Systemic Therapy Strategies

Trial	Regimen	Setting	pCR	EFS / DFS	OS
CheckMate 816	Neoadjuvant nivolumab + chemotherapy → surgery	Neoadjuvant	24%	Median EFS 60 mo (HR 0.68)	5-year OS 65.4% (HR 0.72)
KEYNOTE-671	Neoadjuvant pembrolizumab + chemotherapy → surgery → pembrolizumab (1 yr)	Perioperative	18%	Median EFS 47 mo (HR 0.59)	3-year OS 71% (HR 0.72)
AEGEAN	Neoadjuvant durvalumab + chemotherapy → surgery → durvalumab (1 yr)	Perioperative	17%	2-year EFS 63% (HR 0.68)	Not reported (immature)
KEYNOTE-091	Surgery → +/- chemotherapy → adjuvant pembrolizumab (1 yr)	Adjuvant only	N/A	Median DFS 54 mo (HR 0.76)	3-year OS 82% (HR 0.87)
ADAURA	Surgery → +/- chemotherapy → osimertinib (3 years)	Adjuvant only	N/A	Median DFS 66 mo (HR 0.27)	5-year OS 88% (HR 0.49)
ALINA	Surgery → alectinib (2 years)	Adjuvant only	N/A	3-year DFS 89% (HR 0.24)	Not reported (immature)

Prior to 2020 – we only had adjuvant chemotherapy!

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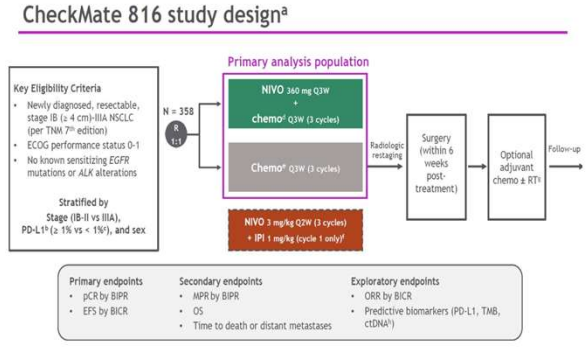
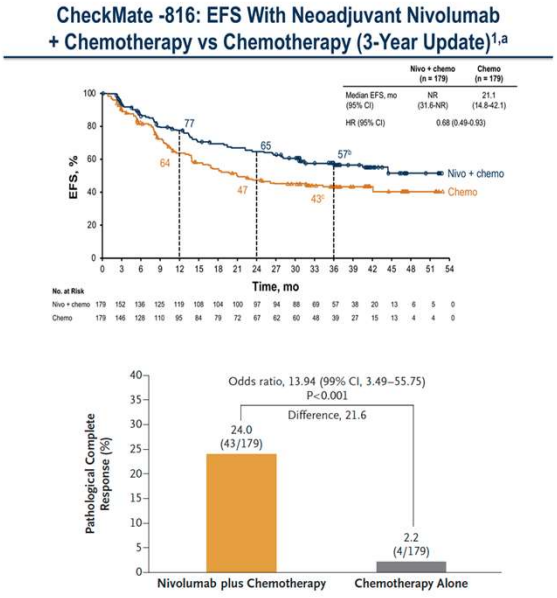
Checkmate 816





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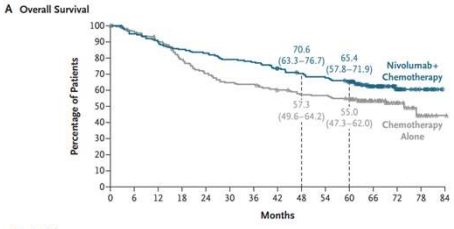
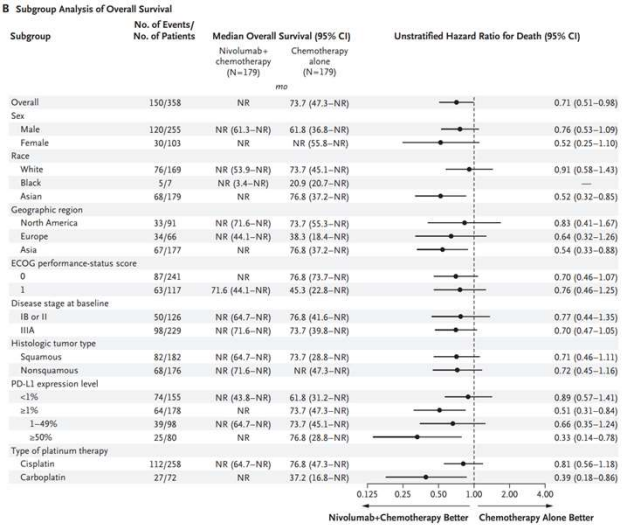


