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Lung Cancer 2023

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

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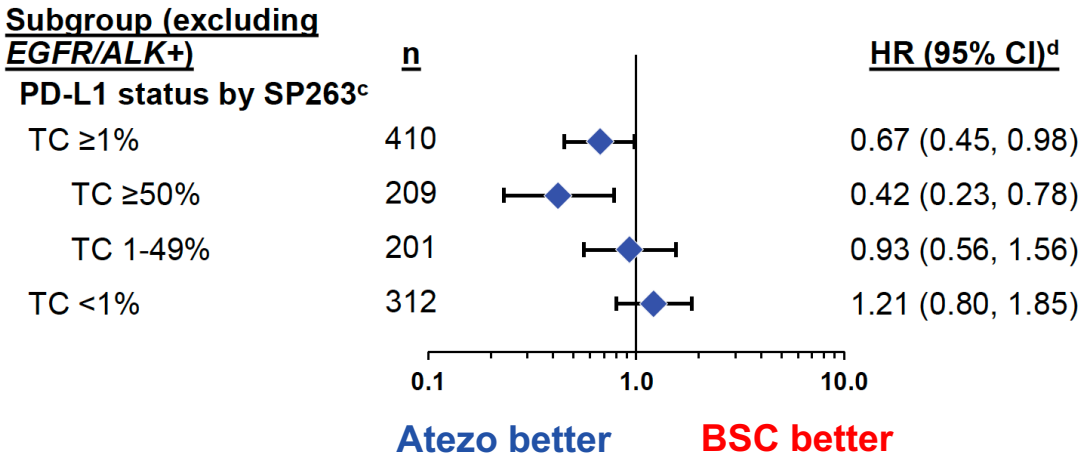
Discussion Question

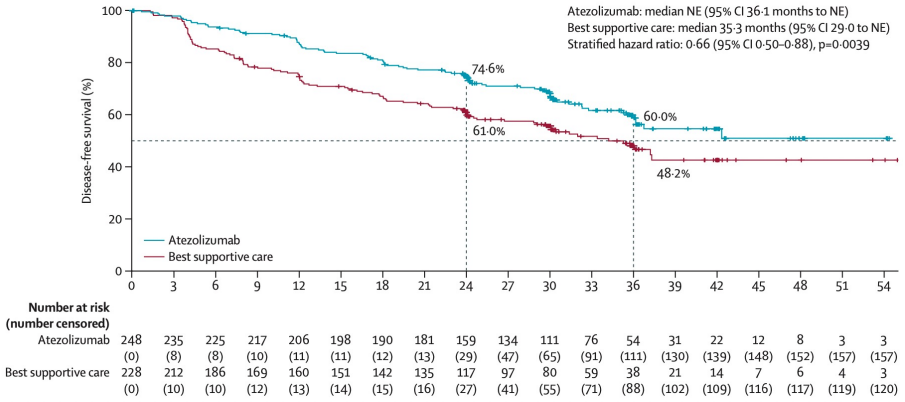
Which patients with localized NSCLC should receive adjuvant therapy with an immune checkpoint inhibitor? How do you choose between adjuvant osimertinib and an anti-PD-1/PD-L1 antibody for your patients with EGFR mutations?

RTP
RESEARCH
TO PRACTICE

Adjuvant Therapy for NSCLC

- Recurrence risks are high even after complete resection
  - Adjuvant chemotherapy offers modest benefit (stage II/III)
- Adjuvant immunotherapy improves DFS
  - IMpower010 showed atezolizumab (after chemotherapy) improved DFS for resected stage II/III PD-L1+ NSCLC (HR 0.66)
    - Greatest benefit in PD-L1 high (HR 0.43)
    - FDA approved for PD-L1+ October 15, 2021

