Novel Drug Development of the Next-Generation T790M Mutant Specific Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for the Treatment of Advanced Non-Small Cell Lung Cancer

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Short Communication

Lung cancer is a leading cause of cancer death worldwide. Lung cancer accounts for over 1 million mortalities annually and non-small cell lung cancer (NSCLC) accounts for almost 85% of all cases. Epidermal growth factor receptors (EGFR) mutations are found in approximately 10% and 30% of patients with NSCLC in North American/European and East Asian countries, respectively. EGFR activating mutations result in increased malignant cell survival, proliferation, invasion, metastatic spread and tumor angiogenesis in NSCLC. The two most common EGFR mutations are short-in-frame deletions of exon 19 (del ex19), and a point mutation (CTG to CGG) in exon 21 at nucleotide sequence 2,573 resulting in the substitution of leucine for arginine in codon 858 (L858R). These mutations account for approximately 90% of EGFR mutations in NSCLC. Patients with the most common EGFR mutations, exon 21 L858R and deletions in exon 19, typically have good responses to therapy with reversible first generation EGFR inhibitors such as erlotinib or gefitinib. Toxicity associated with these first generation EGFR inhibitors includes skin rash and diarrhea related to inhibition of the WT (wild-type, normal) EGFR in skin and intestine, respectively. Despite the impressive initial response to treatment by first generation EGFR-TKIs, disease progression generally occurs after 9-15 months of erlotinib or gefitinib therapy administration, driven in approximately 50-60% of cases by a second site EGFR mutation in exon 20 called T790M (the “gatekeeper” mutation) which mediates resistance to first-generation EGFR inhibitors. This mutation was sometimes associated with amelioration of the EGFR gene as well. Some patients have developed amplification of another gene that drives tumor growth (MET gene amplification and mutations in the PI3KCA gene). To overcome this acquired resistance, novel drug development of several promising “next-generation” 3rd generation pyrimidine-based EGFR TKIs designed to have potency and high selectivity for EGFR T790M over wild-type EGFR has been ongoing. X-ray crystallography reveals structurally they form a covalent bond with cysteine 797 in the adenosine triphosphate (ATP)–binding site. In general, the T790M mutation increases the ATP affinity of the oncogenic exon 21 L858R mutation and alters the drug binding within the ATP-binding pocket of EGFR, thus reducing the potency of any ATP-competitive EGFR-TKI as the primary mechanism by which the T790M mutation confers drug resistance. Available effective treatment options for NSCLC patients who develop acquired resistance T790M-mutation were quite limited until the emergence of recent novel drug development of highly selective 3rd–generation EGFR TKIs targeting T790M mutant specific. Several such novel inhibitors, including osimertinib (AZD9291), rociletinib (CO-1686), BI 1482694 (HM61713), EGFR61 and ASP8273, have been investigated in early to late phase clinical studies. On November 2015, the US Food and Drug Administration (FDA) has approved osimertinib (AZD9291) for the treatment of patients with EGFR T790M mutation-positive metastatic NSCLC, as detected by an FDA-approved test, patients have progressed on or after initial EGFR TKI therapy and this is the first approved drug indicated for NSCLC patients harboring EGFR T790M mutation. In this short review, summary of current drug development status of each novel potent and highly selective T790M-mutant specific 3rd generation EGFR TKIs will be introduced and discussed.

Osimertinib (AZD9291)

