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Immunotherapy in Lung Cancer

3/29/19
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Disclosures

- I have served as a paid consultant to AstraZeneca

- MSKCC has received money for research support conducted by me from:
  - Novartis
  - Merck
  - Takeda

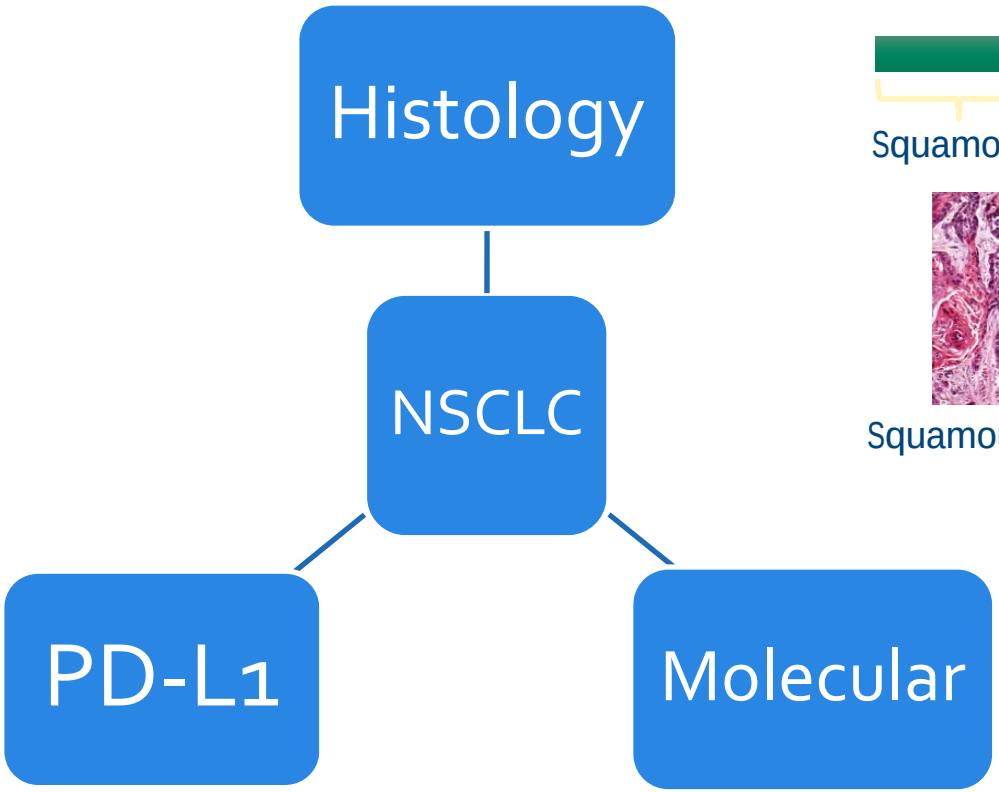
Agenda

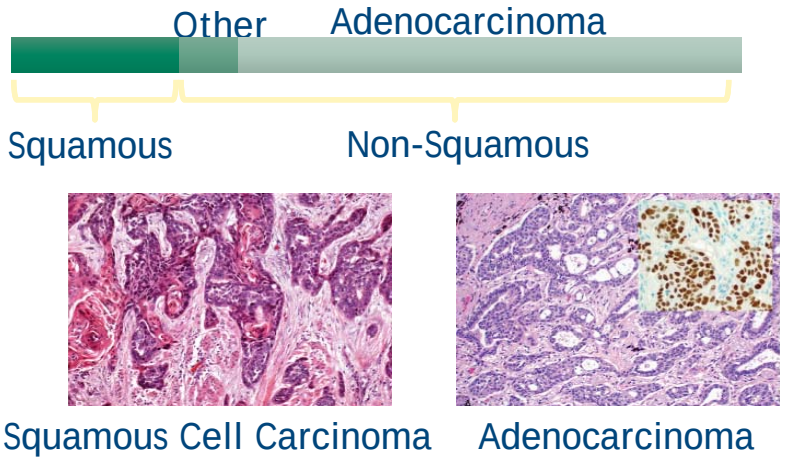
- Rationale for immunotherapy in lung cancer

- Current lung cancer treatment landscape
  - Role in metastatic NSCLC
  - Role in Stage III NSCLC
  - Role in SCLC

- Potential toxicities of immunotherapy and management

Diagnosis of Lung Cancer in 2019





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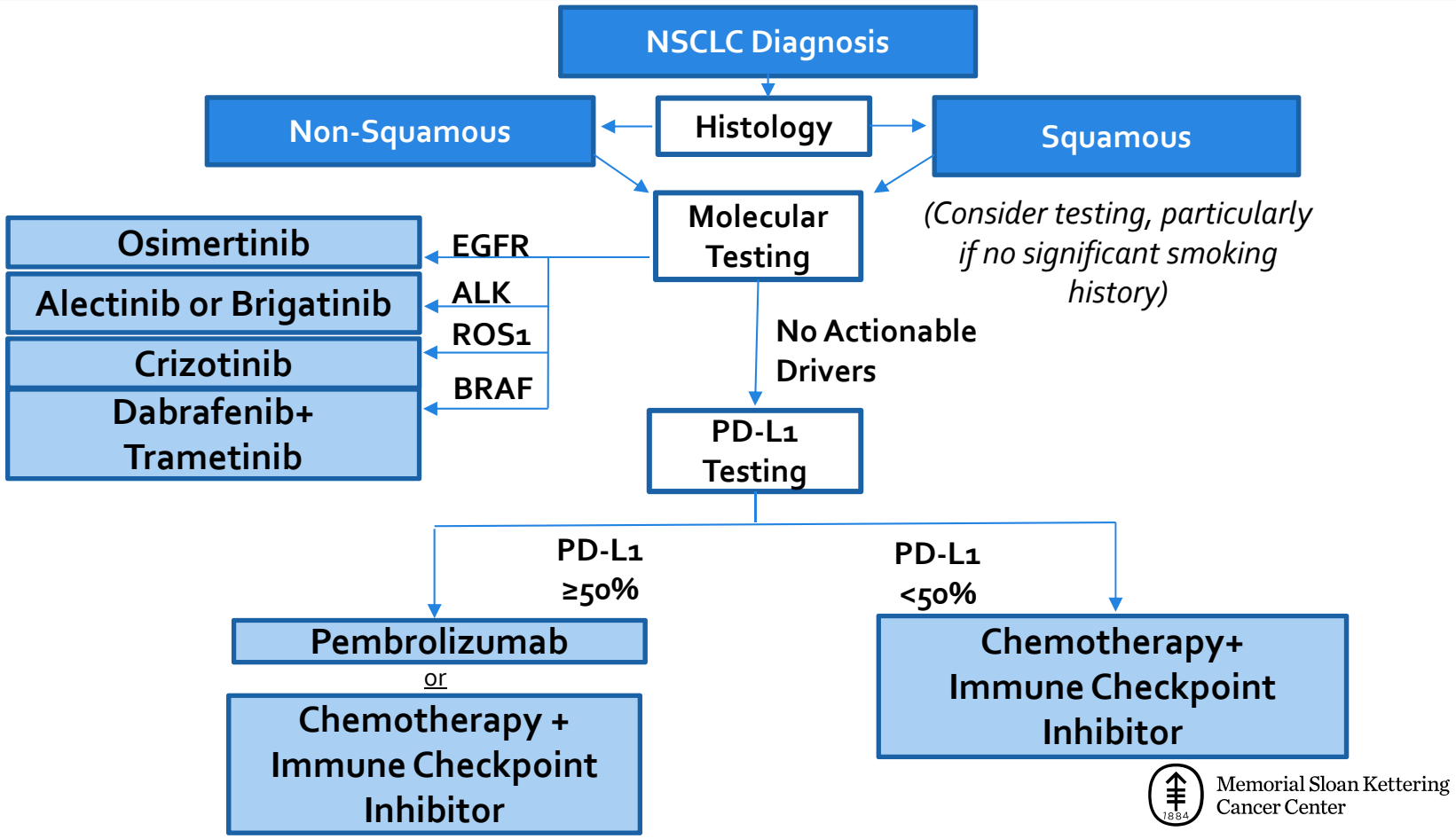
Treatment of Stage IV Lung Cancer in 2019



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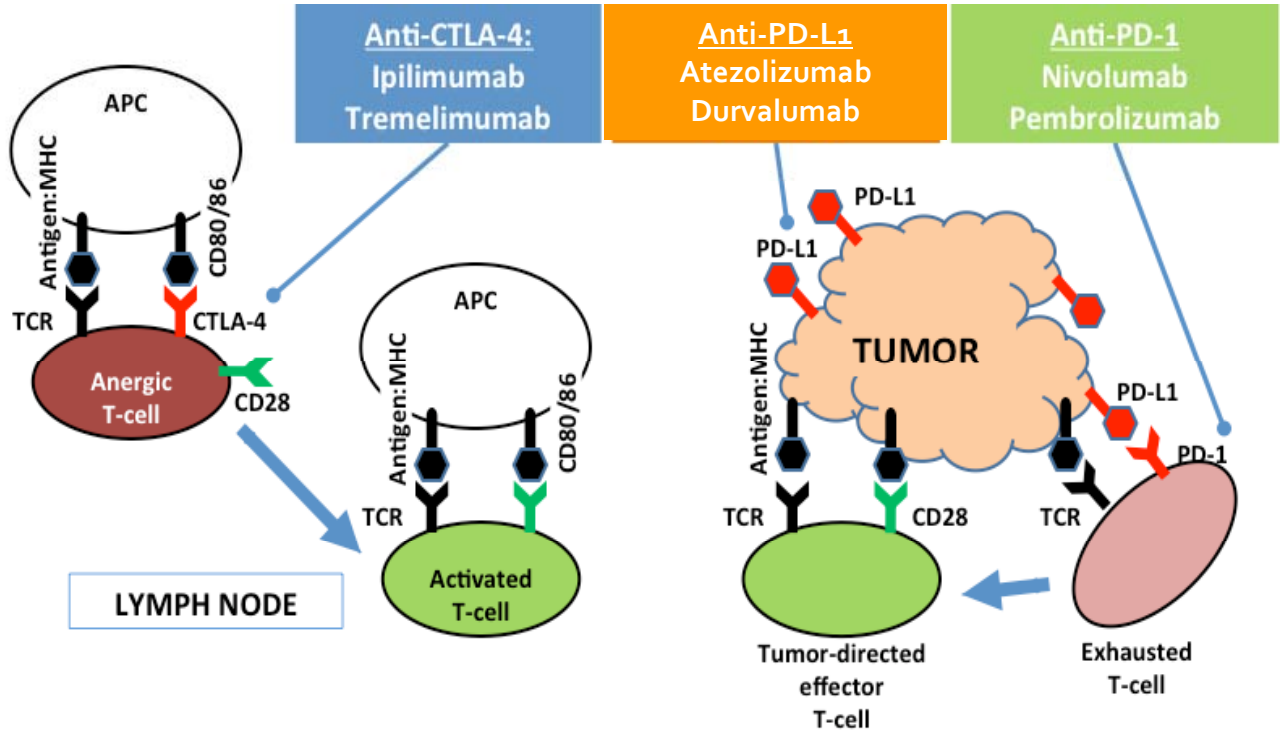
Immune Checkpoint Inhibitors



Adapted from Intelkofer and Thompson, TLB, 2015 & Callahan and Wolchok, TLB, 2013

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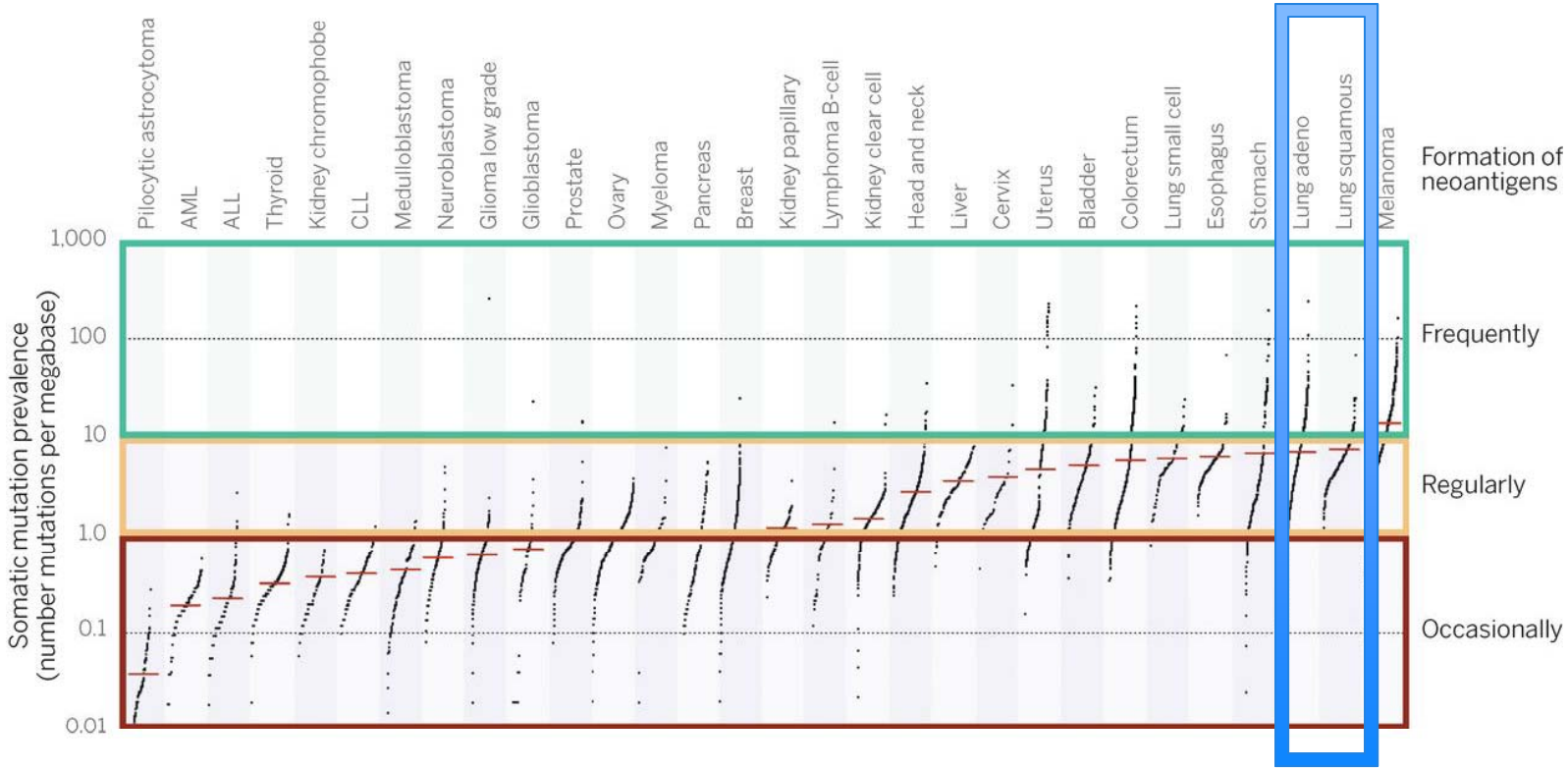
Somatic Mutation Burden in Cancer



