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Reviewer Comments:

1. This review focused on the challenges of neoadjuvant targeted therapy for early stages NSCLC pts is potentially interesting, clinically relevant, and in line with recent efforts to test the validity of this healing approach. Several considerations by the author are quite insightful. Unfortunately, the MS suffers significantly from its presentation. It appears too long, verbose, and repetitive in several places. It is often based on convoluted sentences that are difficult to interpret. A thorough revision of the text' s phrasing is recommendable.

Thank you for your comments, I have corrected the manuscript as much as I could, shortened it and eliminated most of the repetitions, splitted up and rephrased convoluted sentences.

2. Moreover, despite the author' s remarkable effort in presenting a comprehensive review of the neoadjuvant usage of EGFR-TKIs, some additional data on other forms of neoadjuvant targeted therapy could have been discussed too.

I have added some lacking data on neoadjuvant therapy as well.

Specific points (several are minor)

Dear Reviewer, thank you for all your valuable comments. I have done all the corrections and made all changes in the manuscript based on your comments and suggestions.

1. The title should be slightly changed to make even more sense: “Challenges of neoadjuvant targeted therapy in early stage non-small-cell lung cancer - A narrative review”

Thank you, I have changed the title as you have suggested. Now it is:
“Challenges of neoadjuvant targeted therapy in early stage non-small-cell lung cancer - A narrative review”

2. The author should try to shorten the MS and avoid too many repetitions. Underneath, there are just a few suggestions.

Thank you, I have shortened the manuscript as much as I could and modified in the way you have suggested. I have eliminated the repetitive sentences as well.

3. The review essentially limits the discussion of neoadjuvant targeted therapy to that by EGFR-TKIs, which indeed has been the most used so far. Only one study evaluating the neoadjuvant usage of the ALK-TKI crizotinib (ref. 47) is mentioned. Yet, other publications on neoadjuvant/adjuvant

usage of TKIs could be cited. One is a recent review by Liu S-Y et al. (PMID: 35644704, from May 2022, thus after the cutoff of December 2021 for the author's review), who describe how targeted therapy for ALK, ROS1, NTRK, BRAF V600, and RET molecular alterations is currently being assessed in the adjuvant and neoadjuvant settings. Related to that, McCoach CE et al. describe a trial in which pts with early stage NSCLC harboring ALK- or ROS1-fusions or MET ex14 skipping mutations are treated with the ALK/ROS1/MET TKI Crizotinib (PMD: 27378174, 2016).

Thank you, regarding comments listed, I have added the part related to points 3 and 4, after point 4 (below)

4. Furthermore, anecdotal clinical case reports indicate the feasibility of neoadjuvant therapy with Alectinib against ALK-fusions (Leonetti A et al. 2021, PMID: 33762169, which also describes the design of the ALNEO phase II trial for Alectinib as neoadjuvant treatment in surgically resectable stage III ALK+ NSCLC), or with BRAF and MEK inhibitors in BRAF-mutant NSCLC (Liu C et al. 2022, PMID: 36003777).

Thank you, regarding your comments listed at points 3 and 4, I have added accordingly, as follows:

Frequency of genomic alterations in early stage non–small cell lung cancer

Line 100-102: Similar rates were demonstrated in two large Chinese retrospective series of resected stage I–IIIA adenocarcinoma, in 4% out of 689 patients (28) and in 6.6% out of 1056 patients (29).

Selected studies on neoadjuvant targeted therapy

Line 174-176: Another, phase II randomized trial (ANSWER) is evaluating the efficacy of neoadjuvant novel 3rd generation EGFR-TKI Aumolertinib compared with erlotinib or platinum doublet chemotherapy in resectable EGFR-mutant stage IIIA NSCLC, with ORR as the primary endpoint (51). (Table 2).

