



# FLAURA strikes again: efficacy of osimertinib is independent of PD-L1 expression

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Osimertinib, a third generation tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR), achieved impressive results in first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with sensitizing EGFR mutations (1). Numerically, with a median progression-free survival (PFS) and overall survival (OS) of 18.9 and 38.6 months respectively, osimertinib surpasses outcomes of all available treatments in metastatic NSCLC including those of immune checkpoint inhibitors (ICIs) (2,3). However, unlike with ICIs, responses are not durable and disease eventually progresses. Outrunning osimertinib in first-line treatment of metastatic EGFR mutation (EGFR<sup>m</sup>)-positive NSCLC would require novel strategies such as exploring and exploiting the immune environment of EGFR driven disease.

Of 231 tissue blocks available from the screened population in the FLAURA trial, 197 with sufficient tissue were stained for programmed death ligand 1 (PD-L1) expression, using the SP263 Ventana immunohistochemical assay based on tumor cell staining (TC). Immune cell (IC) scoring incorporated into the VENTANA PD-L1 (SP142) assay, was also performed as part of an exploratory analysis. In a recent paper published in the *Journal of Thoracic Oncology*, Brown and colleagues demonstrated that the efficacy of osimertinib in first-line treatment of EGFR<sup>m</sup>-positive metastatic NSCLC was unaffected by PD-L1 expression regardless of the selected staining threshold (1%, 25% or 50%) and the type of immunohistochemical staining

assay (TC or TC and IC). Moreover, EGFR mutations and PD-L1 expression were not mutually exclusive; yet, the prevalence of PD-L1 expression was lower in EGFR<sup>m</sup>-positive tumors and the difference was more accentuated at higher PD-L1 TC thresholds (51% *vs.* 68% at a TC  $\geq$ 1%, 8% *vs.* 35% at TC  $\geq$ 25% and 5% *vs.* 28% at TC  $\geq$ 50%). In EGFR<sup>m</sup>-positive patients who received osimertinib (N=54), median PFS and response rates (RR) matched those obtained in the overall FLAURA population (median PFS 18.9 months, response rate 80%) and were unaffected by PD-L1 expression (TC/IC  $\geq$ 1% versus TC/IC <1% for PFS and TC  $\geq$ 1% versus TC <1% for RR) (4).

The key message in Brown *et al.*'s analysis of the FLAURA population is that the efficacy of osimertinib remains independent of PD-L1 expression which is concordant with Tang *et al.* and Cho *et al.*'s findings (4-6). A few studies reported improved survival endpoints (again endpoints were heterogeneous across studies) in EGFR<sup>m</sup>-positive patients who were also PD-L1 expressers (7,8). Other studies found adverse outcomes in PD-L1 expressers (9,10). All the studies that tried to answer this pending question were retrospective. PD-L1 status was mainly assessed by immunohistochemistry (IHC); yet thresholds varied significantly across studies. Most of these studies were monocentric and used either erlotinib or gefitinib. Data is scarce regarding the interplay between osimertinib, a more potent EGFR TKI, and PD-L1 expression. EGFR T790 mutant NCI-H1975 cell lines treated with

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osimertinib had a reduced PD-L1 expression regardless of cell death (11). Osimertinib both induced PD-L1 degradation by proteasomes and reduced PD-L1 mRNA expression (11). The consequence of osimertinib-modulated PD-L1 downregulation is unclear and requires further *in vivo* studies. ATHENE (NCT03029858) is an ongoing observational study that measures PD-L1 value change by TC/IC staining as well as PD-L1 expression positive rate change from the baseline to progressive disease in patients with advanced NSCLC with confirmed T790 mutation after prior EGFR-TKI treatment.

