

1. Biomarker-driven access to vemurafenib in BRAF-positive cancers: Second study of the French National AcSé Program.

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Background: Vemurafenib (V) is registered in monotherapy for the treatment of adult patients (pts) with BRAF V600 mutation (mut) unresectable or metastatic melanoma but responses were observed in other tumor types. To avoid off-label use and allow for a nationwide safe access to V for pts with BRAF mut, the French National Cancer Institute (INCa) launched the AcSé V program, funding both access to molecular diagnosis in the 28 INCa molecular genetic centers and an exploratory phase II trial testing V in pts with BRAF mut tumors. AcSé V was launched following the AcSé crizotinib study. **Methods:** BRAF mut identification is proposed to pts with advanced cancers including lung, ovarian, bladder, thyroid, prostatic cancers; cholangiocarcinoma, sarcoma/GIST, multiple myeloma, Chronic Lymphocytic Leukemia (CLL) and Hairy Cell Leukemia (HCL), all known from literature to harbor this mut. If not eligible to another academic or industry trial targeting the same mut, a pt with BRAF V600 mut may be included in the appropriate pathology cohort to receive V 960 mg BID. Pts with BRAF non-V600 mut (on exon 11 or 15) or other BRAF alteration identified through a pangenomic tumor profile are also eligible in a miscellaneous cohort. Emerging new data are examined by a steering committee who may propose to open additional cohorts. Objective Response (OR) is evaluated every 8 weeks using RECIST V1.1 for solid tumors and appropriate criteria for myeloma, CLL and HCL. A Bayesian approach allows continuous monitoring of the OR. Sequential analyses are performed in each cohort to allow early stopping using an inefficacy bound for OR of 10% until a maximum sample size of 30 to 50 pts (efficacy bound at the end of the study: 30%). From Oct. 2014 to Jan. 2016, 70 pts out of > 1200 screened were included. A dermatological monitoring has been established with regular consultations carried out by dermatologists belonging to the network of the Skin Cancer Group from the French Society of Dermatology. Moreover 3 specialists have been appointed by the Group to provide expertise and advice on the management of BRAF inhibitors specific skin toxicities. Around 3,000 molecular tests and up to 500 pts treated in 150 centers are planned over 3 years.

2. Analysis of medical practices for French patients with BRAF mutant metastatic colorectal cancer.

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Background: BRAF V600E mutations are rare in metastatic colorectal cancers (mCRC). Recent results showed that BRAF mutant tumors usually have a poor prognosis, resist to anti-EGFR treatment and may be more sensitive to a bevacizumab plus chemotherapy (CT) triplet combination. **Methods:** We retrospectively reviewed 153 consecutive patients' files with BRAF mutated mCRC treated in 9 French Cancer Centers between May 2004 and November 2014. We report here the first results on clinical and biological features, treatment received and progression-free and overall survival. **Results:** There were 78 women and 75 men with a median age of 65 years [range 30-90]. In 15% of cases, patients (pts) had familial history of CRC. Primary tumor was most frequently localized in the right colon (54%). Peritoneum was the third most-frequent metastatic site (32%), after liver and lung (respectively 62% and 37%). Almost all pts had V600E BRAF mutation, and only one had a G596R mutation. MMR status was lacking for 65 pts (42.5%) and 15 (10%) of the BRAF mutant tumors exhibited a deficient MMR status (microsatellite instability). 142 pts (92.8%) received a 1st line chemotherapy, based on oxaliplatin in 82 (57.7%), irinotecan in 29 (20.4%) and 5FU only in 15 pts (10.5%). Only 11 pts (7.7%) received folfinirinox first-line chemotherapy. 52 pts (36.6%) received an antiangiogenic (bevacizumab) including 4 with folfinirinox. 14 (9.8%) received an anti-EGFR therapy. The 1st line chemotherapy was usually stopped because of tumor progression in 37% but also for chemotherapy holidays (33%). The median PFS in first line setting was 5.4 months, CI95% [4.1-6.7]. Only 99 patients (65%) initiated second-line chemotherapy and 62 (41%) a third-line. 12 patients (8%) had a secondary resection of liver metastases. **Conclusions:** BRAF mutant represent a distinct molecular subset of mCRC and an early identification could allow a more adequate management. In 1st line, few of them receive a triplet CT plus bevacizumab combination in clinical practice. Clinical guidelines and prospective clinical trials with innovative chemotherapy regimens and/or targeted treatment are strongly needed.