Line 201-226: Few studies have reported on early stage ALK-positive lung cancer patients (41,55,56) due to the rarity of this distinct subtype of NSCLC. The first one from 2016 (41) treated patients with early stage NSCLC harboring ALK- or ROS1-fusions or MET ex14 skipping mutations with the ALK/ROS1/MET TKI Crizotinib with the aim to evaluate resected tumor samples for pathologic response to induction therapy, ORR, disease free survival and to identify early mechanisms of resistance to targeted therapy. Another one (55) reported 11 cases of pathologically confirmed N2 ALK-positive NSCLC treated with neoadjuvant crizotinib followed by surgery, 10 of which achieved R0 resection and 2 achieved pCR, but one of them with rapid postoperative relapse (59). The ongoing phase II multicenter ALNEO trial with MPR as the primary endpoint evaluates the efficacy and safety of neoadjuvant alectinib in (potentially) resectable ALK-positive NSCLC (any T stage with N2, T4N0–1) (58) (Table 3).

There are several case reports on neoadjuvant crizotinib (57-59), and alectinib (60-63) as well, pointing to neoadjuvant ALK TKI approach as feasible, efficient and well tolerated.

The increasing number of approved targeted therapies – including for KRAS G12C mutations, ROS1, BRAF V600E, MET exon 14 alterations, HER2 exon 20 insertion, NTRK and RET rearrangements – brings novel opportunities for personalized, oncogene-driven treatment approach

in (neo)adjuvant setting (64) Two case reports have been published, one on pCR to neoadjuvant crizotinib in adenocarcinoma with a MET Exon 14 skipping mutation (65), and the other on MPR induced by neoadjuvant BRAF and MEK inhibitors in a patient with stage IIIA lung adenocarcinoma harboring BRAF V600E-mutation (66).
Geometry-N, a phase II trial of neoadjuvant and adjuvant capmatinib in NSCLC with MET exon 14 mutations and/or high MET amplification is ongoing (NCT04926831) (67). The Lung Cancer Mutation Consortium (LCMC) has initiated the PROMISE umbrella trial in resectable stage I–III NSCLC with matched targeted therapies in neoadjuvant setting (68). Another ongoing trial, NAUTIKA1 evaluates neoadjuvant and adjuvant alectinib, entrectinib, vemurafenib plus cobimetinib, or pralsetinib in patients with resectable stage II–III NSCLC with ALK, ROS1, NTRK, BRAF V600, or RET molecular alterations (NCT04302025) (69,70). (Table 3).

4. Abstract line 9 and Introduction line 35, "Five-year survival rates for radically resected early stage NSCLC remain pretty disappointing": in light of technical surgical improvements in recent years (for ex., from pneumonectomy to lobectomy and from that to now segmentectomy for some pts), perhaps the statement could be milder "Five-year ….. remain disappointing" (w/o "pretty").

Thank you for your comment, I have erased the word pretty

5. Composite words such as EGFR-mutant, ALK-positive, oncogene-driven etc. should be consistently hyphenated throughout the text (right now, they are only sometimes).

Thank you for your comment, I have done accordingly.

6. Introduction, line 32, "Increased use of CT screening has led to detection of more NSCLC patients with early-stage disease who should be treated": this issue is still debated (as a matter several countries have not implemented it yet), thus a reference to support it would be appropriate here.

Thank you for your comment, I have added the relevant references:

Increased use of CT screening has led to detection of more NSCLC patients with early-stage disease who should be treated (1-6).

7. Line 46-48, "On the other hand, important disadvantages are that neoadjuvant approach might delay the surgical treatment and increase the risk of further disease progression potentially leading to an undesirable change from resectable into unresectable tumor": What is the evidence for this assumption? Any references to support it?

Thank you, I have rephrased this sentence and added the relevant references:

On the other hand, significant concern exists that neoadjuvant approach might delay the surgery and increase the risk of further disease progression potentially leading to switch from resectable into unresectable tumor (9-12)

8. Line 51, "either as monotherapy combined with chemotherapy": it should have been "either as monotherapy or combined with chemotherapy". The same applies to line 113.

Thank you, I have added "or"

9. Line 55-56, "As mutant non–small cell lung cancer has": it should be NSCLC, as the abbreviation has been defined already on line 32 and used several times before. The same on line 78.