Even though they are not mutually exclusive, epidemiological studies found a lower PD-L1 expression in EGFR-driven tumors. In a pooled analysis of 18 studies with 3,969 patients, Soo *et al.* obtained a 41% lower likelihood of PD-L1 expression in EGFRm-positive patients (12). Despite the heterogeneity of study designs and PD-L1 testing assays, these results were corroborated by three additional analyses (13-15). In the FLAURA trial, EGFRm-positive patients with PD-L1 expression  $\geq 1\%$  (N=52) were more likely to be of Asian ethnicity (37% *vs.* 20% in PD-L1 negative patients) and to harbor L858R mutations (42% *vs.* 33%). Conversely, non-expressers of PD-L1 were more likely to be of white Caucasian ethnicity (80% *vs.* 63% in PD-L1 expressers) and to harbor exon 19 deletions (63% *vs.* 56%). Smoking status did not vary between the two groups (4). However, these data are merely observational as no multivariate analysis was performed. The majority of related studies evaluate the association between PD-L1 expression and clinicopathologic features including EGFR mutations but provide very little information about the characteristics of PD-L1 expressers among EGFRm-positive patients (14,16). Therefore, characterization of this group of EGFRm-positive patients who are also PD-L1 expressers is pertinent and might help identify which patients benefit from ICIs after EGFR-TKIs. Interestingly, in a study of 25 EGFRm-positive patients who received nivolumab after disease progression on EGFR-TKI therapy, Haratani *et al.* observed a higher PD-L1 expression in T790M-negative versus T790M-positive patients (17).

The activation of the PD-1/PD-L1 pathway negatively regulates immune responses and allows for cancer progression and metastasis. PD-L1 expression level is currently used as a predictive biomarker for anti-PD-1/PD-L1 ICIs in the treatment of NSCLC (18). However, this biomarker is far from perfect and did not predict response to first-line nivolumab in stage IV or recurrent NSCLC (19). Furthermore, a phase II trial of pembrolizumab in TKI-

naïve EGFRm-positive and PD-L1 positive (PD-L1  $\geq 1\%$ ) patients with advanced NSCLC was prematurely ceased due to lack of efficacy despite a PD-L1 expression  $\geq 50\%$  in 73% of patients (20). Indeed, EGFR mutated tumors do not seem to respond well to immunotherapy. The biological basis for the lack of efficacy remains unclear and the majority of the trials testing the efficacy of ICIs excluded patients with driver mutations (2,21). Conversely, IMpower 150 was the first randomized phase 3 trial of an ICI combined with chemotherapy and bevacizumab that demonstrated improved PFS and OS in patients with sensitizing EGFR mutations who were previously treated with EGFR-TKIs for advanced non-squamous NSCLC (22). *Table 1* lists the main studies of ICIs in advanced NSCLC that included EGFRm-positive patients (3,20,22-32). CheckMate 722 and Keynote-789 are 2 ongoing studies comparing the combination of chemotherapy with Nivolumab (with or without ipilimumab) or Pembrolizumab, respectively, to chemotherapy alone in TKI-resistant advanced non-squamous EGFRm+ NSCLC (NCT02864251 and NCT03515837). Additional information on post-study ICI use in Brown *et al.*'s analysis of FLAURA would have been particularly instructive. PD-L1 might not be the best biomarker to predict the efficacy of immunotherapy in EGFRm-positive tumors. Other biomarkers were studied in NSCLC, namely the tumor mutational burden (TMB) measured as the number of mutations in the whole exome or per megabase and the tumor microenvironment (TME). TMB was a strong predictor of PFS irrespective of PD-L1 expression in a phase III trial combining nivolumab and ipilimumab as first-line treatment of advanced NSCLC without driver mutations (21). A significant association between TMB and EGFRm-negative status (P=0.0111) was noted in a multivariate analysis (33). On the other hand, Gainor *et al.* found that a low expression of PD-L1 and CD8 positive tumor infiltrating lymphocytes (TILs) within the TME might explain the disappointing results of immunotherapy in EGFRm-positive tumors (34). In opposite, type 1 TME phenotype with both high PD-L1 and CD8 positive TILs might be a promising predictor of efficacy of anti-PD-1/PD-L1 therapy in NSCLC including EGFRm-positive disease (10,35).