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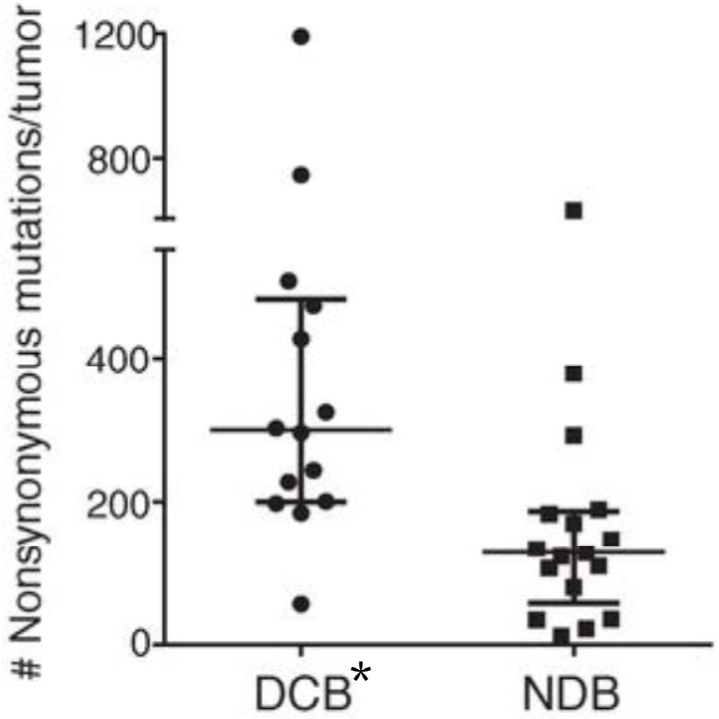
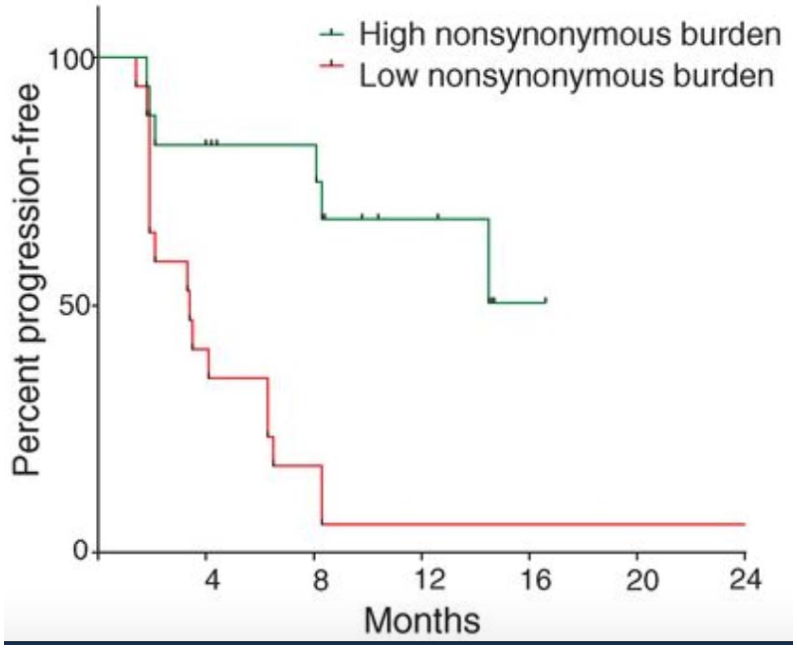
Tumor Mutation Burden Associated with Response to PD-1 Inhibition





* Durable Clinical Benefit (6 month PFS)

Rizvi et al. Science. 2015

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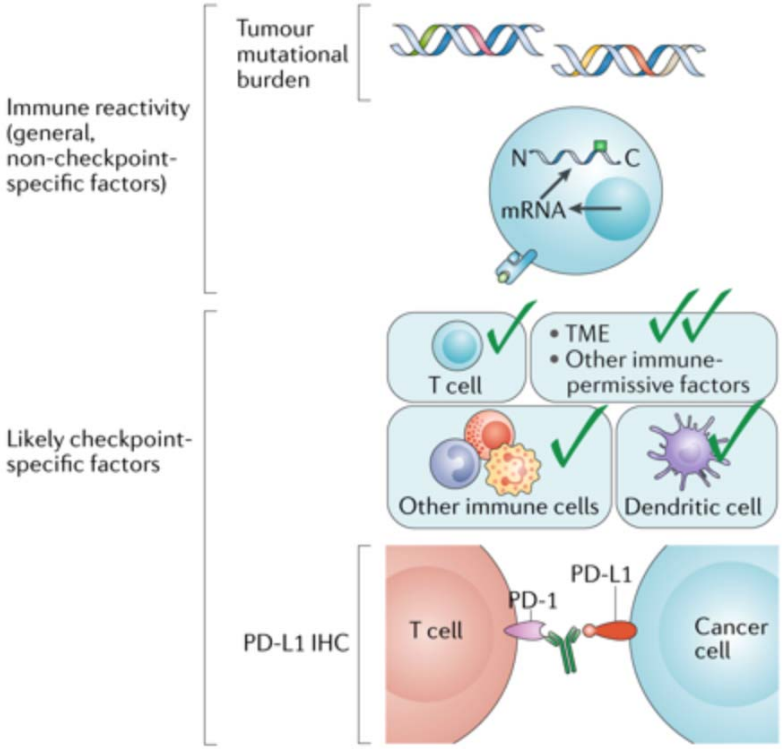
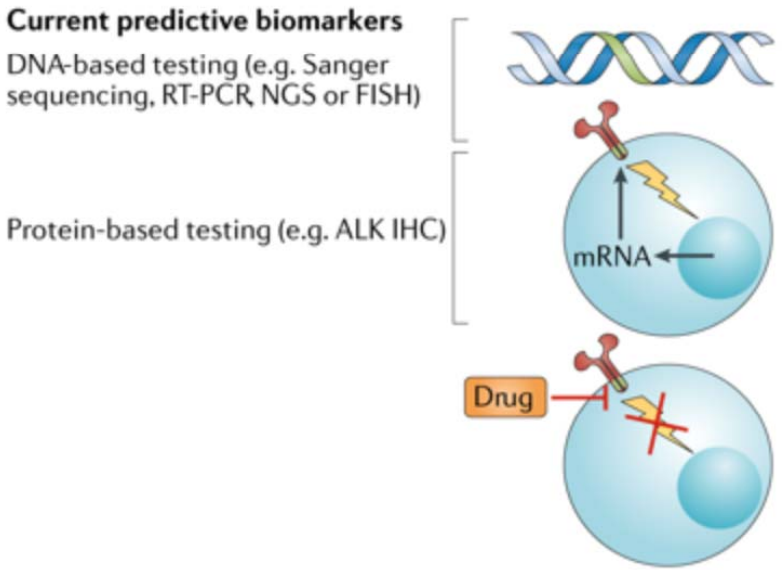
Not All Biomarkers are Created Equal…

Biomarkers to predict response to Immune Checkpoint Inhibitors



Biomarkers to predict response to targeted therapy



Camidge, Doeble, and Kerr. Nat Rev Clin Onc. 2019

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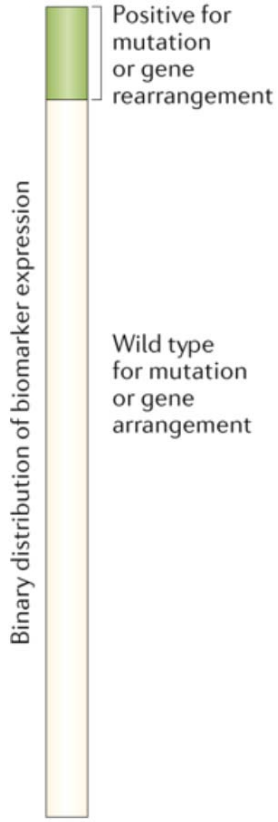
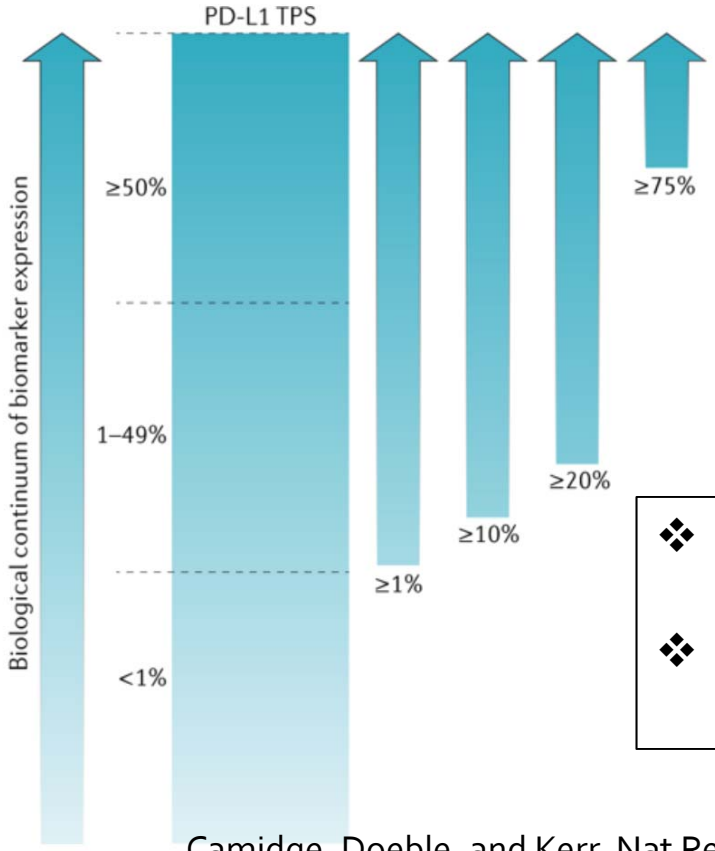
Not All Biomarkers are Created Equal…

EGFR Mutation



PD-L1 IHC



Biomarker Challenges in Immunotherapy

- PD-L1 expression variable within tissue?
- Ideal cutoff to use?
- Potential differences between assays
- TMB and PD-L1 are independent variables

❖ Response rate to EGFR TKI in patients with EGFR mutation: 80%
❖ Response rate to PD-1 Inhibitor in patients with "high" PD-L1: 45%

Camidge, Doeble, and Kerr. Nat Rev Clin Onc. 2019

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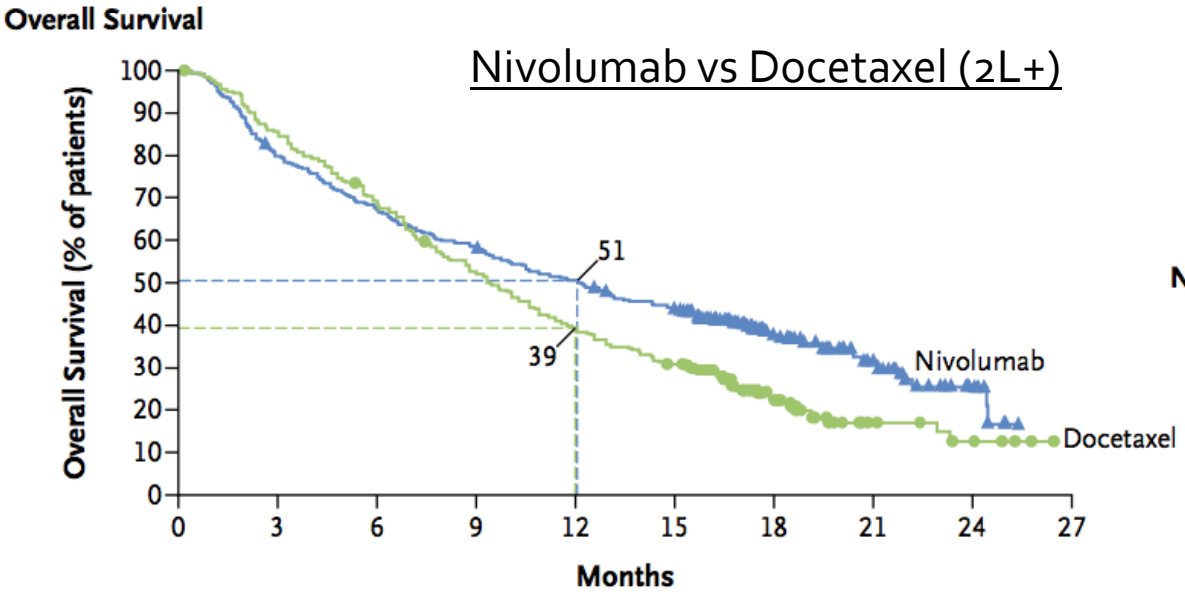
PD-1 Inhibitors in the Metastatic Setting



