MA11 EXPANDING TARGETABLE GENETIC ALTERATIONS IN NSCLC
IASLC 2020 World Conference on Lung Cancer, Singapore.

MA11.07 Phase 1/2 TRIDENT-1 Study of Repotrectinib in Patients with ROS1+ or NTRK+
Advanced Solid Tumors

INTRODUCTION:
Repotrectinib is a next-generation ROS1/TRK TKI with >90-fold greater potency than crizotinib and entrectinib against ROS1 and >100-fold greater potency than larotrectinib against TRK in engineered Ba/F3 cell proliferation assays. In the Phase 1 portion of TRIDENT-1 study, repotrectinib demonstrated encouraging overall clinical activity in patients (pts) with ROS1 fusion+ NSCLC and TRK fusion+ solid tumors, especially in those pts with ROS1+ NSCLC who are TKI naive.

METHODS:
In Phase 1 portion of the study, the Recommended Phase 2 Dose (RP2D) for repotrectinib was determined to be 160 mg QD for 14 days followed by 160 mg BID if tolerated. Currently, this global trial (Clinical trial information: NCT03093116) is actively enrolling pts whose cancers harbor a ROS1 or NTRK1/2/3 fusion in six phase 2 expansion cohorts (see table). The primary endpoint for the Phase 2 portion is confirmed overall response rate (cORR) by Blinded Independent Central Review (BICR) using RECIST v1.1. An early interim analysis on 39 pts enrolled in Phase 2 was conducted using investigator assessment.

RESULTS:
Phase 1: Utilizing a 22 July 2019 data cutoff, cORR was 91% by BICR in 11 ROS1 TKI-naïve pts with 5 responses ongoing. The median duration of response (DOR) for the 10 confirmed responders was 23.1 months (95% CI: 5.6–not reached [NR]) and median progression-free survival (PFS) was 24.6 months (95% CI: 7.2 – NR). As of 6 April 2020, with an additional 8.5 months of follow-up, 4 of the 5 previously responding TKI-naive pts remained in a partial response (PR) per physician assessment data and 7 TKI-naive pts remained on treatment, range (17.3+ - 34.2+ months). Phase 2: The early Phase 2 TRIDENT-1 dataset utilizing a July 10, 2020 data cutoff includes the first 39 treated pts across six cohorts who have had at least one post-baseline scan. Data are summarized in table below:

Repotrectinib was well tolerated, with predominantly grades 1/2 adverse events. TEAEs in >25 % of pts were dizziness (62%), fatigue (39%), constipation (33%), dysgeusia (33%), and dyspnea (28%). 90% of 39 treated pts in Phase 2 escalated to 160 mg twice daily (BID) after 14 days per the study defined dose titration approach. There were no Grade 4 or Grade 5 TRAEs.

CONCLUSION:
Repotrectinib was well tolerated and continues to demonstrate encouraging overall clinical activity in pts with ROS1 fusion-positive NSCLC and TRK fusion-positive solid tumors.

P09 HEALTH SERVICES RESEARCH/HEALTH ECONOMICS - REAL WORLD OUTCOMES
IASLC 2020 World Conference on Lung Cancer, Singapore.

P09.53 Comparative Effectiveness of Crizotinib versus Entrectinib in ROS1+ Non-Small
Cell Lung Cancer (NSCLC) using Clinical Trial and Real-World Data

INTRODUCTION:
Crizotinib and entrectinib are licensed for treating ROS1+ advanced NSCLC.No head-to-head studies of crizotinib versus entrectinib exist; however, a prior analysis compared entrectinib clinical trial clinical trial outcomes to crizotinib real-world data (RWD). Here, we compared the antitumor activity of entrectinib and crizotinib in clinical trial populations and different crizotinib RWD sources.

