

2015 EUROPEAN CANCER CONGRESS

25-29 September 2015

Vienna, Austria

SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

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TRANSLATIONAL RESEARCH

High frequency of potentially targetable ERBB2 extracellular domain mutations detected in multiple cancer types by comprehensive genomic profiling

Lead author Jeffrey Ross, Pathology Department, Medical Centre, Albany, USA and Medical Director of Foundation Medicine, Inc., Cambridge, USA, presented findings from comprehensive genomic profiling (CGP) of a large series of tumour samples that determined the incidence of mutations within the extracellular domains (ECD) of ERBB2 that can be targeted by existing anti-HER2 therapies. Most oncogenic mutations in the ECD are generally mutually exclusive of ERBB2 amplifications and occur in a wide variety of human cancers. Most ERBB2 ECD mutations involve S310F and S310Y base substitutions; recent reports have linked tumours having these genomic alterations with good responses to anti-HER2 targeted therapies, including currently available kinase inhibitors and antibodies.

CGP was done on 37,772 clinical FFPE cancer samples using hybridisation capture of exonic regions from 315 cancer-related genes and select introns from 19 genes commonly rearranged in cancer. The investigators used ≥ 50 ng samples of DNA, which were extracted and sequenced to high, uniform median coverage (623X) to identify clinically relevant genomic alterations (CRGA), defined as sequences that correspond to targets of existing anti-cancer drugs that are either on the market or being used in registered clinical trials.

CGP revealed that S310F or S310Y ERBB2 ECD mutations occurred in 177 (0.5%) of the 37,772 clinical samples that were sequenced, while just 34 (0.01%) non-ECD ERBB2 point mutations were identified in this series. The majority (76%) of the ERBB2 ECD mutations were confined to 7 tumour types, including bladder/kidney urothelial carcinoma (UC), carcinoma of unknown primary (CUP), biliary tract carcinoma (BTC), lung cancer, colorectal carcinoma, breast cancer, and gastroesophageal carcinoma. The incidence of ERBB2 ECD extracellular domain alterations was significant compared to other tumour types: Incidence was 18% in both UC and CUP with mutations occurring in 3.20% ($p < 0.0001$) and in 0.96% of tumours, respectively, ($p = 0.00049$), and 7% in BTC, where it was present in 1.10% of tumours ($p = 0.0045$).

ERBB2 ECD mutation was also highly associated with the micropapillary variant of UC compared to conventional UC ($p < 0.0001$). More than 30 other tumour types accounted for the remaining 24% of the ERBB2 ECD mutations identified.

Tumour Type	Tumours with <i>ERBB2</i> ECD Mutations			
	Total Cases	% of Total <i>ERBB2</i> ECD Mutations	% in this Tumour Type	Comparison of this Tumour Type to All Tumour Types
Bladder/Kidney Urothelial Carcinoma (UC)	32	18%	3.20%	P<0.0001
Unknown Primary Carcinoma (CUP)	32	18%	0.96%	P=0.0004
Lung Carcinoma	22	12%	0.35%	NS
Breast Carcinoma	14	8%	0.26%	NS
Biliary Tract Carcinoma (BTC)	13	7%	1.10%	P=0.0045
Gastroesophageal Carcinoma	12	7%	0.71%	NS
Colorectal Carcinoma	10	6%	0.19%	NS

Caption: Frequency of Targetable *ERBB2* Extra-Cellular Domain (ECD) Mutations across Multiple Tumour Types