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

- Nivolumab approved in the 2nd line setting, all patients, regardless of PD-L1
- Pembrolizumab approved in the 2nd line setting, PD-L1 >1%
- Atezolizumab approved in the 2nd line settings, all patients, regardless of PD-L1

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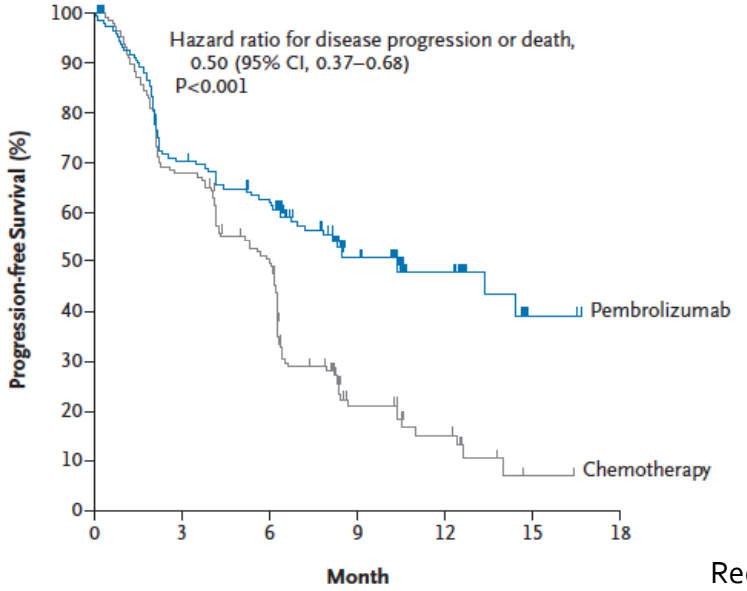
Pembrolizumab is Superior to Platinum-based Chemo in Patients with PD-L1≥50% (KEYNOTE-024)

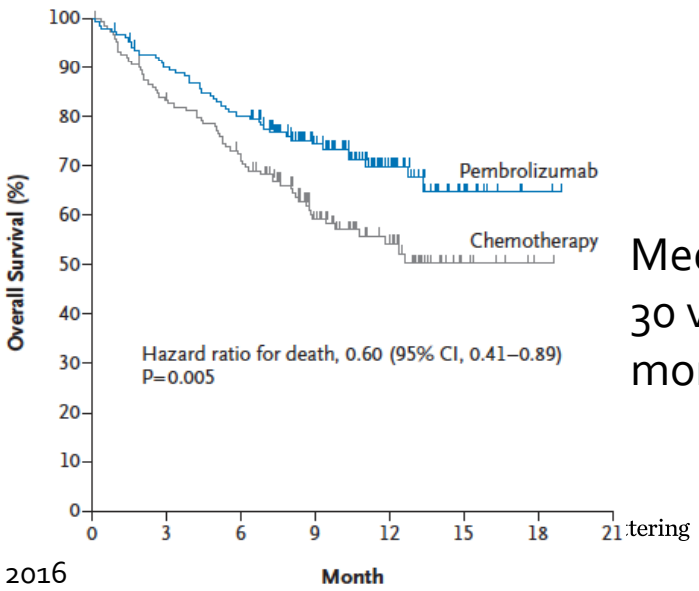
Key Eligibility Criteria

- Metastatic NSCLC (any histology)
- PD-L1 TPS ≥50%
- EGFR and ALK negative
- No untreated or unstable CNS metastases

Randomize 1:1

- Pembrolizumab Q3W
- Carboplatin + Paclitaxel Q3W OR Carboplatin + Pemetrexed Q3W

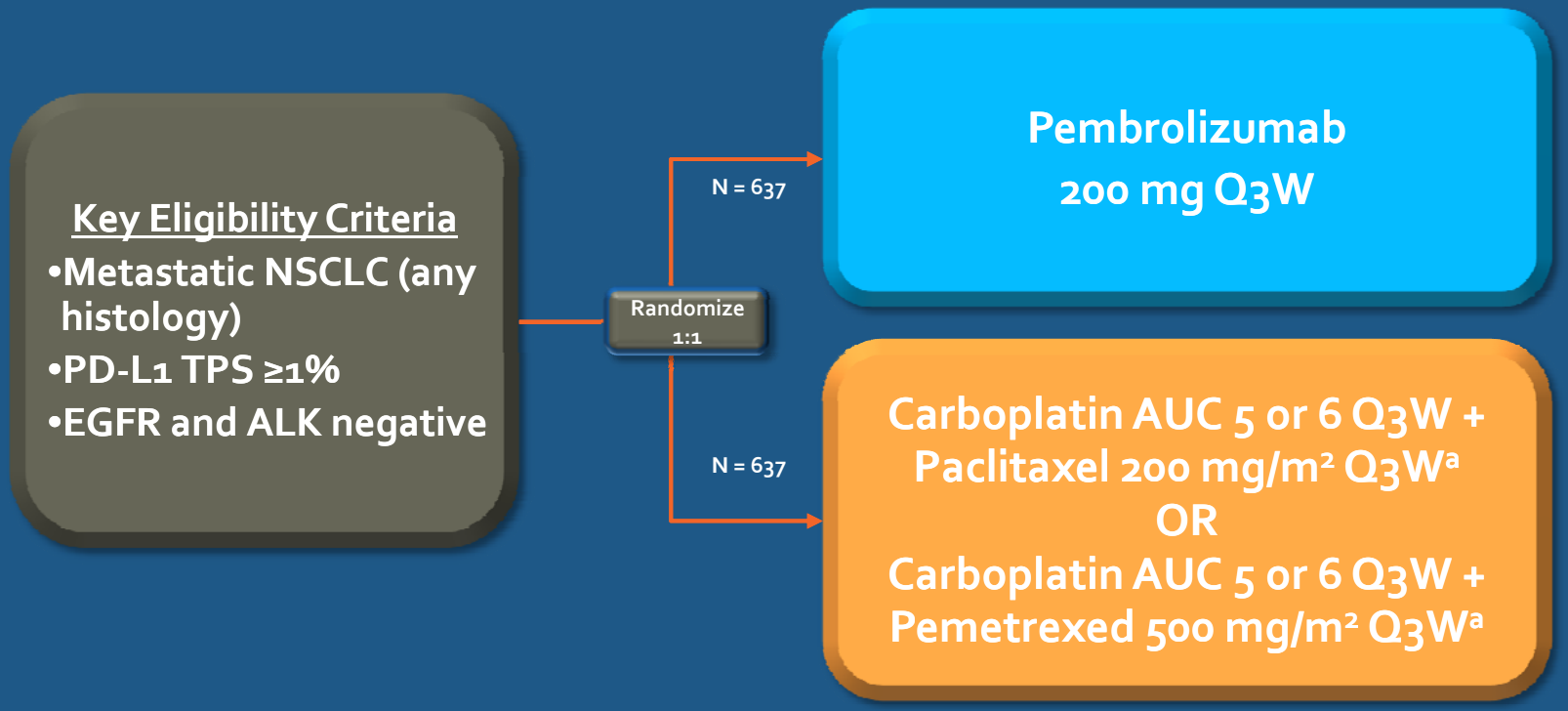




Median OS 30 vs 14.2 months

Reck et al, NEJM 2016

Randomized Trial of Pembrolizumab and Platinum-based Chemotherapy in Patients with PD-L1 ≥1%



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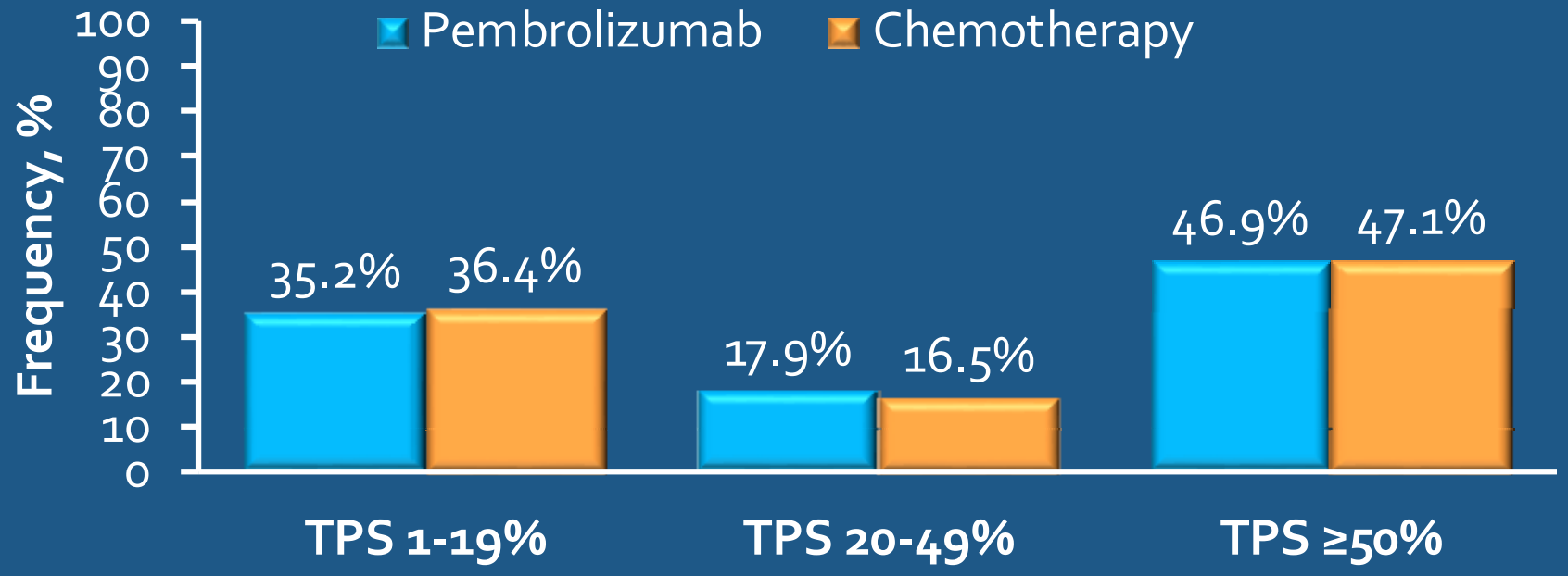
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥1%



Gilberto Lopes ASCO 2018

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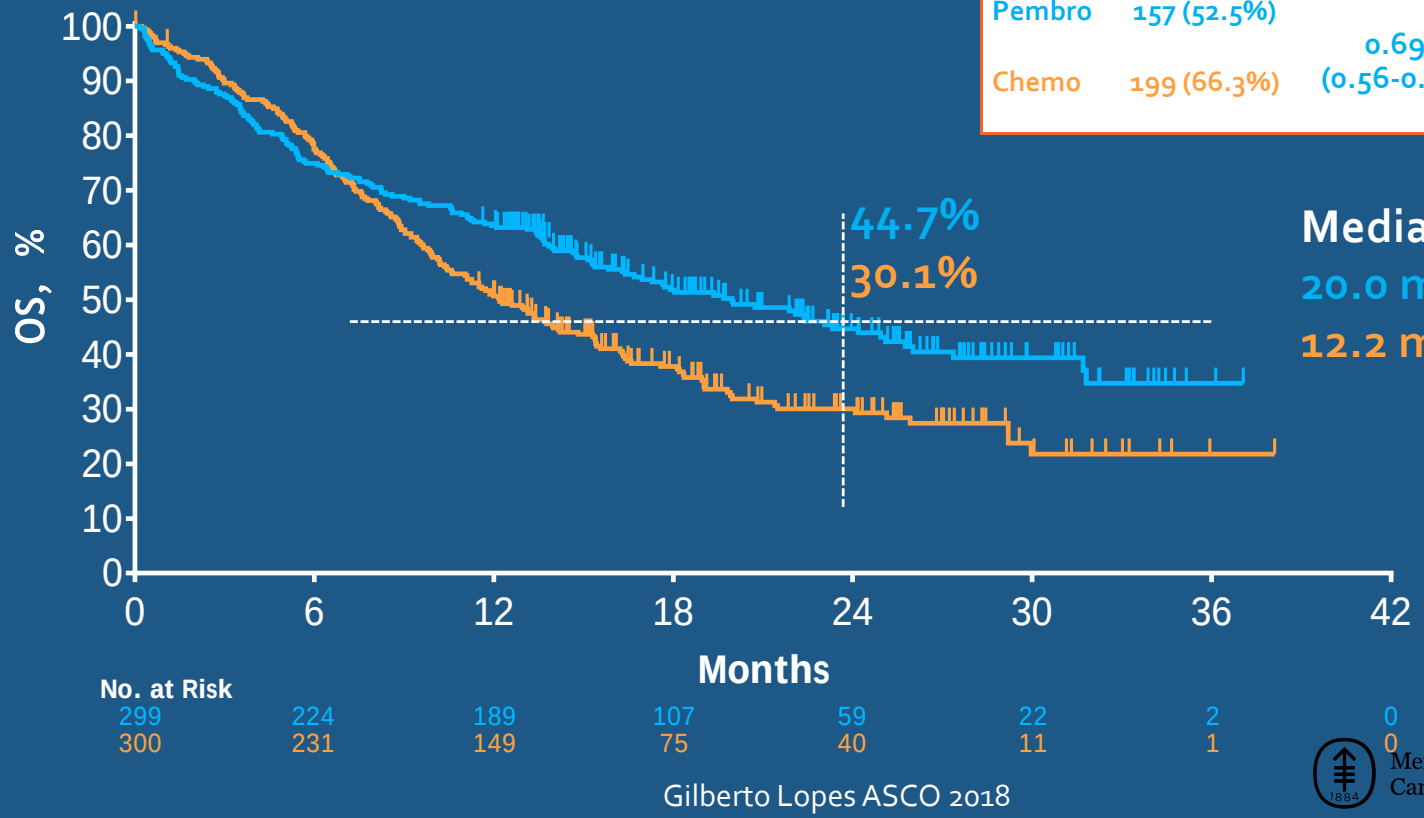
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥50%



