Peer Review File

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Reviewer A: Minor Revision

Comments:

Authors reviewed whether molecular-targeted TKIs as neoadjuvant settings are effective in early-stage and locally advanced oncogenic-driven lung cancer in detail. I am satisfied with the updated review. I have only two comments.

Comment 1: line 68: EGFR mutations constitute the second most common oncogenic driver event. What is the first most common oncogenic driver event, TP53? Please describe the driver.

Reply 1: Thanks for the observation. The most common oncogenic driver is *Kristen Rat Sarcoma viral oncogene (KRAS)*. Based on the suggestion of the reviewer, we have re-written the phrase as follows (page 3/line 71: "*EGFR* mutations constitute the second most common oncogenic driver, after the Kristen Rat Sarcoma viral oncogene (KRAS). Unfortunately, KRAS mutations have not been targeted successfully similar to EGFR mutations (Schffler et.al.)".

Comment 2: In general, patients with exon 19 deletion benefited from EGFR-TKI compared to those with L858R mutation in metastatic EGFR mutant-NSCLC. The difference between exon 19 deletion and L858R might be described in EGFR-mutant stage III NSCLC.

Reply 2: The reviewer raises an interesting point. Some of the clinical trials included in our review, stratified the patients by EGFR mutation type, in order to perform subgroup analysis. This is the case of the adjuvant phase III ADJUVANT and ADAURA trials, and the phase II EVAN and Li et al. trials. All these studies consistently agree that patients harboring the exon 19 deletion seem to derive major benefit to TKIs than patients with L858R in terms of median DFS. Likewise, in the neoadjuvant setting, Zhang et. al. obtained similar results:

-ADJUVANT/CTONG1104: Ex19del HR 0.55 (P .024); L858R HR 0.62 (P .071)
-ADAURA: Ex19del HR 0.12 (P .07); L858R HR 0.35 (P .21)
-EVAN: Ex19del HR 0.19; L858R HR 0.38
-Li: Ex19del (P .016); L858R (P .407)
-Zhang: Ex19 33.5m; L858R 25.3m (P .921)

Based on the suggestion of the reviewer we have included a sentence in line 397: “Some of the abovementioned adjuvant clinical trials, stratified the patients by EGFR mutation status (Ex19del or L858R) in order to perform subgroup analysis. This is the case of the adjuvant phase III ADAURA and ADJUVANT/CTONG1104 trials (ref) and the phase II EVAN trial (ref). In the Li et al. trial analysis by mutation subgroups was also preplanned (ref). All these studies, consistently agree that patients harboring the ex19del seem to derive a major benefit to TKIs than patients with L858R in terms of DFS.

Reviewer B: Minor Revision

Comments:

This review summarized treatment results of neoadjuvant/adjuvant in EGFR-mutant/ALK-rearranged NSCLC. The molecular targeted therapies against EGFR-mutant/ALK-rearranged have significantly improved the clinical outcomes of NSCLC patients with advanced stages; however, clinical benefits of the targeted therapies for the patients with early stages remain unclear. In this review, the results of clinical trials are well written, and sharing the information will be truly important for clinical field. The reviewer has few minor comments.

Comment 1. Uncommon EGFR mutations, such as G719X in exon18 and L861Q in exon21, are well-known to show limited responses to the first-generation EGFR-TKIs, while a recent post-hoc analysis in the Lux-Lung trials showed that second-generation EGFR-TKI was active in patients with uncommon EGFR mutations. It would be informative to describe whether the previous or ongoing clinical trials targeting EGFR-mutant NSCLC with stage III have included uncommon EGFR mutations.

Reply 1. Thanks for the observation. Most of the trials in the perioperative setting only considered those tumors harboring one of the 2 common sensitive *EGFR* mutations (Ex19del and L858R). Only three trials allowed the inclusion of patients with uncommon mutations such as G719X and L861Q. The SELECT trial included 2 patients with the G719X mutation and 1 patient with the L861Q mutation. Feng et al. included 1 patient with an uncommon mutation and it was allocated in the arm of chemotherapy. And finally, the ongoing NeoAdaura trial allows the inclusion of patients with the two common mutations either alone or in combination with other *EGFR* mutations (ie, T790M, G719X, Exon20 insertions, S7681 and L861Q).

Based on the reviewer’s suggestion we have modified the text as follows:

In line 311 we have added a specification for SELECT trial: "… In this phase II study, one hundred patients with resected stage IA to IIIA and sensitive EGFR mutations (3 patients with uncommon mutations G719X and L861Q), were….".

In the line 487 we have added a specification for the NeoAdaura trial: "…randomize (1:1:1) 300 patients with sensitizing *EGFR* mutations (Ex19Del or L858R either alone or in combination with other *EGFR* mutations) to receive placebo plus…"

Comment 2. In table 1-2, it would be readable to make X-Y axis of the columns in table 2 compatible with that of table 1.

Reply 2. Based on the reviewer's suggestion we have inverted the X-Y axis in table 2, It is now shown as follows:

Trial	**Phase**	**Stage**	**N**	**Study design**	**EGFR-TKI duration**	**Primary endpoint**	**Results**	**Results for survival rates (mo)**
Zhong et al.(67) **CSLC-0702**	II random	IIIA (N2)	24	Erlotinib (*EGFR*+) vs Platinum-based CT x 3 cycles (EGFR-WT)	6 weeks	ORR	**ORR 58.3% vs. 25% (P=.18)** RRR 50% vs 71% MPR no reported CPR no reported pLND 17% vs 25%	PFS 6.9 vs 9 (HR 2.26) OS 14.5 vs 28 (HR 1.79)
Zhong et al.(68) **CTONG1103 (EMERGING)**	II random	IIIA (N2)	72	Erlotinib (NA and A) vs Platinum-based CT x 2 cycles (NA and A)	NA: 6 weeks A: up to 12 mo	ORR	**ORR 54.1% vs 34.3% (P=.092)** RRR 73% vs 63% MPR 9.7% vs. 0% CPR 0% pLND 11% vs 3%	PFS 21.5 vs 11.4 (HR 0.39) OS 45.8 vs 39.2 (HR 0.77)
Xiong et al.(69) **(ESTERN)**	II	IIIA (N2)	19	Erlotinib	8 weeks	RRR	ORR 42.1% **RRR 68.4%** MPR no reported CPR 0%	PFS 11.2 OS 51.6

							pLND 21.1%	
Zhang et al.(70) **NCT01833572**	II	II-IIIA	35	Gefitinib	6 weeks	ORR	**54.5%** RRR 89% MPR 24.2% CPR 12.1% pLND no reported	DFS 33.5 OS not reached
Tan et al.(71) **(PROGRESS)** Ongoing data on n=16	II	I-IIIA	16	Gefitinib	Minimum 4 weeks	EGFR TKI sensitivity biomarkers determination	**ORR** 62% (n=16) RRR 100% (n=16) MPR 8% (n=16) pLND 31% (n=16)	-