Credit: Jeffrey Ross

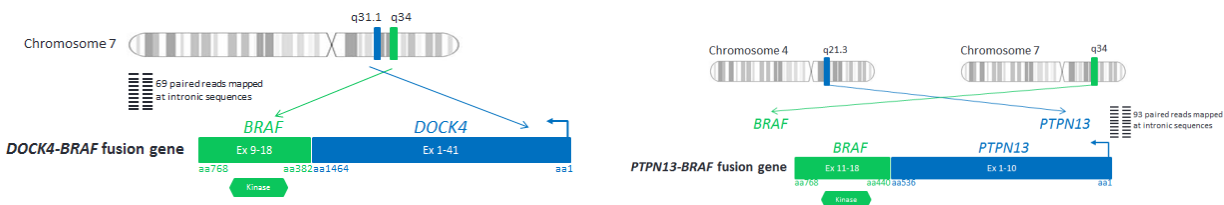
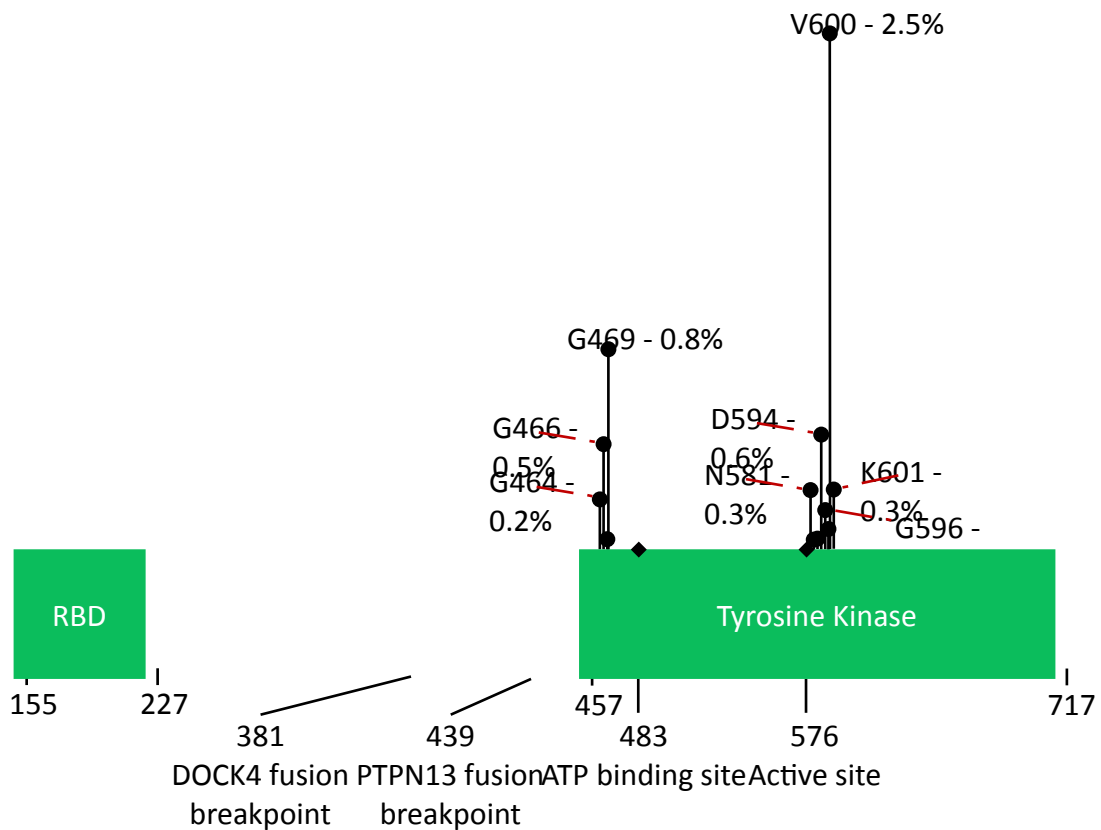
CGP detected genomic sequence alterations that are not detectable by IHC and FISH and thus are missed when *ERBB2* status is determined by conventional methods; normal *ERBB2* copy number was detected in 154 (87%) of the *ERBB2* ECD mutated cancers and, therefore, would not have been identified as *ERBB2* “positive” by FISH or IHC testing. The authors emphasised that, although *ERBB2* ECD mutations are rare, they represent important targetable genomic alterations occurring across a wide range of tumour types and are enriched in specific tumours. Ross et al. Abstract P144.

Practice point and future research opportunities

Therapeutically relevant extracellular domain mutations in ERBB2/HER2 were observed across multiple tumour types that may show good responses to already existing anti-HER2 targeted therapies. These ERBB2 sequence alterations remain undetectable by other modalities, and represent the utility of comprehensive genomic profiling to personalise treatment for patients with advanced and refractory malignancies.