	Events	HR (95% CI)	*P*
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		

Median OS (95% CI)

20.0 mo (15.4-24.9)

12.2 mo (10.4-14.2)

Gilberto Lopes ASCO 2018

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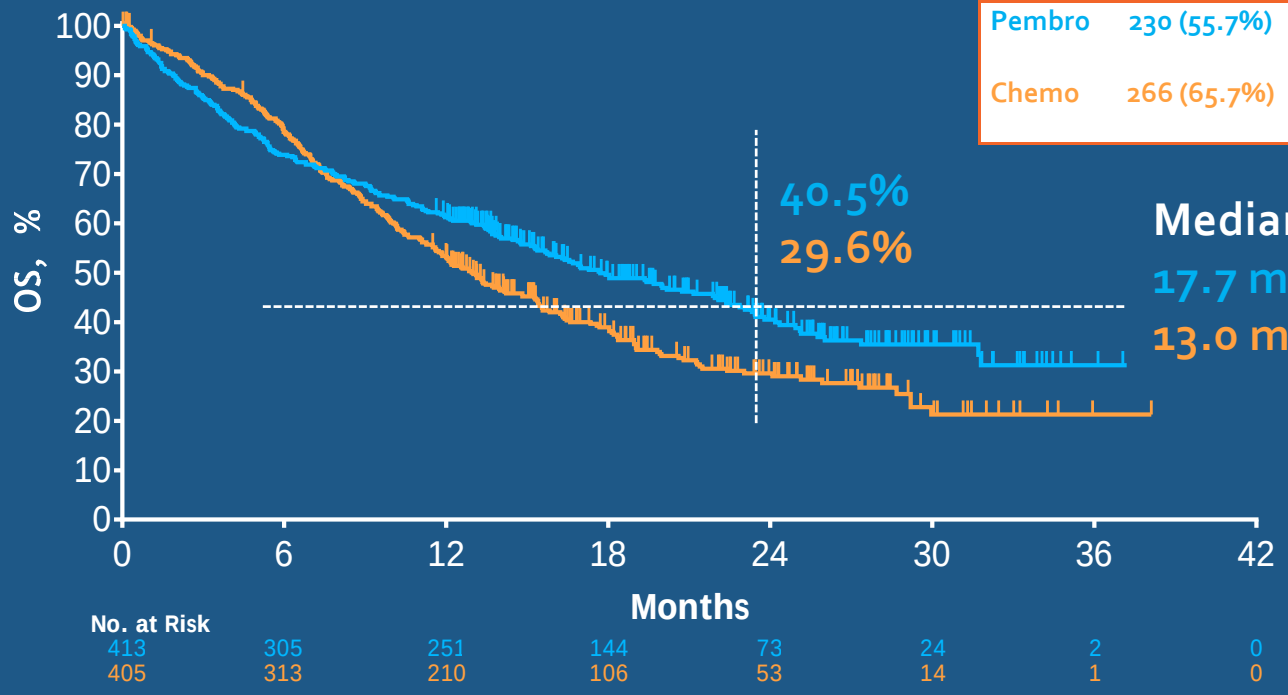
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥20%



	Events	HR (95% CI)	*P*
Pembro	230 (55.7%)	0.77 (0.64-0.92)	0.0020
Chemo	266 (65.7%)		

Median OS (95% CI)

17.7 mo (15.3-22.1)

13.0 mo (11.6-15.3)

Gilberto Lopes ASCO 2018

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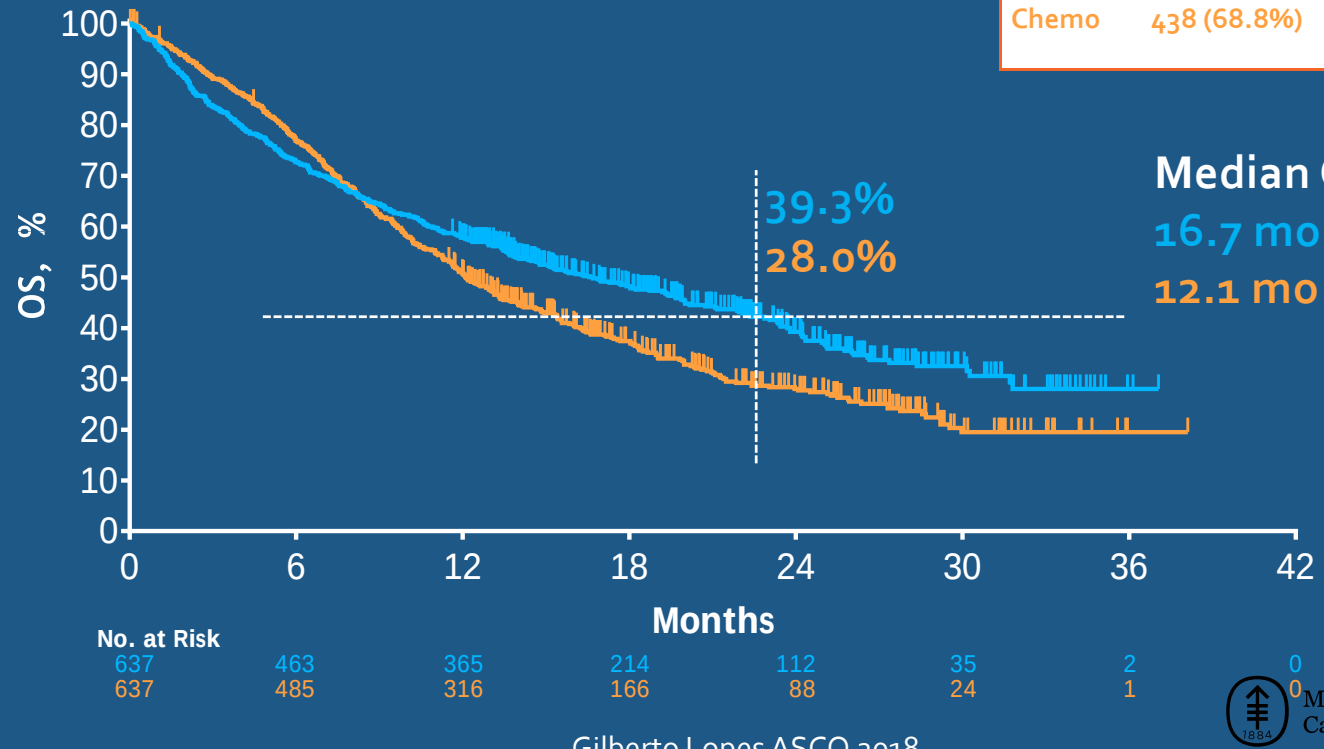
Pembrolizumab vs Platinum-based Chemo in Patients with PD-L1 ≥1%

	Events	HR (95% CI)	*P*
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		



Median OS (95% CI)

16.7 mo (13.9-19.7)

12.1 mo (11.3-13.3)

No. at Risk							
637	463	365	214	112	35	2	0
637	485	316	166	88	24	1	0

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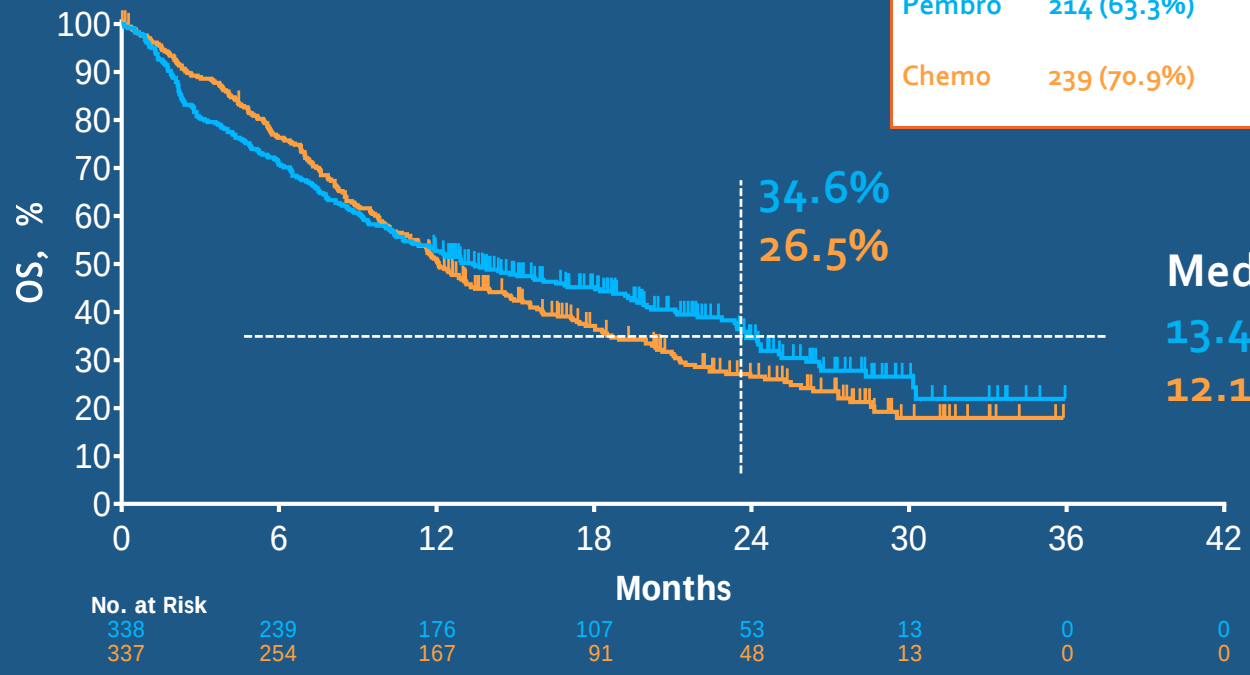
Pembrolizumab vs Platinum-based Chemotherapy:PD-L1 ≥1-49%



	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

Median OS (95% CI)

13.4 mo (10.7-18.2)

12.1 mo (11.0-14.0)

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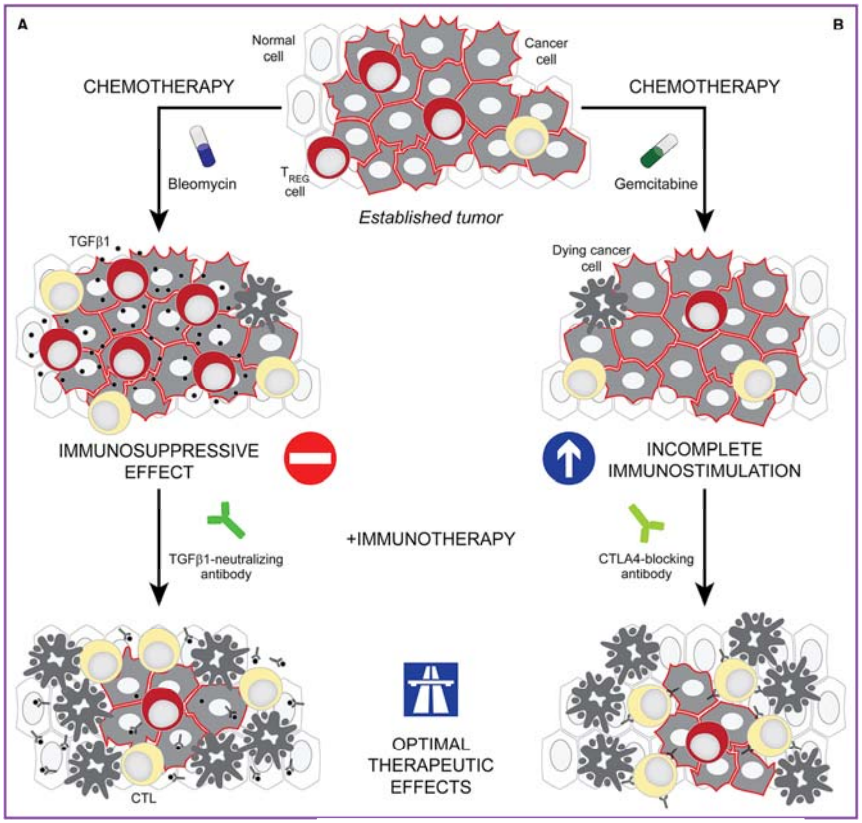
Chemo + IO rationale in Lung Cancer

- Chemotherapy may:
  - Increase antigen cross presentation after tumor cell death
  - Inhibition of MDSCs
  - Increase ratio of cytotoxic T-cells to regulatory T-cells

