

# 2015 EUROPEAN CANCER CONGRESS

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## 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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## LUNG CANCER

### Highly specific rovalpituzumab tesirine shows clinical benefit as single agent in second and third-line treatment of SCLC

M. Catherine Pietanza, Memorial Sloan Kettering Cancer Center, New York, USA reported results from a phase I/Ib multicentre study showing that the antibody-drug conjugate, rovalpituzumab tesirine, had strong clinical activity as second- and third-line treatment of patients with small-cell lung cancer (SCLC). This study was the first-in-human trial of rovalpituzumab tesirine, which comprises a humanised monoclonal antibody to the delta-like protein 3 (DLL3), a dipeptide linker, and a pyrrolobenzodiazepine dimer toxin. DLL3 is a Notch ligand that is not expressed in normal tissue but is overexpressed in SCLC tumour-initiating cells. Clinical activity was strongest in the subset of patients with tumours having high expression of DLL3, the drug target.

The trial enrolled 79 patients previously treated for progressive SCLC; 33 patients were female and the overall median age was 62 (range 44 to 81) years. Rovalpituzumab tesirine was given to 34 patients every 3 weeks (Q3W) and to 45 patients Q6W in escalating doses of 0.05, 0.1, 0.2, 0.4 and 0.8mg/kg until dose limiting toxicities were observed. Maximum tolerated doses (MTD) of 0.2mg/kg Q3Wx3 cycles and 0.3mg/kg Q6Wx2 cycles were taken further to the Ib expansion cohorts. Pharmacokinetic data revealed a longer-than-expected half-life, encouraging a Q6W schedule. The investigators developed a DLL3 antibody, which was used to assess antigen expression in 48 archived tumour specimens, with 33 (69%) being DLL3-positive.

The combined clinical benefit rate was 66% in the 29 patients with confirmed DLL3-positive tumours and who received the MTD; of these, 10 (34%) patients had partial response and 9 (31%) patients achieved stable disease. The duration of response in patients with confirmed responses at the recommended phase 2 dose (RP2D) of 0.3mg/kg Q6W was 178+ (range: 58 to 266+) days. Of particular interest were the significant response rate of 17% observed among 35 patients receiving the MTD in the third-line setting, where no standard-of-care currently exists. This response rate was further enriched to 42% in 15 patients who were DLL3-positive.

The most commonly reported treatment emergent adverse events (TEAEs) of any grade occurring in  $\geq 20\%$  of patients were fatigue (47%), dyspnoea (24%), nausea (24%), and decreased appetite (22%). Serious TEAEs included serosal effusions reported in 11 (14%) patients and thrombocytopenia in 3 (4%) in patients. Phase II studies are being planned. NCT01901653  
Pietanza *et al.* Abstract 7LBA.

### Practice point and future research opportunities

Currently, for SCLC there is no standard third line treatment, so rovalpituzumab tesirine is likely to fulfill an unmet need for these patients. Rovalpituzumab tesirine demonstrated substantial single-agent anti-tumour activity and durability in patients with relapsed or refractory DLL3-positive SCLC, which may also have identified a predictive biomarker, DLL3, that is associated with drug efficacy, allowing for a targeted treatment in SCLC. Additional, larger trials are warranted.

### Mutation profile in stage III NSCLC shows prognostic value for progression-free survival

Angela Boros from Institut Gustave Roussy, Villejuif, France, presented results on behalf of colleagues who evaluated the prognostic value of specific gene alterations, including EGFR, KRAS, BRAF mutation, or ALK rearrangement by reviewing data from 190 consecutive patients receiving chemotherapy or radiotherapy with a curative intent, the standard for stage III non squamous non-small cell lung cancer (NSCLC); the prognostic value of alteration in these genes had to date been unknown. The investigators collected paraffin embedded tissue blocks from these patients and DNA was extracted for gene mutation analysis by next generation sequencing; ALK, ROS1 and RET rearrangements were detected by FISH analysis. The survival analysis used Kaplan–Meier methods, log-rank test, and Cox proportional hazards models that adjusted for performance status (0 versus  $\geq 1$ ), stage (IIIA versus IIIB) and whether patients received thoracic surgery. Radiotherapy was delivered at a median dose of 66 Gy (range: 46 to 70 Gy). Platinum-based chemotherapy was administered concomitantly to 108 patients and as induction/consolidation treatment in 170 patients; 15 patients received no chemotherapy.