3. Updated survival and biomarker analyses of a randomized phase II study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR).

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Background: Atezolizumab (atezo, MPDL3280A), a humanized engineered mAb, is the first anti-PD-L1 agent to show improved OS vs docetaxel (doc) in NSCLC. These results correlate with PD-L1 expression on tumor cells (TC) and/or tumor-infiltrating immune cells (IC) and have shown improvement over time as reflected by the continued late separation of OS curves. **Methods:** Pts were randomized to receive atezo 1200 mg IV q3w or doc 75 mg/m² IV q3w. Tumors were prospectively evaluated for PD-L1 expression using the SP142 IHC assay and scored from low to high (0-3). Gene expression was analyzed using a Fluidigm platform. The primary endpoint was OS and the primary analysis included 173 events among 287 randomized pts (event/patient ratio [EPR] 60%; min follow up 13 mo). Here we present data as of Dec 1, 2015 with a min follow up of 20 mo. **Results:** With longer follow up and 200 events (EPR 70%) further separation in survival curves and improvement in OS HR were seen for atezo over doc for ITT (HR 0.69, 95% CI 0.52-0.92) and across PD-L1 and histology subgroups

(Table). Longer mDOR was seen for atezo vs doc (18.6 vs 7.2 mo). Improved OS with atezo over doc correlated with high tumor expression of T_{eff}/IFN γ -associated genes (unstratified HR 0.52, 95% CI 0.32–0.83). Atezo continues to have a tolerable safety profile distinct from doc. **Conclusions:** Extended follow up reveals further separation late in OS curves and increased benefit with atezo monotherapy vs doc. Relative to the primary analysis, OS benefit is improved in ITT and PD-L1 subgroups, including TC0 and IC0, and in pts with squamous NSCLC. In addition, PD-L1 expression measured by IHC and the tumor T_{eff}/IFN γ gene signature, which reflects pre-existing immunity, can identify pts most likely to benefit from atezo.

4. Avelumab (MSB0010718C; anti-PD-L1) + best supportive care (BSC) vs BSC $\pm$ chemotherapy as third-line treatment for patients with unresectable, recurrent, or metastatic gastric cancer: The phase 3 JAVELIN Gastric 300 trial.

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Background: Programmed death-1 receptor ligand (PD-L1) is a key therapeutic target in the reactivation of the immune response against multiple cancers. Avelumab* is a fully human anti-PD-L1 IgG1 antibody that has shown promising efficacy and an acceptable safety profile in multiple tumor types, including adenocarcinoma of the stomach or gastroesophageal junction (AS/GEJ). This open-label phase 3 trial (NCT02625623) compares avelumab + best supportive care (BSC) vs BSC $\pm$ chemotherapy as third-line treatment for patients (pts) with AS/GEJ. **Methods:** The primary objective of this global, multicenter trial is to demonstrate superiority, defined by overall survival, of avelumab + BSC vs BSC $\pm$ chemotherapy. Approximately 330 pts stratified by region (Asia vs non-Asia) will be randomized. Main eligibility criteria include: histologically confirmed unresectable locally advanced or metastatic AS/GEJ, fresh or archival tumor tissue for PD-L1 expression assessment, ECOG PS 0-1, 2 prior lines of systemic treatment, no prior therapy with any drug targeting T cell coregulatory proteins, and no concurrent anticancer treatment or immunosuppressive agents. Pts are not preselected for PD-L1 expression. Pts receive either BSC with avelumab 10 mg/kg as a 1h intravenous infusion Q2W or BSC $\pm$ chemotherapy (physician's choice of irinotecan 150 mg/m² Q2W or paclitaxel 80 mg/m² weekly for 3 out of 4 weeks, in a 4-week treatment cycle for pts eligible to receive chemotherapy). Pts not eligible for chemotherapy will receive BSC only. Treatment is given until disease progression, unacceptable toxicity, or consent withdrawal. Secondary endpoints include progression-free survival, objective response rate, quality of life (assessed via EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22), safety as per NCI-CTCAE v4.03, and tumor biomarkers. Responses are evaluated according to RECIST 1.1 and adjudicated by a blinded independent review committee. Trial enrollment began in Dec 2015. *Proposed INN.

5. FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—Prodige 14 – ACCORD 21 (METHEP-2), a unicancer GI trial.

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Background: Liver metastases (LM) from colorectal cancer (CRC) are initially resectable in only 10-15% of patients (pts). The conversion to resectability following induction chemotherapy is an important strategy to increase survival. Our study was designed to determine the most appropriate chemotherapy (associated with a targeted therapy) for CRC pts with LM considered as initially unresectable. **Methods:** This French phase II, multicenter, prospective trial, randomized pts between bi-chemotherapy (BiCT) versus tri-chemotherapy (TriCT). The population was initially stratified by targeted therapy depending on KRAS status and then by RAS status (from 02 Dec 2013 due to the change in cetuximab's [Cet] marketing authorization): Cet for wt(K)RAS pts and bevacizumab (Bev) for mtRAS pts. The hypothesis was to increase the rate of LM resection (R0-R1) from 50% with BiCT to 70% with TriCT (bilateral α -test 5%; power 90%). **Results:** 256 patients were randomized in 33 sites from February 2011 till April 2015: 126 BiCT (FOLFIRI [56 pts]; FOLFOX4 [70 pts]) and 130 TriCT (FOLFIRINOX). The resection rate (R0 or R1; CI95%) of the LM was 45.2% [36; 54] for pts treated with BiCT vs 56.9% [48; 66] for TriCT ($p = 0.062$). The LM resection rate (R0 or R1; CI95%) was 44.7% [35; 55] for pts treated with Bev (mtRAS) vs 55.6% [47; 64] for Cet (wtRAS) ($p = 0.087$). At the time of data analysis, the median follow-up (CI95%) was 22.5 months [19.6; 29.5] for the BiCT pts and 23.5 months [19.8; 28.8] for the TriCT pts and at analysis 78 patients had died. The median overall survival (OS) is significantly different ($p = 0.048$): in the TriCT Arm the median OS was not reached and is 36 months [23.5; 40.6] in the BiCT Arm. The severe toxicity rate was 37.6% for BiCT vs 41.7% for TriCT ($p = 0.503$). 38 BiCT pts and 34 TriCT pts had surgical complications, with two deaths in each arm. **Conclusions:** First line FOLFIRINOX chemotherapy, in association with a targeted therapy, showed a higher rate of LM R0/R1 resections than standard BiCT (FOLFIRI or FOLFOX4) combined with the same targeted therapy, with a statistically significant difference in terms of OS.

6. An open-label phase II trial of dabrafenib (D) in combination with trametinib (T) in patients (pts) with previously treated *BRAF* V600E-mutant advanced non-small cell lung cancer (NSCLC; BRF113928).

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Background: *BRAF* V600E mutations occur in 1% to 2% of lung adenocarcinomas and act as an oncogenic driver. The *BRAF* inhibitor D has demonstrated clinical activity (33% overall response rate [ORR], with a median progression-free survival [PFS] of 5.5 months as monotherapy in 78 previously treated pts with metastatic *BRAF*V600E–mutant NSCLC (cohort A). The combination of D + T has demonstrated significant improvements in efficacy vs *BRAF* inhibitor monotherapy in *BRAF* V600–mutant metastatic melanoma. Here, the primary analysis of pts with NSCLC who experienced failure of ≥ 1 prior platinum-based therapy for advanced disease and were treated with combination D + T is presented (cohort B). **Methods:** This is a multicohort, sequentially enrolled phase 2 trial in pts with metastatic *BRAF* V600E–mutant NSCLC. The primary endpoint was investigator-assessed ORR according to RECIST v1.1. Secondary efficacy endpoints included PFS and duration of response [DOR]. D was dosed at 150 mg orally twice daily and T at 2 mg orally once daily. **Results:** Between December 2013 and January 2015, 57 pts received D + T as $\geq$ second-line treatment and were evaluable for response. Median age was 64 y (range, 41–88 y). Most pts were female (51%), white (86%), adenocarcinoma (95%), and current or former smokers (73%). All pts had nonsquamous histology. 22 pts (37%) remain on therapy, and 37 have stopped (28 with disease progression, 8 due to adverse events [AEs], 1 due to pt decision). 52 pts were evaluable for efficacy (confirmed response). The ORR was 63% (95% CI, 49%-75%), with a disease control rate (ORR + ≥ 12 weeks of stable disease) of 79% (95% CI, 66%-89%). The median PFS was 9.7 mo (95% CI, 6.9-19.6 mo) and the median DOR was 9.0 mo (95% CI, 6.9-18.3 mo). Of the pts with a confirmed response, 50% remained in response at the time of analysis. The most common AEs ($> 25\%$) included pyrexia, nausea, vomiting, diarrhea, asthenia, decreased appetite, and dry skin. **Conclusions:** D + T was highly efficacious in *BRAF*V600E–mutant NSCLC, with a manageable AE profile. This study is the first reported combination trial of a *BRAF* inhibitor and MEK inhibitor in *BRAF* V600E–mutant NSCLC.

