TARGETED THERAPIES IN NON-SMALL CELL LUNG CANCER (NSCLC)

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TRIAL SUMMARY: Ceritinib as first-line treatment for advanced NSCLC

De Castro G Jr, Tan DS, Crinò L, et al. First-line ceritinib versus chemotherapy in patients with ALK-rearranged (ALK+) NSCLC: A randomized, phase 3 study (ASCEND-4). World Conference on Lung Cancer, Vienna, Austria, December 6, 2016, Abstract PL03.07. ID 4987

Ceritinib is a second-generation oral anaplastic lymphoma kinase inhibitor (ALKi) with evidence for improved progression-free survival (PFS) in the second-line setting for patients with ALK translocation (ALK+) advanced non-small cell lung cancer (NSCLC) whose tumours progressed on first-line ALKi therapy. ASCEND-4 is a randomized, open-label, phase 3 study of ceritinib vs platinum-pemetrexed doublet as first-line therapy for ALK+ advanced non-squamous NSCLC. A total of 376 patients were enrolled, with 189 randomized to ceritinib 750 mg/day, and 187 randomized to 4 cycles of platinum-pemetrexed followed by maintenance pemetrexed; 80 patients crossed over to ceritinib at progression. The primary endpoint was PFS; secondary endpoints included overall survival (OS), overall response rate (ORR), and safety.

Results: After a median followup of 19.7 months, ceritinib significantly improved PFS (median, 16.6 [12.6, 27.2] vs 8.1 months [5.8, 11.1], HR=0.55, p<0.001) compared with chemotherapy. OS was immature at time of analysis. Ceritinib also demonstrated higher ORR (72.5% vs 26.7%), and duration of response (median, 23.9 vs 11.1 months) versus chemotherapy. Intracranial ORR was also higher with ceritinib that chemotherapy (72.7% [49.8, 89.3] vs 27.3% [10.7, 50.2]). Finally, ceritinib demonstrated less drug-related treatment discontinuation compared with chemotherapy (5.3% vs 11.4%). The most common adverse events (AEs) with ceritinib included diarrhea (84.7%), nausea (68.8%), vomiting (66.1%), and increases in alanine aminotransferase (ALT; 60.3%) and aspartate aminotransferase (AST; 52.9%).

TRIAL SUMMARY: Next-generation sequencing of ctDNA

Mack P, Banks KC, Riess JW, et al. Clinical utility of circulating tumor DNA (ctDNA) analysis by digital next-generation sequencing of over 5,000 advanced NSCLC patients. World Conference on Lung Cancer, Vienna, Austria, December 6, 2016, Abstract OA06.01 ID 6096.

Next-generation sequencing (NGS) of circulating tumour (ctDNA) is a non-invasive genotyping platform with potential usefulness in clinical decision-making at the time of diagnosis and disease progression in NSCLC patients who are on, or candidates for, targeted therapies. In this study, Guardant360 was used to analyze NGS on 8388 ctDNA plasma samples targeting 54 to 70 genes in patients with advanced-stage NSCLC. The frequency and distribution of known genetic alterations were compared to those described in The Cancer Genome Atlas (TCGA; Pearson and Spearman correlations). The clinical impact of ctDNA testing was evaluated by identification of resistance mechanisms emerging at progression on targeted therapies, and through analysis of additional driver mutations detected by ctDNA at baseline in 362 consecutive NSCLC patients with tissue mutation data available. The positive predictive value (PPV) of ctDNA sequencing was assessed in 229 patients with known tumour driver alterations.

Results: ctDNA alterations were detected in 87% of cases; EGFR mutations in 26%, KRAS mutations in 17%, MET amplification in 6%, BRAF mutations in 3%, ALK fusion in 1%, and other rare but potentially actionable alterations in 5%. Mutation patterns among driver oncogenes were highly consistent with those from TCGA (Pearson r=0.9 excluding T790M and C797S for EGFR, r=0.99 for KRAS, and r=0.99 for fusion breakpoint locations). PPV of ctDNA-detected variants was 100% for EGFR [L858R], 98% for EGFR [E19del], 96% for ALK, RET or ROS1 fusions, and 100% for KRAS [G12/G13/Q61] mutations. In 362 cases with tissue information available, 63%

(229/362) were tissue-quantity-insufficient or undergenotyped (QNS/UG). ctDNA analysis identified driver mutations in 51 of the 229 QNS/UG cases, a 38% increase in detection rate over tissue alone. Among 1,111 EGFR-mutant cases, resistance mutations were identified at progression at frequencies consistent with published literature: EGFR [T790M] 47%, MET amp 5%, ERBB2 amp 5%, FGFR3 fusions 0.4%, ALK/other fusions 1%, BRAF mutations 1.8%, PTEN inactivation 2.5%, NF1 inactivation 3%, RB1 inactivation 3%, KRAS mutations 1.9%. In 143 consecutive NSCLC patients with detailed followup and serial analysis seen at the UC Davis Cancer Center, informative driver mutations were observed in 48 (34%).