	Median Overall Survival (95% CI) mo
Nivolumab+Chemotherapy (N=179)	NR (NR–NR)
Chemotherapy Alone (N=179)	73.7 (47.3–NR)

Hazard ratio for death, 0.72 (95% CI, 0.523–0.998)
P=0.048



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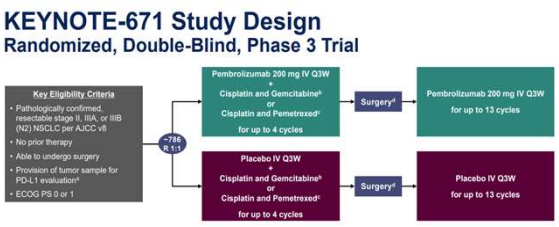
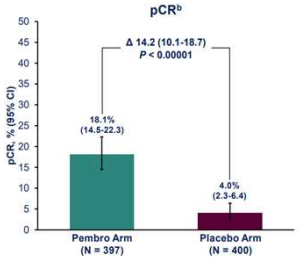
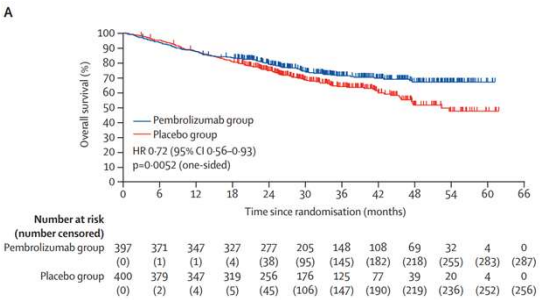
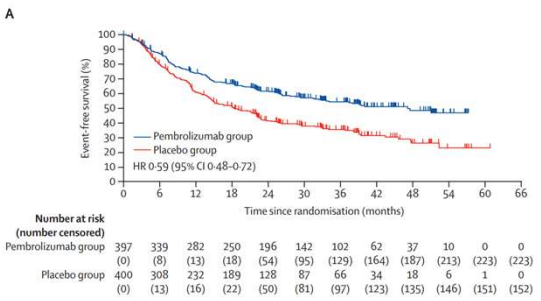
KEYNOTE-671









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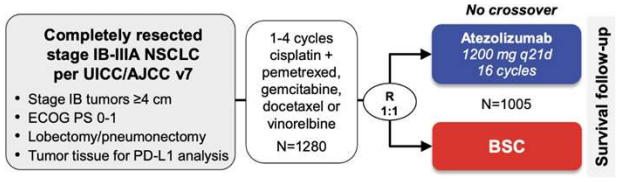
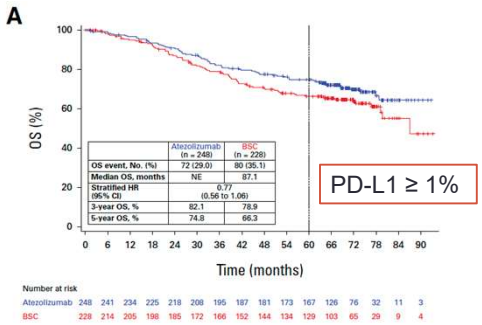
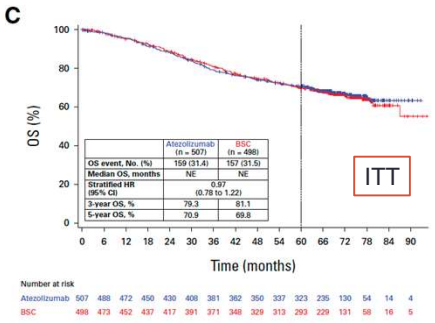
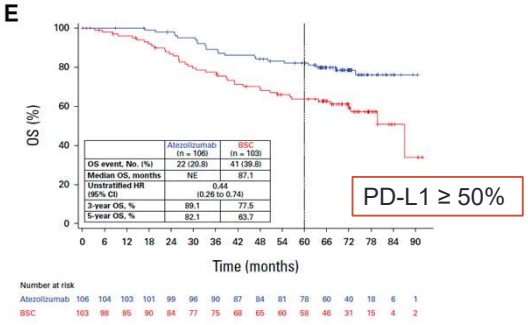
IMPOWER010