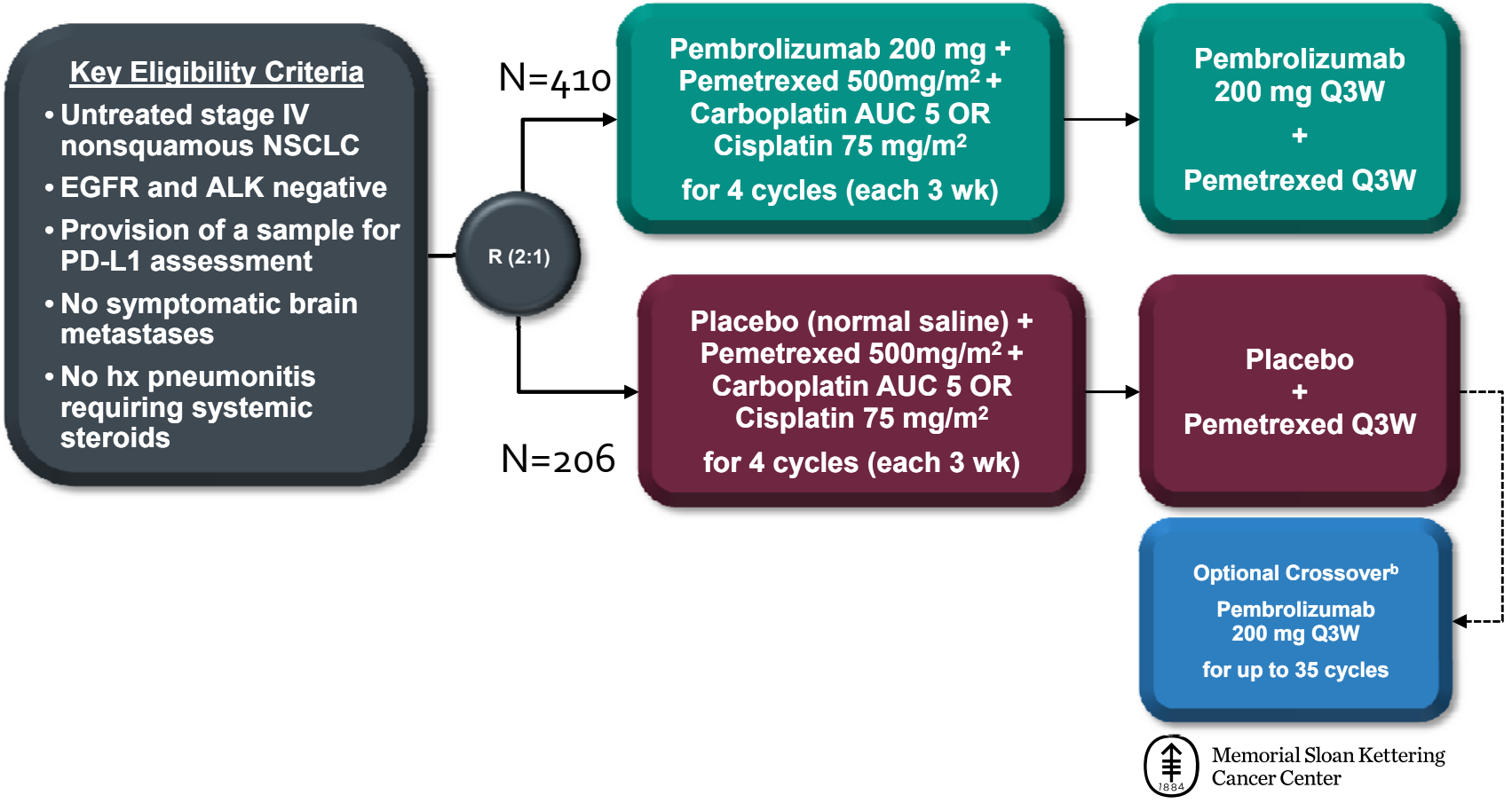
→ Enabling immune checkpoint inhibitors to work better

→ Many patients do not receive 2nd line therapy



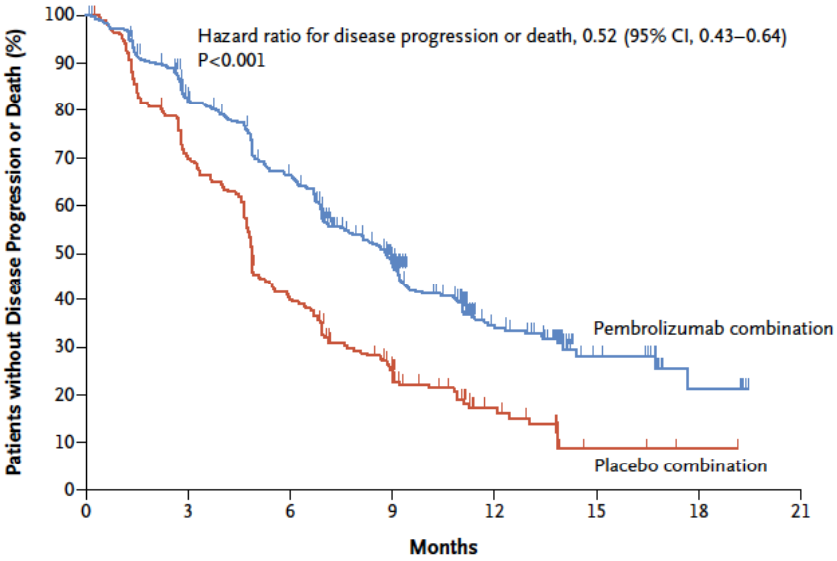
Galluzzi et al. Cancer Cell. 2015

Chemotherapy + Pembrolizumab in Metastatic Non-squamous NSCLC



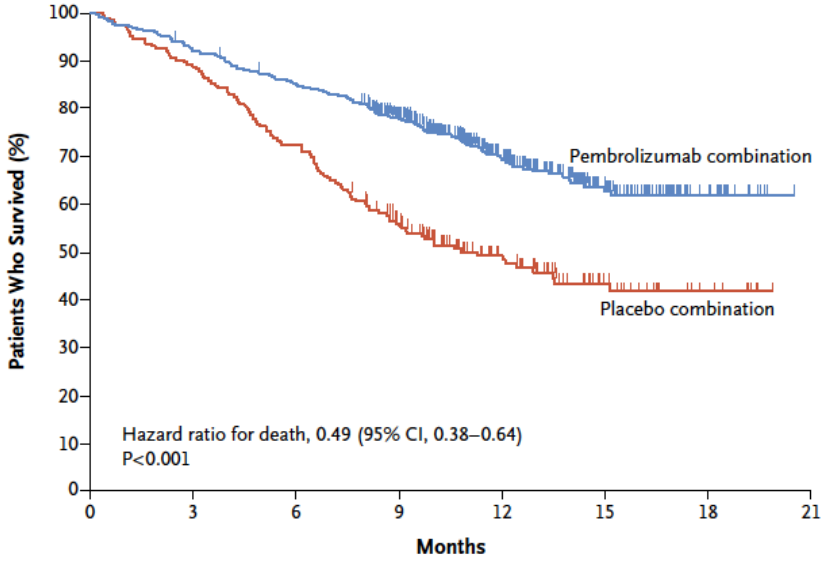
Chemotherapy + Pembrolizumab in Metastatic Non-squamous NSCLC

Progression-free Survival



- 12 month PFS 34% vs 17%
- median PFS 8.8 vs 4.9 months
- ORR 47% vs 19%

Overall Survival



- 12 month OS 69% vs 49%
- mOS NR vs 11.3 months
- Median follow up 10.5

Gandhi et al NEJM 2018

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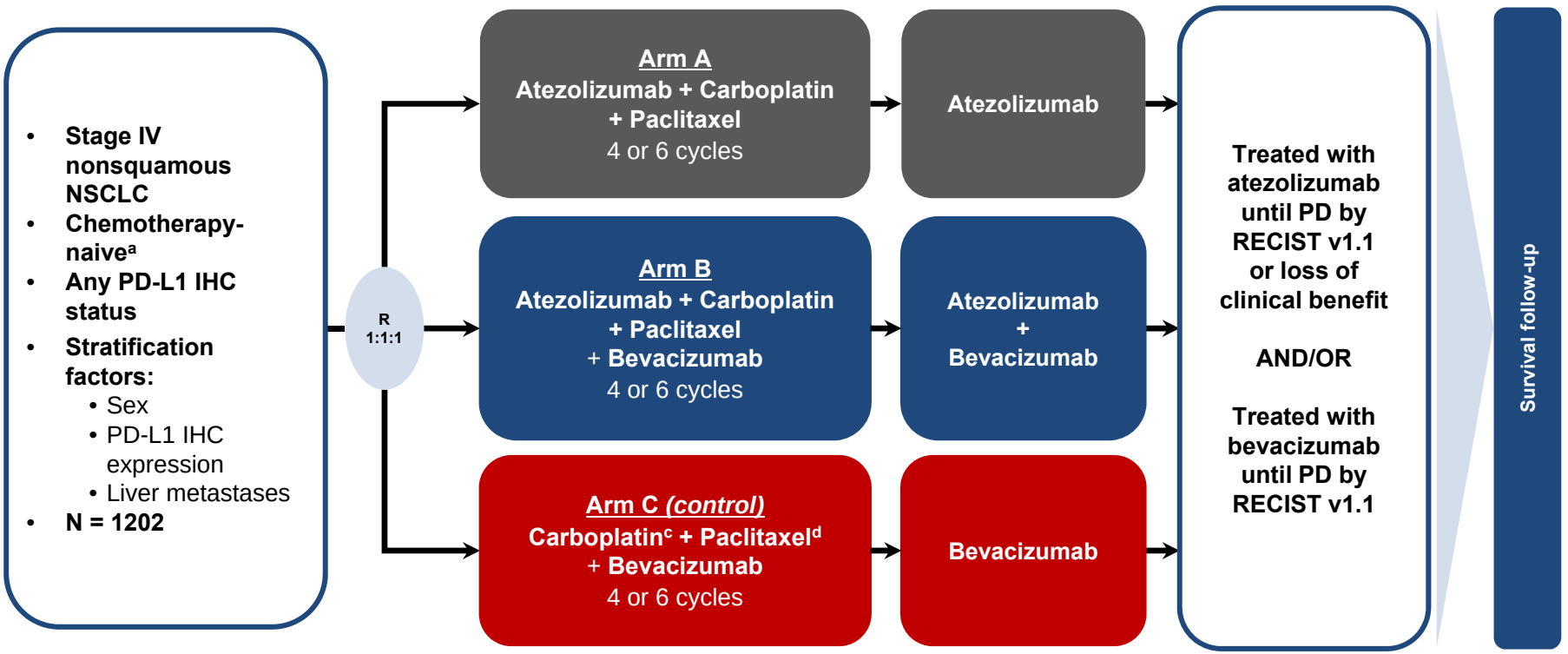
Chemo + Atezolizumab + Bevacizumab in Non-squamous Lung Cancer



Socinski et al, ASCO 2018

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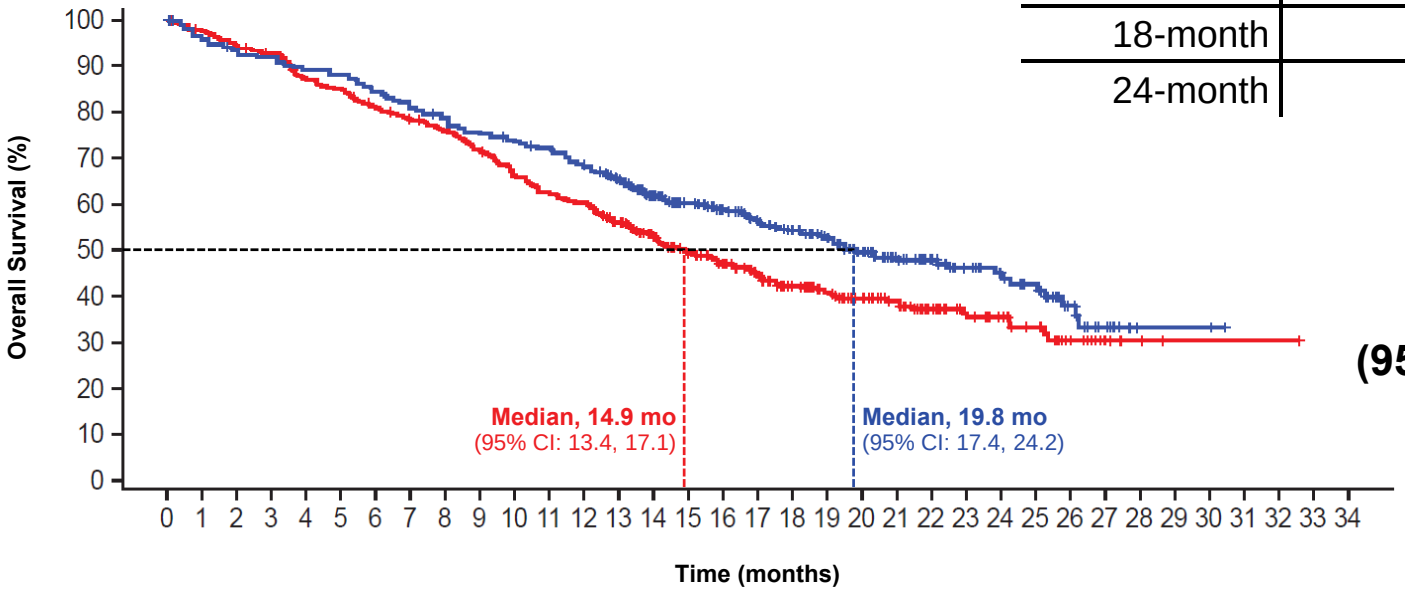
Chemo + Atezolizumab + Bevacizumab in Non-squamous Lung Cancer

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	68%	61%
18-month	54%	42%
24-month	45%	36%



HR, 0.77
(95% CI: 0.63, 0.93)