METHODS:
PROFILE 1001 (crizotinib), and the integrated analysis of ALKA-372-001, STARTRK-1, and STARTRK-2 (entrectinib) were deemed feasible for indirect treatment comparison (ITC). Simulated treatment comparisons (STC) were performed adjusting mutually reported baseline characteristics (BLC) to simulate the conditional mean adjusting BLC’s in PROFILE 1001 to those reported in the entrectinib studies. BLCs imbalanced between studies and included in the stepwise STC model were: age, sex, ethnicity, ECOG performance status, and smoking status. CNS metastatic status was not available to address across all studies. Outcomes analyzed included progression free survival (PFS),
12-month overall survival (OS12), objective response rate (ORR), and duration of response (DOR). A naïve comparison with crizotinib RWD from Flatiron and US Oncology/McKesson was conducted to evaluate the generalizability of the RWD outcomes to clinical trial cohort; at the time of analysis entrectinib RWD were unavailable.

RESULTS:
Median PFS of crizotinib (n=53) versus entrectinib (n=53) showed an adjusted STC mean difference (MD) of 2.15 months (95% CI: -16.78, 17.38) favoring crizotinib. Adjusted OS12 risk ratio (RR) was 1.08 (95% CI: 0.87, 1.41) favoring crizotinib. Adjusted ORR was RR=0.90 (95% CI: 0.74, 1.16) favoring entrectinib. Median DOR showed a MD of 4.18 months (95% CI: -18.96, 19.16) favoring crizotinib. Imbalances were observed between crizotinib clinical data versus RWD for the same BLC as for crizotinib clinical data versus entrectinib clinical data (Table). Both a shorter median real-world PFS and OS were observed among crizotinib RWD versus crizotinib clinical data; RWD source influenced outcomes.

CONCLUSION:
While the STC analysis between crizotinib and entrectinib trials suggest numerical superiority for crizotinib in PFS, OS, and DOR and for entrectinib in ORR, these differences were not statistically significant. Limited sample size and data-gaps concealing relevant possible imbalances such as in baseline CNS represent major limitations of this approach. Comparisons to RWD may also have relevant data-gaps impacting balance, but RWD outcomes appear worse than trial datasets, limiting the usefulness of RWD as an artificial control arm versus trial data. In the future, a more accurate comparison using balanced RWD for both entrectinib and crizotinib is needed to draw firmer inferences.

ES28 TARGETING KRAS
IASLC 2020 World Conference on Lung Cancer, Singapore.