Besides selecting the adequate population and finding the correct predictive biomarker, combination therapy might allow ICIs to find their place in EGFR-driven disease. Studies suggested an active role for the EGFR oncogene in remodeling the TME. EGFRm-positive tumors may be characterized by host T cell exhaustion specifically through

**Table 1** EGFRm-positive patients in studies of immune checkpoint inhibitors in the treatment of advanced NSCLC

Study (author, year)	Design and summary	Number of EGFRm+ patients	PDL1 expression in EGFRm+ patients	ORR of EGFRm+ patients	Median OS of EGFRm+ patients	Median PFS of EGFRm+ patients
CHECKMATE 057 (23) (Borghaei et al., 2015)	Randomized open-label, Ph3, nivolumab vs. docetaxel, advanced NON-squamous NSCLC, L >1	82 (overall population 582, 14%); 44 of 82 had nivolumab; 53 of 582 received EGFR TKIs	No data	No data	EGFRm+ HR 1.18 (95% CI 0.69-2.00); EGFRm- HR 0.66 (95% CI, 0.51-0.86)	EGFRm+ HR 1.46 (95% CI, 0.9-2.37); EGFRm- HR 0.83 (95% CI, 0.65-1.06)
KEYNOTE 010 (24) (Herbst et al., 2016)	Randomized open-label Ph2/3, Pembrolizumab vs. docetaxel, advanced PD-L1 TPS ≥ 1% NSCLC, L >1	86 (overall population 1,033, 8%); EGFRm+ pretreated with EGFR TKIs; 60 of 86 had pembrolizumab	TPS ≥ 50% in 34 patients (overall population 442 with TPS ≥ 50%); 21 of 34 received pembrolizumab	No data	EGFRm+ HR 0.88 (95% CI 0.45-1.70); EGFRm- HR 0.66 (95% CI, 0.55-0.8)	EGFRm+ HR 1.79 (95% CI, 0.94-3.42); EGFRm- HR 0.83 (95% CI, 0.71-0.98)
OAK (25) (Rittmeyer et al., 2017)	Randomized open-label Ph3, Atezolizumab vs. docetaxel, advanced NSCLC, L >1	85 (overall population 850, 10%); EGFRm+ pretreated with EGFR TKIs; 42 of 85 had Atezolizumab	No data	No data	EGFRm+; HR 1.24 (95% CI 0.71-2.18); EGFRm- HR 0.69 (95% CI, 0.57-0.83)	No difference in PFS between EGFRm+ and EGFRm-
JAVELIN LUNG 200 (26) (Barlesi et al., 2018)	Randomized open-label Ph3, avelumab vs. docetaxel, advanced NSCLC, L >1 (EGFRm-positive pretreated with EGFR TKI—later amendment)	24 (overall population 792, 3%); EGFRm+ pretreated with EGFR TKIs; 11 of 24 had avelumab	PD-L1 ≥ 1% on TC in 12 EGFRm+ patients (overall population 529 PD-L1 ≥ 1%); 5 of 12 had avelumab	No data	No data	No data
IMpower 150 (3,22) (Socinski et al., 2018 and Reck et al., 2019)	Randomized open-label Ph3, atezolizumab + carboplatin + paclitaxel (ACP) vs. bevacizumab + carboplatin + paclitaxel (BCP), or atezolizumab + BCP (ABCP) followed by maintenance with atezolizumab and/or bevacizumab, advanced non squamous NSCLC, L1	ABCP vs. ACP vs. BCP: 124 EGFRm+; 91 EGFR sensitizing mutations (overall population 1,202, 8%); 59 of 91 had Atezolizumab (ABCP or ACP); 13 of 91 (14%) EGFRm+ were not pretreated with EGFR TKIs	ABCP: 21 of 34 (62%) EGFRm+ were PD-L1 negative (<1% on TC and IC) vs. 167 of 359 (47%) EGFR WT; overall ITT population, PD-L1 ≥ 50% on TC or ≥ 10% on IC: 13 (10%) EGFRm+ patients vs. 199 EGFR WT (17%)	ABCP: ORR 24 of 34 (71%) EGFRm+ vs. 224 of 397 (56%) overall ITT population; ACP: ORR 16 of 45 (36%) EGFRm+ vs. 163 of 401 (41%) overall ITT population; BCP: ORR 18 of 43 (42%) EGFRm+ vs. 158 of 393 (40%) overall ITT population	ABCP vs. BCP/ subgroup with sensitizing EGFR mutations: OS NE vs. 17.5 months, HR 0.31 (95% CI, 0.11-0.83); ACP vs. BCP/subgroup with sensitizing EGFR mutations: no difference in OS	ABCP vs. BCP/ subgroup with sensitizing EGFR mutations: longer PFS 10.3 vs. 6.1 months, HR 0.41 (95% CI, 0.23-0.75); ACP vs. BCP/subgroup with sensitizing EGFR mutations: no difference in PFS