COMMENTARY: NSCLC is both a prevalent and deadly cancer, with the majority of patients presenting with advanced, incurable disease.[1] Options for systemic treatment have evolved substantially over the last 2 decades, including the most recent development in immune-checkpoint inhibitors, demonstrating PFS and OS advantages in the first-line setting.[2] Despite the excitement over the potential of immune checkpoint inhibitors, these therapies consistently tend not to work in the subclass of patients with sensitizing driver mutations such as ALK translocations.[3] Frontline treatment for this population tends to be oral targeted therapies. Currently in Canada, patients whose tumour harbours ALK translocations have access to crizotinib as first-line oral systemic targeted therapy.[4] As well, ceritinib has benefit in the second-line setting following progression on crizotinib and prior to consideration of platinum doublet chemotherapy.[5,6]

Presentations at the 2016 World Conference on Lung Cancer demonstrated continued improvement upon existing benchmarks of care for ALK translocations and showcased the potential future of mutation analysis with ctDNA. ASCEND-4 examined ceritinib as an alternative first-line ALK inhibitor, and compared it to platinum doublet therapy. Targeted therapy with ceritinib demonstrated improved PFS (16.6 vs 8.1 months, p<0.001), and higher ORR (72.5% vs 26.7%) vs chemotherapy. Especially high intracranial ORR was once again seen with ceritinib (72.7% vs 27.3%) compared to chemotherapy.

Detection of both de novo sensitizing mutations and resistant clonal populations is crucial in the era of targeted treatment. Philip Mack and colleagues demonstrated the potential of performing highly accurate, deep-coverage NGS testing using plasma ctDNA in over 8,000 patients with advanced NSCLC. This study confirms both the consistency of driver oncogene patterns in advanced NSCLC compared with TCGA samples, as well as resistance mutation percentages at progression.

These studies have already demonstrated clinically significant improvements over existing standards of care, with therapeutics that have more tolerable side effect profiles. Survival for patients with activating mutations is broaching the 2- to 3-year mark. The other exciting signal seen from ASCEND-4 is the activity of small molecule inhibitors on brain metastases, traditionally thought to be a sanctuary site.

Despite the clinically significant gains in PFS, tumours eventually develop resistance to targeted therapies. Thus the landscape of targeted therapies in advanced NSCLC is one of constant change and rapid turnover, bringing us into an era of multiple and frequent mutational testing at times of clinical progression. The study by Mack et al is a proof-of-concept study that will pave the way for future large-scale noninvasive diagnostic developments in the field of lung cancer. ctDNA is already FDA approved and stands to become a goldstandard in advanced lung cancer in Canada as well. Looking forward, we eagerly await results of trials looking at novel targeted therapies in the first-line setting. In the ALK-positive population, the global ALEX study compares a first-line third-generation ALK inhibitor to the first-generation ALK inhibitor crizotinib. Subsequent lines of targeted therapy are already in the works for patients with ALK translocation. Without a doubt, these are exciting times in thoracic oncology.

IN BRIEF

Already known

- Non-small cell lung cancer patients with anaplastic lymphoma kinase (ALK) translocations tend not to respond to immune checkpoint inhibitors.
- More accurate and less invasive tests are needed to identify resistance mechanisms emerging at progression on targeted therapies.

What these studies showed

- The ASCEND-4 trial compared ceritinib to platinum doublet therapy in patients with ALK translocations and found a significant improvement in progression-free survival (PFS) of 16.6 months vs 8.1 months, and higher overall response rate and intracranial response rate.
- Next-generation sequencing of circulating tumour DNA (ctDNA) showed good positive predictive value on a broad range of resistance mutations.

Next steps

- Enter a new era of rapid development of therapies to target mutations responsible for progression and implement new technologies, such as ctDNA, to permit large-scale noninvasive testing for mutations at time of progression.

References

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