Socinski et al, ASCO 2018

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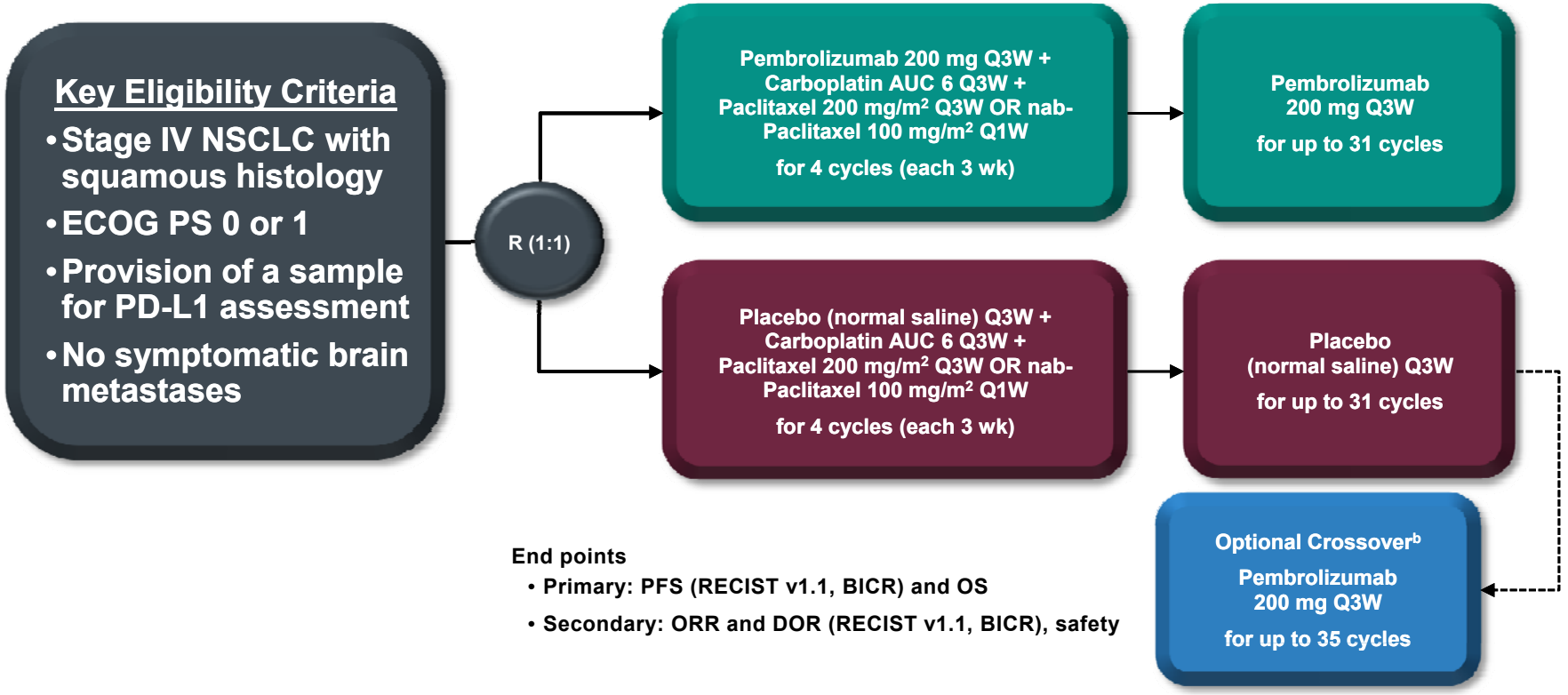
Pembrolizumab with Carboplatin and Taxane in Squamous NSCLC



End points

- **Primary: PFS (RECIST v1.1, BICR) and OS**
- **Secondary: ORR and DOR (RECIST v1.1, BICR), safety**

Paz-Ares ASCO 2018

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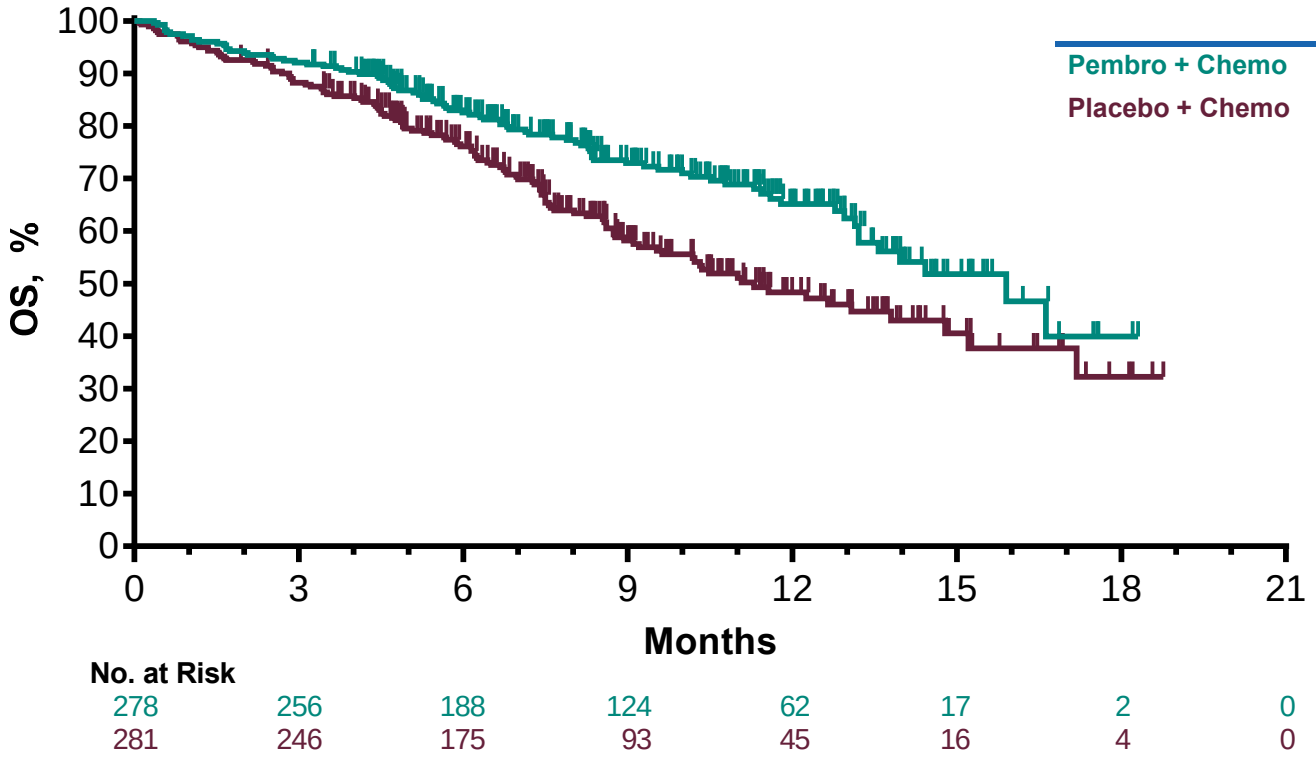
Pembrolizumab with Carboplatin and Taxane in Squamous NSCLC



	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		

Median OS (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

Similar chemo+ atezolizumab study showed PFS benefit but not OS in preliminary analysis

Luis Paz-Ares . NEJM 2018

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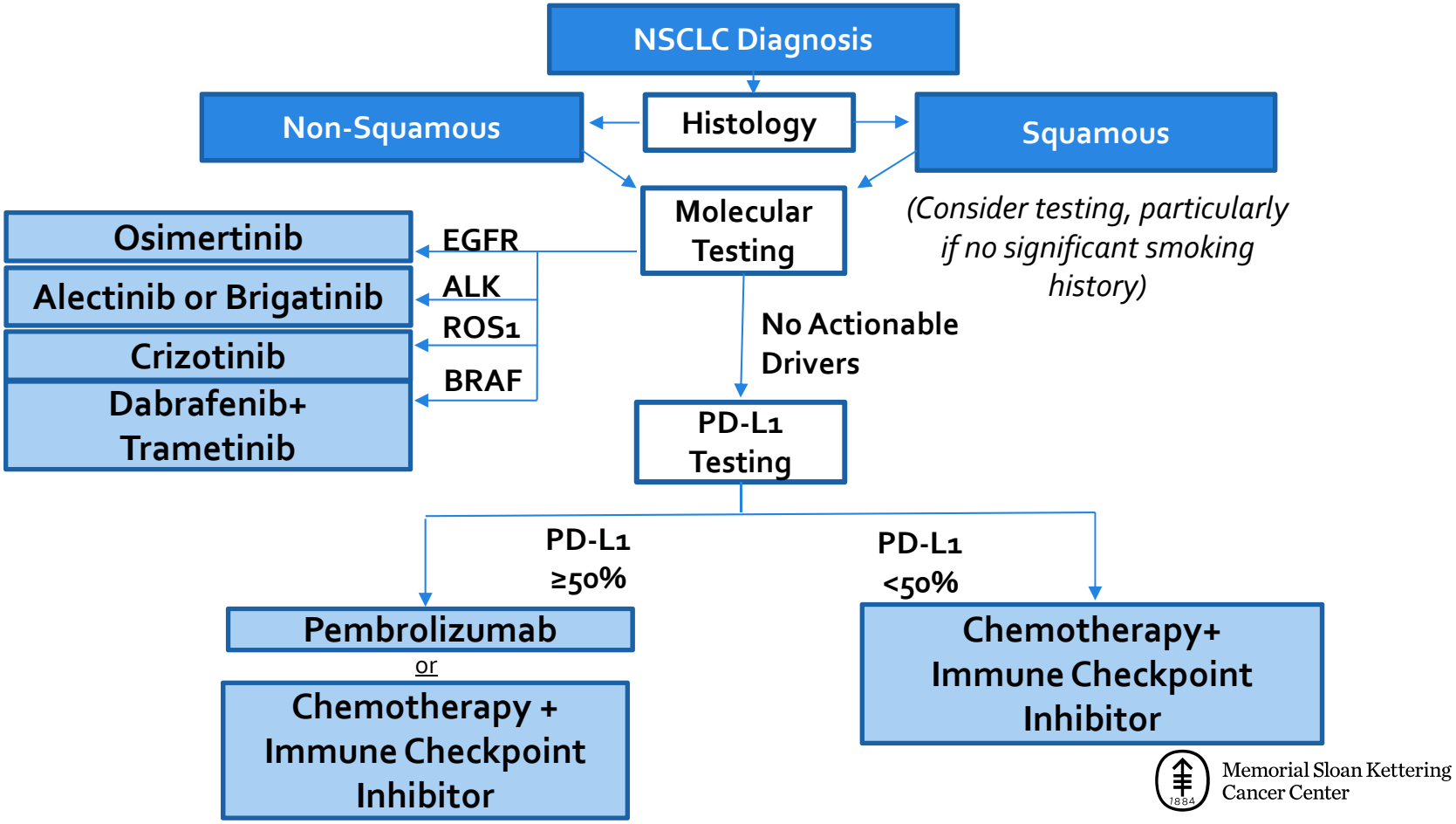
First Line Treatment Algorithm



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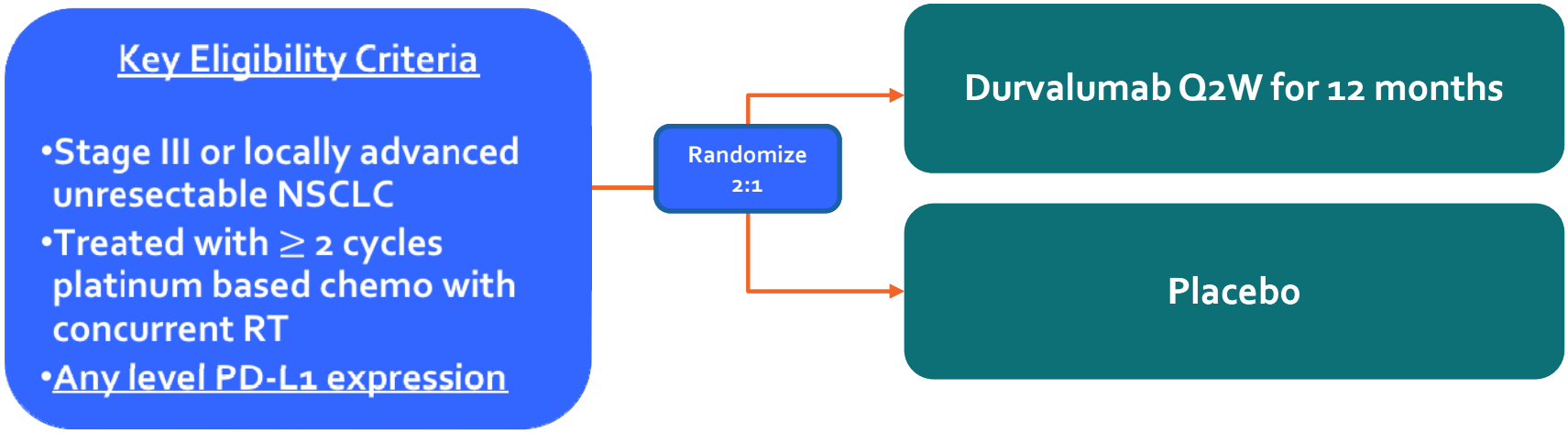
Immunotherapy in Stage III disease