**Table 1** (continued)

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Study (author, year)	Design and summary	Number of EGFRm+ patients	PD-L1 expression in EGFRm+ patients	ORR of EGFRm+ patients	Median OS of EGFRm+ patients	Median PFS of EGFRm+ patients
IMpower 130 (27) (West et al., 2019)	Randomized open-label Ph3, atezolizumab + carboplatin + nab-paclitaxel vs. CT alone, advanced non squamous NSCLC, L1	44 (ITT population 723, 6%); EGFRm+ pretreated with EGFR TKIs; 32 of 44 had atezolizumab	PD-L1 expression similar in ITT and WT populations. No data on PD-L1 expression in EGFRm+ subgroup	No data	No OS benefit of adding atezolizumab in subgroup of patients with EGFR alterations	No PFS benefit of adding atezolizumab in subgroup of patients with EGFR alterations
Lisberg et al., 2018 (20)	Ph2 trial, pembrolizumab in TKI naive EGFRm+, PD-L1 $\geq 1\%$ patients with advanced NSCLC	11; 82% treatment naive	73% had PD-L1 $\geq 50\%$	1 patient (9%); repeat analysis showed he was EGFRm-	No data; ceased for futility	No data; ceased for futility
CHECKMATE012 (28) (Hellmann et al. 2017)	Ph1 multicohort study, nivolumab 1 mg/kg Q2w + ipilimumab 1 mg/kg Q6w (Arm A) vs. nivolumab 3 mg/kg Q2w + ipilimumab 1 mg/kg Q12w (ARM B), vs. nivolumab 3 mg/kg Q2w + ipilimumab 1 mg/kg Q6w 5ARM C), advanced NSCLC, L1	Arm B + C: 8 (overall population 77, 10%); Arm B: 4 EGFRm+ of 38 patients (11%); Arm C: 4 EGFRm+ of 39 patients (10%)	Arm B + C: PD-L1 $\geq 1\%$ in 7 of 8 patients; PD-L1 $\geq 50\%$ in 3 of 8 patients	4 of 8 EGFRm+ (50%)	No data	No data
ATLANTIC (29) (Garassino et al., 2018)	Ph2 durvalumab in advanced NSCLC, L $\geq 3$	97 (overall population 444, 22%); EGFRm+ pretreated with EGFR TKIs	PD-L1 expression on TC in the cohort EGFRm+ or ALK+ (97 EGFRm+ of 111 patients); $< 25\%$ 30 patients (27%); $\geq 25\%$ 77 patients (69%); $\geq 90\%$ 47 patients (42%)	In the cohort EGFRm+ or ALK+; 10 patients of these 10 patients had PD-L1 $< 25\%$ in the cohort EGFRm- and ALK-; OS 9.3 m in PD-L1 $< 25\%$ and 10.9 m in PD-L1 $\geq 25\%$ and 13.3 m in PD-L1 $\geq 25\%$ ; in the cohort EGFRm- and ALK-; OS 9.3 m in PD-L1 $< 25\%$ and 10.9 m in PD-L1 $\geq 25\%$ and 13.3 m in PD-L1 $\geq 25\%$ ; in the cohort EGFRm- and ALK-; OS 9.3 m in PD-L1 $< 25\%$ and 10.9 m in PD-L1 $\geq 25\%$ and 13.3 m in PD-L1 $\geq 25\%$	In the cohort EGFRm+ or ALK+; OS 9.9 m in PD-L1 $< 25\%$ and PFS 1.9 m in PD-L1 $< 25\%$ and 1.9 m in PD-L1 $\geq 25\%$ ; in the cohort EGFRm- and ALK-; PFS 1.9 m in PD-L1 $< 25\%$ and 3.3 m in PD-L1 $\geq 25\%$	In the cohort EGFRm+ or ALK+; PFS 1.9 m in PD-L1 $< 25\%$ and 1.9 m in PD-L1 $\geq 25\%$ ; in the cohort EGFRm- and ALK-; PFS 1.9 m in PD-L1 $< 25\%$ and 3.3 m in PD-L1 $\geq 25\%$
BIRCH (30), a humanized anti-programmed death-ligand 1 (PD-L1) (Peters et al., 2017)	Ph2, atezolizumab in advanced NSCLC, PD-L1 TC or IC $\geq 5\%$ , L $\leq 2$	45 (overall population 543, 8%); 11 had atezolizumab in L1	No data	L1: 3 (23%) patients in EGFRm+ group vs. 20 (19%) in EGFRm- group; L2: 0 (0%) in EGFRm+ vs. 43 (21%) in EGFRm-; L3: 1 (7%) in EGFRm+ vs. 35 (18%) in EGFRm-	L1: 20.1 m in EGFRm+ vs. not estimable in EGFRm-; L2: 9.8 m in EGFRm+ vs. 16.3 m in EGFRm-; L3: 7.4 m in EGFRm+ vs. 14.7 m in EGFRm-	L1: 5.5 m in EGFRm+ vs. 5.5 m in EGFRm-; L2: 1.3 min in EGFRm+ vs. 12.8 m in EGFRm-; L3: 1.4 m in EGFRm+ vs. 12.8 m in EGFRm-

Table 1 (continued)

Table 1 (continued)

Study (author, year)	Design and summary	Number of EGFRm+ patients	PDL1 expression in EGFRm+ patients	ORR of EGFRm+ patients	Median OS of EGFRm+ patients	Median PFS of EGFRm+ patients
IMMUNOTARGET (31) (Mazieres et al., 2019)	Retrospective trial, registry of patients with advanced NSCLC and oncogenic driver alterations treated with immune checkpoint inhibitors (5% in L1)	125 EGFRm-positive (overall population 551, 23%)	Median percentage of cells expressing PD-L1 $\geq 1\%$ : 3.5 (n=38); Significantly Longer PFS in EGFRm+ PD-L1 positive vs. negative patients	PD in 83 (67%) EGFRm+ patients; best response rate for patients with driver mutation except KRAS 12.7%	10 m (95% CI, 6.7–14.2)	2.1 m (95% CI, 1.8–2.7); Significantly different across molecular subgroups, shortest in T790M and complex mutations
Italian Nivolumab Expanded Access Program (EAP) (32) 305 (Garassino et al., 2018)	Retrospective, nivolumab after 1 or more systemic treatments in patients with non-squamous NSCLC	102 (overall population 1,588, 6%); 93 of 102 previously received EGFR TKIs	No data	ORR higher in EGFRm- vs. EGFRm+ patients; 19.6% vs. 8.8% (P=0.007)	No significant difference in OS between EGFRm- and EGFRm+ patients (11 vs. 8.3 m)	No significant difference in PFS between EGFRm- and EGFRm+ patients: 3 months in both groups

