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COMMENTARY

ATTLAS, IMpower151 and ORIENT-31: Dusting off IMpower150 for Post-Osimertinib in *EGFR*-Mutated NSCLC?

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Abstract: Treatment strategies for post-epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) therapy in *EGFR*-mutant non-small cell lung cancer (NSCLC) is an ongoing challenge. Previously, the IMPRESS trial comparing platinum doublet chemotherapy with or without *EGFR*-TKI did not demonstrate any progression-free survival (PFS) benefit. The retrospective subgroup analysis of IMpower150 indicated that the quad regimen (carboplatin, paclitaxel, bevacizumab, atezolizumab) improved PFS and overall survival (OS) in patients with *EGFR*-mutant NSCLC who progressed on first-generation *EGFR*-TKIs. Given the retrospective nature of the analysis, the IMpower150 regimen is not approved in the US for post-*EGFR*-TKI treatment. Currently, osimertinib or other third-generation (3G) *EGFR*-TKIs is the first-line standard of care for advanced *EGFR*-mutant NSCLC. MARIPOSA-2 provided the first randomized trial post-osimertinib in *EGFR*-mutant NSCLC patients with another quad regimen (platinum, pemetrexed, lazertinib, amivantamab). The IMpower150 and MARIPOSA-2 quad regimens differ in the principle of whether to continue or even "double-down" on *EGFR* inhibition. Recently, three prospective randomized trials conducted in Asia offered promising results, showing that a quad regimen of doublet platinum chemotherapy plus anti-angiogenesis agent and ICI may be as efficacious as MARIPOSA-2 with a lower rate of toxicities and accounting for the PFS difference if 1L chemotherapy plus osimertinib instead of osimertinib monotherapy. In particular, the median PFS achieved by the quad regimens of ATTLAS and IMpower151 is 8.5 months. However, only 8.2% and 17.9% of the *EGFR*-mutant NSCLC patients who received the quad regimens progressed on 3G *EGFR*-TKI, respectively. Here, we discuss how the results of IMpower151 and ATTLAS may rejuvenate interest in a non-*EGFR* containing quad regimen as a potential post-osimertinib monotherapy treatment. Randomized trials comparing the results of these studies, including the quad regimen of MARIPOSA-2 versus the quad regimen of IMpower151/Impower150/ATTLAS in post-osimertinib (or other 3G *EGFR*-TKI) progression, are urgently needed.

Keywords: atezolizumab, bevacizumab, chemotherapy, EGFR-mutant, NSCLC, FLAURA-2

Introduction

Immune checkpoint inhibitors (ICIs), including programmed death-ligand 1 (PD-L1), and programmed cell death (PD-1) inhibitors, as monotherapy or in combination with chemotherapy (Keynote-789, Checkmate-722, LIBRETTO-431 [control arm]) have limited efficacy in patients with oncogenic driver molecular alterations in advanced NSCLC.[1] Indeed, the use of immunotherapy as a monotherapy or in combination with chemotherapy for first-line treatment of advanced NSCLC excludes *EGFR*-mutant and ALK-rearranged NSCLC.[2] Until recently in the US, the treatment options for *EGFR*-mutant NSCLC post-*EGFR*-TKI were doublet platinum-based chemotherapies. In Europe in February 2019, the European Medical Agency (EMA) approved the IMpower150 quad regimen (carboplatin, paclitaxel, bevacizumab, atezolizumab) for treatment of *EGFR*-mutant NSCLC after progression with *EGFR*-TKI, based on a small subgroup retrospective analysis with both PFS and OS survival benefits[3,4] (Table 1). Hence, there is a need for consensus on effective post-osimertinib monotherapy.