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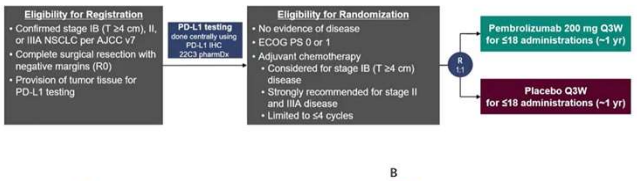
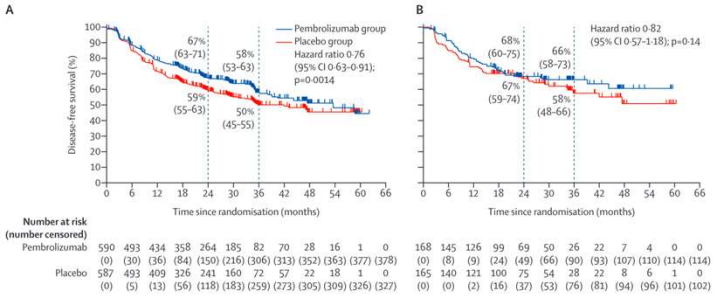
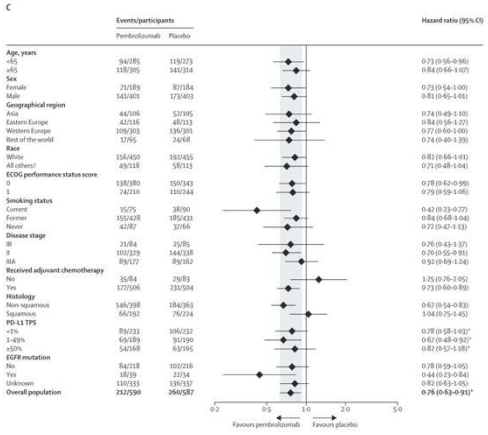
KEYNOTE-091







Overall population

PD-L1 ≥ 50%

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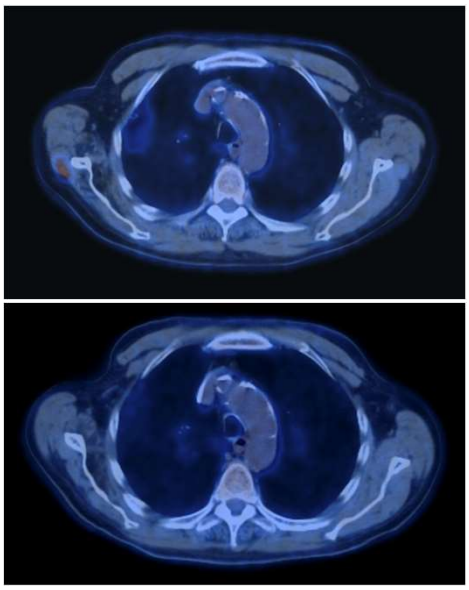
Case 1

- Patient with 4.4 cm right upper lobe mass
- Underwent EBUS with mediastinal staging - only RUL mass involved
- Stage IIA (T2bN0M0) lung adenocarcinoma
- PD-L1 90%, KRAS G12V mutated
- Treated with 4 cycles of neoadjuvant carboplatin/pemetrexed and pembrolizumab



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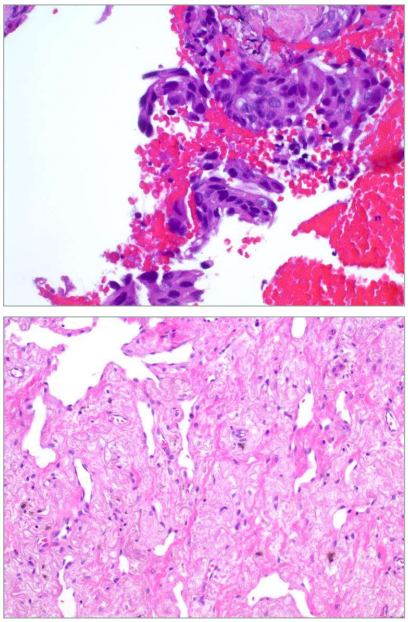
Case 1