The prognostic value of specific gene alterations was investigated in 78 patients having evaluable material; 20 (26%) were female, 47 (60%) were current smokers, 40 (51%) had adenocarcinoma and there were 47 stage IIIA and 31 IIIB cases. The most prevalent mutations identified in this cohort were KRAS (15%), EGFR (12%), BRAF (5%; 3 mutations per 66 gene positive samples), NRAS 3% (1 of 32), CTNNB1 3% (1 of 32), and PI3KCA 2% (1 of 58). All 65 samples containing HER2 showed no mutation. FISH was positive for ALK rearrangement in 5% (3 of 56) of NSCLC samples but no alteration in ROS1, RET, HRAS and AKT1 was found in 32 NSCLC samples in which the test was performed.

The association with patient outcome was evaluated at a median follow-up of 3.1 years and showed specific gene alterations associated with significantly worse progression-free survival (PFS); the 11 patients with EGFR mutated or ALK-positive had poorer PFS of median 0.8 year,

95%CI 0.6, 0.9 year and 17 patients with other mutations had 0.5 year, 95%CI 0.4, 0.8 year compared to 50 patients with wild-type genotype who demonstrated median PFS of 1 year; 95%CI 0.9, 1.3 (multivariate hazard ratio (HR) 1.8 and 2.8, respectively;  $p = 0.004$ ). No significant difference in OS was noted: median OS was 2.4 (95%CI 1.3; NR) for patients with EGFR/ALK, 1.1 (95% CI 0.6, 2.5] for patients with other mutations and 1.9 [95%CI 1.5; 2.5] for patients with wild type genes ( $p = 0.23$ ). OS associated significantly only with the dose of radiotherapy received, HR 0.5 [95%CI 0.3, 1.0 ( $p = 0.04$ ). Boros *et al.* Abstract 3000.

### Practice point and future research opportunities

Specific gene alterations may associate with a poorer progression-free survival in patients with stage III NSCLC treated by chemoradiotherapy or radiotherapy. The prognostic and/or predictive value of these alterations should be further evaluated in larger populations.

## Prevalence of gene mutations in patients with NSCLC: Results from the ETOP Lungscope Project

Lead author Keith Kerr, Aberdeen Royal Infirmary, Aberdeen, UK, presented findings from the ETOP Lungscope Project which assessed whether multiplex mutation analysis could predict the prevalence and clinical implications of gene mutations in patients with resected stage I–III non-small cell lung cancer (NSCLC). The investigators used samples from 2709 patients with resected stage I–III NSCLC with clinical data contained in the ETOP Lungscope Biobank to evaluate the prevalence of mutations and determine their association to clinicopathological features and patient outcome, including overall survival (OS), recurrence-free survival (RFS), and time to relapse (TTR). DNA was extracted from FFPE samples and assessed for gene mutation using Fluidigm technology, a microfluidics-based multiplex PCR platform. Mutant allele detection sensitivity is  $>1\%$  for most of the ~150 (13 genes) mutations covered in the multiplex test. Local quality assurance was verified in a central collaborating laboratory, where samples were standardised before genomic analysis.

Study findings represented multiplex testing evaluation of 1502 (55.4%) patient samples. The patients had a median age of 66.3 years and 64.0% were male; adenocarcinoma occurred in 48.3% of patients and 42.9% had squamous cell carcinoma. Smoking status was 7.2% never, 34.2% current and 52.7% former smokers, and the disease stage was: IA in 22.2%, IB in 26.0%, IIA in 17.2%, IIB in 12.2%, IIIA in 20.3%, and IIIB in 2.1% of cases. FFPE samples dated from 2005 to 2008 but recently extracted DNA quality and quantity was generally good, yielding average of

2.63 µg DNA per case; only 38 (1.4%) cases failed quality control and were excluded from study; 95.1% of included cases allowed the complete panel of mutations to be tested.

The most commonly occurring mutations (prevalence) were KRAS (23.2%), MET (6.3%), EGFR (5.1%) and PIK3CA (4.9%); NRAS and BRAF mutation were found in 11 cases (0.7%), and HRAS in 9 (0.6%). Just one case of AKT1 and MYD88 mutations were identified and no ERBB2, FLT3, JAK2 or KIT mutations were found. EGFR and KRAS mutations were found predominantly in patients with adenocarcinoma, with Exon 19 deletion being the most common EGFR mutation (56.8%) and G12C the most prevalent KRAS mutation (45.0%). EGFR mutations were found most often in females, and never smokers. PIK3CA mutations were most prevalent in patients with squamous cell carcinoma and were detected in 60% of patient samples. MET mutations had a similar prevalence across squamous cell and adenocarcinoma cases.