7. Impact of early tumor response on prognostic of patients with unresectable liver metastases from wt-KRAS colorectal cancer (LM-CRC) treated with hepatic artery infusion of irinotecan, 5-fluorouracil and oxaliplatin plus intravenous cetuximab after failure of systemic chemotherapy (European Phase II OPTILIV).

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Background: Early tumor shrinkage has been associated with improved long-term outcome in patients (pts) with chemotherapy (chemo)-refractory LM-CRC. We examined the prognostic relevance of early tumor response after hepatic artery infusion of triplet chemotherapy combined with intravenous (IV) Cetuximab (Cet) in pts with unresectable LM-CRC. **Methods:** Pts received IV-Cet (500 mg/m²) and HAI of Irinotecan (180mg/m²), 5-Fluorouracil (2800 mg/m²), and Oxaliplatin (85mg/m²) every two weeks. Tumor response (RECIST) was based on CT scans ± MRI q3 courses. Pts were categorized as early-responders (CR or PR after 3 courses – at » 6 weeks), late responders (CR or PR > 3 courses) and non-responders (SD or PD). The rate of conversion to liver surgery (R0-R1), progression free survival (PFS) and overall survival (OS) were compared. **Results:** 57/64 registered pts (89%) received ≥ 3 courses. They were assessed for response, which occurred early for 16/57 pts (28%), late for 10 pts (17.5%) or not at all for 31 pts (54.4%). The early-responders had similarly extensive disease as the other pts (median of 12 LM, median largest diameter = 37 mm, bilateral LM for 81% pts). Grade 3-4 diarrhea and asthenia were least in the early responders (6.3% vs 22.0%, and 0% vs 26.8%, p = 0.024, respectively). R0-R1 resection rate was twice as high in the early response group as compared to the other group (7/16; 43.8% vs 10/41; 24.4%, p = 0.10). PFS curves did not differ. In contrast, median OS was significantly longer in the 16 early-responders - 34.5 months [32.1 -36.9] - as compared to both the 41 non-early responders - 20.2 [13.6 – 26.8]; p = 0.010; and the 10 late responders - 12.0 [6.9 -17.2]; p = 0.001. **Conclusions:** Best clinical tolerability, LM conversion-to-resection, and survival outcomes were obtained in pts achieving an early tumor response on combined triplet hepatic artery infusion and IV Cet. The rapid disease-modifying effect of HAI is an important asset for curative intent medico-surgical strategies, and awaits prospective confirmation.

8. Sorafenib (Soraf) and irinotecan (Iri) combination for pretreated RAS-mutated metastatic colorectal cancer (mCRC) patients: A multicentre randomized phase II trial (NEXIRI 2-PRODIGE 27).

