In 1L metastatic EGFRm NSCLC

TREAT FIRST WITH AN EGFR TKI—NOT IO—REGARDLESS OF PD-L1 EXPRESSION

- NCCN recommends testing patients for actionable mutations to identify potentially efficacious targeted therapies and avoid therapies unlikely to provide clinical benefit[1]
- EGFR mutations commonly coexist with PD-L1 expression in patients with mNSCLC[2-5]
- Treatment guidelines and FDA approvals do not include the use of immunotherapy as first-line treatment in EGFRm mNSCLC[1,7-9]
- SITC guidelines recommend IO for EGFRm patients only after targeted therapy and chemotherapy[6]
- The only known trial in a few TKI-naïve EGFRm NSCLC patients suggests that IO may be ineffective as first-line treatment in patients with metastatic EGFRm NSCLC[24]
- Without a full molecular profile, patients may not receive optimal treatment

NCCN GUIDELINES®

NCCN recommends treatment with targeted therapy take precedence over treatment with immunotherapy in patients with mNSCLC and oncogenic drivers, even when PD-L1 expression levels are elevated.[1]

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.2.2020. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed December 23, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Akamine T, Takada K, Toyokawa G, et al. Association of preoperative serum CRP with PD-L1 expression in 508 patients with non-small cell lung cancer: a comprehensive analysis of systemic inflammatory markers. *Surg Oncol.* 2018;27(1):88-94. **3.** D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. *Br J Cancer.* 2015;112(1):95-102. **4.** Liu SY, Dong ZY, Wu SP, et al. Clinical relevance of PD-L1 expression and CD8+ T cells infiltration in patients with EGFR-mutated and ALK-rearranged lung cancer. *Lung Cancer.* 2018;125:86-92. **5.** Yoneshima Y, Ijichi K, Anai S, et al. PD-L1 expression in lung adenocarcinoma harboring EGFR mutations or ALK rearrangements. *Lung Cancer.* 2018;118:36-40. **6.** Brahmer JR, Govindan R, Anders RA, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *J Immunother Cancer.* 2018;6(1):75. **7.** Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2020. **8.** Tecentriq [package insert]. South San Francisco, CA: Genentech Inc.; 2019. **9.** Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2019. **10.** Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1–positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823-1833. **11.** Clinicaltrials.gov. Study of MK-3475 (pembrolizumab) versus platinum-based chemotherapy for participants with PD-L1-positive advanced or metastatic non-small cell lung cancer (MK-3475-042/KEYNOTE-024). https://clinicaltrials.gov/ct2/show/NCT02220894. Accessed August 15, 2019. **12.** Langer CJ, Gadgeel SM, Borghaei H, et al; KEYNOTE-021 Investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497-1508. **13.** Borghaei H, Langer CJ, Gadgeel S, et al. 24-month overall survival from KEYNOTE-021 Cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non–small cell lung cancer. *J Thorac Oncol.* 2019;14(1):124-129. **14.** Broderick JM. Frontline pembrolizumab combo improves survival in phase III NSCLC trial. https://www.onclive.com/web exclusives/frontline-pembrolizumab-combo-improves-survival-in-phase-iii-nsclc-trial. Published January 16, 2018. Accessed August 15, 2019. **15.** Carbone DP, Reck M, Paz-Ares L, et al; CheckMate 026 Investigators. First-line nivolumab in stage IV or recurrent non–small-cell lung cancer. *N Engl J Med.* 2017;376(25):2415-2426. **16.** Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med.* 2018;378(22):2093-2104. **17.** Clinicaltrials.gov. A study of nivolumab and ipilimumab combined with chemotherapy compared to chemotherapy alone in first line NSCLC (CheckMate 9LA). https://clinicaltrials.gov/ct2/show/NCT03215706. Accessed January 10, 2020. **18.** EU Clinical Trials Register. A phase III clinical study to evaluate the efficacy and safety of atezolizumab in combination with carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel in patients with stage IV non-squamous non-small cell lung cancer. EudraCT number 2014-003206-32. https://www.clinicaltrialsregister.eu/. Accessed August 15, 2019. **19.** West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):924-937. **20.** Kowanetz M, Socinski MA, Zou W, et al. IMpower150: efficacy of atezolizumab plus bevacizumab and chemotherapy across PD-L1 expression subgroups defined by the SP142 and SP263 IHC assays confirm all-comer benefit in 1L metastatic NSCLC. Presented at: AACR; April 14-18, 2018; Chicago, IL. **21.** Papadimitrakopoulou VA, Cobo M, Bordoni R, et al. IMpower132: PFS and safety results with 1L atezolizumab + carboplatin/cisplatin + pemetrexed in stage IV non-squamous NSCLC [oral presentation]. Presented at: IASLC WCLC; September 23-26, 2018; Toronto, Canada. **22.** Spigel D, de Marinis F, Giaccone G, et al. IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. Presented at: European Society for Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Abstract LBA78. **23.** Clinicaltrials.gov. A study of atezolizumab (MPDL3280A) compared with a platinum agent (cisplatin or carboplatin) + (pemetrexed or gemcitabine) in participants with stage IV non-squamous or squamous non-small cell lung cancer (NSCLC) [IMpower110]. https://clinicaltrials.gov/ct2/show/NCT02409342. Accessed January 10, 2020. **24.** Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. *J Thorac Oncol.* 2018;13(8):1138-1145.

