ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Abstract #301033

Translational analysis of esophageal adenocarcinoma (EAC) patients treated with oxaliplatin and capecitabine (Xelox) +/- the dual ErbB inhibitor AZD8931 in the DEBIOC study.

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Background:

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 DEBIOC to evaluate the impact of neoadjuvant Xelox +/-AZD8931 on biological pathways using a unique software driven solution.

Methods:

24 pre-treatment FFPE EAC biopsies and 17 matched surgical resection specimens were transcriptionally profiled using the Almac Diagnostics Xcel Array. Gene expression data was analyzed using the Almac clara^{T} total mRNA report V3.0.0, reporting on 92 gene expression signatures and 7337 single genes associated with 10 key biologies. 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.

Results:

15 patients received Xelox+AZD8931 and 9 Xelox alone. Hierarchical clustering of biopsies identified 4 major clusters: Inflammation active, Genomic Instability active, EGFR & MAPK active, and EMT & Angiogenesis active. Comparison of signature scores pre- and post-neoadjuvant treatment demonstrated a significant reduction in scores relating to DNA damage repair (DDR) deficiency (Almac DNA Damage assay, $p< 0.0001$; BRCAness Profile, $p= 0.0025$; HRD Gene Signature, $p< 0.0001$; BRCA1ness Signature, $p= 0.0004$) and a significant increase in angiogenesis signatures (Almac Angiogenesis Assay, $p= 0.0002$; Angio

Predictive G model, *p*= 0.0228; Angiogenesis Signature A, *p*= 0.0034) and EMT signatures (EMT Signature, *p*= 0.0031, EMT Enrichment Score, *p*= 0.0013, Pan-Can EMT Signature B, *p*= 0.0001).

Comparing pre- and post-treatment signature scores in patients treated with Xelox +/-AZD8931 revealed a significant reduction in EGFR Sensitivity Signature (*p*= 0.0088), ERBB2-specific Gene Expression Signature (*p*= 0.0127) and Hallmark PI3K-AKT-MTOR Signaling (*p*= 0.0195) in those treated with Xelox + AZD8931 in keeping with the mechanism of action of AZD8931. Downregulation of AKT signaling was confirmed in AZD8931 treated and resistant cell lines.

Conclusions:

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. Neoadjuvant treatment was associated with a reduction in DDR deficiency and an increase in angiogenesis and EMT signatures whilst a reduction in EGFR, Her2 and AKT pathways was noted with AZD8931 treatment.

Merit Award Application Material:

Merit Award Application Materials:

- ASCO Merit Award letter of reference for Dr Anita Lavery.pdf (143.8KB) - Letter of Support
- Dr Anita Lavery CV February 2020.pdf (86.2KB) - Curriculum Vitae

Title:
Translational analysis of esophageal adenocarcinoma (EAC) patients treated with oxaliplatin and capecitabine (Xelox) +/- the dual ErbB inhibitor AZD8931 in the DEBIOC study.

Submitter's E-mail Address:
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Is this a late-breaking data submission?
No

Is this abstract a clinical trial?
No

Research Funding Source:
Pharmaceutical/Biotech Company

Research Funding Source Name:
AstraZeneca

Are there additional sources of funding for your study?
Yes

Additional sources of funding for your study:
Health Research Board Ireland Other Government Agency, Cancer Research UK, OGcancerNI, Wellcome Trust Other

Are patients still being accrued to the trial reported in this abstract?
No

Would like to be considered for a Merit Award:
Yes

Have the data in this abstract been presented at another major medical meeting?
No

Has this research been submitted for publication in a medical journal?
No

Type of Research:
Retrospective

Research Category:
Translational

Continued Trial Accrual:
No

Received Grant funding:
No

Sponsor:
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