No difference in OS, RFS, or TTR was found between patients with or without EGFR, KRAS, MET and PIK3CA mutations. Kerr *et al.* Abstract 3001.

#### Practice point and future research opportunities

Accurate assessment of specific genetic mutations in NSCLC, especially identification of driver mutations, is crucial in determining the appropriate personalised therapy. The Lungscope Project demonstrated that archival FFPE samples from patients with NSCLC can provide adequate material for multiplex mutation analysis and allow molecular characterisation in a predominantly European, clinically annotated cohort.

### Atezolizumab out performs docetaxel in patients with NSCLC and tumours expressing PD-L1 in the phase II POPLAR trial

Johan Vansteenkiste, [University Hospitals Leuven](#), Belgium presented findings from the randomised, phase II POPLAR trial of atezolizumab, a PD-L1 antibody, in the second- and third-line settings in unselected patients with metastatic or locally advanced non-small cell lung cancer (NSCLC). POPLAR randomised 287 previously treated patients to receive atezolizumab (n = 144) or docetaxel (n = 143); atezolizumab was administered at 1200 mg i.v. every 3 weeks and docetaxel at 75 mg/m<sup>2</sup> i.v. every 3 weeks. The primary objective was estimated overall survival (OS) by intention-to-treat (ITT) analysis and by PD-L1 expressions subgroups. Secondary objectives included estimated progression-free survival (PFS), objective response rate (ORR), and duration of response by ITT and by PD-L1 expression. The median patient age was 62 years and one-third of the patients received atezolizumab or docetaxel as third-line therapy.

Across all PD-L1 expression levels, as determined using the SP142 IHC assay, the ORR was 15% with both treatments. The value of patient selection by PD-L1 expression was demonstrated by the higher response rates seen in patients with the highest PD-L1 expression; in patients with high PD-L1 levels on tumour cells/tumour-infiltrating immune cells (TC/IC 3), the median PFS was 7.8 versus 3.9 months, for atezolizumab and docetaxel, respectively (HR 0.60; 95% CI 0.31, 1.16). The ORR was 38% with immunotherapy versus 13% with chemotherapy. In this group, the median OS was 12.6 versus 9.7 months and the median PFS was 2.7 versus 3.0 months, for atezolizumab and docetaxel, respectively. In the subgroup of patients without PD-L1 expression TC/IC 0, no difference in OS was observed and was 9.7 months for both arms. However, PFS favoured docetaxel and was 1.7 versus 4.1 months in the atezolizumab and docetaxel arms, respectively. The ORR was 8% with atezolizumab versus 10% with docetaxel in this subgroup of patients without PD-L1 expression.

The profile of adverse events was in line with data reports from other PD-1/PD-L1 checkpoint inhibitors. Although atezolizumab patients received longer median treatment of 3.7 versus 2.1 months for docetaxel, fewer patients had treatment-related grade 3/4 adverse events (AEs); 11% of atezolizumab patients compared with 39% of docetaxel patients experienced an AE. A randomised phase III study of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who failed platinum therapy is ongoing. NCT01903993. Vansteenkiste *et al.* Abstract 14LBA.

### Practice point and future research opportunities

Atezolizumab may change treatment strategies for patients with refractory PD-L1 positive lung cancer; atezolizumab was granted breakthrough therapy designation for patients with PD-L1-positive NSCLC in February 2015. Efficacy, demonstrated by the response rate, correlated with the degree of PD-L1 expression on tumour and tumour-infiltrating immune cells.

## Atezolizumab is a new addition to rapidly changing treatment paradigms in NSCLC

Lead investigator Benjamin Besse of the Institut Gustave Roussy, Villejuif, and the Paris Sud University, Paris, France reported findings from the BIRCH trial that evaluated the clinical efficacy of atezolizumab as first- and subsequent line, monotherapy in patients with advanced non-small cell lung cancer (NSCLC). Atezolizumab is a humanized antibody targeting PD-L1 that inhibits PD-L1/PD-1 interaction while preserving the interplay between PD-L2/PD-1, which potentially preserves peripheral immune homeostasis.