Thank you, I have put further on NSCLC everywhere where it was necessary

10. Sentence on line 56-61, "Given numerous challenges … and outcomes to EGFR TKI treatment.": the sentence is very long and unclear ("given something" implies a consequence, i.e. "something else occurs"). It'd be appropriate to split it up and rephrase it in more proper form. Indeed, the author could simply name that these various issues/challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that are discussed in the review.

Thank you, I have splitted up and rephrased the sentence:

Line 64-66: Various challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that are discussed in this review. The focus is mainly on EGFR-mutant NSCLC in the context of neoadjuvant approach, as it has been most studied.

11. Line 82-86, "American trial MSK-IMPACT … proteomic analyses (6)": another long convoluted sentence that is difficult to read. It could be divided in two, with the first sentence describing by clearer phrasing the incidence of EGFR-mutations in the MSK-IMPACT cohort and the second separate sentence the frequency in the TCGA cohort.

Thank you, I have done accordingly, so now it is:

Line 86-89: American trial MSK-IMPACT prospectively analyzed 860 multiple lines treated recurrent/metastatic adenocarcinomas for mutations in >300 cancer-associated genes, and evidenced EGFR-mutations in 27% (21). In The Cancer Genome Atlas (TCGA) cohort of 230 treatment-naive resected adenocarcinomas, 11% were EGFR-mutant tumors (16).

12. Line 90-91, "In the adjuvant phase III ADAURA, out of 2447 resected stage IB–IIIA EGFR+ NSCLC, 44% were EGFR mutation positive": in the ADAURA trial, as described in reference 15, 2447 pts with stage IB-IIIA NSCLC were screened and 1087 (44%) of these pts had EGFR-mutation in their NSCLC. Thus, EGFR+ should be eliminated from the sentence.

Thank you, I have eliminated it.

13. Line 93, "Interestingly, in a Chinese retrospective study analyzed 790 early-stage resected tumors": the preposition "in" should be eliminated from the sentence to give it a sense.

Thank you, I have eliminated it.

14. Line 94, "the frequency of EGFR mutations in total were close" : the frequency … was close.

Thank you, I have replaced were with was

15. Line 95-96, "Recent analysis of 244 … detected EGFR mutations were noted in 44.6% in whole cohort" : It should be "A recent analysis of 244 … detected EGFR mutations in 44.6% in the whole cohort" .

Thank you, I have done accordingly.

16. Line 97-98, "Analyzed surgical samples in a big series of 689 South Corean patients with stage I–III lung adenocarcinomas observed EGFR mutations in 438 patients (64%)" : To observe is not an appropriate verb in this sentence. It could be changed to "The analyzed surgical samples ....displayed EGFR mutations in 438 patients" or similar. Furthermore, Korean is with the k.

Thank you, I have done accordingly.

17. Line 109, "the meta-analysis of 15 RCTs" : first time the abbreviation RCTs is used in the text, thus it should be defined here, not on line 204.

Thank you, I have done accordingly, defined in line 107: Several randomized controlled studies (RCTs)…

18. Line 111-114, "In the last several years … have been undertaken" : Again, long convoluted sentence. It'd be proper to split it up in a more reader-friendly manner.

Thank you, I have rephrased it:

Line 111-112: In the last several years, a significant number of neoadjuvant and/or adjuvant studies with molecular targeted agents have been undertaken.

19. Line 120: additionally.

Thank you, I have made the correction regarding the word additionally.

20. Line 122-123, "where early adaptive reactions at the protein level cause insufficient inhibition of the oncogenic driver and thus residual tumor burden" : it is unclear what the authors means with this statement. It should be better explained as it is too generic. It should refer to more specific, described mechanisms of TKI-resistance.