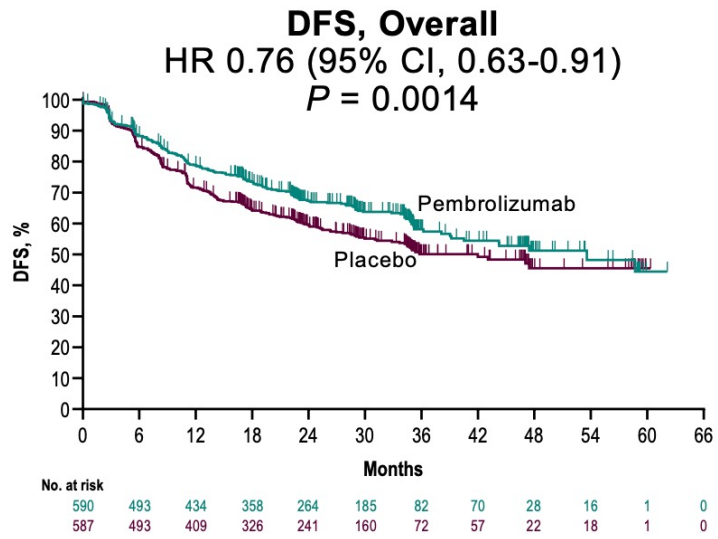


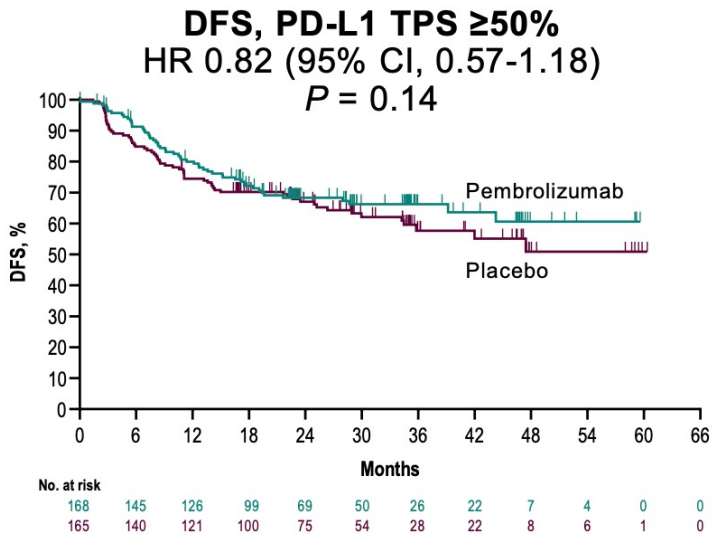


Felip, Lancet 2021; Felip, ESMO 2021, Felip IASLC 2022; Abstract PL03.09

Adjuvant Therapy for NSCLC

- Adjuvant immunotherapy improves DFS
  - PEARLS (KEYNOTE-091) showed pembrolizumab improved DFS for resected stage Ib/II/IIIA NSCLC (HR 0.76)
    - DFS in PD-L1 high subset 0.82 (p=0.14)
    - FDA approved across PD-L1 strata January 26, 2023





Peters, ESMO 2022, O'Brien Lancet Oncol 2022

Adjuvant Therapy for NSCLC

- Who should receive adjuvant immunotherapy after surgery and chemotherapy?
  - Atezolizumab approved for resected stage II/III, PD-L1+
  - Pembrolizumab approved for resected stage Ib/II/III, any PD-L1
- Individualize decisions based on risk of recurrence and risk of toxicity from immunotherapy
  - Strongest consensus for resected II/III, PD-L1 high
  - General acceptance for resected II/III, PD-L1 low
  - My current practice is to consider for any resected NSCLC in the absence of contraindication and absence of driver mutations

