Oncogenic Driver Mutations and Immune Checkpoint Inhibitors

- Oncogenic driver mutations affect diverse molecular pathways, with differing effects on the tumor microenvironment that may impact clinical benefit of immune checkpoint inhibitors (ICIs)
- Early trials of ICI monotherapy found reduced activity in patients with *EGFR* or *ALK* positive disease
- Evidence is limited because:
  - Later prospective trials largely excluded patients with *EGFR* and *ALK* alterations
  - Others did not investigate driver mutation status
- FDA approvals for first line use of ICIs in advanced NSCLC are mostly restricted to patients who do not carry *EGFR* and *ALK* alterations (with the addition of *ROS1* alterations for cemiplimab)
- Ongoing investigation of genomic subsets of NSCLC as well as further predictive markers for ICI benefit will continue to impact practice in this area

EGFR, epidermal growth factor receptor.

FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm; Otano I et al. *Nat Rev Clin Oncol*. 2023;20:143-159.

Benefit from Immune Checkpoint Inhibitor Monotherapy Varies by Type of Driver Mutation in Advanced NSCLC

Driver mutation	Number of trials	Total number of patients	ORR	PFS
EGFR	6	489	0%-12%	2-4 mo
ALK	3	40	0%	2 mo
ROS1	1	6	17%	NR
HER2 (*ERBB2*)	3	86	8%-27%	2-3 mo
RET	3	40	0%-37%	2-8 mo
KRAS	4	1157	19%-37%	3-4 mo
BRAF	6	220	20%-62%	2-8 mo
MET ex14 skipping	4	120	17%-36%	2-5 mo

- *KRAS*, *BRAF* and *MET* exon 14 skipping mutations are enriched in smokers
- Smoking is also associated with high TMB, which is predictive of benefit from immune checkpoint inhibitors

- Evidence largely derived from small trials, retrospective studies, and real-world databases
- Data are even more limited for currently used ICI combinations

ORR, objective response rate; PFS, progression-free survival; mo, months; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; TMB, tumor mutational burden.

Otano I et al. *Nat Rev Clin Oncol*. 2023;20:143-159.

Oncogenic Driver Mutations as Negative Biomarkers for First Line Immune Checkpoint Inhibitor Use in Advanced NSCLC

Agent	Biomarker	First Line Indication(s)
Atezolizumab	No *EGFR* or *ALK* alterations	• Monotherapy in patients with high PD-L1 (TC ≥ 50% or IC ≥ 10%) • In combination with bevacizumab, paclitaxel, and carboplatin, non-squamous only • In combination with paclitaxel protein-bound and carboplatin, non-squamous only
Durvalumab	No *EGFR* or *ALK* alterations	• In combination with tremelimumab-actl + platinum-based chemotherapy
Nivolumab	No *EGFR* or *ALK* alterations	• In combination with ipilimumab with PD-L1 ≥ 1% • In combination with ipilimumab and 2 cycles platinum-doublet chemotherapy
Pembrolizumab	No *EGFR* or *ALK* alterations	Non-squamous • In combination with pemetrexed and platinum-based chemotherapy • As monotherapy in patients with PD-L1 ≥ 1%
Pembrolizumab	**No restriction by oncogenic driver**	Squamous • In combination with carboplatin and paclitaxel or paclitaxel protein-bound
Cemiplimab	**No *EGFR*, *ALK*, or *ROS1* alterations**	• In combination with platinum-based chemotherapy • As monotherapy in patients with high PD-L1 (TPS ≥ 50%)

EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; IC, tumor-infiltrating immune cells; TC, tumor cells; TPS, tumor proportion score.

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