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POSTER perspectives

NSCLC Posters and Abstracts from Chicago

Source: 2016 American Society of Clinical Oncology Annual Meeting held June 3-7, 2016

Target Audience

The target learning audience is oncologists and other health care providers who manage patients with non-small cell lung cancer.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the diagnosis and treatment of NSCLC
- Apply evidence-based research into clinical practice to improve quality of care and clinical outcomes

Faculty

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perspectives

Activity and safety of brigatinib (BRG) in patients (pts) with ALK+ non–small cell lung cancer (NSCLC): Phase (ph) 1/2 trial results

Authors: Corey J. Langer, Scott N. Gettinger, Lyudmila Bazhenova, Ravi Salgia, Kathryn A. Gold, Rafael Rosell, Alice Tsang Shaw, Glen J. Weiss, David J. Dorer, Victor M. Rivera, Frank G. Haluska, David Kerstein, D. Ross Camidge.

Corey J. Langer, MD, director of thoracic oncology, University of Pennsylvania, and professor of medicine, Department of Medicine from the Hematology-Oncology Division at the University of Pennsylvania, discusses Activity and safety of brigatinib (BRG) in patients (pts) with ALK+ non–small cell lung cancer (NSCLC): Phase (ph) 1/2 trial results. Data was presented by Dr. Langer and colleagues at the 2016 ASCO annual meeting held June 3-7, 2016, in Chicago, Illinois.

To improve and expand upon lung cancer therapies based upon histological considerations, one promising strategy involves dividing non–small cell lung cancers (NSCLC) beyond its 3 subtypes (squamous cell carcinoma, large cell carcinoma, and adenocarcinoma) into clinically relevant molecular subsets, according to a classification schema based on specific driver mutations.[1] One such target, anaplastic lymphoma kinase (ALK), undergoes oncogenic activation by gene arrangement.[2] The tyrosine kinase inhibitor (TKI) crizotinib has been approved for use in patients with metastatic ALK-rearranged (ALK+) NSCLC and is currently ourstandard of care in treatment-naïve patients; it demonstrates high initial activity, but poor longer-term results, with most patients experiencing disease progression and drug resistance.

Brigatinib (previously known as AP26113) is a next-generation investigational oral TKI that has demonstrated preclinical activity against ALK-rearranged NSCLC and mutants resistant to crizotinib.[3] This activity included potently inhibiting native ALK and all ALK secondary resistance mutations as well as demonstrating prolonged survival and significantly reduced tumor burden in a mouse model. These observations led to an ongoing phase 1/2 study designed to assess the role of brigatinib in patients with advanced malignancies including crizotinib-exposed ALK+ NSCLC.

In this single-arm, open-label multicenter trial, patients (N=137) received 30-300 mg total daily doses in phase 1, and 90 mg qd, 180 mg qd with 7-day lead-in at 90 mg (90→180 mg qd), or 180 mg/d in phase 2. The primary phase 2 endpoint was investigator-assessed objective response rate (ORR) by RECIST criteria (v1.1)[4]; the reported response rates also included phase 1 patients. Additional secondary per-protocol endpoints included safety, tolerability, best target lesion response, progression-free survival (PFS), and overall survival (OS).

Of the 137 total patients, 79 were ALK+ NSCLC (intention-to-treat population) with a median age of 54 years, 49% female, 82% white, 65% with ECOG performance status 1; 90% had received prior crizotinib. At the time the study was reported at ASCO 2016, 36 (46%) of ALK+ NSCLC patients remained in the study with most discontinuing due to documented progressive disease. Median duration of treatment for ALK+ NSCLC patients was 17.0 months.