Adjuvant Therapy for NSCLC

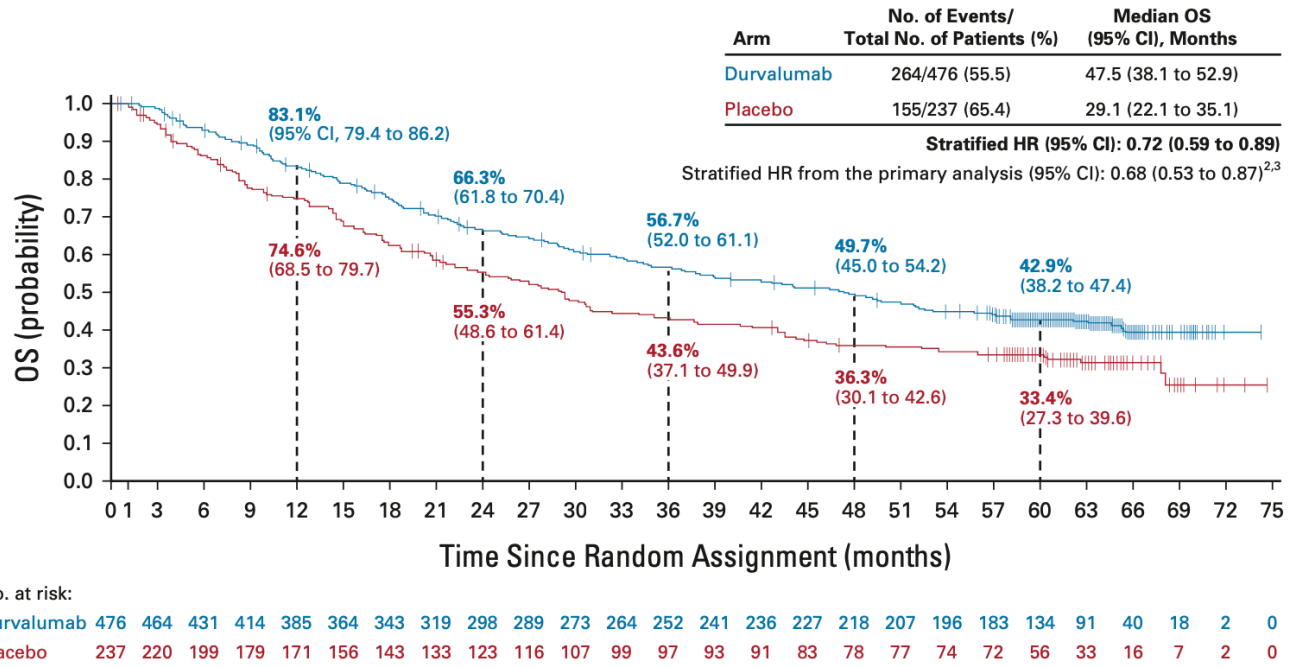
- Choosing between immunotherapy or osimertinib for resected EGFR-mutant NSCLC?
  - Immunotherapy generally ineffective in stage IV EGFR+ NSCLC (even with high PD-L1 expression)
  - Some conflicting data (KEYNOTE-091) but small numbers
  - EGFR TKI after immunotherapy associated with greater toxicity
  - Osimertinib offers profound DFS benefit (HR 0.23) including prevention of CNS spread
  - My current practice is adjuvant osimertinib for resected EGFR+ NSCLC over immunotherapy

Discussion Question

Should all patients with unresectable locally advanced NSCLC who complete definitive chemoradiation therapy receive consolidation therapy with durvalumab? In which situations, if any, do you not administer consolidation durvalumab or consider consolidation therapy with something other than durvalumab (eg, osimertinib)?

Consolidation Therapy for NSCLC

- Consolidation durvalumab after chemoradiation for stage III NSCLC is the clear standard of care
  - Improved PFS (median 16.9 vs 5.6m, HR 0.55)
  - Improved OS (median 47.5 vs 29.1, HR 0.72)



Spigel, JCO 2022

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Consolidation Therapy for NSCLC

- Benefit of durvalumab in EGFR+ NSCLC unclear
  - EGFR+ subset in PACIFIC small (n=43), OS HR 0.85 (ns)
  - In the event of relapse, use of TKI after IO associated with toxicity
  - Consolidation TKI being studied now (LAURA)
  - Given low likelihood of durvalumab benefit and extrapolating profound local/distant/CNS benefit seen in ADAURA, my current practice is to avoid durvalumab for EGFR/ALK NSCLC and discuss consolidation TKI after chemoradiation (off-label use)

Discussion Question

In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient with metastatic NSCLC and various targetable tumor mutations? Does PD-L1 expression have any bearing on this decision?