- LUNG, RIGHT UPPER LOBE, LOBECTOMY (STATUS POST NEOADJUVANT THERAPY):
  - 1. Mass with fibrosis, hemosiderin-laden macrophages, foci of chronic inflammation, and anthracosis (tumor bed 4.3 cm)
  - Negative for residual carcinoma (complete histologic response to neoadjuvant therapy)
  - Pleura with fibrosis and chronic inflammation
  - All margins negative for carcinoma
  - Treatment effect
    - Viable carcinoma 0%
    - Necrosis 0%
    - Stromal fibrosis 100 %
- Patient did not receive adjuvant therapy and is currently in surveillance with no evidence of disease



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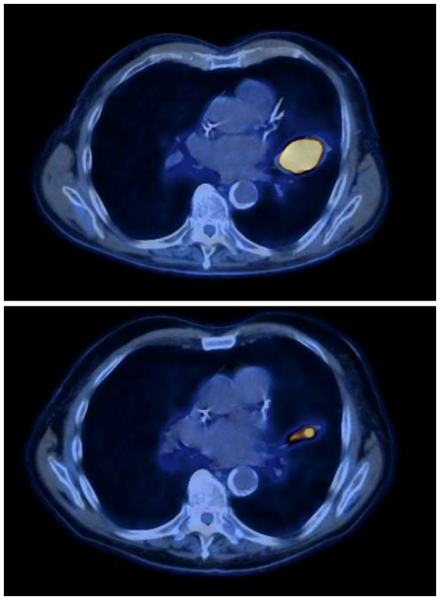
Case 2

- Patient with 4.8 cm left upper lobe mass
- Underwent EBUS with mediastinal staging - only LUL mass involved
- Stage IIA (T2bN0M0) squamous cell lung cancer
- PD-L1 0%, NGS negative
- Enrolled in MK2870-019 clinical trial (TROP2 antibody-drug conjugate)
- Treated with 4 cycles of neoadjuvant carboplatin/paclitaxel and pembrolizumab



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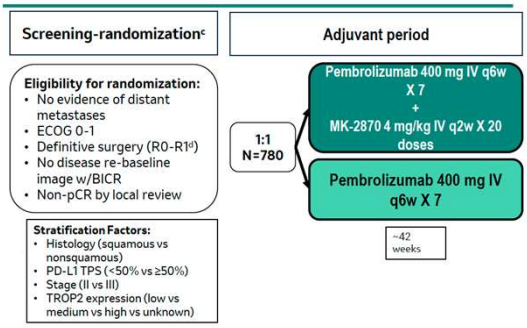
Case 2

- LUNG, LEFT, LINGULA, LINGULECTOMY:
  - Residual invasive, moderately differentiated squamous cell carcinoma with focal keratinization:
    a. Size of tumor: 4.5 cm (ypT2b)
    b. Surgical margins: Negative
    c. Treatment effect:
      i. Viable tumor: 55%
      ii. Necrosis: 35%
      iii. Fibrosis: 10%
- Continued to receive adjuvant therapy
- Randomized to pembrolizumab control arm and completed 1 year of total treatment – no evidence of disease currently



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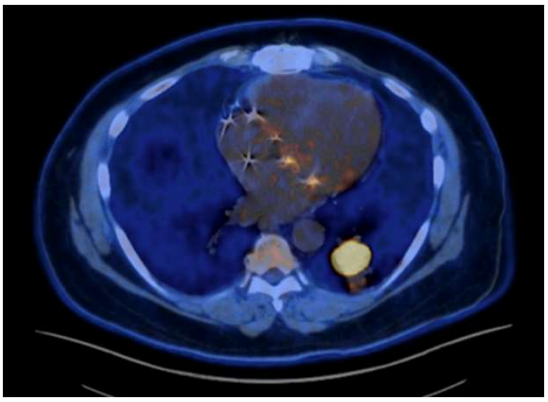
Case 3

- Patient with 3 cm left lower lobe mass
- Underwent EBUS with mediastinal staging - only LLL mass involved
- Stage IA3 (T1cN0M0) squamous cell lung cancer
- Underwent left lower lobe lobectomy with lymph node dissection



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Case 3

- LUNG, LEFT, LOWER LOBE, LOBECTOMY:
  1. Invasive squamous cell carcinoma:
     a. Tumor size: 3.0 cm
     b. Surgical margins: Free of involvement
  2. One of thirteen lymph nodes positive (1/13)
  3. Ancillary testing:
     a. PD-L1: Tumor Proportion Score (TPS): 35%
     b. NGS (lung panel): Positive for HRAS Q61L mutation
- Patient was upstaged to stage IIB (pT1cN1M)
- Received cisplatin/gemcitabine adjuvant therapy for 4 cycles and pembrolizumab for 1 year – no evidence of disease currently