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Mariposa-2

MARIPOSA-2 is the first randomized trial to investigate combination therapy after progression with osimertinib. Briefly, MARIPOSA-2 demonstrated that the quad regimen (platinum doublet chemotherapy + lazertinib [an alternate 3G *EGFR*-TKI] + amivantamab [an *EGFR*/MET bi-specific antibody]) (LACP) confers superior PFS over platinum doublet chemotherapy (CP) alone. The trial included a third investigation arm (chemotherapy + amivantamab, ACP), but was randomized in a 2:2:1, and was not the main primary endpoint for MARIPOSA-2. Essentially, LACP achieved superior PFS over CP (8.3 months vs 4.2 months; HR: 0.44; 95% CI: 0.35–0.56; P<0.001).[5] However, LACP involves significantly higher adverse events requiring dose reduction and a higher incidence of venous thromboembolic disease. While the PFS of LACP was superior to that of CP, whether the regimen is easily administered to the vast majority of patients remains in question.[6]

IMpower151 and ATTLAS

It is within this context that we delve into the role of chemoimmunotherapy plus anti-angiogenic agents in the metastatic, *EGFR*-mutant NSCLC as an alternative to MARIPOSA-2. Previously, preclinical studies have shown that resistance to *EGFR*-TKIs may change the tumor microenvironment, resulting in favorable responses to immunotherapy.[7] However, immunotherapy alone has no benefit in *EGFR*-mutant NSCLC,[8] and the combination with chemotherapy failed to meet its primary endpoint in the KEYNOTE-789[9] and CheckMate-72[10] studies. The role of PD-1 or PD-L1 inhibitors is only supported with the addition of anti-angiogenic agents such as bevacizumab, a vascular endothelial growth factor A (VEGF-A) from the IMpower150[4] and ORIENT-31 trials[11] (Table 1).

Table 1 Comparison of IMpower150, ATTLAS and ORIENT-31 Trials

Trial	IMpower150	IMpower151	ATTLAS (KCSG-LU19-04)	ORIENT-31
Country	26 countries	China	Korea	China
Treatment arm	Atezolizumab plus bevacizumab and chemotherapy (ABCP, N=34)	Atezolizumab plus bevacizumab and chemotherapy (ABCP, N=81)	Atezolizumab plus bevacizumab and chemotherapy (N=154)	Sintilimab plus IB305 plus chemotherapy (N=158)
Comparator arm	Atezolizumab plus carboplatin plus paclitaxel (ACP, N=45) Bevacizumab plus carboplatin plus paclitaxel (BCP, N=43)	Bevacizumab and chemotherapy (BCP, N=82)	Paclitaxel and carboplatin (N=74)	Sintilimab plus chemotherapy (N=156) Chemotherapy alone (N=160)
***EGFR* mutation (N)**				
Exon 19 deletion	15	50	70	80
Exon 21 L858R	11	26	75	70
T790M	1	14	NA	NA
Other	7	5	2	8
Post-3G TKI alone (quad arm)	0%	17.9% (N=14)	8.2% (N=12)	11% (N=7)
Smoking				
Current or former	14	NA for subgroup analysis	57	47
Never	20		97	111
Brain metastasis (N)	NA for subgroup analysis	NA for subgroup analysis	67	59
Primary endpoint	PFS and interim OS in the ITT wild-type population (excluding *EGFR* or *ALK* alteration)	Investigator-assessed PFS in the ITT population	Investigator-assessed PFS	IRRC-assessed PFS
Efficacy endpoints				
ORR	42%	NA for subgroup analysis	69.5%	45%
Median PFS (months)	10.2 (HR, 0.61, 95% CI: 0.36–1.03)	8.5 (HR 0.86, 95% CI: 0.61–1.21)	8.48 (HR 0.62, 95% CI: 0.45–0.86)	7.2 (HR 0.74, 95% CI: 0.57–0.97)
Median OS (months)	NR (HR 0.61, 95% CI: 0.29–1.28)	NA for subgroup analysis	20.63 (HR 1.01, 0.69–1.46)	21.1 (95% CI: 17.5–23.9)

(*Continued*)

Table 1 (Continued).

Trial	IMpower150	IMpower151	ATTLAS (KCSG-LU19-04)	ORIENT-31
Grade 3 or worse TRAEs	64%		53%	56%
Approvals				
FDA	No		No	No
EMA	Yes		No	No

Abbreviations: CI, confidence interval; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HR, hazard ratio; IC, immune cells; IRRC, independent radiologic review committee; intention-to-treat, ITT; N, number; NA, not applicable; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1; programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; TRAEs, treatment-related adverse events.