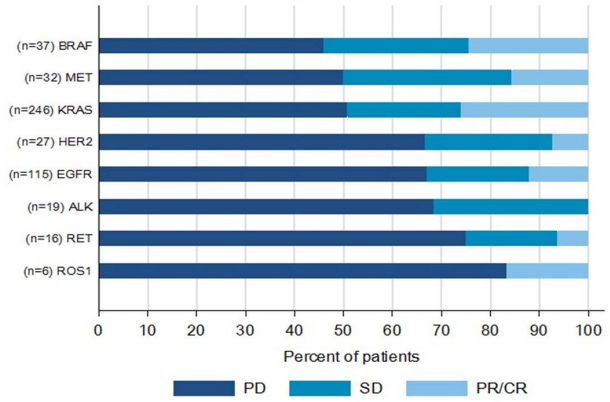
Immunotherapy in Driver+ NSCLC

- Immunotherapy largely ineffective in driver-positive NSCLC even in the context of high PD-L1 expression
  - Phase II study of first-line pembrolizumab in EGFR+ NSCLC
  - No responses observed (even in PD-L1 high)
  - Notable toxicity with subsequent TKI (including fatal pneumonitis)
- TKI after immunotherapy consistently toxic in driver-positive NSCLC
  - More irAEs with EGFR TKIs (hepatitis, colitis, pneumonitis)
  - ALK TKIs associated with hepatitis
  - RET TKIs associated with hypersensitivity reactions

Lisberg, JTO 2018; Schoenfeld, Ann Oncol 2019; McCoach, JTO 2022

Immunotherapy in Driver+ NSCLC

- Exceptions include BRAF V600E and METex14 mutations
  - Two drivers often seen in smokers
- Suggestion that immunotherapy in combination with VEGF can be of benefit in EGFR+ NSCLC
  - IMpower150 (carboplatin + paclitaxel + bevacizumab + atezolizumab)
  - ORIENT-31 (cisplatin + pemetrexed + IBI305 + sintilimab)
- My current practice is to use TKI first
  - Reserve IO after TKI therapies exhausted
  - Avoid if TKI essential (CNS control)
  - Prefer combination trials over standard IO
  - Exception for KRAS G12C



Mazieres, ASCO 2018; Reck, Lancet Resp 2019; Lu, Lancet Oncol 2022

Discussion Question

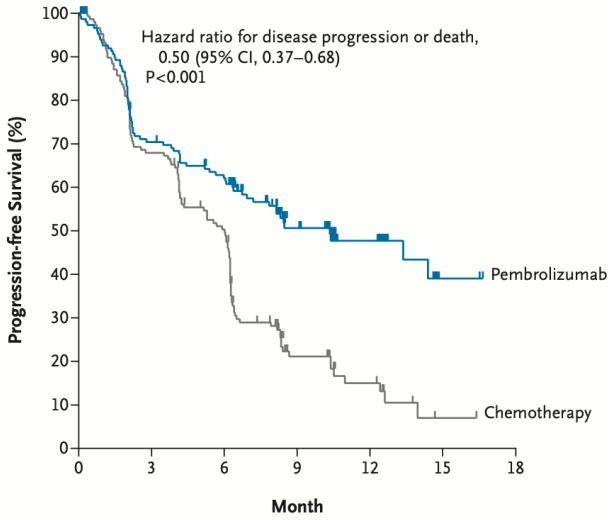
How do you approach the decision to use anti-PD-1/PD-L1 monotherapy versus combined chemoimmunotherapy versus dual immune checkpoint inhibition with and without chemotherapy for patients with newly diagnosed metastatic NSCLC without a targetable tumor mutation?