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Systemic Therapy Strategies

Strategy	Pros	Cons
Neoadjuvant Only	- Treat micrometastatic disease sooner - Tumor downstaging may improve R0 resection rates - In vivo chemosensitivity assessment - Immunotherapy works better in presence of neoantigens - Enables pathologic response assessment (e.g., pCR, MPR) - Better compliance than adjuvant treatment - Can avoid unnecessary surgery in rapid progressors	- May not proceed to surgery due to progression or complications - May delay definitive surgical treatment - Surgery may be difficult after tissue fibrosis or tumor response - No definitive staging until resection - Less data on long-term outcomes
Adjuvant Only	- Avoids delaying surgery - Definitive pathologic staging helps guide therapy - Preferred for EGFR/ALK mutated - Avoids possible surgical complications after fibrotic response - Patient is upstaged during surgery - Optimal strategy if immunotherapy contraindicated	- Missed opportunity to downstage tumors pre-op - Patients may be unfit for post-op therapy - Lower completion rates for planned therapy course - Less effective immune response if antigen load is reduced - Micrometastatic disease left untreated during surgery period
Perioperative	- Combines the benefits of neoadjuvant and adjuvant treatment - Greater treatment intensity may maximize micrometastatic control - Some evidence for better event-free survival - Signal for improved survival in non-pCR and higher PD-L1 levels	- Increased cumulative toxicity - Requires patient fitness for both pre- and post-op treatment - Adjuvant portion may be too aggressive for some patients - More expensive and resource intensive

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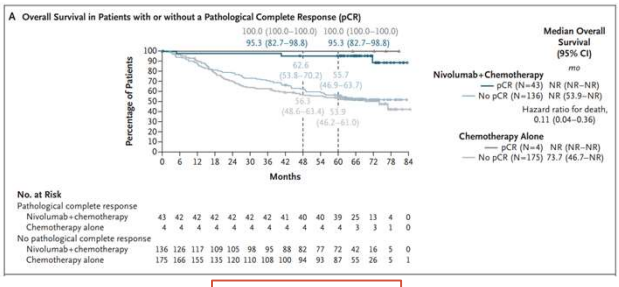
Treatment Considerations – Complete Response



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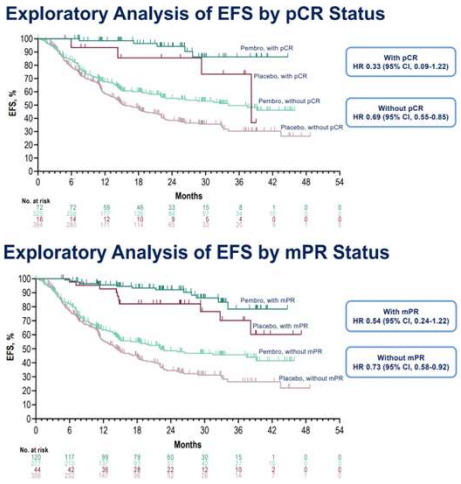

KEYNOTE-671

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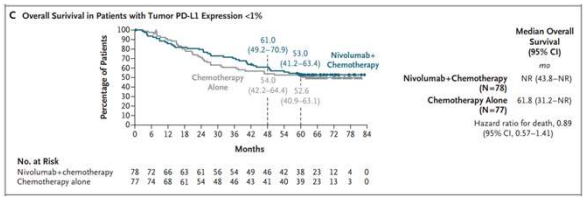
Treatment Considerations – PD-L1 Expression



