

News

Breakthrough cancer medicine and its impact on novel drug development in China: report of the US Chinese Anti-Cancer Association (USCACA) and Chinese Society of Clinical Oncology (CSCO) Joint Session at the 17th CSCO Annual Meeting

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Abstract

The US Chinese Anti-Cancer Association (USCACA) teamed up with Chinese Society of Clinical Oncology (CSCO) to host a joint session at the 17th CSCO Annual Meeting on September 20th, 2014 in Xiamen, China. With a focus on breakthrough cancer medicines, the session featured innovative approaches to evaluate breakthrough agents and established a platform to interactively share successful experiences from case studies of 6 novel agents from both the United States and China. The goal of the session is to inspire scientific and practical considerations for clinical trial design and strategy to expedite cancer drug development in China. A panel discussion further provided in-depth advice on advancing both early and full development of novel cancer medicines in China.

Key words Breakthrough, clinical trial, cancer medicine

The US Chinese Anti-Cancer Association (USCACA) and the Chinese Society of Clinical Oncology (CSCO) successfully held a session titled "Breakthrough cancer medicines: scientific and practical considerations" at the 17th CSCO Annual Meeting on September 20th, 2014 in Xiamen, China. Over 300 participants from academia, hospitals, pharmaceutical and biotechnology industries, and cancer research organizations from China and the United States (US) attended the meeting. With a theme of breakthrough cancer medicines, the conference featured an overview of the

successful cases of breakthrough cancer medicines and regulatory considerations as well as effective early development that lays the foundation of breakthrough medication application.

On behalf of the organizing committee, Dr. Jian Ding from Shanghai Institute of Materia Medica and Dr. Li Yan from USCACA, Co-Chairs of the symposia, opened the meeting by introducing the theme and agenda of the session. Dr. Helen Chen, from National Cancer Institute, USA, started the first half of session by reviewing the global landscape in cancer drug research and development (R&D). She highlighted the progress with molecularly targeted agents, the expanding role of immunotherapy, and advances in the tools for drug discovery, preclinical testing and patient/tumor profiling. Convergence of these developments has provided unprecedented opportunities for further therapeutic breakthroughs. It is recognized that strong basic and translational research will be critical to new discovery and innovation. Furthermore, deeper understanding of the agents and their impacts on tumors will not only enhance the efficiency of drug development but also provide guidance on rational combination or sequence of therapies for optimal patient outcome.

Dr. Hao Liu from Novartis presented a topic titled "Zykadia (ceritinib), a second generation anaplastic lymphoma kinase (ALK) inhibitor for patients with ALK-positive non-small cell lung cancer (NSCLC)." Ceritinib represents an important treatment option for ALK-positive NSCLC patients who relapse after starting initial therapy with crizotinib. On March 6th, 2013, the Food and Drug Administration (FDA) granted ceritinib breakthrough therapy designation based preliminary evidence of clinical activity in patients with metastatic

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ALK-positive NSCLC. This is also because there is a high unmet and urgent medical need for effective therapies in the small population of ALK-positive NSCLC patients whom the standard therapies such as crizotinib, a first generation ALK inhibitor, failed to effectively treat. The drug went through the FDA Accelerated Approval Program, which allows the approval of a drug to treat a serious or life-threatening disease based on clinical data showing the drug has an effect on a surrogate end point reasonably likely to predict clinical benefit to patients. This program provides earlier patient access to promising new drugs. The accelerated approval was based on a clinical trial, ASCEND-1 study^[1], of 163 patients with metastatic ALK-positive NSCLC treated with prior ALK inhibitor. Results showed that ~50% of the participants had their tumors shrink, and this effect lasted for an average of ~7.0 months, the agency noted. The overall response rate (ORR) was 54.6% [95% confidence interval (CI), 47%–62%], and the median duration of response was 7.4 months (95% CI, 5.4–10.1 months). The results from ASCEND-1 study also suggest clinical activity in crizotinib-naïve population and the potential utility of ceritinib for the treatment of brain metastasis of ALK-positive lung cancer^[1].

Dr. Man-Cheong Fung from Janssen Research & Development, LLC., shared an overview of Imbruvica® (ibrutinib). Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK) with efficacy in patients with various B-cell malignancies. BTK is an essential enzyme in the B-cell receptor signaling pathway. Ibrutinib binds covalently to a cysteine residue (Cys-481) in the active site of BTK, which inhibits B-cell receptor signaling within the malignant B cells with downstream mitigation of cell growth and proliferation, survival, adhesion, and migration^[2-5]. Ibrutinib was first synthesized in 2005 and tested in human subjects in clinical studies in 2009. Three breakthrough therapies (BT) were granted for designations by the US FDA in 2013: relapsed/refractory mantle cell lymphoma (MCL), deletion 17p chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinemia (WM). Ibrutinib was first approved by the FDA in November 2013 for the treatment of patients with MCL who have received at least one prior therapy^[6]. It was subsequently approved for the treatment of patients with CLL who have received at least one prior therapy^[7], and received an expanded approval in CLL patients who carry a deletion in chromosome 17 (del 17p)^[8].

Dr. Maria Koehler from Pfizer Company presented data on palbociclib (PD-0332991), an oral and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6 inhibitor), in development for patients with ER⁺/HER2⁻ breast cancer. Palbociclib received breakthrough therapy designation by the US FDA for the potential treatment of patients with breast cancer. The deregulation of the retinoblastoma (RB) tumor suppressor pathway is widespread in cancers, occurring through the direct mutation or loss of RB1, or enhanced signaling through CDK4 and CDK6 via amplification and/or overexpression of D-type cyclins, or loss of p16 (CDKN2A) function. Tumors retaining intact RB1 functions rely on the activity of CDK4/6–Cyclin D complex to inactivate RB1 and promote progression through the G₁ restriction point into S phase. Hormone receptor–positive breast cancers are one tumor type where RB1 remains intact in most tumors and deregulation of CDK4/6–Cyclin D signaling is common.

As such, dependence on CDK4/6 signaling in estrogen receptor (ER)–positive breast cancers was demonstrated using the CDK4/6 inhibitor palbociclib. Preclinical studies identified luminal ER-positive breast cancer cell lines with elevated expression of cyclin D1 and RB as well as reduced expression of p16 as being associated with the sensitivity of palbociclib^[9]. A randomized phase II study was designed as a two-part study evaluating palbociclib plus letrozole in front-line ER⁺/HER2⁻ metastatic breast cancer (MBC)^[10]. Part 1 enrolled post-menopausal patients with this subtype using ER⁺/HER2⁻ biomarkers, whereas Part 2 enrolled patients with the same MBC subtype additionally screened for *CCND1* amplification and/or loss of p16 gene. The final analysis of the primary endpoint showed a statistically significant improvement in PFS for the palbociclib plus letrozole arm (20.2 months) versus letrozole arm (10.2 months) ($P = 0.0004$)^[10]. The most common adverse events in the palbociclib plus letrozole arm were neutropenia, leukopenia, fatigue, and anemia. A randomized, multi-center, double-blinded phase III trial evaluating palbociclib in combination with letrozole versus letrozole alone as a first-line treatment for post-menopausal patients with ER⁺/HER2⁻ locally advanced or metastatic breast cancer is on-going^[11].

Dr. Jean Pierre Armand from French Institute Gustave-Roussy (IGR), the former President of European Society for Medical Oncology (ESMO), further discussed the advancement of new anticancer drug clinical studies in Europe. He used examples of IGR phase I program to illustrate the importance of molecularly matching patients with tumor of particular genetic aberration to targeted agents. "Phase I program tells you all." said Dr. Armand. That was true in his previous experience for irinotecan, sunitinib, taxotere, mTOR inhibitor and even more evident with the very recent targeted therapy to include inhibitors of ALK, epidermal growth factor receptor (EGFR), hedgehog, and the latest immune-modulators such as anti-programmed death 1 (PD1) and anti-programmed death-ligand 1 (PD-L1). The phase III trial is then only conducted to confirm evident phases I and II results. Clinical skills, which integrate everything through the patients, are of paramount importance to add value to the critical early trials. Bilateral agreements between China and France have permitted to conduct the simultaneous phase I program in France and in China. As an example, lucitanib, a promising anti-fibroblast growth factor receptor (FGFR) inhibitor from Servier, is developed at Fudan Hospital, China and Gustave Roussy, France in the phase I program. The reverse with Chinese molecules in Paris is planned before the end of the year through News Summit.

Dr. Li Yan chaired the panel discussion using the development of the series of ALK inhibitors to highlight key aspects of breakthrough medications.