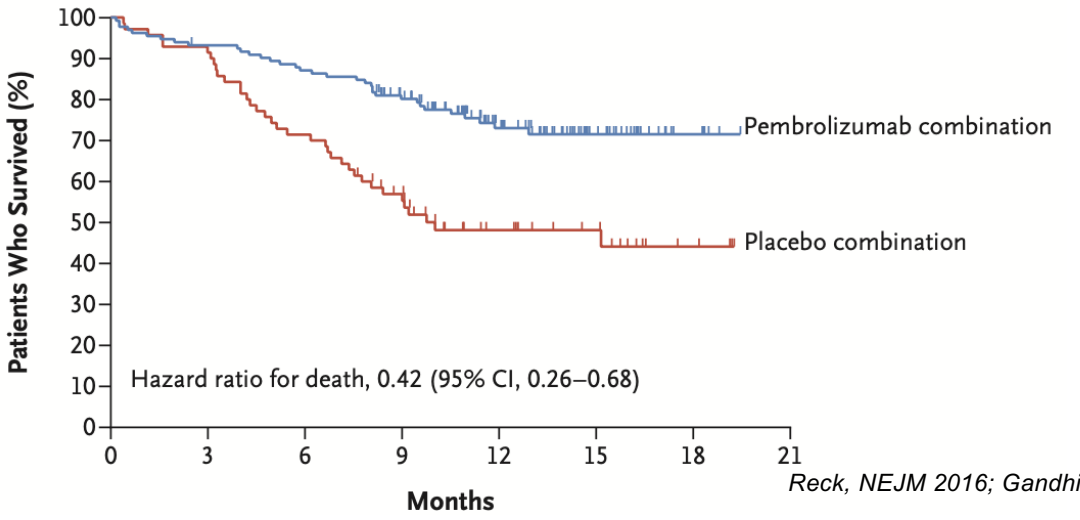
First-Line Immunotherapy

- PD(L)1 monotherapy
  - Atezolizumab (IMpower110) – for PD-L1 ≥ 50%
  - Pembrolizumab (KEYNOTE-024, KEYNOTE-042)) – for PD-L1 ≥ 1%
  - Cemiplimab (EMPOWER-Lung 1) – for PD-L1 ≥ 50%
- Dual checkpoint blockade
  - Nivolumab + ipilimumab) – for PD-L1 ≥ 1%
- Chemo-immunotherapy
  - Platinum + pemetrexed + pembrolizumab (non-sq, KEYNOTE-189)
  - Platinum + taxane + pembrolizumab (sq, KEYNOTE-407)
  - Carboplatin + paclitaxel + bevacizumab + atezolizumab (non-sq, IMpower150)
  - Carboplatin + (*nab*)paclitaxel + atezolizumab (non-sq, IMpower130)
  - Platinum doublet + cemiplimab (EMPOWER-Lung 3)
  - Platinum doublet (x2) + nivolumab + ipilimumab (CheckMate 9LA)
  - Platinum doublet + durvalumab + tremelimumab (x5) (POSEIDON)

Immunotherapy in Driver+ NSCLC

- PD-L1 ≥ 50%
  - My practice is pembrolizumab monotherapy
  - If high tumor burden, significant symptoms, rapid pace, then my preference is chemo-immunotherapy
  - Prefer not to add CTLA-4 inhibition in PD-L1 high NSCLC
    - KEYNOTE-598: adding ipilimumab to pembro in PD-L1 ≥ 50% did not improve OS





Reck, NEJM 2016; Gandhi, NEJM 2018; Boyer, JCO 2021; Abreu ESMO 2022

Immunotherapy in Driver+ NSCLC

- PD-L1 low (1-49%) and negative
  - My practice remains chemo-immunotherapy
  - Dual checkpoint blockade in certain cases
- KRAS and STK11 co-mutations
  - Prefer to include chemotherapy
  - More consideration for dual checkpoint blockade + chemotherapy

Discussion Question

What role, if any, do you believe datopotamab deruxtecan will eventually play in the management of metastatic NSCLC? If this strategy were available today, for which patients would you prioritize its use?

Datopotamab Deruxtecan

- Trop-2 antibody drug conjugate
- TROPION-PanTumor01
  - Heavily pretreated NSCLC
  - RR 24-26%, mPFS 4.3-6.9m
- In NSCLC with actionable genomic alterations (post TKI)
  - RR 35% with mDOR 9.5m (34 pts, mostly EGFR)
- TROPION-Lung02
  - Dato-DXd + pembrolizumab – RR 37% (RR 62% in 1L)
  - Dato-DXd + pembro + chemo – RR 41% (RR 50% in 1L)

Lisberg, JTO 2018; Schoenfeld, Ann Oncol 2019; Meric-Bernstam ASCO 2021, McCoach, JTO 2022

Datopotamab Deruxtecan

- Trop2 ADCs clearly active and a welcome addition
- Still determining best use of these agents
  - Biomarker needed? Biomarker helpful?
- If available today, would use after platinum-doublet chemotherapy and before docetaxel-based therapy
  - Post TKIs in those with drivers
  - Post IO and post chemotherapy for driver-negative NSCLC
  - Need more information on first-line use

Lisberg, JTO 2018; Schoenfeld, Ann Oncol 2019; McCoach, JTO 2022