Thank you for your remarks, I have rephrased that part a bit and now it is as follows:

Line 113-123: Pivotal prospective trials have proven that first line TKI treatment show better efficacy with the high rate of significant responses and less toxicity than chemotherapy in advanced oncogene-driven NSCLC (15, 31-39). These findings support its evaluation in neoadjuvant setting, especially in borderline or potentially resectable tumors or those in which a pneumonectomy would otherwise be indicated. Importantly, this approach enables analysis of tumor specimen before and after targeted treatment and thus additionally provides the opportunity to assess tumor sensitivity, resistance mechanisms to targeted agents and residual tumor burden (40,41). Better insight into the biology of residual disease in oncogene-driven NSCLC might significantly affect the choice of subsequent therapy or combination treatments as well as outcomes.
Moreover, knowing differing characteristics among different TKIs, each generation of targeted therapies needs to be carefully evaluated based on their efficacy, therapy duration and variety of effects on tumor biology characteristics such as intrinsic/acquired resistance mechanisms.

21. Line 130: tumors have shown.

Thank you, I have made the correction putting have instead of has.

22. Line 134-135, "setting. Vast majority of available data for targeted therapy in early stage resectable NSCLC are related to the EGFR-mutation positive subpopulation, while there are ongoing clinical studies in other molecular subtypes as well" : this has been stated already before in the MS and could be eliminated to shorten it.

Thank you, I have eliminated it.

23. Line 148-149, "Three small, but single arm phase 2 studies … The CSLC-0702 (36) was the first phase II trial … ": this trial has two arms; thus, it shouldn't be described as single-arm trial.

Thank you, I have made the correction accordingly, eliminated the word small

24. Line 153: and OS between the two arms.

Thank you, I have made the correction accordingly.

25. Line 162, "Immune regulatory and inflammatory response genes were upregulated leading to infiltration of fibroblasts and T cells" : The sentence is unclear. Which cells upregulated these genes? How did this result in infiltration of fibroblasts and T cells? How was this assessed?

Thank you for your remarks, I have rephrased that sentence based on available data and now it is as follows:

Line 154-156: RNA sequencing revealed that immune regulatory and inflammatory response genes were upregulated compared to the treatment naive cohort, indicating infiltration of fibroblasts and T cells.

26. Line 168, "with deletion 19" : it should be "with exon 19 deletion" .
Thank you, I have rephrased that sentence:

Neodjuvant osimertinib, the third-generation EGFR TKI given 80 mg orally daily for 6 six weeks, is shown to be effective and feasible for patients with stage II-IIIB adenocarcinoma with EGFR common mutations, according to interim report of the NEOS Chinese prospective, multi-center, single-arm study (47)

27. Line 177-178, "The average duration of treatment was 59 days, the objective RR was 46%" : this is already stated on line 175-176 and can be eliminated.

Thank you, I have eliminated it.

28. Line 187-188, "in early-stage EGFR mutated NSCLC was evidenced unlike another earlier meta-analysis (44)" : Reference 44 addressed the prognostic value of EGFR-mutations in resected NSCLC, not the neoadjuvant usage of EGFR-TKIs. Actually, it is explicitly stated in that article that "Patients were excluded if they had received tyrosine kinase inhibitors (TKIs) as neo-adjuvant treatment or adjuvant treatment".

Thank you, I have erased from that part of the text and put it in the part on prognostic significance of EGFR mutation where it belongs.

29. Line 214: could have an impact on the major pathological response rate.

Thank you, I have erased that sentence during shortening the text.

30. Line 227, "The data obtained from the studies on neoadjuvant therapy with TKIs relate mostly to best studied EGFR TKIs evidently" : the sentence should be rephrased in more proper English.

Thank you, I hope this is acceptable:

The data obtained from the studies on neoadjuvant TKI therapy relate mostly to EGFR TKIs.

31. Line 232: Available data from.

Thank you, this has been corrected (form into from).

32. Line 253-258, "There is clearly the need … trials (50, 51)" : another very long, verbose sentence. Please reformulate it in different parts and more clearly.

Thank you, I hope this is better:

Line 255-259: Incorporating a biomarker testing approach into the routine work-up of early-stage NSCLC is needed, but still there are many challenges such as to establish standardized surrogate endpoints of neoadjuvant treatment. Major pathologic response (MPR) defined as 10% or less

residual tumor cells represents a potential surrogate endpoint for OS in NSCLC and a marker for neoadjuvant treatment efficacy (73,74).