ES28.01 Biology of KRAS Targeting Agents
T. Mitsudomi

KRAS biology 1-3
KRAS gene encodes for a 21kDa protein that toggles GDP-bound inactive conformation to and from GTP-bound active conformation. When RAS receives an upstream signal from receptor tyrosine kinases via guanine nucleotide-exchange factors (GEFs), GDP of inactive RAS is exchanged with GTP, resulting in an inactive form of RAS, which activates downstream pathways. GTP-bound RAS returns to GDP-bound RAS by its intrinsic GTPase activity. These processes are called as “RAS cycle.” GTPase activating proteins (RAS-GAPs, NF1) bind to active RAS and stimulate their GTPase activity by several magnitude orders. Mutations at codons 12, 13, and 61 of RAS disrupt GAP-mediated GTP hydrolysis. It is known that active RAS interacts with at least 20 effector proteins and stimulates downstream signaling cascades. Among them, RAF proteins activate the MAPK/ERK pathway resulting in cell proliferation. RalGDS activates small GTPases RalA and RalB that mediate cell transformation and cytoskeletal reorganization. PI3Ks activate the Akt family that plays a vital role in I cell survival, growth, and migration. The Association of RAS proteins with the membrane is essential for activating downstream signaling. This process includes farnesylation, proteolytic cleavage of the CAAX motif, carboxymethylation of the terminal Cys, and palmitoylation. RAS gene activation in lung cancer KRAS mutations usually occur in adenocarcinoma, especially with mucus production/goblet cell morphology. They are more frequent in Caucasians (~30%) than East Asians (~10%) and are associated with smoking exposure. KRAS mutation in lung cancer is characterized by the frequent a G to a T transversion in contrast to the frequent a G to an A transition in colorectal cancer. There are at least six amino acid substitutions in KRAS mutation at codon 12. Mutant KRAS, in general, has weaker GTPase activity; however, G12C has near wild type GTPase activity despite its reduced GAP mediated hydrolysis. In contrast, KRAS G13D has elevated intrinsic nucleotide exchange activity. Besides, KRAS subclassification according to co-mutation of
LKB1 (the KL subgroup), TP53(KP), and CDKN2A/B with low TTF1 (KC) has been proposed, which reflect different biology, patterns of immune-system engagement, and therapeutic vulnerabilities. The prognostic impact of KRAS mutations in lung cancer is variably reported, but in general, it is thought to be a weak negative prognostic factor. How to target KRAS mutated lung cancer It appears that not all cancers with KRAS mutations are dependent on mutant KRAS. Upon treatment of shRNAs to deplete KRAS in lung cancer cell lines harboring KRAS mutations, cell lines with mesenchymal differentiation maintain viability without expressing KRAS. This makes it challenging to develop a treatment strategy against KRAS mutated tumors. The early efforts to make RAS a druggable target include inhibition of membrane binding of RAS. This process is complicated involving several molecules such as farnesyl transferase (FT), geranylgeranyl transferase (GGT), ras-converting enzyme (RCE1), isoensysteine carboxyl methyltransferase (ICMT) and also varies depending on different RAS molecules (HRAS, KRAS 4a, 4b (two KRAS isoforms), NARAS). With inhibition of FT, KRAS but not HRAS could be alternatively prenylated by GGT. Salarisib, farnesyl thiosalicylic acid, inhibits prenylated protein methyltransferase (PPMTase) with potent in vitro activity, including against KRAS; however, failed in a phase II trial. Although RAF-MEK-ERK signaling is an essential downstream pathway of RAS, RAF or MEK inhibitors have been evaluated. For example, the phase 3 trial of MEK inhibitor selumetinib did not show its benefit. This is partly because inhibition of MEK relieves negative feedback from ERK at multiple MAPK signaling levels, leading to re-activation of this pathway. There have been efforts to identify synthetic lethal interactions in cancer cells with KRAS mutation. In other words, it is to find which genes, when silenced by siRNA, kill cells harboring mutant RAS gene but not cells without this mutation. The list of genes with synthetic lethal activity against RAS mutated tumors are expandimgand include THOC1, eNOS, Myc, Survivin, STK33, PLK1, SYK, RON, integrin b6, TBK1, NFKb, WT1, PKC delta, CDK4, JNK, ATR, GATA2, CDK4. Based on these experiments, abemaciclib, a CDK4/6 inhibitor, plus erlotinib was compared with erlotinib in patients with KRAS mutation in a phase III trial. Although PFS and ORR were improved, the primary endpoint of OS was not met. Attempt to directly compete with GTP as in the case of receptor tyrosine kinase inhibition is difficult because of the very high affinity between RAS and GTP. Recently, KRASG12C inhibitors bind covalently to the mutant cysteine residue and occupy a pocket in the switch II region of GDP -bound KRAS. Early results of clinical trials are promising. Other approaches include inhibitors of SOS1-RAS interaction, inhibition of SHP2 (SH2 containing phosphatase 2) that activates RAS-MAPK pathway, immunotherapy targeting mutant KRAS. The RAS targeted therapy has been challenging because 1) there are many RAS-like G proteins in human, 2) not all RAS-mutated tumors are addicted to mutated RAS, 3) pathways involving RAS is extremely complicated and redundant, including feedback loops 4) Different RAS mutations have the different conformation and different biochemical consequences. In this talk, I would like to summarize the RAS activation basics in lung cancer and RAS-targeted drug development history. 1. Simanshu DK, et al.: Cell 170:17-33, 2017 2. Friedlaender A, et al.: Cancer Treat Rev 85:101978, 2020 3. Moore AR, et al.: Nat Rev Drug Discov 19:533-552, 2020 4. Erijman A, et al.: Mini Rev Med Chem 16:370-5, 2016 5. Kobayashi T, et al.: Lancet Oncol 20:2018 6. Goldman JW, et al.: Front Oncol 10:578756, 2020

MA11 EXPANDING TARGETABLE GENETIC ALTERATIONS IN NSCLC IASLC 2020 World Conference on Lung Cancer, Singapore.