Primary Endpoints: Progression free survival and Overall Survival

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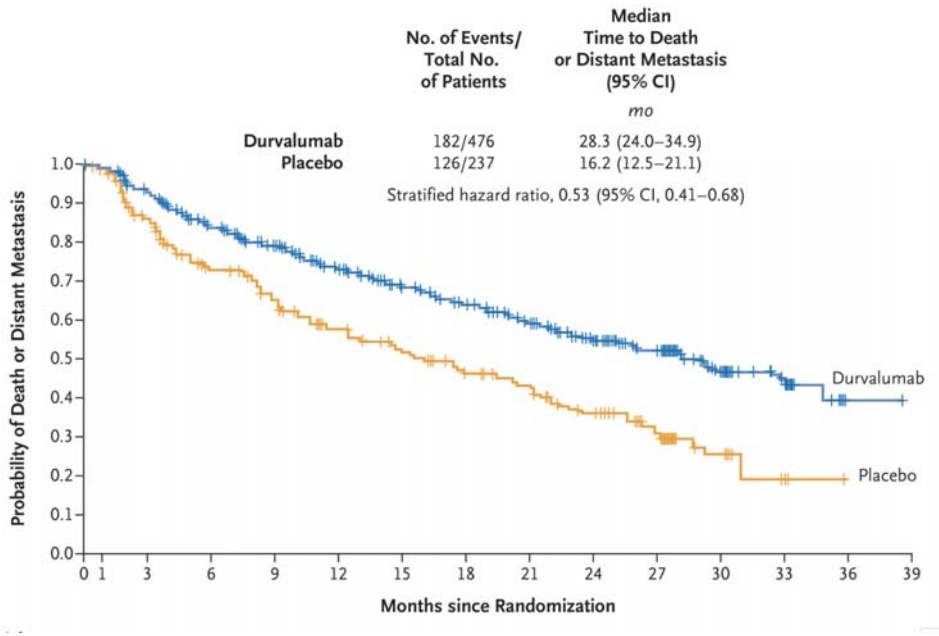
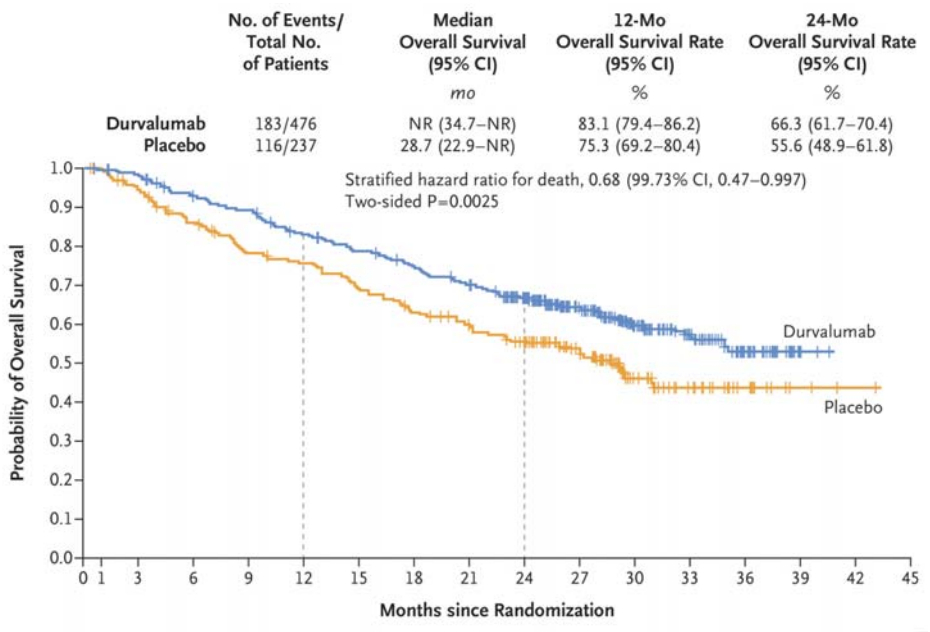
Immunotherapy in Stage III disease





- Risk of pneumonitis: 33.9% of pts on durvalumab and 24.8% on placebo
- No clear benefit if PD-L1 negative -> not approved in Europe for PD-L1 neg patients

Antonia et al. NEJM. 2018

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Extensive Stage Small Cell Lung Cancer

- Standard of care 1L treatment SCLC has been platinum/etoposide chemotherapy for over 20 years
  - Initial responses are robust, recurrent disease often rapid
- Topotecan is the only FDA approved therapy at time of progression (limited efficacy)
- Immunotherapy has demonstrated (minimal) benefit in the 2nd line setting
  - In practice patients most patients received Ipi/Nivo
- Many SCLC patients have rapid decline and may not receive 2nd line therapy

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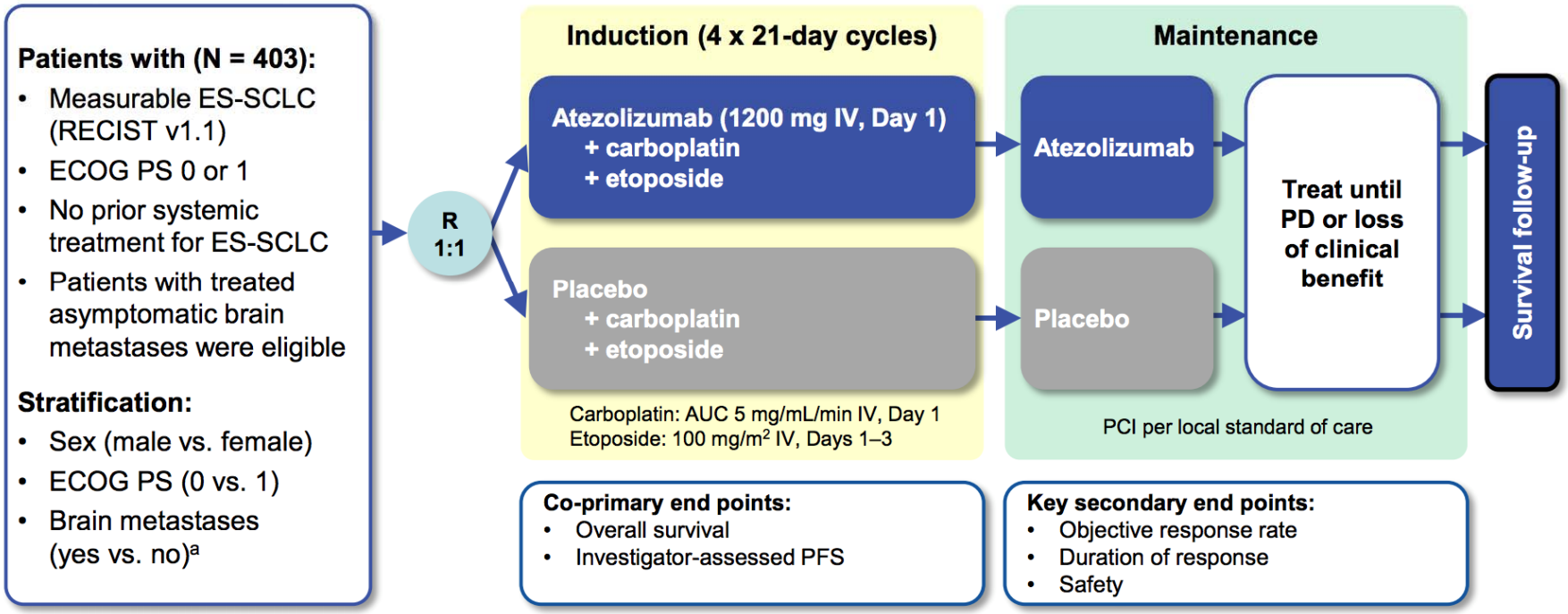
Chemo + IO in Small Cell Lung Cancer



Liu et al. WCLC. 2018

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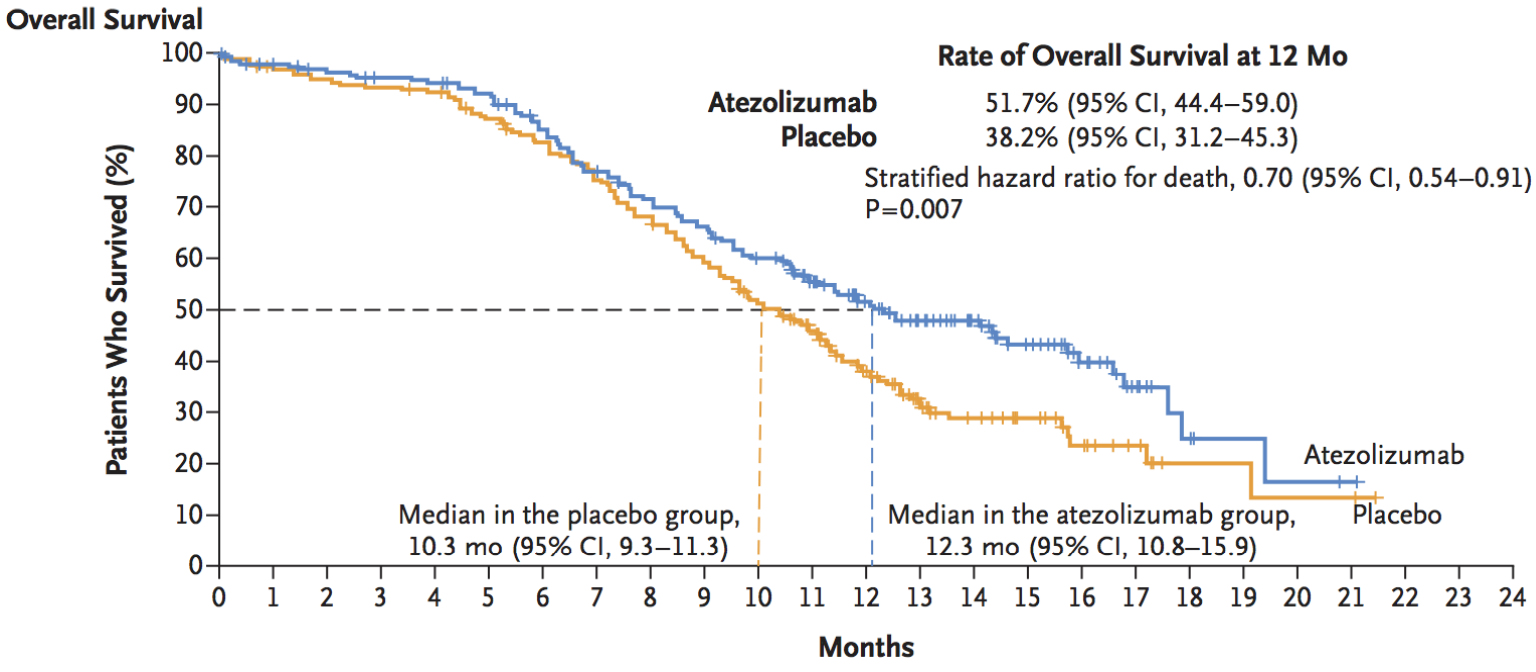
Immunotherapy in Small Cell Lung Cancer



→ Recently FDA approved, quickly adopted as standard of care

Horn et al. NEJM. 2018

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Contraindications to Immunotherapy

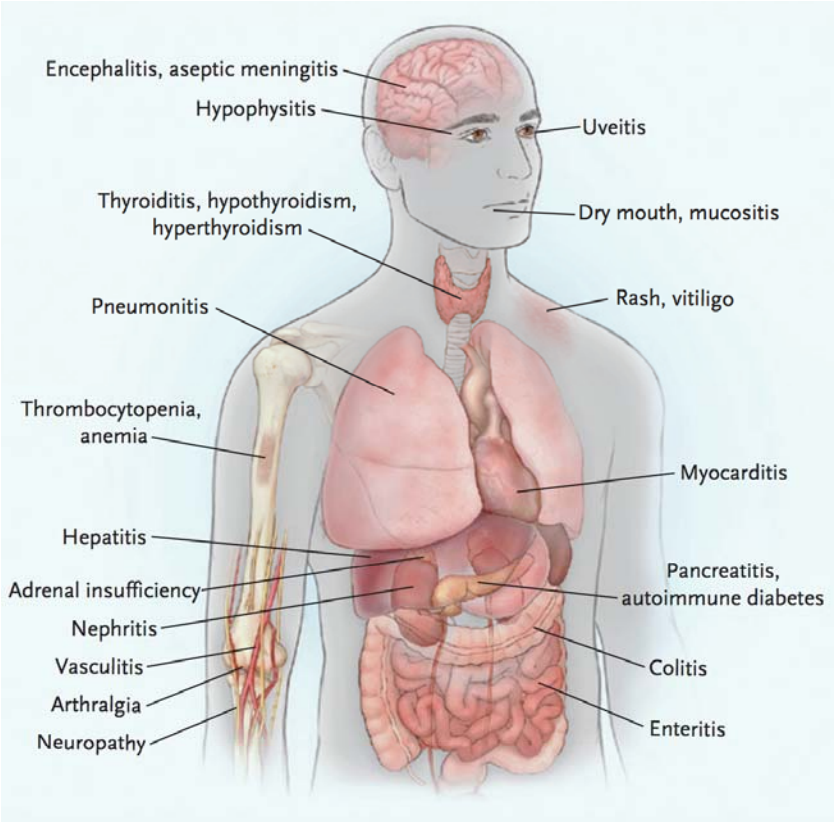
Are there any lung cancer patients that should not receive immunotherapy in the first line setting?

- Patients with targetable oncogenic drivers (EGFR, ALK, ROS1, BRAF)
  - Immunotherapy less effective in these patients, even if high PD-L1
  - May have increased toxicity if TKI used after IO (e.g. osimertinib)

- Patients with known autoimmune conditions who may be at increased risk of toxicity

Immune Related Adverse Events (irAE)

- Toxicities of immunotherapy most likely to occur in initial weeks/months of treatment (but can happen at any time)
- Organ specific toxicities different in PD-1 vs CTLA-4
  - More colitis with anti-CTLA-4
  - More pneumonitis with anti-PD-1
- Patients with preexisting autoimmune conditions may be at higher risk