- *Follow the science to understand the targets as well as the compounds.* To be successful in the fast evolving field of oncology drug R&D, it is utmost important to follow the science and understand the targets as well as the compounds thoroughly. From the discovery of ELM4-ALK fusion in which the echinoderm microtubule-associated protein-like 4 (*EML4*) gene is fused to the anaplastic lymphoma kinase (*ALK*) gene in NSCLC in 2007, it took only 4 years for the first ALK inhibitor, XALKORI (crizotinib), to obtain regulatory approval. This rapid development would not have been

possible if scientists at Pfizer had not followed and acted on the emerging science and properly readjusted the development path of crizotinib, a dual inhibitor of ALK/c-MET, by targeting ALK instead of originally targeting c-MET.

- *Biomarker-driven development strategy is vital to success.* Given the low frequency of ELM4-ALK (~5%), it is estimated that at least over 10,000 patients were screened to enroll the ~250 patients in the first two phases I and II studies to generate exciting results [ORR = 57%, estimated median progression-free survival (mPFS) > 10 months]^[12]. Therefore, it takes resolution and determination to dive into a biomarker-defined subpopulation to be rewarded.

- *Clear differentiation is the key to success of later entries.* It took only another 4 years for the second generation ALK inhibitor, ZYKADIA (ceritinib), to gain US FDA approval. In addition to be impressively active in patients with recurred or relapsed disease after prior crizotinib treatment (ORR = 56%, mPFS = 7.0 months), ceritinib has also demonstrated clear activity in patients with central nervous system (CNS) metastasis^[13]. In September 2014, another new ALK inhibitor, Alecensa (alectinib), gained regulatory approval in Japan based on activity in patients progressed after prior treatment with ALK inhibitors, both crizotinib and ceritinib, and activity in treating CNS metastasis. In addition, alectinib achieved an ORR of ~94% and a PFS of 27.7 months in 46 treatment-naive patients^[14].

- *China can and should be included in global development to gain early access to breakthrough medicines.* The approval of crizotinib by China FDA (CFDA) on February 25th, 2013 was only 18 months after the accelerated approval by US FDA in August 2011, and before the full approval on November 21st, 2013. Xalkori was granted approval in China through the Center for Drug Evaluation (CDE)'s fast-track approval channel in a process lasting 11 months from New Drug Application (NDA) to CFDA clearance. The CDE in January 2013 issued a positive review of Xalkori, which stated that data from 3 phase I, II, and III global trials (rather than trials held in China) were considered. The phase II trial included 234 Chinese patients, and there were 157 Asian patients and 29 Chinese patients in the phase III trial. Dr. Li Xu, the Executive Committee member of USCACA, then the Vice President of Pfizer Oncology (now Senior Vice President and the Head of Oncology Business Unit of Jiangsu Hengrui Medicine Co.), commented, "I had privilege to be part of this memorable, successful Xalkori China development from the beginning to the end. I want to summarize this memorable experience into a few words: compassion, preparation, and persistence, which were implemented throughout entire China development. Guided by an effective overall strategy and plan as well as team-work with strong support of Xalkori global team and headquarters leaders, I must point out 2 critical facts for the success: (1) strong leadership from Chinese key opinion leaders and investigators that led to a high quality and fast speed of execution in this relatively rare tumor in NSCLC; and (2) effective, scientific-based communications between Chinese regulatory agency and development team focusing on the benefits of Chinese cancer patients. We strongly believe that cancer patients in China should have the same opportunity as the cancer patients in other countries—can receive the best available treatment timely."

Taken together, the following criteria should be met to consider designating a compound as a "breakthrough medicine": a) addressing serious medical conditions; b) there is a lack of treatment, or currently available standard-of-care (SOC) are not satisfactory; c) the candidate medicine provides substantial improvement over SOC; and d) acceptable safety.