MA11.09 Efficacy and Safety of Larotrectinib in Patients with Tropomyosin Receptor Kinase (TRK) Fusion Lung Cancer


INTRODUCTION:
Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers that occur in a wide range of tumor types. Larotrectinib, a highly selective Food and Drug Administration and European Medicines Agency approved TRK inhibitor, demonstrated an objective response rate (ORR) of 79% and a median duration of response (DoR) of 35 months across multiple cancers (Hong et al. Lancet Oncol 2020). Here we report updated data for patients with TRK fusion lung cancer assessed by independent review committee (IRC) and investigators (INV).

METHODS:
Patients with lung cancer harboring an NTRK gene fusion enrolled in two clinical trials (NCT02122913 and NCT02576431) were included in this analysis. Larotrectinib 100 mg twice daily was administered on a continuous 28-day schedule. Response was assessed by IRC and by INV per RECIST v1.1.

RESULTS:
As of July 15, 2019, 14 patients with metastatic TRK fusion lung cancer were enrolled: 13 with non-small cell lung cancer (NSCLC) and 1 patient with small cell lung cancer (SCLC). Seven (6 NSCLC, 1 SCLC) patients had baseline central nervous system (CNS) metastases. The median age was 52 years (range 25–76). Eleven patients (79%) had fusions involving NTRK1 and three patients (21%) had fusions involving NTRK3. Patients were heavily pre-treated with a median of three prior therapies (range 1–5). Among 13 IRC-evaluable patients the ORR was 77% (95% confidence interval [CI] 46–95). ORR was 71% (95% CI 42–92) per INV. ORR in patients with CNS metastases was 71% (95% CI 29–96) and 57% (95% CI 18–90) per IRC and per INV, respectively (Table). The overall DoR per IRC ranged from 3.6 to 36.8+ months. The median progression-free survival (PFS) had not been reached (range 1.8 to 30.3+ months), with an estimated PFS rate at 12 months of 69%. Larotrectinib was well tolerated with treatment-emergent adverse events being mainly Grade 1–2.
CONCLUSION:

In this updated dataset, larotrectinib was shown to be highly active in patients with advanced lung cancer harboring *NTRK* gene fusions, including those with CNS metastases. The drug has a favorable safety profile. These results support inclusion of *NTRK* gene fusions in the routine molecular testing of patients with lung cancer.

<table>
<thead>
<tr>
<th>All patients (N=16)</th>
<th>Patients with brain metastases at baseline (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INV</td>
</tr>
<tr>
<td>CHR, N (95% CI)</td>
<td>71 (56-86)</td>
</tr>
<tr>
<td>CR, N (70)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>PD, N (70)</td>
<td>9 (86)</td>
</tr>
<tr>
<td>SD, N (70)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>PD, N (70)</td>
<td>7 (71)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>INV</th>
<th>IRC</th>
<th>INV</th>
<th>IRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRC, N (95% CI)</td>
<td>71 (56-86)</td>
<td>77 (68-86)</td>
<td>57 (48-66)</td>
<td>71 (59-84)</td>
</tr>
<tr>
<td>CR, N (70)</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD, N (70)</td>
<td>9 (86)</td>
<td>6 (82)</td>
<td>4 (57)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>SD, N (70)</td>
<td>2 (25)</td>
<td>3 (37)</td>
<td>2 (29)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>PD, N (70)</td>
<td>7 (71)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

N, number of patients; INV, investigational; IRC, independent review committee; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.