EGFRm+, epidermal growth factor receptor mutation positive; EGFRm-, epidermal growth factor receptor mutation negative; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; CT, chemotherapy; RT, radiation therapy; NSCLC, non-small cell lung cancer; L, treatment line; TC, tumor cell; IC, immune cell; TPS, tumor positive score; PD-L1, programmed death ligand 1; HR, hazard ratio; CI, confidence interval; vs., versus; Ph3, phase 3; Ph2, phase 2; Ph1, phase 1; EGFR TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; nab, nanoparticle albumin-bound; ITT, intention-to-treat; Q, every; w, weeks; m, months; ALK+, anaplastic lymphoma kinase positive; ALK-, anaplastic lymphoma kinase negative; PD, progressive disease; NE, not estimable.

upregulation of the PD-1/PD-L1 pathway (36). In addition, EGFR TKIs have contrasting immunomodulatory effects. Erlotinib and Gefitinib increase the sensitivity of lung cancer cells to natural killer cell-mediated lysis through upregulation of NKG2D ligands (37). They also enhance major histocompatibility index class I (MHCI) and II (MHCII) molecules in response to IFN- $\gamma$  thus increasing T cell mediated tumor killing (38). Conversely, EGFR TKIs also have immunosuppressive effects through inhibition of T-cell proliferation and activation and through inhibition of monocyte differentiation and increase in circulating myeloid derived suppressor cells (39). Akbay *et al.* found a reduction in PD-L1 expression in vitro after treatment with EGFR TKIs (36). Based on the previous findings of immunostimulatory and immunosuppressive functions of EGFR TKIs, one can conclude that the addition of these drugs to ICIs might not be the miraculous solution to implement immunotherapy in EGFRm-positive advanced NSCLC. Moreover, EGFR TKIs and ICIs have overlapping toxicities such as pneumonitis, which could be life-threatening in some cases, thus caution is advised when designing phase I combination studies. In fact, Schoenfeld *et al.* reported severe immune-related adverse events in 15% of patients treated with sequential ICIs followed by osimertinib, especially when the latter was started within the first 3 months following ICIs (40). Also in the multi-arm phase Ib TATTON trial, the combination of osimertinib and durvalumab in patients with EGFRm-positive advanced NSCLC progressing on prior EGFR TKI treatment was associated with interstitial lung disease in 22% of patients including one with a grade 5 pneumonia (41). On the other hand, yes-associated protein (YAP) is the main mediator of the Hippo signalling pathway. Its activation through loss of Hippo signalling by mutation, and downregulation of the core Hippo components, promotes cancer progression, drug resistance and metastasis in NSCLC. The EGFR/MAPK signalling pathway stimulates YAP. Inhibition of YAP could be used in the treatment of NSCLC with acquired resistance to EGFR-TKIs, and to increase sensitivity to BRAF and MEK inhibitors (42,43). Anti YAP therapy could also be combined with ICIs to improve their efficacy in EGFR driven disease. Statins, cucurbitacin E, dasatinib, dobutamine, norcantharidin, JQ1, agave and MLN8237 are some of the molecules that inhibit YAP and that could be tested in combination with immunotherapy in future phase I studies of EGFR driven, TKI resistant tumors (44).

Despite the magnitude and the solid design of FLAURA, the debate about oncogene addiction and immune escape

is far from being closed. Outrunning osimertinib in the first-line treatment of EGFRm-positive advanced NSCLC requires us to deepen our knowledge of the immune microenvironment of EGFR-driven disease, to find consistent prognostic and predictive biomarkers and finally to carefully develop both smart and safe combination therapies.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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