33. Line 259-266: The author properly quotes the IASLC' s "multidisciplinary recommendation for the pathologic assessment of resection specimens, encompassing MPR and pCR (52)" . It might be appropriate to also cite the proposed refinement of MPR assessment after neoadjuvant therapy recently published by Saqi A et al. (DOI:https://doi.org/10.1016/j.jtocrr.2022.100310), which further proves the complexity of defining this parameter in clinical practice.

Thank you, I have done it with this text incorporated:

Line 269-276: Very recently a novel MPR calculator tool (MPRCT) for standardized, comprehensive collection of percentages of viable tumor, necrosis, and stroma in the tumor bed, including tumor width and length in the latter, has been developed (76). It has the potential to validate trials with MPR and pCR as surrogate end points of neoadjuvant therapy efficacy. Data from the ongoing Phase 3 neoadjuvant trials using MPRCT such as IMpower030 are awaited. The MPRCT compared to the IASLC recommendations, might better capture data in areas of tumor heterogeneity and decrease the bias of standard pathology approach selecting viable areas and avoiding necrotic ones, that cause underestimation of pathologic response (76).

34. Line 270: in-depth molecular analysis that is.

Thank you, I have the related sentence rephrased and splitted in two, as follows:

Line 277-280: There is a need for data on precise histological changes after targeted therapy such as EGFR-TKI, not only to compare with the pre-treatment tumor specimen and assess the level of tumor shrinkage, but, even more importantly to perform in-depth molecular analysis. This analysis is essential for making adequate decision on adjuvant approach.

Line 271-272, "histological characteristics of resected specimens differed among the different EGFR-TKIs" : better to write "differed upon treatment with different EGFR-TKIs" .
Thank you, I have made this correction, so now the sentence is:

Line 280-281: Additionally, it remains to be determined whether histological characteristics of resected specimens differed upon treatment with different EGFR-TKIs.

35. The section entitled "The need for comprehensive molecular profiling in the light of complex mechanisms of intrinsic and acquired resistance to TKIs (EGFR TKIs)" is well presented (it could be shortened a little bit) and contains interesting and relevant considerations. The author deserves special credit for that.

Thank you for this comment. I have shortened this part a little bit, and rephrased some parts to provide more clarity. I hope you will find it appropriate:

Line 285-351: A very important issue is related to establishment of reliable genomic/epigenetic

biomarkers at the time of diagnosis, and consequenlty the optimal selection of neoadjuvant approach with possibility to predict who would most likely respond to targeted drugs. NSCLC is a highly complex, heterogeneous tumor with co-occurring genomic alterations i.e. with a variety of spatially and temporally different co-mutations. Given this NSCLC complexity, nowadays widely applied molecular profiling at diagnosis such as PCR panels, targeted NGS, FISH, IHC, do not encompass sufficient number of driver genes unlike comprehensive molecular profiling.

Different resistance mechanisms to EGFR TKIs that are responsible for disease progression in advanced NSCLC, have been detected based on analyses of tumor biopsy samples obtained at the time of tumor progression. Around 20–30% of patients with advanced EGFR-mutant NSCLC do not respond at all or show some response to TKIs for a very brief time (<3 months) as the consequence of intrinsic resistance mechanisms which are not yet fully recognized (13,77). Due to clonal tumor heterogeneity of NSCLC, different genetic alterations may exist in clones before treatment initiated, namely de novo alterations, that are either cause of intrinsic resistance to EGFR TKIs (78), or may reflect prompt adaptive response by some surviving tumor cells, a phenomenon called “drug tolerance” to the TKI therapy. Those surviving cell subpopulations acquire a dormant or “persister” state of cell-cycle arrest and have the potential for further tumor growth and progression (79).