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Background: Sorafenib and irinotecan combination (NEXIRI) showed promising efficacy with a 65% disease control rate (DCR) in pretreated mutated (mt) KRAS mCRC. In this single arm study, CCND1 rs9344 A/A polymorphism had a predictive value (Samalin et al. 2014). This multicentre randomized phase II trial aimed to determine the 2-month progression-free survival rate (2-PFS) of NEXIRI vs Iri or Soraf monotherapies in these patients (pts) after failure of all approved active drugs at the time of the study. **Methods:** Pts PS ≤ 1 with

progressive non-resectable mtKRAS (then RAS) mCRC pretreated with irinotecan, oxaliplatin, fluoropyrimidines and bevacizumab (none with regorafenib), were randomized in 3 arms: NEXIRI (biweekly Iri IV 120, 150, 180mg/m² at C3 combined with a fixed dose of Soraf 400mg twice daily) vs Iri (180mg/m²) alone vs Soraf alone, until progression or toxicity, with cross-over to NEXIRI at progression. Primary endpoint was the 2-PFS (RECIST v1.1). Pharmacokinetic, pharmacogenetics and pathologic translational studies were undertaken. **Results:** We included 173 pts (age 62 [31-82]; PS 0/1: 38/61%) between 2012 and 2014 in 17 French centres. Main results were (median follow-up 17.5 months): See table. **Conclusions:** We confirmed the NEXIRI regimen efficacy in a randomized study for refractory mtRAS mCRC pts. CCND1 rs9344 may identify patients who benefit from this combination. These results justify comparing NEXIRI to Regorafenib or TAS 102 monotherapies in CCND1 rs9344 A/A pts subgroup. Other results from ancillary studies will be presented at the meeting.

9. REMINET: A European, multicentre, PHASE II/III randomized double-blind, placebo-controlled study evaluating lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours.

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Background: Patients (pts) with metastatic or locally advanced, non-resectable, Well-Differentiated Duodeno-Pancreatic (WDDP) NETs are treated following European guidelines. Pts with more aggressive disease, i.e. progressive and/or symptomatic metastases, significant hepatic invasion (> 30-50%), and/or bone metastases, combination chemotherapy is considered; otherwise biotherapy (everolimus or sunitinib) is an option. The recommendations are to stop chemotherapy once disease control is obtained. The concept of maintenance therapy is well established in several cancer types. In this study we will evaluate the role of a somatostatin analogue (LAN) as maintenance in patients with stable/responding disease after 1L therapy (which may have been interrupted for tolerability issues) until progression. Somatostatin analogues are well tolerated and have demonstrated anti-proliferative effect making them ideal candidates for maintenance therapy. **Methods:** REMINET is an academic randomized, double-blind, placebo-controlled, phase II/III study. A total of 222 adults patients pts with a metastatic (synchronous or metachronous) or locally advanced, non-resectable, grade 1 or 2 WDDP NETs (WHO 2010 classification; Ki-67 ≤ 20%) and documented stable disease or objective response after 1L therapy at least 4 weeks prior to randomization, will be enrolled and randomly assigned in a 1:1 ratio to receive 120 mg LAN or placebo, every 28 days, until disease progression or unacceptable toxicity. Stratification factors: Centre, Grade 1 vs. 2, 1L treatment (chemotherapy vs. biotherapy). The primary endpoint of the phase III part is Progression-Free Survival (PFS) assessed by the investigators (RECIST v1.1). The aim of the phase II part is to demonstrate a 6-months PFS > 45% in LAN arm. Main

secondary endpoints are PFS according to central review, overall survival, safety and quality of life. Frozen blood samples (-80°C) will be BioBanked for ancillary studies. The study is currently open in Europe. **Status:** A total of 13 patients are already randomized.

10. Non-classical response measured by immune-modified RECIST and post-progression treatment effects of atezolizumab in 2L/3L NSCLC: results from the randomized phase II study POPLAR.

