Peer Review File

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Review Comments:

Comment # 1: Some data are available from ASCO 2020 with regard to relationship between METex14 alteration and PD-L1 expression, it could be interesting to briefly address this issue in the introduction section [Award M presentation, ASCO 2020]

Response # 1: The data regarding METex14 and PD-L1 interaction was published in 2018 in Annals of Oncology by Mark Awad and his colleagues and it is not new. He just added his and his colleague work from 2018 paper in his ASCO 2020 annual presentation. This data is already included in our manuscript on page 7 line 161 and 162 with reference to his work which is published in Annals of Oncology in 2018.

Changes to the text: None. As this data is already mentioned in the original version of our manuscript on page 7 line 161 and 162.

Comment #2: Line 135: Authors should clarify crizotinib G1-G2 adverse events. Reviewers have asked to describe G1-G2 adverse events (AEs) of Criztotinib

Response # 2: Will add G1-2 AEs that occur in ≥ 20% of patients. See below in red the updated version of the text.

Changes to the text: Adverse events (AEs) that were reported in ≥ 20% of patients include vision disturbances, diarrhea, peripheral edema, vomiting, constipation, elevated aminotransferases, dysgeusia and headaches. Most of these AEs were grade1-2. Grades 3-4 toxicities that occurred in 10% or more patients include elevation of aminotransferases and neutropenia. See line #

Comment # 3: Line 143, with regard to GEOMETRY-trial, authors have to specify that results reported are referred to METex14 alteration, while different results are now available for MET amplification (GCN>10) from ASCO 2020 and should be added [Wolf et al, ASCO 2020].

Response # 3: Will add the new data presented/reported at ASCO 2020 annual meeting.

Changes/Addition to the Text: Cohort 1a (pretreated) and 5a (treatment naïve) enrolled 69 and 16 evaluable patients respectively with high-level of MET amplification (gene copy number [GCN] ≥10). The ORR in pretreated and treatment naïve patients with MET amplification was 29% and 40% respectively. Median PFS in both high MET amplified cohort was similar (4.07 vs 4.17 months) (1). See line #

Comment # 4: Line 266: Some data are available from ASCO 2020 regarding Sym015. Authors have to update new data in the main text, in the figure and in the table.

Response # 4: Appreciate the request to include ASCO 2020 Sym015 data. Will add the following text in the new version and include the Amivantamab and REGN5093 as their data was also reported.

Changes/addition to the text: following text is added. Newer agents like Amivantamab (JNJ-61186372), Sym015 and REGN5093 are under active investigation in various settings. Amivantamab is a bispecific antibody targeting EGFR/MET receptors. CHRYSALIS is an ongoing phase I study evaluating Amivantamab in EGFR exon20 ins NSCLC patients. In 39 out of 50 response evaluable patients, 36% showed ORR. The most common AEs were rash (72%), infusion related reaction (60%), paronychia (34%), stomatitis (16%), pruritus (14%), and diarrhea (6%) (2). Future studies should select patients very carefully for further drug development. Sym015 comprises a mixture of two humanized antibodies directed against nonoverlapping epitopes on the MET extracellular domain (SEMA-α), allowing receptor internalization and degradation. In pre-clinical model, it showed activity against *MET*ex14 skip^{+} and amplified tumors (3). In an ongoing phase I/II study, 45 NSCLC patients with *MET*ex14 skip^{+} or amplification received Sym015. Of 20 patients, 5 had confirmed response (2/8 MET^{Amp} and 3/12 $MET^{Ex14\Delta}$); 11 develop SD (6/8 MET^{Amp} and 5/12 $MET^{Ex14\Delta}$); 2 progressed (2/12 $MET^{Ex14\Delta}$); and 2 were not evaluable. Median PFS was 5.5 m overall. The most common treatment related AE in ≥10% patients

were fatigue (13.3%) and peripheral edema (11.1%) (4). REGN5093 is also a bispecific antibody that binds to two distinct epitopes of MET, blocking HGF binding and inducing internalization and degradation of MET. Preclinical data is very encouraging, and currently investigating NSCLC patients with various *MET* alterations in a dose finding study {Rowlands, 2020 #1315}.

Comment # 5: Line 312: FDA recently approved Capmatinib for the treatment of advanced NSCLC (6 May 2020).
Response #5: Sure. We will change the text to reflect that.
Change to the text: Based on GEOMETRY mono-1 data, FDA has granted accelerated approval Capmatinib in patients with *METex14* skip alterations. Tepotinib is currently awaiting FDA approval in US however approved in Japan for the same indication

Comment # 6: Although it is not the topic of this review, authors should briefly mention the role of MET alterations in development of acquired resistance in 'oncogene addicted' disease, especially in EGFR mutant patients treated with Osimertinib and subsequently develop resistance due to MET aberration.
Response # 6: We agree with reviewers that this is relevant and that's why we have described the role of MET alterations in EGFR mutant NSCLC at more than a few occasions throughout this manuscript. However, since it is not the focus of this review therefore it may seem that these details are lacking mainly because they are stated in pieces. We have mentioned the significance of MET in EGFR mutant NSCLC in the sections of "*MET* Alterations in NSCLC", "Capmatinib", "Savolitinib", "S49076", and "Targeting MET with Antibodies". We even reported the data of TATTON study under section of Savolitinib for the same reason.
Changes to the Text: None. Please see response above.