elsevier.

METHODS

- 24 pre-treatment FFPE EAC biopsies and 17 matched surgical resection specimens were transcriptionally profiled using the Almac Diagnostics Xcel Array.
- 15 patients received Xelox+AZD8931 and 9 Xelox alone.
- Gene expression data was analyzed using the Almac clara^T total mRNA report V3.0.0.
- Paired Wilcoxon tests (5% significance level) were used to evaluate changes in clara^T scores pre- and post-treatment.
- EGFR and Her2 expression were assessed by IHC and FISH.

HIERARCHICAL CLUSTERING OF BIOPSY SAMPLES

1. Hierarchical clustering of biopsies identified 4 major clusters:

Cluster 1: IFNg & Inflammation active

Cluster 2: Genomic instability & Evading Growth active

Cluster 3: Proliferation (EGFR) and MAPK active

Cluster 4: EMT and Angiogenesis active

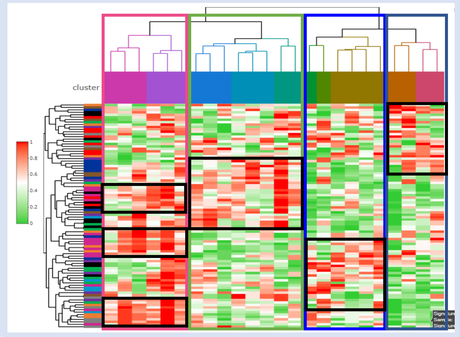

Figure 3: Hierarchical clustering of DEBIOC biopsy samples.

CLARA^T SIGNATURE SCORES AND NEOADJUVANT TREATMENT

2. Comparing signature scores pre- and post- neoadjuvant treatment demonstrated a significant reduction in scores relating to **DNA damage repair (DDR) deficiency** and an increase in **angiogenesis** signatures and **EMT** signatures.

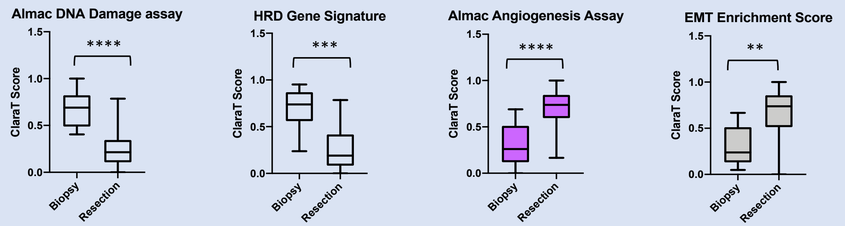

Figure 4: clara^T signature scores pre- and post-neoadjuvant treatment (Xelox +/-AZD8931).

3. Comparing pre- and post-treatment signature scores in patients treated with Xelox +/-AZD8931 showed a significant reduction in EGFR Sensitivity Signature, ERBB2-specific Gene Expression Signature and Hallmark PI3K-AKT- MTOR Signaling in those treated with Xelox + AZD8931 in keeping with its mechanism of action.

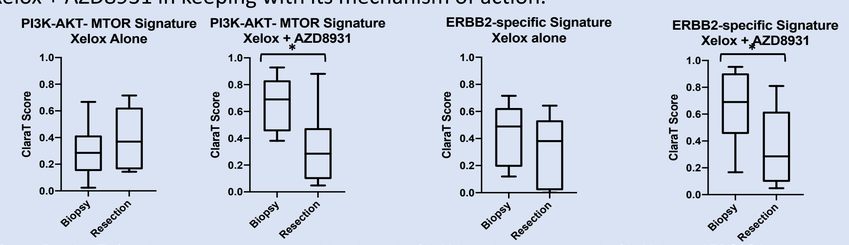

Figure 5: claraT signature scores pre and post treatment with Xelox alone compared with Xelox + AZD8931.
* p<0.05; **p<0.01 ***p<0.001; ****p<0.0001

AZD8931 TREATED AND RESISTANT CELL LINES

4. Downregulation of AKT signaling was confirmed in AZD8931 treated and resistant cell lines.

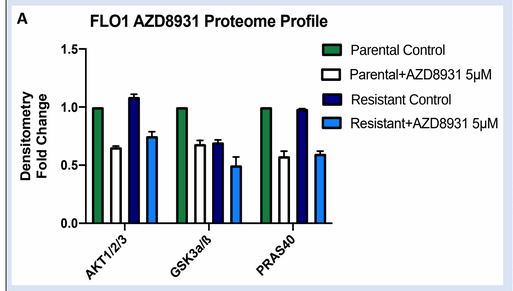

Figure 6 A+B: Proteome array demonstrating downregulation in AKT pathway signaling in FLO1 parental and AZD8931-resistant EAC cell lines when treated with AZD8931 5μM.

CONCLUSIONS AND FUTURE DIRECTIONS

- We report the use of a novel software tool to apply 92 gene expression signatures to EAC biopsy and resection specimens from the DEBIOC trial to provide insight into mechanisms of action and potential resistance pathways.
- Neoadjuvant treatment was associated with a reduction in DDR deficiency and an increase in angiogenesis and EMT signatures.
- AZD8931 treatment was associated with a reduction in EGFR, Her2 and AKT pathways.
- These data are being further explored to discover resistance mechanisms to AZD8931.

ACKNOWLEDGEMENTS

The DEBIOC trial was sponsored by the University of Oxford and funded by AstraZeneca and Cancer Research UK (an ECMC/AstraZeneca alliance trial). This work was supported by Invest Northern Ireland and Almac Diagnostics. The Northern Ireland Molecular Pathology laboratory has received funding from Cancer Research UK, Friends of the Cancer Centre and the Seán Crummey Foundation. The Northern Ireland Cancer Trials Network are supported by Cancer Research UK and the Northern Ireland HSC Research & Development Division through the Experimental Cancer Medicine Centre Network initiative. This work was supported by and occurred as part of the Wellcome-HRB ICAT Programme.