Osimertinib (AZD9291) “TAGRISSO” is the first approved drug indicated for patients with metastatic EGFR T790M mutation-positive NSCLC in US and EU. Astra Zeneca 3rd generation EGFR-TKI, osimertinib (AZD9291) is a potent, orally available selective small molecule irreversible TKI of both EGFR mutation sensitizing and T790M-resistance mutants that spares WT EGFR. Osimertinib (AZD9291) has a distinct chemical structure from the other novel 3rd generation EGFR-TKIs, characterizing that it has mono-anilino-pyrimidine compound and also offers a pharmacologically differentiated profile from earlier generation (gefitinib, erlotinib, afatinib and dacomitinib) EGFR TKIs. Chemical structural formula of AZD9291 shows that its pyrimidine core forming two hydrogen bonds to the hinge region (Met-793), orientation of the indole group adjacent to the “gatekeeper” residue, the amine moiety positioned in the solvent channel and the covalent bond formed to cysteine 797 via the acrylamide group of AZD9291[1]. On November 2015, the US FDA has approved osimertinib (AZD9291) 80 mg once-daily under the FDA’s accelerated approval process for the treatment of patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. Osimertinib (AZD9291) has also approved in the EU on February 2016 based on the clinical data from two phase II studies (AURA extension and AURA2) (NCT02094261) and the AURA phase I expansion study, which demonstrated efficacy in 474 patients with EGFR T790M mutation positive NSCLC who had progressed on or after an EGFR-TKI. In the combined phase II studies (AURA extension and AURA2), the objective response rate was 66% and progression-free survival (PFS) was 9.7 months (median duration of response was not reached). Safety profile of osimertinib (AZD9291) showed that most common AEs were generally mild to moderate including diarrhea (42%), rash (41%), dry skin (31%). Grade 3/4 toxicities were uncommon and 80 mg once-daily (QD) dosing is generally well tolerated [2-4]. In the first-line setting of AZD9291, both a phase III, randomized study of AZD9291 versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic...
T790M mutation positive NSCLC whose disease has progressed with previous EGFR-TKI therapy (AURA3, NCT02151981) and a phase III study of AZD9291 versus gefitinib or erlotinib in treatment-naïve patients with advanced NSCLC and an EGFR-TKI-sensitizing mutation (FLAURA, NCT02296125) are currently ongoing. In Japan, osimertinib (AZD9291) was also granted Accelerated Assessment and Priority Review status.

Rociletinib (CO-1686)

Clovis Oncology 3rd generation EGFR-TKI, rociletinib (CO-1686) is a potent, orally available small molecule irreversible TKI that selectively targets mutant forms of the EGFR while sparing wild type (WT) EGFR. Rociletinib (CO-1686) received the US FDA's breakthrough therapy designation in May 2014 for NSCLC patients with the T790M mutation after progression on EGFR-directed therapy. The TIGER (Third-generation Inhibitor of mutant EGFR in lung cancER) program is accelerated clinical development program for rociletinib (CO-1686) in patients with EGFR mutant NSCLC. The TIGER program consists of four categories of several stages of clinical trials; TIGER-X is evaluating rociletinib (CO-1686) in two groups of advanced NSCLC patients; the first group patients include immediate after progression on first-line and only EGFR-directed TKI therapy (gefitinib or erlotinib), who have developed the T790M mutation. The second group includes later-line T790M-positive refractory advanced metastatic NSCLC patients after progression on second-line or later EGFR-TKI therapy or subsequent systemic chemotherapy; TIGER-1 is a randomized phase II/III "head to head" study versus erlotinib in newly-diagnosed patients as first-line setting (NCT02186301); TIGER-2 is a single arm, global phase II study in both T790M-positive and T790M-negative patients immediate after progression on first-line and only EGFR-TKI therapy (NCT02147990). TIGER-3 is a randomized phase III study versus single-agent chemotherapy in both T790M-positive and T790M-negative patients who have developed acquired TKI resistance (NCT02322281). In TIGER-X phase II expansion cohorts, objective response rate was 60% at 500 mg BID rociletinib HBr (hydrobromide) cohort (n = 48) and all phase II doses (500, 625 and 750 mg BID) of rociletinib were clinically active and well tolerated in patients with advanced NSCLC [5-7]. The most common treatment-related AEs (all grades) occurring in > 10% of patients were hyperglycemia, diarrhea, nausea, decreased appetite and QTc prolongation and toxicities were generally well tolerated. Active metabolite of rociletinib, M502 is an IGF1R (insulin-like growth factor 1 receptor) - inhibitor and it accumulates in humans causing hyperglycemia. Incidence of hyperglycemia increases with dose and is associated with M502 metabolite concentration. In general, rociletinib induced hyperglycemia is well managed with appropriate oral hypoglycemic agents so far. Based on these results of dose optimization of rociletinib for EGFR mutated NSCLC, the recommended dose was considered to be 500 mg BID.