The second half of session was devoted to the topic of novel cancer agent development in China. Dr. Lei Jiang from Shanghai Institute of Materia Medica shared the data of early phase clinical trials of lucitanib, an oral inhibitor of the tyrosine kinase activity of FGFR1/2, vascular endothelial growth factor receptors 1–3 (VEGFR1–3), and platelet-derived growth factor receptor α/β (PDGFR α/β) developed for patients with solid tumors in China. The spectrum of activity observed in the ongoing phases I and II studies in Europe demonstrates clinical benefit in both fibroblast growth factor (FGF)-aberrant and angiogenesis-sensitive populations (ie, thyroid cancer and renal cell carcinoma). In the subgroup of 12 patients with FGF-aberrant breast cancer, the disease-control rate reached 100%, with 6 patients achieving partial response and 6 patients with stable disease; the PFS was close to 10 months^[15]. A global phase II program and clinical trial in China are under way with preliminary activity seen in Chinese patients.

Dr. Xiao Xu from ACEA Biosciences presented a topic of AC0010MA, a third generation wild-type sparing EGFR inhibitor for NSCLC patients with EGFR mutation and acquired T790M mutation. Approximately 50% of NSCLC patients who received the first generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib developed the acquired T790M mutation, which resulted in the resistance to the first generation EGFR TKIs; the optimal treatment for EGFR TKI resistance has not been defined. During the last 5 years, a novel therapeutic concept for the third generation EGFR inhibitor has been investigated in both preclinical and clinical studies. The third generation EGFR inhibitor is an irreversible kinase inhibitor designed to covalently bind to Cys 797 in the EGFR kinase domain and to overcome T790M gatekeeper mutation-mediated resistance. Notably, the third generation EGFR inhibitors spare wild-type EGFR showing great tolerability in animals. Most recently, results from phase I/II clinical trials have been reported on 2 third generation EGFR inhibitors, CO1686 and AZD9291. Treatment of patients carrying the T790M mutation with the third generation inhibitors resulted in approximately 60% response rate and importantly, unlike first generation EGFR inhibitors, no severe adverse effects were observed. A novel third generation EGFR inhibitor, AC0010MA, has also been developed by ACEA Biosciences. In the preclinical study, AC0010MA overcame T790M-mediated resistance in xenograft models of NSCLC bearing T790M mutation, with no inhibitory effect against wild-type EGFR. In comparison with other 2 EGFR TKIs currently in the clinical trial in the US, AC0010MA showed better selectivity and potent inhibitory activity against EGFR T790M mutation in preclinical studies. The AC0010MA clinical trial in China has started, and this is the first clinical trial for a third generation EGFR TKI in China, where lung cancer cases account for one third of the global cases. With great development efforts recently focused on the third generation EGFR inhibitors, the patients will soon benefit

from this endeavor of the novel molecular targeted therapy.

Dr. Ge Zhang from Jiangsu Hengrui Medicine presented how Hengrui successfully completed Apatinib phase III registration trial on treatment of advanced gastric cancer (GC). Apatinib significantly prolonged overall survival time in advanced GC patients (apatinib vs. placebo, 6.5 months vs. 4.7 months, $P = 0.015$), and was recently approved for advanced GC in China^[16]. Dr. Zhang also shared the preclinical data of pyrotinib, an oral irreversible, potent and selective inhibitor of HER2 and EGFR, and the early development plan to evaluate pyrotinib.

Following 3 presentations, Dr. Feng Roger Luo from Janssen Pharmaceutical R&D and USCACA overviewed the essential goals of early clinical development trials for molecularly targeted agents and the principal of pharmacological audit trail, and then discussed 3 presentations and remarked on these 3 new agents by using the key evaluation criteria for phase I or I/IIa trial.

With rapid advances in molecular understanding of tumor types prevalent in China^[17,18], increased investment in pharmaceutical R&D and clinical trial infrastructure, global partnership and alliance^[19,20], and new talents with global vision^[21-24], it is anticipated that China cancer medicine R&D will rapidly enter the golden era to address the challenges of unmet medical needs for cancer patients in China^[25].

About the USCACA

The US Chinese Anti-Cancer Association (USCACA, 美中抗癌

协会, <http://www.uscaca.org/>) is a non-profit professional organization founded in 2009. With members from academia, industry and government, USCACA facilitates collaboration among cancer research and physicians in the United States and China. Our current focus is on expediting novel cancer drug development by fostering clinical trial networks, sharing best practices and knowledge of clinical trials, and providing education and training opportunities. USCACA collaborates with Chinese Anti-Cancer Association (CACA, 中国抗癌协会), Chinese Society for Clinical Oncology (CSCO), and other professional associations. Our mandate is to improve cancer treatment through research, education, and collaboration.

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