Among ALK+ NSCLC pts with prior crizotinib exposure, the ORR was 72% (95% CI: 60%-82%) accounting for 51 of 71 patients, including 44 confirmed responses. With respect to dosing, the ORR was 77% for 90 mg qd, 80% for 90→180 mg qd, and 65% for 180 mg/d. Among crizotinib-naïve patients, all 8 achieved confirmed objective responses (3 complete) with neither median PFS nor median survival reached at the time of the presentation. Median PFS was 12.9 months and probability of OS at 1 year 77% in crizotinib-exposed ALK+ NSCLC patients. Beyond disease progression, serious adverse events, defined as those occurring in ≥2% of all patients were dyspnea (7%), pneumonia (7%), hypoxia (5%), pulmonary embolism (3%), malignant pericardial effusion (2%), and pneumonitis (2%). The pulmonary events tended to occur early during the course of treatment, and in some subjects, they proved severe enough to warrant suspension of protocol therapy.

Of the 79 ALK+ NSCLC patients, 50 (63%) had intracranial central nervous system metastases at baseline, 46 were evaluable for an intracranial response. Of these, 19 (41%) had a confirmed intracranial ORR, which rose to 57% in the subset of patients with no prior brain radiotherapy (12 of 21). The median intracranial PFS was 15.6 months.

The results demonstrated substantial antitumor activity with brigatinib with an acceptable safety profile. Compared to the 90 mg/d dose, the 90→180 mg qd dose did not appear to increase the risk of early pulmonary adverse events, and these 2 doses have since been investigated in a randomized phase 2 trial (ALTA) in crizotinib-resistant ALK+ NSCLC patients. This trial has completed accrual. A phase 3 trial (ALTA-1L) comparing 90→180 mg qd brigatinib to crizotinib in advanced ALK+ NSCLC ALK inhibitor-naïve patients also has opened.

Assuming these data hold up in the randomized phase 2 and phase 3 settings, it is anticipated that brigatinib will join ceritinib and alectinib in the pantheon of approved agents for individuals with progressive, ALK+, crizotinib-exposed NSCLC.

References

1. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol*. 2011;12:175-180.
2. Yau NK, Fong AY, Leung HF, et al. A pan-cancer review of ALK mutations: implications for carcinogenesis and therapy. *Curr Cancer Drug Targets*. 2015;15:327-336.
3. Zhang S, Nadworny S, Wardwell SD, et al. The potent ALK inhibitor AP26113 can overcome mechanisms of resistance to first and second-generation ALK TKIs in preclinical models [abstract 781]. *Cancer Res*. 2015;75(15 suppl).
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

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POSTER perspectives

Outcomes for patients treated with or without bevacizumab on SWOG S0819: A randomized, phase III study comparing carboplatin/Paclitaxel or carboplatin/Paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced non-small cell lung cancer (NSCLC)

Authors: Thomas John Semrad, Mary Weber Redman, Roy S. Herbst, Edward S. Kim, Lyudmila Bazhenova, Gregory A. Masters, Kurt R. Oettel, Perry Guaglianone, Christopher M. Reynolds, Anand B. Karnad, Susanne M. Arnold, Marileila Varella-Garcia, James Moon, Philip C. Mack, Charles David Blanke, Fred R. Hirsch, Karen Kelly, David R. Gandara

Corey J. Langer, MD, director of thoracic oncology, University of Pennsylvania, and professor of medicine, Department of Medicine from the Hematology-Oncology Division at the University of Pennsylvania discusses Outcomes for patients treated with or without bevacizumab on SWOG S0819: A randomized, phase III study comparing carboplatin/Paclitaxel or carboplatin/Paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced non-small cell lung cancer (NSCLC). Data was presented by Dr. Semrad and colleagues at the 2016 ASCO annual meeting held June 3-7, 2016, in Chicago, Illinois.

In 2016, nearly 225,000 new cases of lung cancer are expected in the United States, where lung cancer will claim more than 158,000 lives, making it the leading cause of cancer death for both men and women. Approximately 85% of these patients have non–small cell lung cancer (NSCLC).

Bevacizumab, an antiangiogenic monoclonal antibody against vascular endothelial growth factor, has been shown to improve survival in patients with advanced, non-squamous NSCLC and good performance status when combined with chemotherapy consisting of carboplatin/paclitaxel.[1] However, in the decade since this trial was published, researchers have debated optimal patient selection criteria as well as the benefit of bevacizumab in certain populations.[2-4]

Nevertheless, combination paclitaxel/carboplatin and bevacizumab remains an approved regimen in the United States. More recently, in the FLEX trial, the epidermal growth factor receptor (EGFR) inhibitor cetuximab, in combination with vinorelbine and cisplatin, led to an overall survival improvement compared to chemotherapy alone in treatment-naïve patients with advanced NSCLC.[5] However, these results did not lead to a formal drug approval in the United States; and the role of this agent grafted onto a standard US regimen was never formally explored in a cooperative group trial until S0819 was initiated.