Comprehensive molecular profiling of tumor biopsy samples at the time of diagnosis has evidenced the co-existence of multiple genetic, epigenetic, and functional mechanisms underlying variety of EGFR-dependent and/or EGFR-independent processes that may cause TKI-resistance (13,16,21,78,80,81). It appears that acquired resistance is the result of combined expansion of certain pre-existing clones and newly developed resistance mechanisms that reflect adaptive tumor response to EGFR TKIs therapy. Some of mechanisms are shared by these two types of resistance, but with clear temporal differences. Thus, since the majority of advanced EGFR-mutant NSCLC do not depend on EGFR only, but also on multiple co-occurring oncogenic events (82), different mechanisms underlying intrinsic and acquired resistance may be identified concomitantly. All this contribute to the complexity of this important aspect for targeted treatment (83). Sensitizing EGFR mutations represent early clonal events in the process of tumor development, while most advanced NSCLCs exibit heterogeneous regions having late clonal driver aberrations that are in fact TKI-resistance mechanisms, such as mutations in TP53, RB, and genes related to the RAS-RAF-MAPK or PI3K-AKT-PTEN-mTOR pathways, cell cycle regulation, Wnt/β-catenin pathway, DNA damage repair, chromatin remodeling, and histone methylation (82,83,84). While being treated with the EGFR TKIs, further on during tumor evolution some of those pre-existing clones that most effectively foster tumor progression may be selected to proliferate as the predominant cell subpopulation reflecting prevailing resistance mechanism (13,23,78). Co-occurring TP53 mutation is a highly prevalent mutation and the most frequent co-mutation found in 30% to over 60% of EGFR-mutant tumors. These TP53 alterations reduce responsiveness to EGFR-TKIs and worsen prognosis in EGFR-mutant NSCLC patients (45,84 -89).

The fact that diverse and heterogeneous intrinsic TKI-resistance mechanisms may co-exist in the same EGFR TKI-resistant NSCLC, is particularly challenging for treatment in the neoadjuvant setting, but the only way to detect those mechanisms is to endorse comprehensive molecular profiling tests such as NGS in routine clinical practice in early stage disease. In this context, it becomes necessary not only to define EGFR-mutant patients subpopulations who are suitable for neoadjuvant targeted therapy, but also to identify which EGFR TKI to be recommended in an

individual case. Comprehensive molecular profiling is of great importance for treatment decision which EGFR TKI to be administered as some of the EGFR-dependent resistance mechanisms cause resistance to EGFR TKIs of all three generations, while others are sensitive to 2. or 3. generation TKIs, whereas on the other hand most of the EGFR-independent resistance mechanisms are common to EGFR TKIs of all three generations.
Selecting the appropriate combination targeted therapy at the diagnosis as well requires the use of extensive molecular profiling. Thus discovered alterations might become additionally actionable targets having then potential to be predictive biomarkers in certain subpopulations of patients (13,17,21,76,80). Consequently, the combination of drugs targeting alterations that are detectable already at the time of diagnosis might have potential to prevent or at least to postpone the predominant proliferation of resistant cancer cells, and thus impact the outcomes in early stage oncogene-driven NSCLC.
Still, there is a risk that certain tumor cell subpopulations harboring other resistance-mechanisms exist while not been discovered (80). Thus, EGFR-mutant NSCLC with its complexity and diversity of baseline co-existing TKI-resistance mechanisms that are not even recognized or/and not targeted, may additonally explain why in a number of studies there has been no evidence of OS benefit or of decreased risk of relapse following neoadjuvant EGFR TKIs treatment.
Moreover, even with extensive molecular profiling tools such as NGS, of most frequently a small tumor biopsy sample at diagnosis, the aspect of tumor heterogeneity is underestimated (82,90,91).
It should be underlined that circulating tumor DNA (ctDNA) that has been analyzed to discover acquired-resistance mechanisms to TKIs (92-95), might have potential as well to detect alterations relevant for selection of optimal treatment approach in early stage disease.
Another very important aspect is that more extensive use of comprehensive molecular profiling in early-stage NSCLC will enable the detection of other, rare oncogene-driven mutations such as ALK, NTRK, RET, BRAF, HER, MET, for which the expanding number of efficient targeted drugs have been developed, but large trials enrolling patients with tumors harbouring any of them are not realistic.