Comprehensive genomic profiling of BRAF in a large series of lung cancer samples

Siraj Ali, Foundation Medicine, Inc., Cambridge, USA discussed the incidence of molecular alterations in the BRAF gene derived from analysis of 3300 consecutive lung cancer samples using next generation sequencing (NGS). He reported results from a large-scale genomic evaluation that reviewed biopsies that were obtained in the course of clinical care for alterations thought to activate BRAF using comprehensive genomic profiling (CGP). In all, 2179 lung adenocarcinoma (LADCA) samples, 535 non-squamous non-small cell lung cancer (NSCLC), 385 squamous cell cancer (SCC), and 201 small-cell lung cancer (SCLC) tumour samples were analysed. DNA was extracted from 40 microns of FFPE and CGP was performed on hybridisation-captured, adaptor ligation based libraries to a mean coverage depth of >500X for 3,769 exons of 315 cancer-related genes plus selected introns from 28 genes that are known to be frequently rearranged in cancer. The results were evaluated for all classes of genomic alterations. Clinically relevant genomic alterations (CRGA) were defined as genomic alterations linked to the response to drugs already on the market or under evaluation in clinical trials.



Caption: BRAF genomic alterations in 2179 case of lung adenocarcinoma assayed by genomic profiling in the course of clinical care (mutation: frequency).

Credit: Siraj Ali

The oncogenic BRAF alterations identified included mutation, fusion, and amplification. Mutations were most commonly detected in 5.5% of LADCA, 3.0% of non-squamous NSCLC, and in 0.8% of SCC samples, but not in SCLC, which had the smallest sample size of 201 cases. Previous reports estimate that BRAF V600E driver mutations are found in approximately 2-3% of patients with NSCLC and are generally mutually exclusive of other oncogenic drivers. BRAF V600 was the most frequently occurring mutation in this series and was detected in 2.5% of LADCA and 0.4% of non-squamous NSCLC samples. In addition to V600E, a subset of other BRAF genetic alterations,

including certain fusions, may also be oncogenic as they activate either the kinase domain or downstream targets; other alterations more frequently identified were G469 in 0.8% versus 1.3%, G466 at 0.5% versus 0.6%, and D594 at 0.6% versus 0.0% of LADCA and non-squamous NSCLC samples, respectively. Alterations in BRAF G469 and D594 were detected in 0.3% of SCC samples. Alterations occurring in less than 0.5% of tumour types included G464, N581, and K601. Two LADCA samples harboured novel fusions, DOCK4-BRAF and PTPN13-BRAF; of these, one patient developed acquired resistance to vemurafenib, but response was restored with the addition of everolimus.

The authors summarised that CGP can be used successfully to identify all classes of BRAF alterations in NSCLC, which reached nearly a 5% frequency of alteration. The rates of specific alterations differed between histologic subtypes, with approximately 50% of BRAF V600E mutations seen in LADCA compared to non-squamous NSCLC, where just 12.5% of BRAF V600E alterations were detected but contained 87.5% of intermediately activating BRAF alterations. They suggest that limited benefit can be obtained from BRAF testing in SCLC wherein no BRAF alterations were found and possibly SCC, where less than 1% of samples contained BRAF mutations. They also suggested that patients with NSCLC harbouring other activating alterations of BRAF may also benefit from treatment from BRAF V600E inhibitors in ongoing NSCLC clinical trials. Ali et al. Abstract 3007.

Practice point and future research opportunities

BRAF is a key component of the RAS-RAF-MEK-ERK signalling pathway, an important component of the downstream molecular network activated by a number of receptor tyrosine kinases, that provides the oncogenic potential for aberrant signalling in this pathway. BRAF activation by a number of molecular mechanisms is one way the pathway may be activated in cancer. Mutations reported in this study include those substitution mutations at position 600, the commonest of which is V600E, which activate the BRAF kinase and are oncogenic in vitro; the physiological effect of the non-V600 mutations is much less clear. The finding of BRAF fusion is interesting but a rare phenomenon. The distribution of mutations by histology is discussed but few data exist with which to compare these results. The few reports of BRAF mutation in squamous cell carcinoma tend to be non-V600 mutations; with limited comparators, it is difficult to draw any conclusion regarding the dominance of non-V600 mutations in the non-squamous NSCLC group.

The NGS approach in this study has presumably generated data that will be of interest. Mutation prevalence data may be confounded by the technology used to find the mutations if it is allele

specific, which is not an issue in this study and the population studied, where there is case selection, especially when there is uneven distribution of mutations by histology.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

ACKNOWLEDGMENT

ESMO would like to thank Virginia Powers, PhD for editorial assistance in preparation of the report.

ESMO would like to thank Drs Jeffrey Ross, Siraj Ali, Christoph Zielinski, Eva Segalov, Toni Choueiri, Richard Cathomas, Paul Nghiem, James Yao, Grant McArthur, and Rolf Issels for giving their permission to publish images from the studies presented during the ECC 2015 in the ESMO media channels.