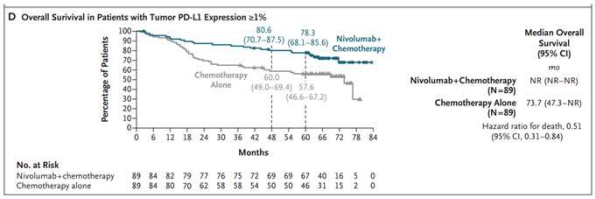


Table: LBA57 Efficacy outcomes by tumor PD-L1 expression

	Tumor PD-L1 ≥ 1%		Tumor PD-L1 < 1%	
	N + C (n = 89)	C (n = 89)	N + C (n = 78)	C (n = 77)
EFS				
Median, mo (95% CI)	NR (44.4–NR)	26.7 (13.4–NR)	26.4 (14.8–NR)	20.8 (13.9–42.1)
HR (95% CI)	0.46 (0.28–0.77)		0.87 (0.57–1.35)	
OS				
Median, mo (95% CI)	NR (NR–NR)	NR (45.1–NR)	NR (48.6–NR)	NR (31.2–NR)
HR (95% CI)	0.37 (0.20–0.71)		0.81 (0.48–1.36)	
pCR rate, % (95% CI)	32.6 (23.0–43.3)	2.2 (0.3–7.9)	16.7 (9.2–26.8)	2.6 (0.3–9.1)
MPR rate, % (95% CI)	44.9 (34.4–55.9)	5.6 (1.8–12.6)	29.5 (19.7–40.9)	14.3 (7.4–24.1)

NR, not reached.

CheckMate 816

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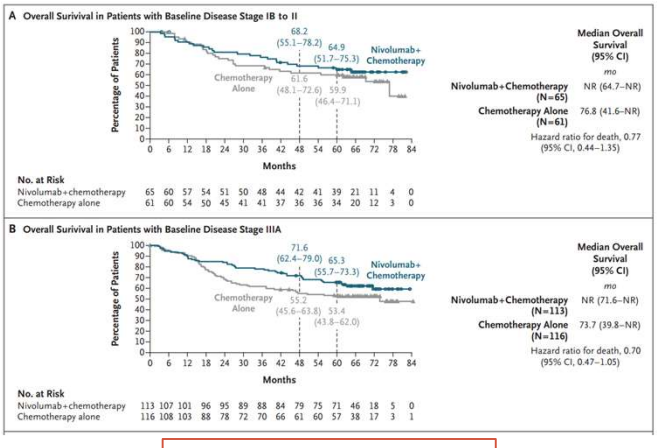
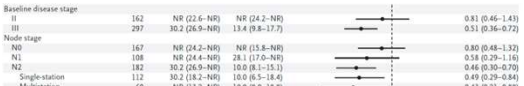
Treatment Considerations – Early Stage



CheckMate 816 OS by Stage

KEYNOTE-671 Subgroup Analysis



CheckMate 77T Subgroup Analysis

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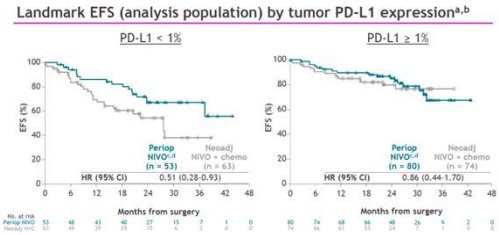
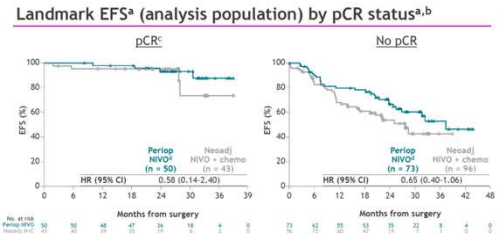
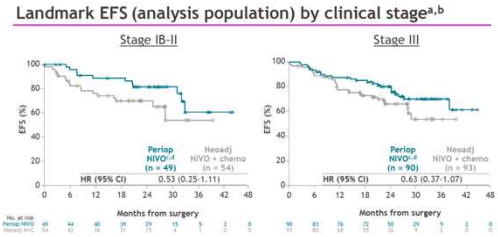
Systemic Therapy Strategies

Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,[1] Solange Peters,[2] Jessica Donington,[3] Stephanie Meadows-Shropshire,[4] Phuong Tran,[4] Stefano Lucherini,[5] Cinthya Coronado Erdmann,[6] Hong Sun,[6] Tina Cascone[7]







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Systemic Therapy Strategies

- Ongoing questions
  - Base treatment decisions on PD-L1 – correlation between high expression and better outcomes
  - General consensus is to stop therapy if patient achieves a complete response
  - Reasonable to consider up front surgery in some patients (small, negative nodes, stage IIA, PD-L1 negative)

- How to choose treatment strategy in non-oncogene driven tumors:
  - Most start with neoadjuvant chemotherapy + immunotherapy: 3 vs 4 cycles of treatment
  - Surgery then evaluate pathological response
  - If complete response - most would stop
  - If no complete response - adjuvant immunotherapy to complete 1 year of treatment
  - Strongly consider enrolling patients in clinical trials

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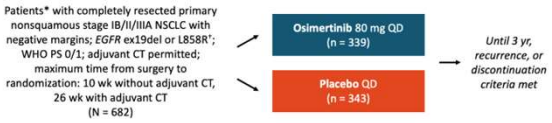
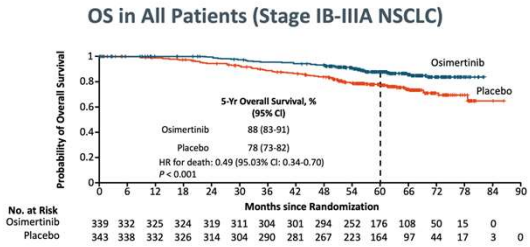
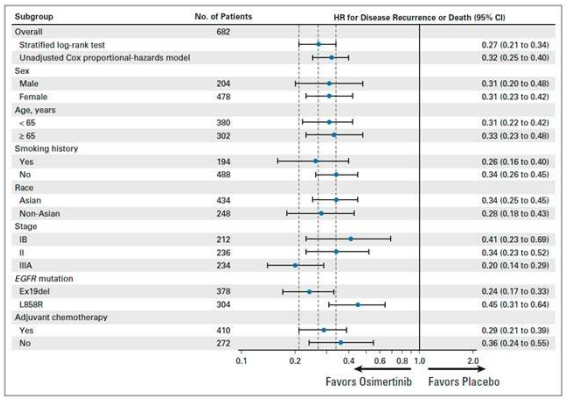
ADAURA – EGFR Mutated Disease







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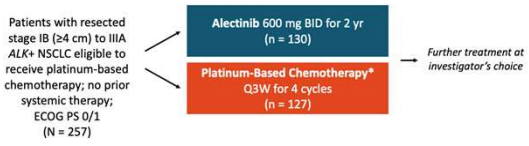
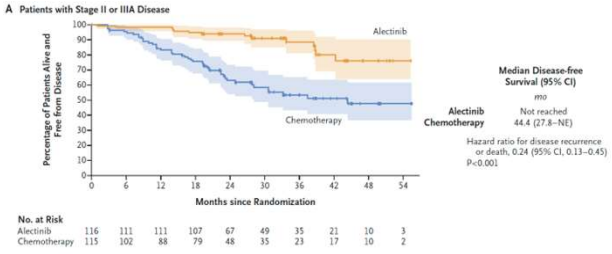
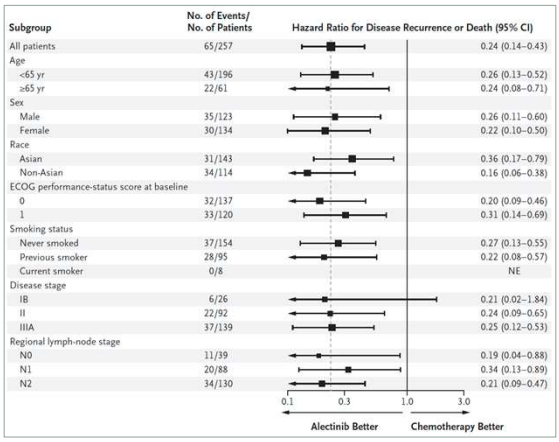
ALINA – ALK Mutated Disease







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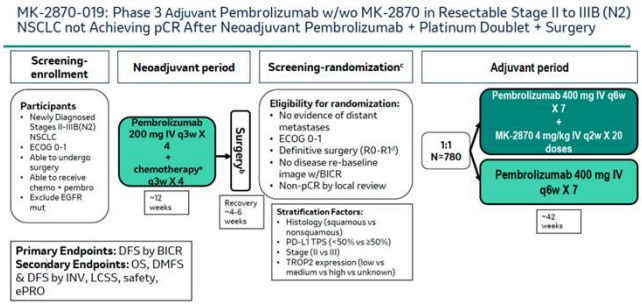
Future Directions

- Clinical trials
  - Antibody-drug conjugates
  - Alternative immunotherapies
  - Targeted agents
  - Neoantigen/cancer vaccines
- Biomarkers for patient selection
  - Driver mutations
  - Gene expression profiling
  - Proteomic classifiers
- ctDNA testing
  - May help guide treatment intensity/duration



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