36. Line 342-346, "With all this advancement in increasing knowledge about EGFR TKI resistance … into unresectable tumor": The concept in this sentence has already been mentioned several times before in the MS and could be eliminated, as it does not add anything essential.

Thank you, this sentence has been eliminated.

37. Line 382-383, "There are some convincing data that the abundance of EGFR mutation is related to the efficacy of targeted treatment that can not be detected by commonly used PCR test as well": what does "as well" mean here?
Thank you, "as well" has been erased.

38. Line 394, "loss of function RBM10 mutation was associated with tumors lacking pathologic response": it would benefit the review if it could be briefly explained, how the RBM10 mutation might negatively impact the PR.

Thank you, this is with the explanation sentence added:

Line 388-392: According to updated results from the ongoing phase 2 trial (49) of neoadjuvant osimertinib, a loss-of-function RBM10 mutation was evidenced in tumors lacking pathologic response. This might be explained by the fact that loss-of-function mutation in RBM10 tumor suppressor gene contributes to the pathogenesis of adenocarcinoma, cell proliferation and disease progression (111).

39. Line 412-413, "higher tumor mutational burden (TMB)": the abbreviation TMB has been useds several times before in the text and should have been defined the first time (line 23).

Thank you, I have made the correction accordingly.

40. Line 418-420: rephrase the sentence more clearly ("but" is used too many times).
Thank you for your suggestion, I have rephrased it and splitted up as follows:

Line 426-429: It has been speculated that mostly the emergence of initially subclonal mutations drive the increase in TMB after 1st/2nd generation EGFR TKI treatment, but unable to increase effective immunogenicity. Further investigation in the 3rd generation EGFR TKI is of interest as well.

41. Line 422-425: too long a sentence. It' d be proper to have period after "wild-type patients" and begin the next sentence as "These results underline the potential".
Thank you, I have made the suggested correction.

42. Line 427-429, "Limitations are … focused clinical problems": It is a rather cryptic sentence that seems unnecessary and should be eliminated to shorten and make the MS more readable.

Thank you, this sentence has been eliminated.

43. Summary, line 436-441, "Challenges of neoadjuvant targeted … outcomes to EGFR TKI treatment": Very long sentence. As noted above for line 55-61, it could be appropriate to split it up and rephrase it in more proper form by simply mentioning that these various issues/challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that have discussed in the review.

Thank you, this has been done:

Line 439-445: Various challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that are discussed in this review. Based on available published data several important issues include treatment efficacy, aspects of neoadjuvant targeted treatment relevant for surgery outcomes, response assessment on resection specimens after neoadjuvant treatment, the need for comprehensive molecular profiling in the light of complex resistance mechanisms, prognostic and predictive impact of oncogenic driver alterations in early-stage NSCLC, relationship between TMB and outcomes.

44. Line 442: interpreted with caution.

Thank you, I suppose this is what you have meant:

Line 446-448: It should be underscored that conflicting results of studies in last decade interpreted with causion, in particular because of commonly used PCR testing limited to mutations in exons 18-21 only in most of them.

45. Reference list, line 605: reference 21 is repeated between ref. 48 and 49 on line 605-607 and should be eliminated from here.

Thank you, this has been erased.

46. Table 1: why are studies with neoadjuvant Osimertinib not included (reference 40-41)? And those with ALK-TKIs? The table would gain in value with those data and the MS would gain in clarity with the results of trials and meta analyses presented as overview in the table.

Thank you, I have made a new Table 1 following your advice, and additionally made two tables more: Table 2. Ongoing clinical trials investigating neoadjuvant EGFR TKIs, and
Table 3. Ongoing clinical trials investigating neoadjuvant TKIs for ALK rearrangement and other rare mutations (all in the enclosed file under name: TABLES Neoadjuvant targeted therapy Nov 2022.

47. Table 1 - column "Study" : the reference numbers rather than 1st author et al. should be shown as more reader-friendly presentation of the table.

Thank you, I have made a corrected Table 1 following your advice including the reference numbers in the brackets.