BIRCH was an open-label, single-arm phase II study of atezolizumab administered either as first-line or as subsequent second- or third-line in patients with advanced NSCLC. Participants were from 200 centres in 19 countries worldwide and selected for high PD-L1 expression by immunohistochemistry (IHC) done on both archival and fresh tissue samples. Patients with stage IIIB/IV or recurrent NSCLC but no active central nervous system metastases were enrolled. In all, 659 patients were treated and evaluated for efficacy and safety. Atezolizumab was given at 1200 mg i.v. at 3-week intervals as first-line to 142 patients with no prior chemotherapy (cohort 1) until disease progression or unacceptable toxicity, as second-line to 271 patients who had received one prior platinum therapy, and to 254 patients who had undergone 2 or more prior chemotherapy regimens (cohort 3) until loss of clinical benefit was seen. Patients in cohorts 2 and 3 had progressed after chemotherapy. All enrolled patients showed PD-L1 expression at high levels on tumour cells (TC) or tumour-infiltrating immune cells (IC) as TC2/3 or IC2/3 or on both cell types. Patient characteristics were balanced across cohorts; the median age was 64 years, 35% were ECOG PS 0, 28% had squamous NSCLC and 17% of patients were never-smokers. EGFR and KRAS mutation was identified in 327 and 177 patients overall, respectively.

BIRCH met its primary efficacy endpoint, overall response rate (ORR), according to IRF per RECIST v1.1 for defined subgroups. Key secondary endpoints were duration of response (DoR), progression-free survival (PFS) by IRF and investigator, ORR by investigator, overall survival (OS) and safety. At a minimum follow-up of 6 months, 61% of responses were ongoing. Tumour shrinkage was observed in up to 27% of patients and who expressed PD-L1 at higher levels ( $p = 0.0001$ ). The median treatment duration across all cohorts was 4.2 (range: 0 to 15) months. The ORR in cohort 1 was 19% and 17% in cohorts 2 and 3 in patients with TC2/3 or IC2/3 expression. Stronger response was seen in patients with higher expression; ORR rates were 26%, 24% and 27% in cohorts 1, 2, and 3 in patients with PD-L1 expression of level TC3 or IC3.

OS data are not yet mature; however, 6-month OS was achieved by 76%, 75%, and 71% of patients in cohorts 1, 2, and 3 having TC2/3 or IC2/3 expression levels and by 79%, 82% and 80% of patients in cohorts 1, 2, and 3 having TC3 or IC3 expression levels, respectively. At median follow-up of 8.8, 7.9, and 8.6 months median OS was 14 months, not reached (NR) and NR across cohorts 1, 2, and 3, respectively. Improved PFS also mirrored higher PD-L1 expression; 6 month PFS rates were 29, 39, 31 with PD-L1 expression of TC2/3 and IC2/3 and 48%, 46% and 34% in patients with TC3 or IC3 levels in cohorts 1, 2, and 3, respectively.

The safety profile was consistent with that demonstrated in other studies; treatment-related adverse events (TRAEs) occurred in 11% of patients overall and TRAEs leading to study



discontinuation occurred in 5% of patients. All cause adverse events (AEs) grades 3/4 were reported in 38% of patients. The most commonly reported AEs were fatigue and nausea, which occurred in 18% and 10% of patients, respectively. Data analysis according to EGFR mutation status is ongoing. NCT02031458. Besse *et al.* Abstract 16LBA.

### Practice point and future research opportunities

The PD-L1 antibody atezolizumab showed remarkable activity in a large number of patients regardless of the line of treatment in the BIRCH trial. Atezolizumab benefit associated with the extent of PD-L1 expression on tumour cells and tumour infiltrating cells, with the highest activity seen in patients demonstrating expression on both cell types, showing the utility of selecting patients based on PD-L1 expression for anti-PD-L1 therapy. While first-line treatment with atezolizumab in patients with PD-L1 high expressing tumours is promising, the combination of atezolizumab with platinum-based chemotherapy remains an attractive option and is currently being investigated in large randomized phase III trials.

### Nivolumab improves benefit over docetaxel in patients with non-squamous NSCLC: Long-term update from CheckMate

The risk of death was decreased by 28% with nivolumab versus docetaxel for patients with previously treated non-squamous non-small cell lung cancer (NS-NSCLC), according to lead investigator Leora Horn from the Vanderbilt-Ingram Cancer Centre who presented updated findings from the phase III, open-label CheckMate-057 study. CheckMate randomised 582 patients with advanced NS-NSCLC who had progressed on platinum-based doublet chemotherapy to nivolumab at 3 mg/kg i.v. every 2 weeks (n = 292) or docetaxel at 75 mg/m<sup>2</sup> i.v. every 3 weeks (n = 290). The median patient age was 62 years and the majority had an ECOG performance status of 1. Prior maintenance with bevacizumab, pemetrexed, or erlotinib was allowed, as was tyrosine kinase inhibitor (TKI) therapy for those with known EGFR mutations or ALK translocation; 40% and 38% of patients in the nivolumab and docetaxel arms, respectively, had received prior maintenance therapy. In the nivolumab arm, 15% of patients were EGFR-positive and 4% were ALK-positive compared with 13% and 3% in the docetaxel group. A median 6 doses versus 4 of nivolumab were administered versus a median 4 doses of docetaxel.