In September 2015, at the World Conference on Lung Cancer, results from the phase 3 SWOG S0819 trial were presented, demonstrating that the addition of cetuximab to chemotherapy reduced the risk of death by 44% for patients with advanced squamous NSCLC with EGFR+ tumors.[6,7] In an update of this trial presented at ASCO 2016, researchers focused on whether inclusion or exclusion of bevacizumab (BI or BE, respectively) would impact treatment outcome in EGFR fluorescence *in situ* hybridization-positive (FISH+) patients. Beyond investigator/patient discretion (BE-Choice), bevacizumab exclusion was defined by protocol (BE-Inappropriate), the criteria for which included: >50% squamous cell (SCCA) histology; cavitary lung lesion on CT; antecedent hemoptysis; coagulopathy; central nervous system metastasis (until 6/2013); non-healing wound or fistula; or need for anticoagulation or platelet inhibitor, or baseline INR >1.5.

In total, 759 patients were BE; with 75.4% being BE-Inappropriate. The largest exclusion group was >50% SCCA (44.4%); 18.8% were in the BE-Choice group. Approximately 30% of patients overall were EGFR FISH+, although that percentage fell to 26% in the BE-Choice group. There were no statistically significant differences in baseline characteristics among these groups; patients were a median 63 years old, 86% were non-Hispanic white, and >90% were current or former smokers.

BI patients experienced significantly longer overall survival (12.1 vs 8.5 months; $p<0.001$) and progression-free survival (5.7 vs 4.0 months; $p<0.0001$) compared to BE patients. In FISH+ patients, bevacizumab inclusion also produced significantly longer overall survival (11.2 vs 6.2 months; $p=0.02$). The researchers found that although EGFR FISH positivity was not linked to improved efficacy in non-squamous NSCLC patients, such an association existed in patients with squamous NSCLC.

Whether this trial might ever lead to approval by the Food and Drug Administration of cetuximab in advanced NSCLC, especially FISH+ patients, is likely moot, at this point. More recently, necitumumab, a second-generation monoclonal antibody targeting EGFR, has been approved for use in combination with chemotherapy in advanced squamous NSCLC, based on the SQUIRE trial,[8] a vindication of sorts for agents targeting EGFR in a population whose cancers are not driven by oncogenic markers.

References

1. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542-50.
2. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol*. 2008;26:60-5.
3. Zhu J, Sharma DB, Gray SW, Chen AB, Weeks JC, Schrag D. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. *JAMA*. 2012;307:1593-601.
4. Lauro S, Onesti CE, Righini R, Marchetti P. The use of bevacizumab in non-small cell lung cancer: an update. *Anticancer Res*. 2014;34:1537-45.
5. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet*. 2009;373:1525-31.
6. Redman MW, Crowley JJ, Herbst RS, Hirsch FR, Gandara DR. Design of a phase III clinical trial with prospective biomarker validation: SWOG S0819. *Clin Cancer Res.* 2012;18:4004-12.
7. Herbst RS, Redman MW, Kim ES, et al. A randomized, phase III study comparing carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced non–small cell lung cancer (NSCLC): SWOG S0819. Presented at: 2015 World Conference on Lung Cancer; September 6-9, 2015; Denver, CO. PLEN04:01.
8. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2015;16:763-74.

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POSTER perspectives

Lung-MAP (S1400) Lung Cancer Master Protocol: Accrual, demographics, and molecular markers

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Corey J. Langer, MD, director of thoracic oncology, University of Pennsylvania, and professor of medicine, Department of Medicine from the Hematology-Oncology Division at the University of Pennsylvania, discusses Lung-MAP (S1400) Lung Cancer Master Protocol: Accrual, demographics, and molecular markers. Data was presented by Dr. Papadimitrakopoulou and colleagues at the 2016 ASCO annual meeting held June 3-7, 2016, in Chicago, Illinois.