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Background: Cancer immunotherapy (CIT) can induce unconventional response patterns due to tumor immune infiltration or delayed response, reducing the ability of RECIST-based endpoints to predict OS benefit. Atezolizumab (atezo; MPDL3280A) demonstrated OS benefit compared with docetaxel (doc) in the ITT population of 2L/3L NSCLC patients (pts) in the POPLAR primary analysis (HR, 0.73; mOS 12.6 mo for atezo vs 9.7 mo for doc). However, PFS and ORR improvement was restricted to pts with high PD-L1 expression, suggesting that many pts experience atezo benefit after classical radiographic progression. **Methods:** Advanced NSCLC pts were randomized to atezo 1200 mg IV q3w until loss of clinical benefit or doc 75 mg/m² IV q3w until PD per RECIST v1.1 (RECIST). The primary endpoint was OS. In addition to secondary endpoints of PFS and ORR per RECIST, atezo pts were evaluated per immune-modified RECIST (imRECIST) and for post-PD radiographic changes. Both arms were evaluated for OS post PD (data cutoff, May 8, 2015; median follow up, 15 mo). **Results:** Of 287 pts, 144 were randomized to atezo. Among these pts, ORR per imRECIST vs RECIST was 17% and 15%, respectively; the rate of CR+PR+SD was 65% and 52%, respectively. mPFS was longer per imRECIST vs RECIST (4.2 vs 2.7 mo). Among 57 atezo arm pts continuing treatment post PD, 14% had subsequent ≥ 30% decrease in target lesions relative to baseline, and 33% had a change of +20% and -30%. mOS from the time of first RECIST PD was 11.1 mo for atezo arm pts continuing atezo post PD (n = 57) and 8.3 mo for atezo pts receiving different anti-cancer therapy post PD (n = 30). Doc arm pts receiving subsequent therapy post PD (n = 46) had mOS of 9.6 mo from the time of PD. **Conclusions:** ORR and PFS were increased in atezo pts per imRECIST vs RECIST, and 47% of pts continuing atezo after PD had subsequent stable/reduced target lesions relative to baseline. The mOS of 11.1 mo post PD for pts continuing atezo treatment is suggestive of atezo benefit following PD that contributes to the OS benefit vs doc in all-comer pts. These results also highlight the utility of imRECIST as response evaluation criteria to assess the efficacy of atezo/CIT.

11. Targeting RET in patients with *RET*-rearranged lung cancers: Results from a global registry.

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Background: Alongside prospective clinical trials for patients (pts) with non-small cell lung cancers (NSCLC) driven by rare genomic alterations, registries can provide complementary information on response to targeted therapies. We present the results of a global registry of *RET*-rearranged NSCLC, providing the largest data set on outcomes with *RET*-directed therapy so far. **Methods:** Pts were identified by a global, multicenter network of thoracic oncologists. IRB approval was obtained according to local requirements. Eligibility included a diagnosis of NSCLC harboring a *RET* fusion by FISH, RT-PCR or NGS. Anonymized data (age, gender, smoking, histology, stage, systemic therapy, survival) were collected centrally and evaluated by an independent statistician. In an analysis of pts treated off-protocol with multikinase inhibitors known to target *RET*, the primary endpoint was best objective response (RECIST). **Results:** 132 pts with *RET*-rearranged NSCLC from the USA, Asia, and Europe were registered. Median age at diagnosis was 61 years (range: 28-89), 52% were female, 62% were never-smokers, 97% had adenocarcinoma, and 91% had stage III/IV disease. 41 pts (31%) received *RET* inhibitor therapy off-protocol: cabozantinib (14), vandetanib (11), sunitinib (10), sorafenib (2), alectinib (1), lenvatinib (1), nintedanib (1), and ponatinib (1). Most pts received a *RET* inhibitor in the third-line setting (range: 1st-8th line). Median PFS was 2.9 months (95%CI: 1.3-5.6), OS 6.8 months (95%CI: 3.9-14.3), median duration of therapy 2.2 months (range: 0.5-12.2). 8 pts remain on treatment. In 35 pts with serial imaging evaluated by RECIST, ORR was 23% (1 CR, 7 PR, 12 SD, 14 PD, 1 not measurable) and DCR 57%. Individual ORR (DCR) for cabozantinib and vandetanib was 31% (62%) and 18% (46%), respectively. No unexpected adverse effects were reported. **Conclusions:** *RET* inhibitors are active in a proportion of pts with *RET*-rearranged NSCLC. Consistent with results from an ongoing phase II trial of cabozantinib (Drilon, ASCO 2015), this proportion is lower than that observed with targeted therapy for *EGFR*-mutant and *ALK*-rearranged NSCLC. New therapeutic approaches and an improved understanding of tumor biology and response are needed.