At a minimum follow-up of 17.2 months, the overall survival (OS) rate with nivolumab was 39% versus 23% with docetaxel; median OS with nivolumab was 12.2 versus 9.4 months with docetaxel, HR 0.72; 95% CI 0.60, 0.88 (p < 0.001). The 1-year progression-free survival (PFS) rates were 19% and 8% and the objective response rates (ORR) were 19% and 12%, with

nivolumab and docetaxel, respectively. Patients receiving nivolumab demonstrated median time to response of 2.1 months versus 2.6 months with docetaxel. The median duration of response (DoR) was 17.2 months with nivolumab versus 5.6 months with docetaxel.

In 455 (78%) patients with quantifiable PD-L1 expression, a greater benefit with nivolumab over docetaxel was seen in patients with  $\geq 1\%$  staining; in patients with PD-L1 expression  $\geq 1\%$ , ORR of 31% and a DoR of 16 months was seen in 123 nivolumab patients versus an ORR of 12% and a DoR of 5.6 months in 123 patients receiving docetaxel. Patients with the highest expression of PD-L1 ( $\geq 10\%$ ), demonstrated an ORR with nivolumab of 37%, with a median DoR of 16 months compared with an ORR of 13% and a DoR of 5.6 months with docetaxel, odds ratio 4.1 (95% CI 1.8, 10.1). However, patients with expression  $< 1\%$  had an ORR of 15% with docetaxel (n = 101) compared with 9% with nivolumab (n = 108).

Adverse events (AEs) occurred significantly less frequently with nivolumab: Rates of all-grade AEs were 69% and 88%, with nivolumab and docetaxel, respectively, and grade 3/4 AEs occurred in 10% of nivolumab patients compared with 54% for docetaxel. The most common grade 3/4 AEs with nivolumab were fatigue, nausea, and diarrhoea, which each occurred in 1% of patients. With docetaxel, 27% of patients had grade 3/4 neutropenia versus 0 in the nivolumab arm. Toxicity-related discontinuations occurred in 5% of patients receiving nivolumab versus 15% of patients receiving docetaxel. These data were simultaneously published in the NEJM [Borghaei *et al.* N Engl J Med 2015; 373:1627-1639]. Horn *et al.* Abstract 3010.

### Practice point and future research opportunities

The longer-term survival results for nivolumab in advanced, non-squamous non-small cell lung cancer support the potential for this agent in treating lung cancer patients.

## KEYNOTE-001 shows robust activity with pembrolizumab in patients with previously treated advanced NSCLC

Jean-Charles Soria, Institut Gustave Roussy in Villejuif, France reported that nearly 30% of previously treated non-small cell lung cancer (NSCLC) patients with elevated PD-L1 expression had objective responses following treatment with 2 mg/kg of pembrolizumab, and the rate increased to 40% at a 10 mg/kg dose. The investigators conducted the phase I KEYNOTE-001 trial in previously treated and treatment-naive patients with advanced or metastatic NSCLC; however, the data presented at the ECC involved the subset of 449 previously treated patients. Investigators studied the safety and efficacy of pembrolizumab at either 2 mg/kg (n = 55) or 10 mg/kg (n = 238)

administered every 3 weeks or and 10 mg/kg given every 2 weeks (n = 156). The evaluation included patients with PD-L1–positive and negative tumours. Patient characteristics showed even distribution between men and women among the groups, a median age of 62 to 63 years, and 82% non-squamous histology. A majority (53%) of the 394 patients treated at the 10 mg/kg dose had received 3 or more prior lines of therapy, as compared with 36% of the patients receiving 2 mg/kg. The overall response rate (ORR) at both dose levels was 18.7% (95% CI 15.2, 22.6). The response rate increased with increasing PD-L1 expression in patients treated with either dose. Median overall survival (OS) for all patients treated with the 10 mg/kg dose was 11.1 months and median progression-free survival (PFS) was 3.0 months. However, in the subgroup of patients with PD-L1 expression  $\geq 50\%$ , OS increased to median 15.5 months and median PFS increased to 5.8 months. The 6-month OS was 63% in all patients treated with 10 mg/kg of pembrolizumab compared with 71.6% for PD-L1–positive patients. The 6-month PFS increased from 34.0% in patients overall to 49.9% for those with PD-L1 levels  $\geq 50\%$ . In this subgroup, 74.2% of patients had some degree of tumour reduction with pembrolizumab, as compared with 51.7% of patients who had less than 50% PD-L1 tumour expression.