EGFR816

Novartis 3rd generation EGFR-TKI, EGFR816 is a potent, ATP-competitive, WT EGFR-sparing, mutant-selective EGFR inhibitor of activating (L858R and Ex19Del) and T790M resistant mutations. X-ray structures of EGFR816 analogs with EGFR T790M. Inhibitors occupy ATP-pocket and covalently bind to Cys797 [11]. Aside from multicenter, open-label phase I/II study (NCT02108964), combination studies with PD-1 antibody as well as c-MET inhibitor are currently under investigation (NCT02323126 and NCT02335944).

ASP8273

Astellas 3rd generation EGFR-TKI, ASP8273 is an orally available, irreversible, potent mutant selective EGFR-TKI that inhibits the kinase activity of T790M resistance mutation as well as EGFR activating mutations. First in human phase 1 study using Bayesian CRM as dose escalation procedure was conducted in Japan and overall ASP8273 has been well tolerated across 25-400 mg dose levels and 600 mg has been expected to be over MTD dose [12,13]. Regarding AEs of ASP8273, GI toxicities including diarrhea, vomiting and nausea have been the most common AEs and quite few events of both hyperglycemia and QTc prolongation. ASP8273 showed anti-tumor activity in NSCLC with both EGFR activating mutations and T790M mutation. RECIST responses have been observed at doses of ≥ 100 mg. In interim report of phase I/II study of ASP8273 in Asian NSCLC patients with EGFR activating and T790M mutations, based on the findings from phase 1, once-daily (QD) ASP8273 MTD and RP2D were determined to be 400 mg and 300 mg. Although the number of patients is very small, partial responses have been observed in 89% of evaluable patients (n = 8/9). Adverse events reported in ≥ 20% of patients in phase 2 were diarrhea, vomiting, nausea, and increased alanine transaminase. No interstitial lung disease-like or hyperglycemia events have been reported thus far [12-14]. Both this global phase I/II study of ASP8273 in patients with EGFR-mutant NSCLC in East Asia (Japan, Korea and Taiwan) (NCT02192697) and phase III study of ASP8273 vs. erlotinib or gefitinib in first-line treatment of patients with stage IIIB/IV NSCLC with EGFR activating mutations (SOLAR) are currently ongoing (NCT02588261).

Conclusions

To overcome the acquired resistance of the first generation EGFR TKIs, both resistance mechanisms and novel therapeutic strategies have been intensively developed and accelerated. Secondary mutation in exon 20 called T790M (the "gatekeeper" mutation) and activation of several molecular bypass signaling pathways are identified as possible key mechanisms of acquired resistance to the first generation EGFR TKIs. Even in using the second-generation inhibitors including afatinib (irreversible covalent inhibitor of EGFR/HER2) and
dacomitinib (irreversible pan ErbB family TKIs of HER1/EGFR, HER2, and HER4), clinical activity is limited in treatment of the first generation EGFR TKIs pretreated NSCLC patients. Recent several therapeutic approaches such as next-generation (the 3rd generation) EGFR TKIs targeting T790M mutant specific, immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies) and combinational therapies have been showed promising therapeutic efficacy in various kind stage of early to late phase clinical trials. Regarding the safety profile, most of AEs caused by 3rd generation EGFR-TKIs are generally mild-to-moderate and well managed with appropriate standard supportive care. Novel AEs including interstitial lung disease, hyperglycemia and QTc prolongation are also manageable, although the exact mechanism is not clear except for possible explanation of both chemical structures and active metabolites. Other important issue, the increasingly importance of re-biopsy of tumor at the time of disease progression, and the matching appropriate effective treatment platform based on the identification of molecular profiling of tumors are emerging. Utilizing circulating tumor DNA (ctDNA) is a promising biomarker for noninvasive techniques. However, standardizing new technologies of ctDNA with both appropriate analysis and clinical validation remained to be exploratory. It is obvious that the emergence of these novel drugs will bring a breakthrough for the treatment of advanced metastatic NSCLC patients and these biomarkers driven treatment strategy also provides information on personalized cancer treatment. Addressing the issue of how to use these next generation mutant specific EGFR-TKIs in an appropriate sequence to optimize clinical efficacy and overcome resistance with appropriate patients selection is absolutely defining moment.

References