While ORIENT-31 was positive for the quad regimen over chemotherapy, it was conducted in a single country (China)[11] and the applicability of the results outside China remains to be determined.[12] Two similarly designed trials from China (IMpower151)[13] and the Republic of Korea (ATTLAS)[14] supported the role of the quad regimen. IMpower151 used a similar design to IMpower150, except that half of the patients had either an *EGFR* mutation or ALK rearrangement in IMpower151. ATTLAS had only two arms comparing platinum/paclitaxel + bevacizumab + atezolizumab (ABCP) to platinum/paclitaxel (CP) (Table 1).

The IMPOWER151 study was negative and did not meet its primary endpoint of investigator-assessed PFS in the intention-to-treat (ITT) population (9.5 vs 7.1 months, HR: 0.84). Of the 53% of patients enrolled with *EGFR* mutation and ALK rearrangement, there was no difference in PFS between the ABCP and BCP regimen (median PFS 8.5 vs 8.3 months, HR: 0.86). On the other hand, ATTLAS achieved its primary endpoint of improved PFS of ABPC over PC (median PFS, 8.48 months [95% CI: 8.18–10.28] versus 5.62 months [95% CI: 4.27–7.22; HR: 0.62, 95% CI: 0.45–0.86]). Importantly, the quad regimen in both trials achieved a median PFS of 8.5 months, which is within the range of LACP of MARIPOSA-2. The quad regimen theoretically achieves a PFS1 + PFS2 from osimertinib to IMpower151/ATTLAS of about 29 months, which is similar to the median PFS achieved in FLAURA-2 when osimertinib is combined with platinum-based chemotherapy.[15]

There was no subgroup analysis by PD-L1 expression for the *EGFR*-mutant NSCLC in IMpower151 from the WCLC 2023 presentation. The ABCP regimen in the ATTLAS trial showed PFS benefit as increased PD-L1 expression. Interestingly, exploratory analysis by PD-L1 (SP263) and distribution and density of tumor-infiltrating lymphocytes (TILs) in the tumor bed using artificial intelligence-powered Lunit SCOPE IO showed that an inflamed score of 20% or more demonstrated PFS benefit. However, this finding is hard to reproduce in clinical settings, and TILs remain largely exploratory. PD-L1 expression in *EGFR*-mutant NSCLC is highly heterogeneous, and is not a reliable predictive or prognostic biomarker for advanced non-squamous NSCLC without actionable genomic alteration.

FLAURA-2 and MARIPOSA

Recently, the improvement in PFS over osimertinib alone with the addition of chemotherapy (FLAUA-2)[15] or with amivantamab (MARIPOSA)[16,17] has changed the treatment landscape for treatment-naïve patients. It is unknown whether chemotherapy or amivantamab were used in the front-line setting or if the second-line setting included chemotherapy and/or amivantamab rechallenge. In the future, specific second-line trials will have to be designed based on the initial treatment regimen and may complicate the sequential treatment landscape of advanced *EGFR*-mutant NSCLC.[18]

Proposed Second-Line Post-Osimertinib (3G) Clinical Trial Design

The IMpower151, ATTLAS and ORIEN-31 trials provided promising results suggesting that the quad regimen may be a effective for post-first-line *EGFR*-TKI. We thus propose a head-to-head comparison between the quad regimen of MARIPOSA-2 versus the quad regimen of IMpower151/Impower150/ATTLAS. We propose a randomized second-line immediate post-osimertinib/3G *EGFR*-TKI trial (Figure 1). Given the likely equivalency of both quad regimens, the primary endpoint could be non-inferiority design.