Similar safety was seen across the two doses of pembrolizumab; grade 3/4 adverse events (AEs) occurred in 10.5% of patients, and 4.0% of patients discontinued due to a treatment-related AE. Three treatment-related deaths from cardiorespiratory arrest, interstitial lung disease, and respiratory arrest occurred.

The phase II/III randomised KEYNOTE-010 trial is ongoing and compares pembrolizumab at 2 mg/kg and 10 mg/kg doses administered every 3 weeks with docetaxel in patients with previously treated NSCLC. NCT01905657. Soria *et al.* Abstract 33LBA.

### Practice point and future research opportunities

In the pivotal KEYNOTE-001 trial, efficacy with pembrolizumab in patients pretreated for NSCLC was shown to increase in patients having 50% or greater PD-L1 tumour expression. Accelerated approval for pembrolizumab in patients with metastatic NSCLC whose tumours express PD-L1 (determined by an FDA-approved test) with disease progression on or after platinum-containing chemotherapy was granted in October 2015 by the US FDA. Patients with tumours harbouring EGFR or ALK genomic aberrations should have experienced disease progression on FDA-approved therapy specific for these aberrations prior to receiving pembrolizumab.

### Rociletinib is active in patients with EGFR mutant NSCLC and a history of CNS metastases

Andrea Varga, Institute Gustave Roussy, Villejuif, France presented preliminary findings from a subgroup of patients with advanced EGFR-positive non-small cell lung cancer (NSCLC) progressive disease after  $\geq 1$  EGFR tyrosine kinase inhibitor (TKI), participating in the TIGER-X trial of rociletinib. TIGER-X is a phase I/II open-label study wherein an overall response rate of 67% has previously been reported for T790M positive patients [Soria 2014]. Rociletinib (CO-1686) is a novel, oral, irreversible TKI with activity against the activating mutations, L858R and Del19, plus the dominant acquired resistance mutation, T790M, but not against wild-type EGFR.

The subgroup comprised 170 patients with a history of CNS disease that was stable and asymptomatic; patients developing progressive disease (PD) while on rociletinib were allowed to continue, if deemed clinically beneficial by the investigator. The primary endpoint was RECIST overall response rate (ORR).

As of 16 March 2015, a total of 401 patients had received therapeutic dose levels of rociletinib (500, 625 and 750 mg BID) including 170 patients in the CNS disease subgroup, who showed a RECIST response rate of 41%. Among these patients, 42 have continued rociletinib post-progression. Patients continuing rociletinib for at least 14 days post progression demonstrated average treatment duration beyond PD of 89 days (range: 14 to 336 days). In this cohort, 22 patients also received brain radiation and continued rociletinib treatment (held on radiation days only) for an average of 120 days (range: 22 to 336 days) after PD.

The cohort of patients with a history of CNS disease showed a similar safety profile to the overall TIGER-X patient population, with hyperglycemia, diarrhoea and nausea reported most commonly. Additional efficacy data are not yet mature for this subgroup. Varga *et al.* Abstract 3009.

### Practice point and future research opportunities

Rociletinib has demonstrated activity by RESIST and has safely been administered in patients with a history of CNS disease, which is associated with a poorer prognosis. Continued rociletinib use after disease progression and CNS radiation suggests an ongoing systemic benefit to these patients. The role of rociletinib in NSCLC patients with CNS involvement will be further evaluated in the ongoing TIGER clinical development programme. Data from the TIGER-X and TIGER-2 trials supported an application to the European Medicines Agency for patients with pretreated EGFR T790M-mutant NSCLC, which was granted an accelerated assessment. The US FDA granted Breakthrough Therapy designation for rociletinib as treatment for mutant NSCLC in patients with the T790M mutation after progression on EGFR-directed therapy in 2015; the New Drug Application is set for review by the Oncologic Drugs Advisory Committee in 2016.

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## AFFILIATION AND DISCLOSURE

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### Disclosure

No conflicts of interest to disclose.

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