Research Question:

What is the response rate of chemo vs Keytruda vs targeted agents -EGFR, ALK, ROS, RET, MET and BRAF lung cancer response rate?

Research Summary:

Our search did not reveal any conclusive data comparing chemotherapy versus pembrolizumab versus targeted agents in lung cancer patients expressing the six mutations. Network meta-analyses and systematic reviews have attempted to compare pembrolizumab versus other ICIs for use in lung cancer, but these analyses are limited by few eligible studies. Clinical data on pembrolizumab use in advanced lung cancer typically included patients who were naïve to targeted therapy (e.g., TKI) or had progressed; minimal comparative data between pembrolizumab and targeted therapy for lung cancer exists.

Background:

A recent 2022 review provided current data regarding the response rate of certain ICI for patients presenting with BRAFV600E mutation in non-small cell lung cancer. Observed ICI include vemurafenib, dabrafenib, sorafenib, BGB-283, and LXH254+LTT462), none of which seem to compare with pembrolizumab. For patients with BRAF mutation, ongoing clinical trials will investigate the combination of pembrolizumab plus trametinib. [1]
A 2021 review details current evidence of immunotherapy in non-small cell lung cancer. While the assessment provides details regarding pembrolizumab therapy with regards to specific genetic properties, there is no comparative evidence presented regarding chemotherapy. The authors identified ongoing trials comparing immunotherapy to chemotherapy, but the majority of these are scheduled for completion in 2024. [2]

A 2021 review included four randomized trials (CheckMate9LA, KEYNOTE-021G, KEYNOTE 189, KEYNOTE407) involving 2,017 patients to assess the indirect treatment comparison (ITC). Nivolumab + ipilimumab +two cycles of chemotherapy (N-I + chemo) revealed comparable ITC results versus pembrolizumab +chemotherapy (Pem + chemo) in overall survival with a hazard ratio [HR] 1.03 (95% confidence interval [CI]0.82- 1.30) and objective response rate [ORR] of 0.81 (95% CI 0.62-1.06). However, progression-free survival (PFS) was shown to be inferior in N-I + chemotherapy compared to Pem + chemo (HR 1.28, 95% CI 1.04-1.59). Overall, Pem + chemo was preferable in providing superior overall survival (OR) benefit compared to NI + chemo with no significant difference in safety profile relative to N-I + chemo combination therapy. [3]

A 2020 systematic review and network meta-analysis included four phase III trials to compare the efficacy and safety of nivolumab (Niv) plus ipilimumab (Ipi) combination therapy (Niv + Ipi) and existing regimens with immunotherapies, pembrolizumab (Pem) plus platinum-based

chemotherapy (PBC) (Pem + PBC), Pem, Niv, or PBC. Overall, for PFS, Niv + Ipi was revealed to be inferior to Pem + PBC and superior to Pem, Niv, or PBC alone. The combination of Pem + PBC had the highest ranking for PFS, followed by Niv + Ipi, Niv, PBC, and Pem. Niv + Ipi was significantly superior in PFS improvement to Pem, Niv, and PBC with HR (0.770 [95%credible intervals (CrI), 0.632 to 0.930]; 0.832 [0.710 to 0.970], and 0.823 [0.708 to 0.950]), respectively. There was a significant PFS improvement with Pem + PBC compared to Pem, Niv, and PBC with HR and 95%CrI (0.436 [0.346 to 0.542], 0.474 [0.352 to 0.624], and 0.465 [0.384 to 0.558]), respectively. The authors noted although heterogeneity among the trials was not significant, it could have affected the conclusion.[4]

An analysis (N= 384; 371 adenocarcinomas, 13 squamous cell carcinomas or not otherwise specified) evaluating the impact of MET expression in advanced non-small cell lung cancer on clinical outcomes found no association of MET expression with chemotherapy outcome. While high MET expression negatively affected the outcome under EGFR-targeting therapy (n= 45 patients with EGFR-mutated NSCLC receiving TKI therapy [afatinib, erlotinib, gefitinib or Osimertinib]; p= 0.053), it was associated with favorable outcomes under PD-1/PD-L1 therapy (n= 51 patients receiving nivolumab or pembrolizumab).The OS and time-to-treatment failure (TTF) of anti-PD-1/PD-L1-treated patients were superior in high MET expressors (OS IO: HR= 0.26, p= 0.052, TTF IO: HR= 0.58, p= 0.277). Notably, pembrolizumab yielded inadequate response in two patients with MET exon 14 and high PD-L1 expression. [5]

References:

[1] Yan N, Guo S, Zhang H, Zhang Z, Shen S, Li X. BRAF-Mutated Non-Small Cell Lung Cancer: Current Treatment Status and Future Perspective. Front Oncol. 2022 Mar 31;12:863043. doi: 10.3389/fonc.2022.863043. PMID: 35433454;PMCID: PMC9008712.[2] Mielgo-Rubio X, Uribe larrea EA, Cortés LQ, Moyano MS. Immunotherapy in non-small cell lung cancer: Update and new insights. J Clin Transl Res. 2021 Jan 20;7(1):1-21. PMID: 34104805; PMCID: PMC8177026.[3] Jiang P, Mao Z, Wang Q, Jia X, Geng L, Xu H, Jiang L, Yang C, Jiao M, Guo H. An Indirect Comparison Between Nivolumab + Ipilimumab + Two Cycles of Chemotherapy vs. Pembrolizumab + Chemotherapy as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer. Front Oncol. 2021 Sep 13;11:698199. doi: 10.3389/fonc.2021.698199.PMID: 34589422; PMCID: PMC8473819.[4] Ando K, Kishino Y, Homma T, et al. Nivolumab plus Ipilimumab versus Existing Immunotherapies in Patients withPD-L1-Positive Advanced Non-Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis. Cancers (Basel). 2020;12(7):1905. Published 2020 Jul 15. doi:10.3390/cancers12071905[5] Reis H, Metzenmacher M, Goetz M, et al. MET Expression in Advanced Non-Small-Cell Lung Cancer: Effect on Clinical Outcomes of Chemotherapy, Targeted Therapy, and Immunotherapy. Clin Lung Cancer. 2018;19(4):e441-e463.doi:10.1016/j.cllc.2018.03.010