Tumor Board Tuesday – Dr. Nathan Pennell, 10/03/2022:
3rd Line Treatment NSCLC with *EGFR* Mutation

Posttest Rationale

1. **What initial treatment would you select for a 50-year-old female never-smoker who presents with mNSCLC (T1bN0M1a, adenocarcinoma, TTF1+) that has *EGFRdel19* & 70%+ PD-L1 expression on NGS?**

    a. Afatinib
    b. Chemo + pembro
    c. Osimertinib
    d. Pembro alone

Rationale: Osimertinib is the NCCN preferred (category 1) choice for patients with *EGFRdel19* and PS ≤4; afatinib is listed as an "other recommended" option (category 1) for these patients. Platinum doublet chemotherapy plus pembrolizumab or pembrolizumab alone are preferred (category 1) options for patients with ≥50% PD-L1 expression and PS ≤2 who are negative for actionable molecular biomarkers.

Reference: National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer (v5.2022). Updated September 26, 2022. Accessed September 29, 2022. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

2. **What subsequent treatment would you select for a 50-year-old female never-smoker who presents with mNSCLC (adenocarcinoma, *EGFRdel19*, PD-L1 70%+), new liver lesions, & worsening effusion 6 months after SRS to brain lesions & continued osimertinib treatment?**

    a. Continue osimertinib
    b. Datopatomab-DXd
    c. Patritumab-DXd
    d. Pembrolizumab

Rationale: The NCCN guidelines recommend systemic therapy for patients progressing on osimertinib who develop multiple systemic lesions. Patritumab-DXd, an investigational antibody-drug conjugate (ADC) consisting of a HER3 antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker, is likely the best choice for this patient; the FDA granted breakthrough therapy designation to patritumab-DXd in December, 2021, for the treatment of patients with metastatic or locally advanced *EGFR*-mutated NSCLC with disease progression on or after treatment with a third-generation TKI and platinum-based therapies based on phase 1 results that demonstrated an ORR of 39% and an mPFS of 8.2 months (N=57). Datopotamab-DXd has also demonstrated positive phase 1 results in this population (ORR: 24% to 26%), but it has not received breakthrough designation. The evidence is weak for recommending pembrolizumab as subsequent therapy for patients with *EGFR* mutations; among patients with *EFGR* exon 19 deletions or L858R mutations, no improvement in OS has been noted in phase 3 trials assessing subsequent therapy with pembrolizumab compared to docetaxel, but statistical significance could not be determined due to the low number of patients with these mutations. Continuation of osimertinib with consideration of definitive local therapy (in this case, liver resection) may be considered for patients with limited systemic metastases (generally, <3-5 metastases).

References: Janne PA, Baik C, Su WC, et al. Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer. *Cancer Discov*. 2022;12(1):74-89. doi:10.1158/2159-8290.CD-21-0715

Garon E, Johnson M, Lisberg A, et al. MA03.02 TROPION-PanTumor01: Updated Results From the NSCLC Cohort of the Phase 1 Study of Datopotamab Deruxtecan in Solid Tumors. *J Thorac Oncol*. 2021;16(10):S892-S893. doi:10.1016/j.jtho.2021.08.118

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer (v5.2022). Updated September 26, 2022. Accessed September 29, 2022. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf