

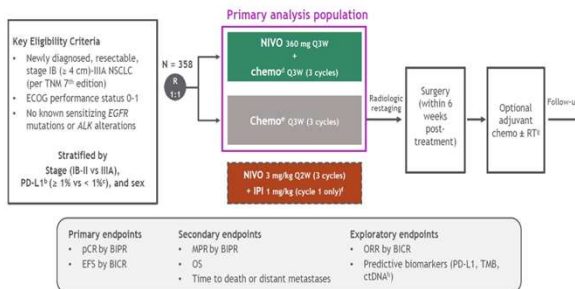
Systemic Therapy Strategies

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)
Prior to 2020 – we only had adjuvant chemotherapy!					
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)

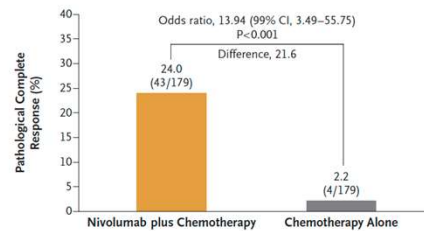
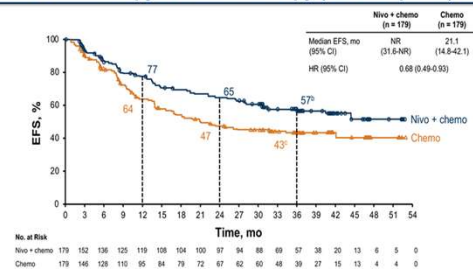
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Checkmate 816

CheckMate 816 study design^a

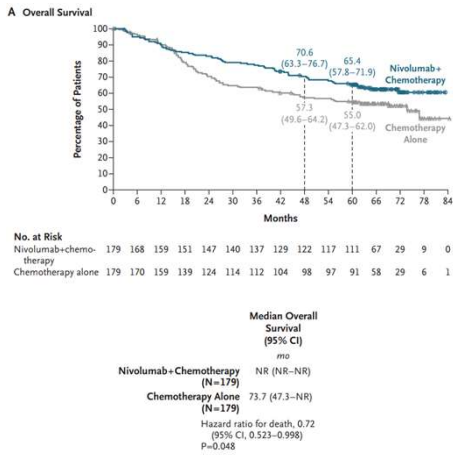


CheckMate -816: EFS With Neoadjuvant Nivolumab + Chemotherapy vs Chemotherapy (3-Year Update)^{1,a}



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Checkmate 816



B Subgroup Analysis of Overall Survival

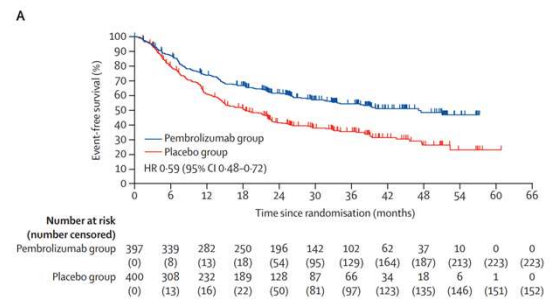
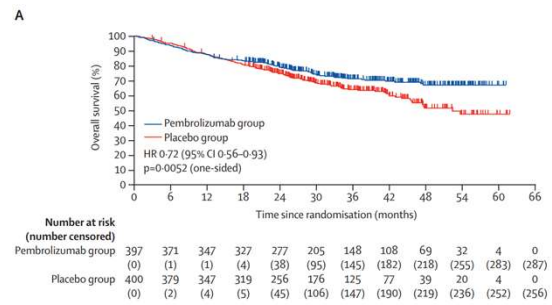
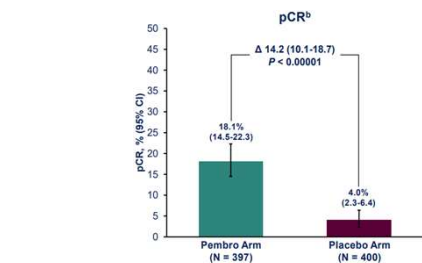
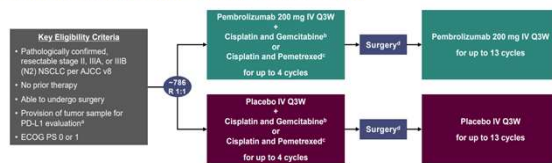
Subgroup	No. of Events/ No. of Patients	Median Overall Survival [95% CI]		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab+chemotherapy (N=179)	Chemotherapy alone (N=179)	
Overall	150/358	NR	73.7 (47.3-NR)	0.71 (0.51-0.98)
Sex				
Male	120/255	NR (61.3-NR)	61.8 (36.8-NR)	0.76 (0.53-1.09)
Female	30/103	NR	NR (55.8-NR)	0.52 (0.25-1.10)
Race				
White	76/169	NR (53.9-NR)	73.7 (45.1-NR)	0.91 (0.58-1.43)
Black	5/7	NR (3.4-NR)	20.9 (20.7-NR)	—
Asian	68/179	NR	76.8 (37.2-NR)	0.52 (0.32-0.85)
Geographic region				
North America	33/91	NR (71.6-NR)	73.7 (55.3-NR)	0.83 (0.41-1.67)
Europe	34/66	NR (44.1-NR)	38.3 (18.4-NR)	0.64 (0.32-1.26)
Asia	67/177	NR	76.8 (37.2-NR)	0.54 (0.33-0.88)
ECOG performance-status score				
0	87/241	NR	76.8 (73.7-NR)	0.70 (0.46-1.07)
1	63/117	71.6 (44.1-NR)	45.3 (22.8-NR)	0.76 (0.46-1.25)
Disease stage at baseline				
IB or II	50/126	NR (64.7-NR)	76.8 (41.6-NR)	0.77 (0.44-1.35)
IIIA	98/229	NR (71.6-NR)	73.7 (39.8-NR)	0.70 (0.47-1.05)
Histologic tumor type				
Squamous	82/182	NR (64.7-NR)	73.7 (28.8-NR)	0.71 (0.46-1.11)
Nonsquamous	68/176	NR (71.6-NR)	NR (47.3-NR)	0.72 (0.45-1.16)
PD-L1 expression level				
<1%	74/155	NR (43.8-NR)	61.8 (31.2-NR)	0.89 (0.57-1.41)
≥1%	64/178	NR	73.7 (47.3-NR)	0.51 (0.31-0.84)
1-49%	39/98	NR (64.7-NR)	73.7 (45.1-NR)	0.66 (0.35-1.24)
≥50%	25/80	NR	76.8 (28.8-NR)	0.33 (0.14-0.78)
Type of platinum therapy				
Cisplatin	112/258	NR (64.7-NR)	76.8 (47.3-NR)	0.81 (0.56-1.18)
Carboplatin	27/72	NR	37.2 (16.8-NR)	0.39 (0.18-0.86)

0.125 0.25 0.50 1.00 2.00 4.00
Nivolumab+Chemotherapy Better Chemotherapy Alone Better

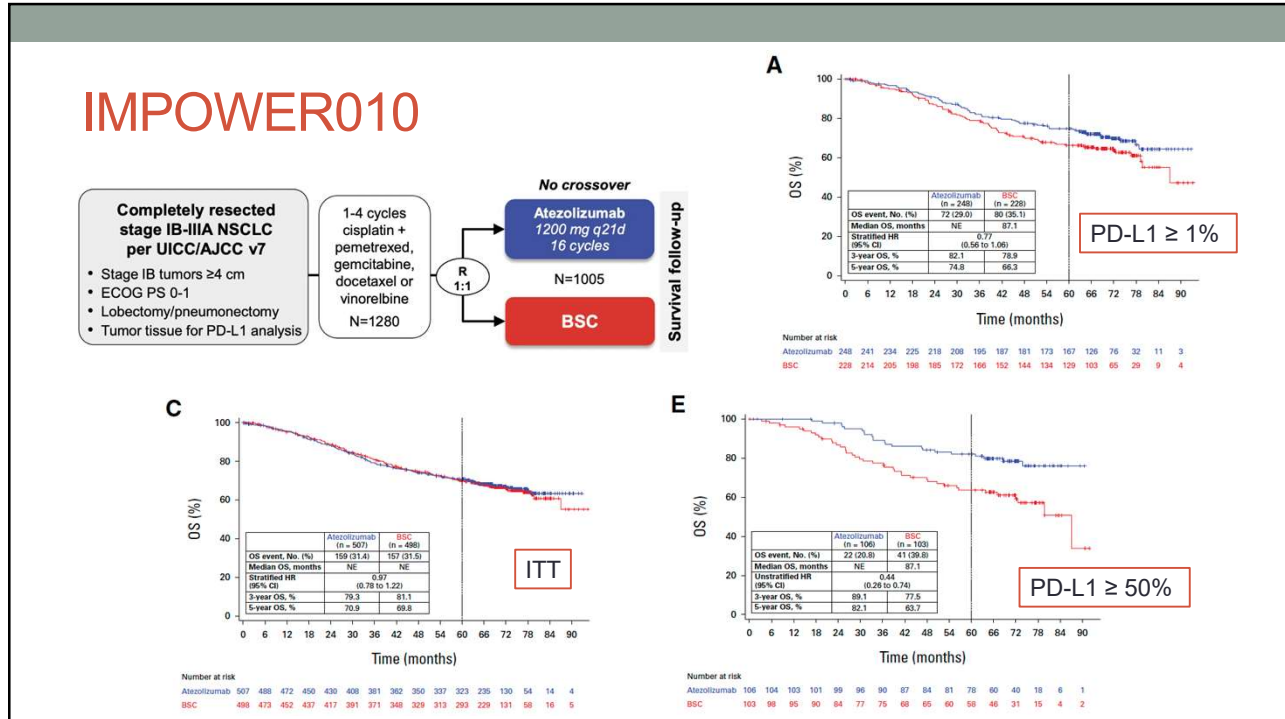
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KEYNOTE-671

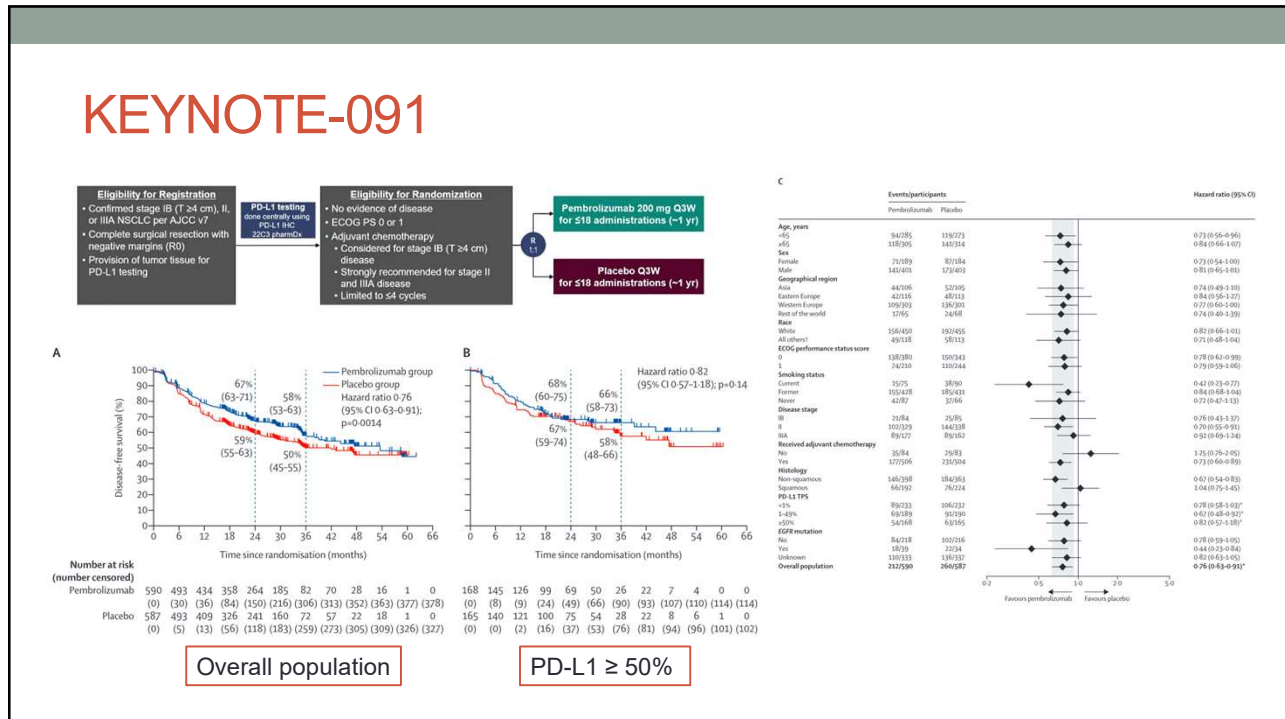
KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



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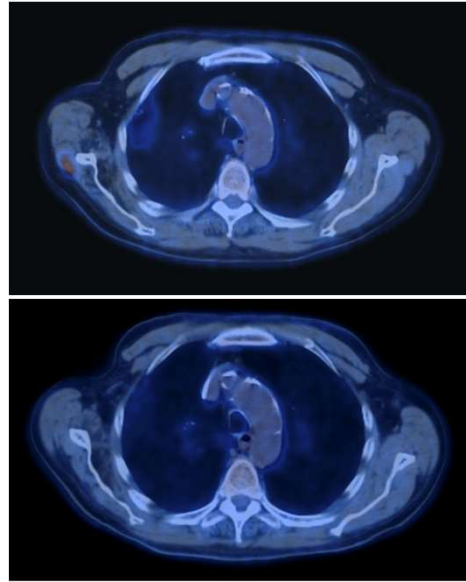
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Case 1

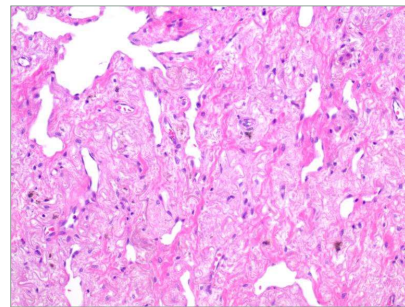
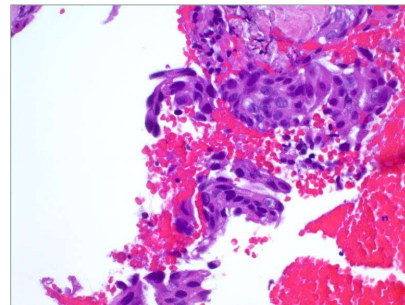
- Patient with 4.4 cm right upper lobe mass
- Underwent EBUS with mediastinal staging - only RUL mass involved
- Stage IIA (T2bN0M0) lung adenocarcinoma
- PD-L1 90%, KRAS G12V mutated
- Treated with 4 cycles of neoadjuvant carboplatin/pemetrexed and pembrolizumab



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Case 1

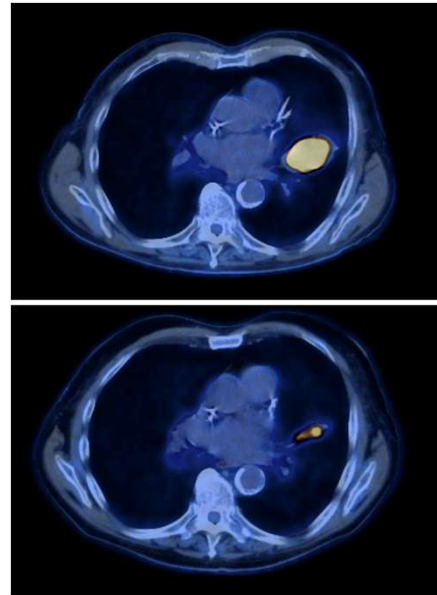
- LUNG, RIGHT UPPER LOBE, LOBECTOMY (STATUS POST NEOADJUVANT THERAPY):
 - 1. Mass with fibrosis, hemosiderin-laden macrophages, foci of chronic inflammation, and anthracosis (tumor bed 4.3 cm)
 - Negative for residual carcinoma (complete histologic response to neoadjuvant therapy)
 - Pleura with fibrosis 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

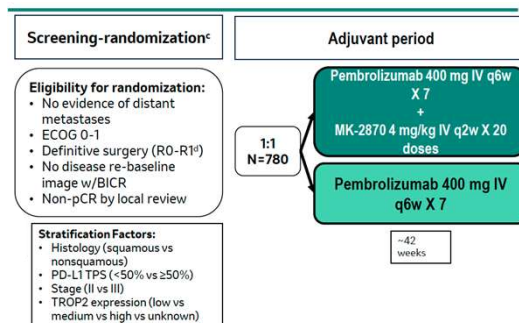
- Patient with 4.8 cm left upper lobe mass
- Underwent EBUS with mediastinal staging - only LUL mass involved
- Stage IIA (T2bN0M0) squamous cell lung cancer
- PD-L1 0%, NGS negative
- Enrolled in MK2870-019 clinical trial (TROP2 antibody-drug conjugate)
- Treated with 4 cycles of neoadjuvant carboplatin/paclitaxel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



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Case 2

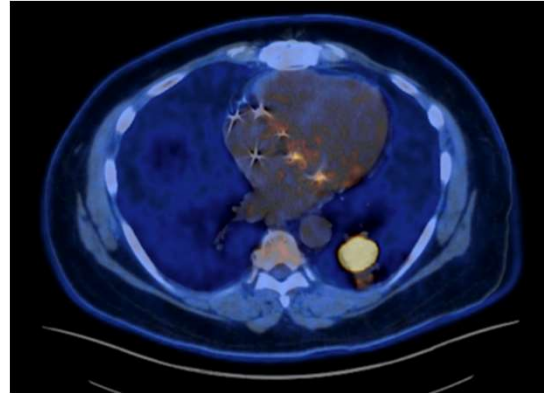
- LUNG, LEFT, LINGULA, LINGUECTOMY:
 - Residual invasive, moderately differentiated squamous cell carcinoma with focal keratinization:
 - a. Size of tumor: 4.5 cm (ypT2b)
 - b. Surgical margins: Negative
 - c. Treatment effect:
 - i. Viable tumor: 55%
 - ii. Necrosis: 35%
 - iii. Fibrosis: 10%
- Continued 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

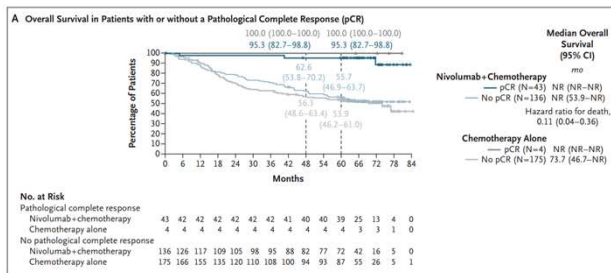
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Systemic Therapy Strategies

Strategy	Pros	Cons
Neoadjuvant Only	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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

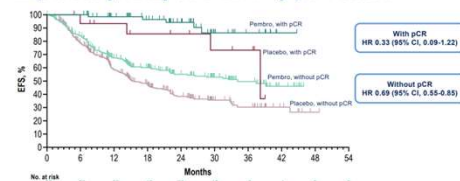
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Treatment Considerations – Complete Response

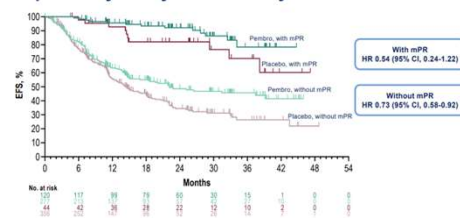


CheckMate 816

Exploratory Analysis of EFS by pCR Status



Exploratory Analysis of EFS by mPR Status



KEYNOTE-671

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Treatment Considerations – PD-L1 Expression

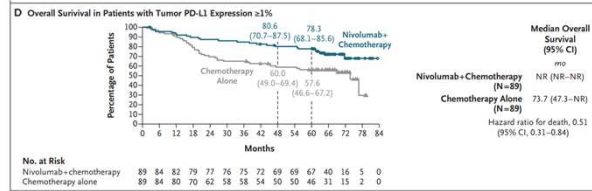
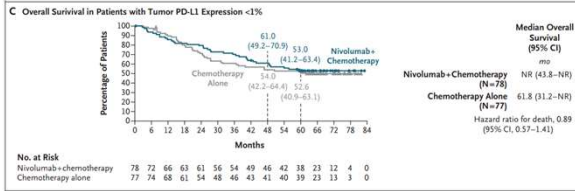


Table: LBA57 Efficacy outcomes by tumor PD-L1 expression

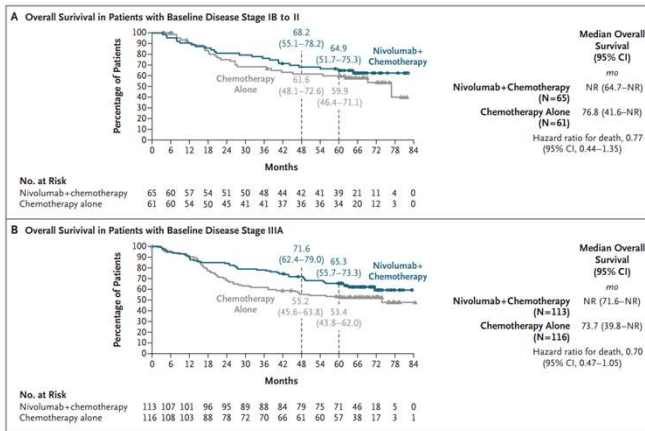
	Tumor PD-L1 ≥ 1%		Tumor PD-L1 < 1%	
	N + C (n = 89)	C (n = 89)	N + C (n = 78)	C (n = 77)
OS				
Median, mo (95% CI)	NR (44.4-NR)	26.7 (13.4-NR)	26.4 (14.8-NR)	20.8 (13.9-42.1)
HR (95% CI)	0.46 (0.28-0.77)		0.87 (0.57-1.35)	
OS				
Median, mo (95% CI)	NR (NR-NR)	NR (45.1-NR)	NR (48.6-NR)	NR (31.2-NR)
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.

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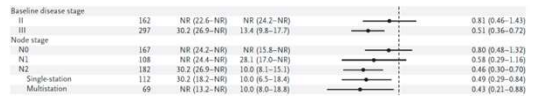
Treatment Considerations – Early Stage



CheckMate 816 OS by Stage



KEYNOTE-671 Subgroup Analysis



CheckMate 77T Subgroup Analysis

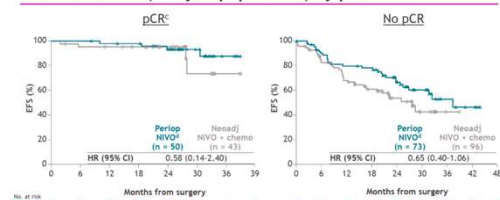
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Systemic Therapy Strategies

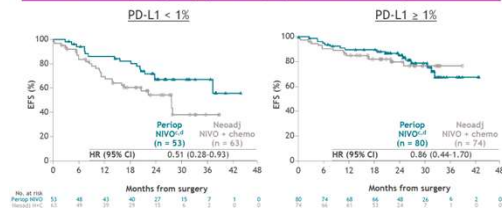
Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,¹ Solange Peters,² Jessica Donington,³ Stephanie Meadows-Shropshire,⁴ Phuong Tran,⁴ Stefano Luchnerini,⁵ Cinthya Coronado Erdmann,⁶ Hong Sun,⁶ Tina Cascone⁷

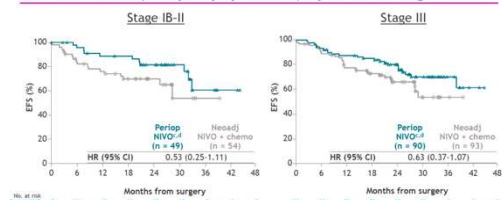
Landmark EFS^a (analysis population) by pCR status^{a,b}



Landmark EFS (analysis population) by tumor PD-L1 expression^{a,b}



Landmark EFS (analysis population) by clinical stage^{a,b}



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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

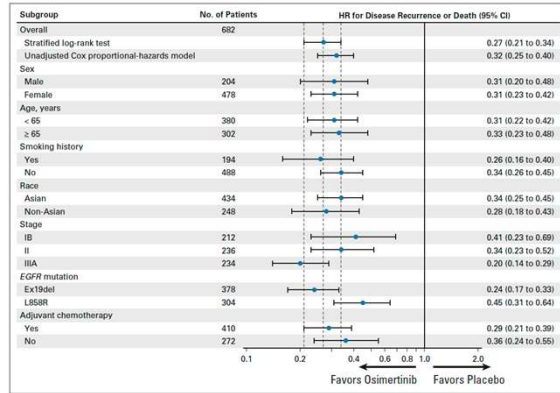
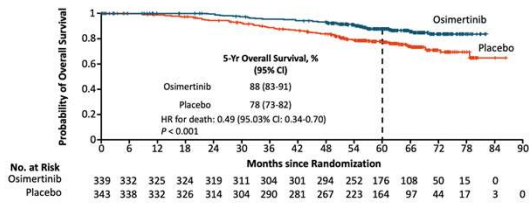
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ADAURA – EGFR Mutated Disease

Patients* with completely resected primary nonsquamous stage IB/IIA NSCLC with negative margins; EGFR ex19del or L858R*; WHO PS 0/1; adjuvant CT permitted; maximum time from surgery to randomization: 10 wk without adjuvant CT, 26 wk with adjuvant CT (N = 682)

Osimertinib 80 mg QD (n = 339) → *Until 3 yr, recurrence, or discontinuation criteria met*
Placebo QD (n = 343)

OS in All Patients (Stage IB-IIIa NSCLC)



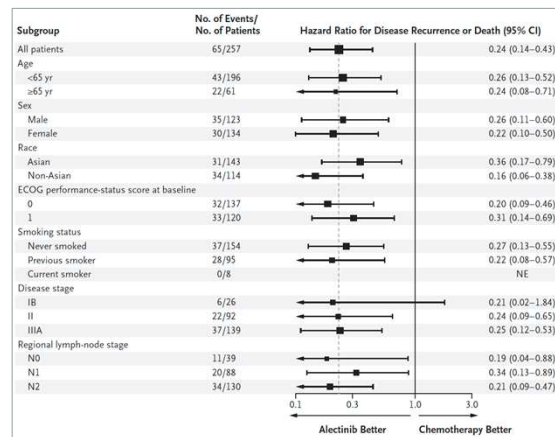
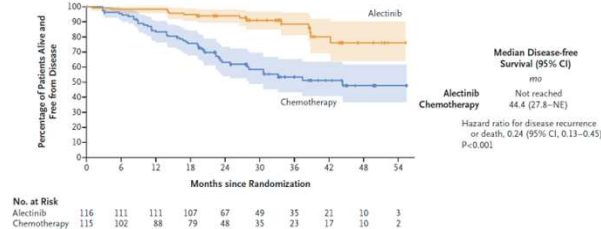
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ALINA – ALK Mutated Disease

Patients with resected stage IB (≥4 cm) to IIIA ALK+ NSCLC eligible to receive platinum-based chemotherapy; no prior systemic therapy; ECOG PS 0/1 (N = 257)

Alectinib 600 mg BID for 2 yr (n = 130) → *Further treatment at investigator's choice*
Platinum-Based Chemotherapy* Q3W for 4 cycles (n = 127)

A Patients with Stage II or IIIA Disease

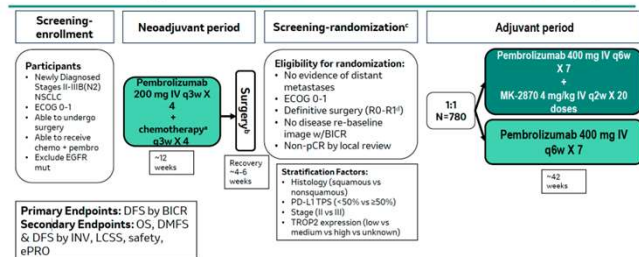


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Future Directions

- 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

MK-2870-019: Phase 3 Adjuvant Pembrolizumab w/wo MK-2870 in Resectable Stage II to IIIB (N2) NSCLC not Achieving pCR After Neoadjuvant Pembrolizumab + Platinum Doublet + Surgery



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