No more than 10% of drugs developed for oncologic diseases that enter phase 1 clinical trials successfully complete phase 3 trials. Various methods proposed to improve those rates include: (1) adopting rigorous experimental randomized designs at the animal testing phase; (2) choosing smaller biomarker-driven groups with higher plausibility for biomarker-drug pair matches; (3) applying the power of genomics in patient selection; and (4) expediting diagnostic development with broader platforms that promote greater flexibility.

The latter can be seen in 2 new trial strategies to which researchers are turning: basket and umbrella designs.[1] While the basket design allows investigators to test the effect of a drug or drugs on 1 or more single mutations in a variety of cancer types, the umbrella design tests the impact of different drugs on different mutations in a single type of cancer; testing is usually performed in a national network of clinical sites with targeted trials that employ a common genetic or molecular screening platform. Both have the goal of accelerating therapeutic testing time, as well as providing a more efficient method to identify patient subgroups more likely to benefit from a new therapy or protocol.

Lung-MAP (or the Lung Master Protocol), coordinated by the Southwest Oncology Group (SWOG) on behalf of the National Clinical Trials Network (NCTN), is a first-in-kind master "umbrella" protocol (S1400) in partnership between government, academia, patient advocacy organizations, and industry.[1] It is designed to simultaneously and independently test multiple biomarker-driven therapies for patients with chemo-refractory squamous cell lung cancer (SCCA), a disease for which major unmet needs exist.

Comments from Dr. Papadimitrakopoulou, lead author of the study.

- Lung-MAP will improve genomic profiling of patients beyond academic centers.
- All studies are registration-intent, therefore potentially offering new therapeutic options to patients.
- Two new substudies (1 matched and 1 nonmatched) are expected in 2016 and 2 more matched studies are planned for 2017.

Patients eligible for Lung-MAP must have stage IV or recurrent SCCA of the lung, pathologically confirmed by tumor biopsy with no mixed histologies, EGFR mutations, or *ALK* fusion permitted. Lung-MAP currently includes 3 biomarker-driven sub-studies, with patients molecularly matched and assigned to: S1400B evaluating taselisib, a P13K inhibitor; S1400C with palbociclib, a CDK 4/6 inhibitor (cell cycle gene alternation); or S1400D testing AZD4547, a fibroblast growth factor receptor (FGFR) inhibitor. Patients with no biomarker match participate in the recently activated S1400I comparing nivolumab/ipilimumab to nivolumab alone, the latter considered by many to be state-of-the-art in second line SCCA of the lung. Sub-studies S1400A with MEDI4736 and S1400E with rilotumumab/erlotinib previously closed.

Between June 16, 2014, and January 20, 2016, 418 sites have opened in North America; 525 patients have registered to the screening component of the trial and 210 patients have been registered to a substudy: 116 to S1400A, 17 to S1400B, 36 to S1400C, 24 to S1400D, 9 to S1400E, and 6 to S1400I. Over 5 years, total sample size is projected to be 5,000.

To date, the median patient age is 67 years (range: 35-92 years); 68% are male and 85% Caucasian; 93% are former or current smokers, 80% are ECOG performance status 0-1, and 16% performance status 2.

Of 507 patients genomically screened, 450 (89%) had sufficient tissue for adequate screening. Prevalence of the biomarkers being targeted in the S1400 substudies included FGFR 16.8%, CDK 18%, and PIK3CA 9.1%. Overall, 60% of patients had no match, while 0.2% had all 3.

Thus far, the investigators have concluded that this novel master protocol has demonstrated feasibility of genomic screening and confirms the anticipated prevalence of targeted alterations in SCCA. In so doing, this study challenges current drug development and registration paradigms, and may delineate a way forward for similar trials in the future, allowing multiple parallel studies in a single disease entity to be combined under a single institutional review board approval.

References

1. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)-A biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res.* 2015;21:1514-24.