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**Timing of responses to crizotinib (PF-02341066) in anaplastic lymphoma kinase (ALK)-positive patients with advanced non-small cell lung cancer (NSCLC)**

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**Background:** Crizotinib is a selective, ATP-competitive, orally bioavailable inhibitor of ALK. Patients with advanced NSCLC positive for an *ALK* fusion gene were enrolled to characterise the clinical activity and safety in this molecularly defined patient population.
**Methods:** Patients with *ALK*-positive advanced NSCLC, as determined using a FISH break-apart probe to *ALK,* were enrolled regardless of their number of prior therapies. Treated brain metastases were allowed. Crizotinib was administered orally at a dose of 250 mg BID. Responses were determined using RECIST v1.0 with radiographic studies planned every 8 weeks.
**Results:** In total, 82 patients with *ALK*-positive advanced NSCLC have been treated (as of April 7, 2010) and were evaluable for response; objective response rate was 57% (47/82) and disease control rate was 87% at 8 weeks. Responses occurred quickly, with the majority (74%) documented by 12 weeks and with the fastest within 30 days (Table). FLT PET responses were noted as early as 4 weeks.

| Time to response | n (%) [N = 47] |
|---|---|
| <8 weeks | 21 (44.7) |
| 8–<12 weeks | 14 (29.8) |
| 12–<16 weeks | 4 (8.5) |
| 16–<20 weeks | 4 (8.5) |
| 20–<24 weeks | 2 (4.3) |
| 24–<28 weeks | 1 (2.1) |
| 28–<32 weeks | 0 |
| ⩾32 weeks | 1 (2.1) |

In this ongoing study, most patients (70%) remain in follow-up for progression-free survival (PFS). Median follow-up for PFS was 6.4 months (95% CI: 3.5, 10); however, median PFS has not been reached. The estimated probability of PFS at 6 months was 72% (95% CI: 61, 83). New lesions at progression included liver, brain, lung, lymph nodes and pleura, with liver the most common. Gastrointestinal toxicities, including nausea (54%), diarrhoea (48%) and vomiting (44%) were the most frequent adverse events, with the majority being mild or moderate. Data on improvement or resolution of baseline adverse events such as dyspnoea will be presented.
**Conclusions:** The majority of patients with *ALK*-positive advanced NSCLC had some degree of tumour shrinkage or disease stabilisation. Response to crizotinib occurred rapidly, with most responses by 12 weeks. Crizotinib was associated with a good safety profile. Based on the response rate and preliminary PFS, crizotinib has the potential to become a new standard of care for patients with *ALK*-positive NSCLC.

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**A phase Ib study of escalating doses of Vascular Endothelial Growth Factor (VEGF) tyrosine kinase inhibitor Tivozanib and FOLFOX6 in patients with advanced gastrointestinal (GI) tumors**

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**Background:** Tivozanib (AV-951), a highly potent and selective tyrosine kinase inhibitor of all three VEGF receptors, has shown additive antitumor activity with 5-FU in preclinical studies. A phase 1b study was conducted to determine maximum tolerated dose (MTD), Dose-Limiting Toxicities (DLTs), PK and anti-tumor activity of escalating doses of Tivozanib and standard dose FOLFOX6 in patients (pts) with advanced GI tumors.
**Methods:** Tivozanib was administered orally once daily for 21 days in 28-day cycles, with FOLFOX6 administered every 14 days. Pts were allowed to continue Tivozanib following discontinuation of FOLFOX6.
**Results:** 20 pts (M/F 13/7), median age 58 y (40–75), were enrolled in cohorts of Tivozanib 0.5 mg (n = 9), 1.0 mg (n = 3) and 1.5 mg (n = 8). Pts received a median of 7.6 weeks (range 0.1–27.9 weeks) of FOLFOX6 and 7.7 weeks (range 0.1–43.1 weeks) of Tivozanib DLT consisted of one episode of reversible grade 4 transaminases at Tivozanib 0.5 mg and one episode of reversible grade 3 vertigo at Tivozanib 1.5 mg. Other grade 3/4 drug related adverse events (AEs) included hypertension and neutropenia. There was no indication that drug related AEs of this combination were more frequent or severe than those observed with FOLFOX6 or Tivozanib alone. The PK profiles of 5FU, oxaliplatin and Tivozanib will be presented.Partial responses were observed in pts with pancreatic and esophageal cancers. Additional safety and efficacy data are being obtained in 10 pts at the recommended dose of Tivozanib 1.5 mg.
**Conclusion:** The combination of Tivozanib and FOLFOX6 is feasible and safe with Tivozanib given at its recommended dose of 1.5 mg. Observed clinical activity merits further exploration in several GI tumors, and these studies are being planned.

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**Phase 2 randomized discontinuation trial (RDT) of XL184 in patients (pts) with advanced solid tumors**

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**Background:** XL184 is an oral, potent inhibitor of MET, VEGFR2 and RET that exhibits anti-tumor and anti-angiogenic activity in preclinical tumor models. An ongoing Phase 2, double blind, placebo controlled RDT is evaluating the clinical efficacy and safety of XL184 in nine tumor types: breast (B), gastric/GEJ (G), non-small cell lung (NS), ovarian (O), pancreatic (PA), prostate (P), small cell lung (S) cancer, hepatocellular carcinoma (H) and melanoma (M). Indications were selected based on the role of MET and VEGFR2 in tumor biology.
**Methods:** Approximately 600 pts will be enrolled to receive open-label XL184 at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response per mRECIST is assessed every 6 wks. Pts with partial or complete response (PR or CR) at week (wk) 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with stable disease (SD) at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. Pharmacokinetics of XL184 will be analyzed by tumor type.
**Results:** A total of 198 pts have been enrolled. Evidence of tumor regression was observed in multiple tumor types. Most frequently observed adverse events regardless of causality (all grades, Grade ⩾3) include: fatigue (29%, 4%); diarrhea (28%, 4%); nausea (24%, 2%); decreased appetite (21%, 1%); vomiting (14%, 3%); hypertension (13%, 3%); rash (12%, 1%); dysphonia (12%, 0%); constipation (11%, 1%); abdominal pain (10%, 2%); and dysgeusia (10%, 0%). The dose reduction rate for pts on study for at least 6 wks was 26%. Six pts achieved a confirmed PR (2 H, 2 NS, 1 M, 1 P) and 3 pts an unconfirmed PR (3 O) in the Lead-in Stage. Of the 105 pts who were evaluable (minimum 12 wks follow up) to date, 43 pts achieved SD and were randomized (11 M, 8 NS, 5 H, 5 PA, 5 P, 4 G, 4 O, 1 S). The overall disease control rates at wk 12 were 88% (7 out of 8 evaluable pts) in H, 86% (6/7) in O, 67% (6/9) in P, 50% (12/24) in M, and 50% (10/20) in NS. Ten pts crossed over to XL184 upon PD while on placebo in the Randomized Stage. No results are currently available for the breast cancer cohort.
**Conclusions:** Preliminary results indicate that XL184 is active in multiple solid tumor types and is generally well tolerated. Updated efficacy and safety results will be presented.