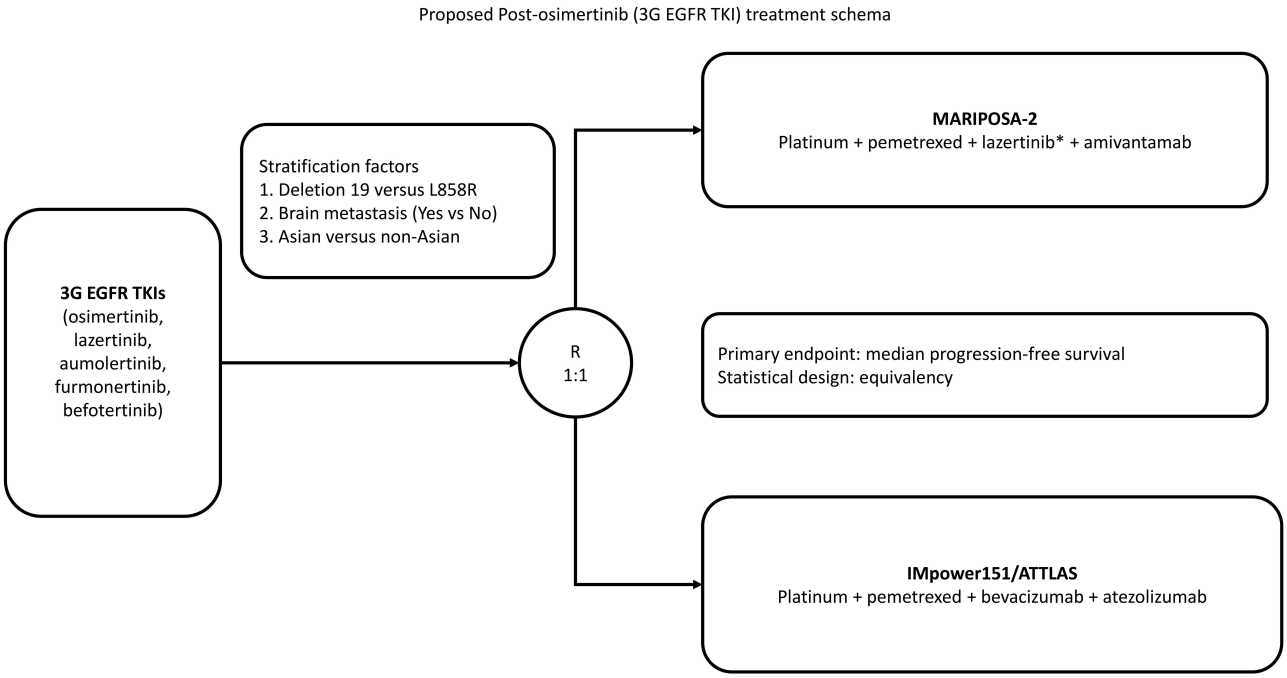

Figure 1 A hypothetical schema comparing the quad regimen of MARIPOSA-2 to the quad regimen of IMpower151/ATTLAS.

Summary

1. The treatment landscape for advanced *EGFR*-mutant NSCLC is rapidly evolving. The standard of care resulting from osimertinib as the first-line treatment is being challenged by the success of FLAURA-2 and MARIPOSA. These trials differ in that FLAURA-2 utilized chemotherapy upfront while MARIPOSA utilized "maximum" *EGFR* inhibition with both an *EGFR*-TKI and *EGFR* mAb.

2. All three trials (IMPower151, ATTLAS, and ORENT-031) were conducted in Asian countries. However, there is strength in numbers and all three trials point to a hypothesis-generating observation that chemotherapy in combination with anti-angiogenesis and ICI may be potentially an effective subsequent treatment, given the low frequency of *EGFR*-mutant NSCLC patients who had only exposure to 3G *EGFR*-TKI (N=33). Randomized trials comparing two quad regimens, MARIPOSA-2 versus IMpower151/ATTLAS post-osimertinib (or other 3G *EGFR*-TKI) progression, is urgently needed. We propose a simple head-to-head trial comparing the two quad regimens of MARIPOSA-2 and IMpower151/ATTLAS.

Disclosure

Dr Sai-Hong Ignatius Ou reports grants, personal fees from Pfizer, JNJ/Janssen, Daiichi Sanyo; grants from Mirati, Revolution Medicine, grants and stock ownership from Nuvalent; personal fees from DAVA Oncology LLC, OncLive, BMS; stock ownership from MBrace Therapeutics, BlossomHill Therapeutics, Turning Point Therapeutics, and Elevation Oncology, outside the submitted work. The authors report no other conflicts of interest in this work.

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