AstraZeneca

In metastatic EGFRm non-small cell lung cancer (NSCLC)

TREAT THE DRIVER OF DISEASE

National Comprehensive Cancer Network® (NCCN®) recommends testing eligible patients with mNSCLC for targetable genetic alterations to[1]*:

- Identify potentially efficacious targeted therapies
- Avoid therapies unlikely to provide clinical benefit

*The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.

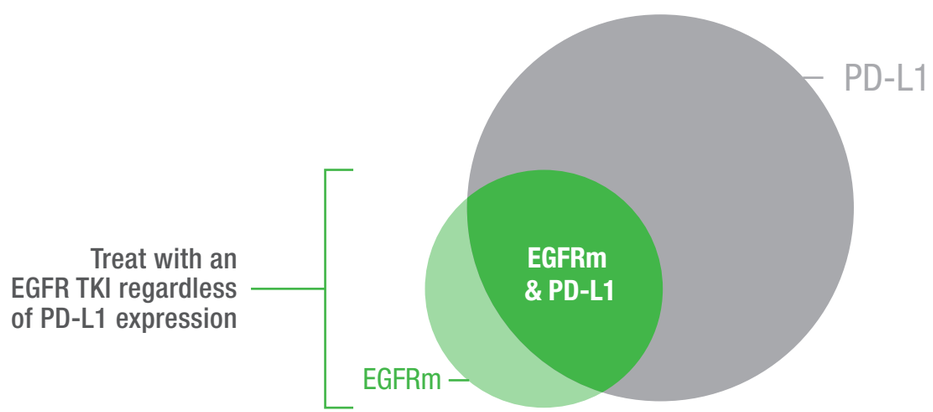
AstraZeneca

When metastatic EGFRm NSCLC patients express PD-L1

EGFR TKIs—NOT IO—ARE THE GUIDELINE RECOMMENDED FIRST-LINE TREATMENT

PD-L1 expression is common in patients with EGFR mutations[2-5]

- PD-L1 expression and actionable driver mutations are not mutually exclusive; up to 70% of EGFRm patients express at least 1% PD-L1



NCCN GUIDELINES® **NCCN recommends treatment with targeted therapy take precedence over treatment with immunotherapy in patients with mNSCLC and oncogenic drivers, even when PD-L1 expression levels are elevated.[1]**

Only AFTER treatment with an EGFR TKI is immunotherapy an option for metastatic EGFRm NSCLC patients[1,6-9]*

- Treatment guidelines and FDA approvals include the use of immunotherapy for EGFRm patients only after EGFR TKIs have been exhausted

*Data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.

IO, immunotherapy.

In metastatic NSCLC

NO EVIDENCE SUPPORTS TREATING EGFRm PATIENTS WITH IMMUNOTHERAPY FIRST

Eleven large and robust 1L IO trials EXCLUDED treatment-naïve EGFRm patients[10-23]

Therapy	Trial	Allowed treatment-naïve EGFRm patients
Pembrolizumab monotherapy	KEYNOTE-024	NO
	KEYNOTE-042	NO
Pembrolizumab + doublet chemotherapy	KEYNOTE-021 Cohort G	NO
	KEYNOTE-189	NO
Nivolumab monotherapy	CHECKMATE 026	NO
Nivolumab monotherapy ± ipilimumab or doublet chemotherapy	CHECKMATE 227	NO
Nivolumab + ipilimumab + chemotherapy	CHECKMATE 9LA	NO
Atezolizumab + doublet chemotherapy	IMpower130†	NO
Atezolizumab ± bevacizumab + doublet chemotherapy	IMpower150†	NO
Atezolizumab ± doublet chemotherapy	IMpower132	NO
Atezolizumab monotherapy	IMpower110	NO

The only known trial of IO in treatment-naïve EGFRm NSCLC patients was stopped early due to lack of efficacy[24]

- Enrollment in the phase 2 study (NCT02879994) was ceased after 11 of 25 planned patients were treated; no responses were observed in 10 of the 11 EGFRm NSCLC patients that were treated, even though the majority of patients were PD-L1 high (TPS ≥50%)
  - The patient who did have a response was revealed to be EGFR wild-type upon repeat analysis

No IO therapies, either as a single agent or in combination, are FDA approved for treatment-naïve EGFRm mNSCLC patients[7-9]

IN EGFRm mNSCLC, PD-L1 EXPRESSION IS IRRELEVANT—CHOOSE 1L THERAPY THAT TREATS THE DRIVER OF DISEASE

†EGFRm and ALK positive patients were allowed only after progression or intolerance to treatment with one or more approved targeted therapies.

AstraZeneca