Sidlow, Hellmann, and Postow. NEJM. 2018

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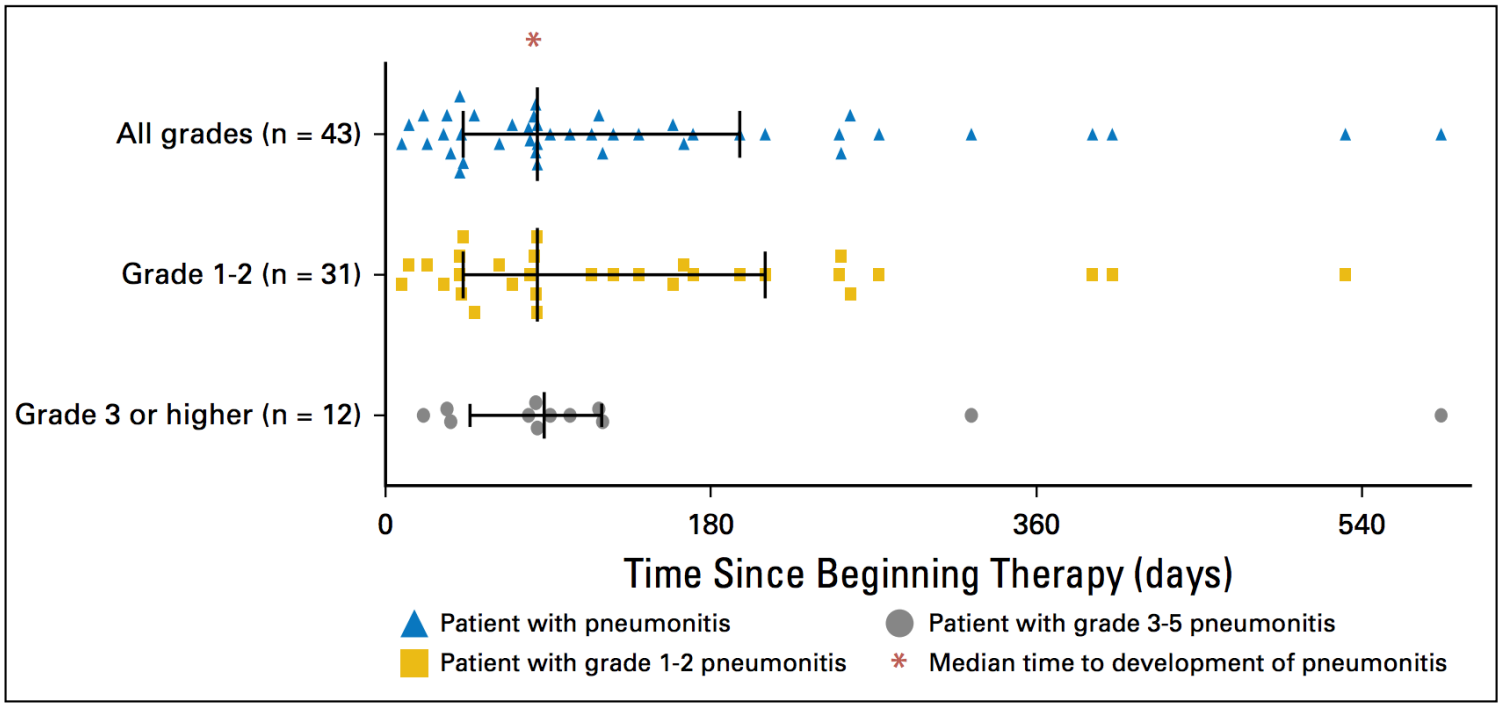
Immunotherapy Toxicities: Pneumonitis



Risk of pneumonitis (all grades): ~5%
Risk of Grade 3-5 pneumonitis: ~ 1%

Risk higher with combination therapy (PD-1+CTLA-4)

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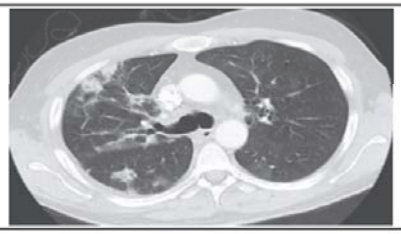
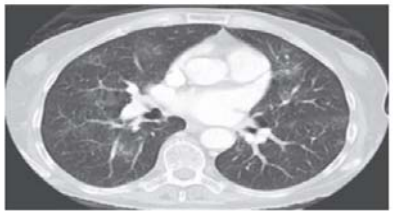
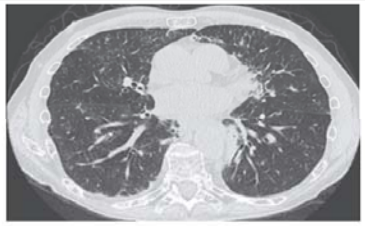
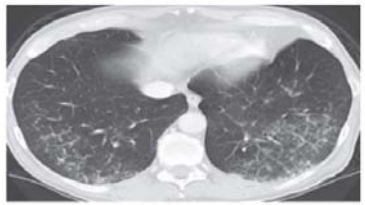
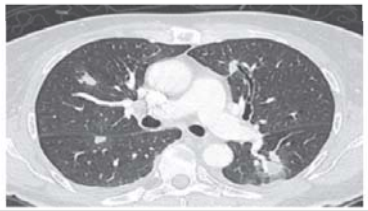
Naidoo et al. JCO 2016.

Immunotherapy Toxicities: Pneumonitis

Multiple potential radiographic patterns of pneumonitis related to immunotherapy

Cryptogenic organizing pneumonia-like (n = 5, 19%)	
Ground glass opacities (n = 10, 37%)	

Interstitial (n = 6, 22%)	
Hypersensitivity (n = 2, 7%)	
Pneumonitis not otherwise specified (n = 4, 15%)	

Naidoo et al. JCO 2016.

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Management of irAEs: Pneumonitis

Consensus Guidelines from ASCO (no prospective trials to guide management)

G1: **Asymptomatic**; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.	•Hold treatment, repeat CT in 3-4 weeks •May resume ICPi with radiographic evidence of improvement •If no improvement, should treat as G2 (with steroids)
G2: **Symptomatic**; involves more than one lobe of the lung or 25 to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL.	•Hold until resolution to G1 or less. •Prednisone 1 to 2 mg/kg/day and taper by 5 to 10 mg/week over 4-6 weeks. •Consider bronchoscopy with BAL. •Consider empirical antibiotics.
G3: Severe symptoms; **hospitalization required**; involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated.	**•Permanently discontinue immunotherapy** •Empiric antibiotics; methylpred IV 1 to 2 mg/kg/day • If no improvement after 48 hours, consider infliximab or mycophenolate mofetil or IVIG or cyclophosphamide, taper corticosteroids over 4-6 weeks •Bronchoscopy with BAL ± transbronchial biopsy.
G4: Life-threatening respiratory compromise; urgent intervention indicated **(intubation)**	

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Immunotherapy Toxicities

- Rates of irAEs are higher in patients with response to treatment
- Prompt initiation of steroids is important
- Treatment with steroids for irAEs does not reduce efficacy of treatment
- If Grade 3-4 toxicity occurs, agents should be permanently discontinued
  - Responses can be maintained off therapy
  - Current practice is often to restart other treatments only with clear clinical/radiographic signs of progressive cancer

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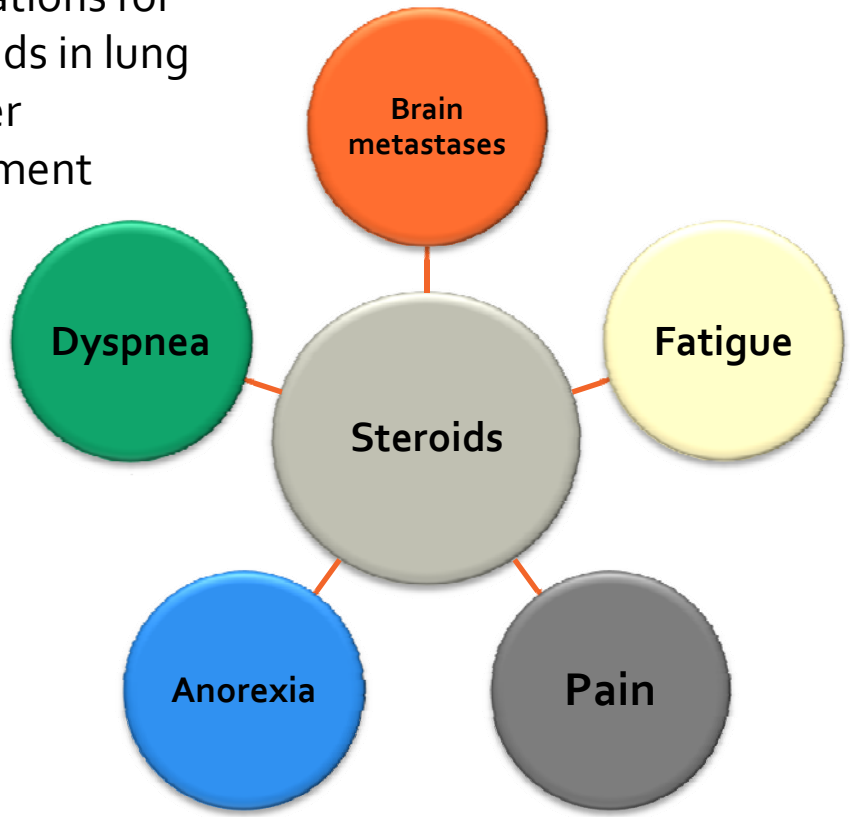
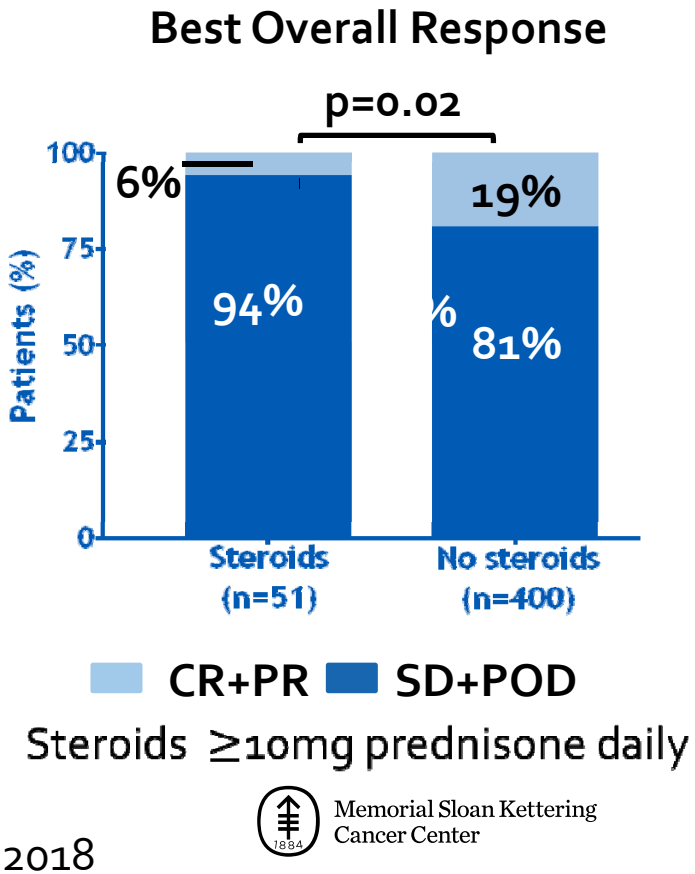
Impact of Baseline Steroids on PD-(L)1 Efficacy: Lower Overall Response Rate

Indications for steroids in lung cancer treatment





Arbour et al. JCO 2018

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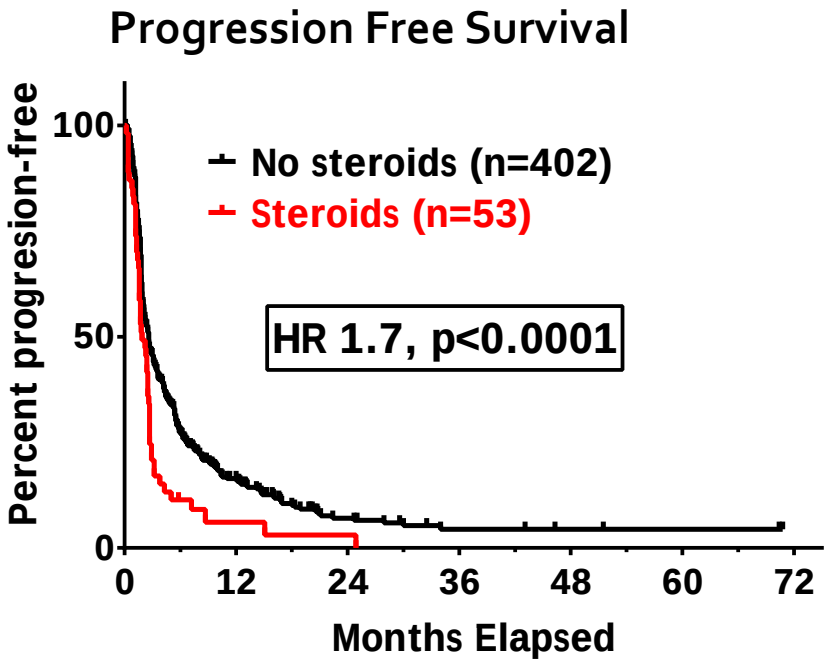
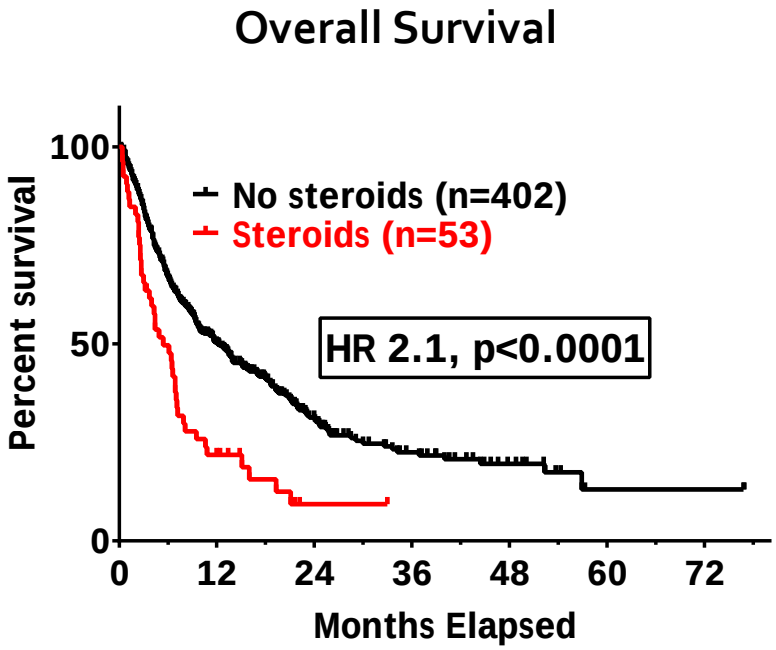
Impact of Baseline Steroids on PD-(L)1 Efficacy: Inferior PFS and OS





Arbour et al. ASCO 2018

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Conclusions

- PD-1 and PD-L1 inhibitors have dramatically changed the treatment landscape of metastatic NSCLC and SCLC
- PD-L1 staining is most established biomarker, though TMB being increasingly recognized
- Immunotherapy offers the promise of durable disease control for patients with lung cancer
- irAEs can develop in patients treated with PD-1/L1 inhibitors, including pneumonitis
  - Prompt initiation of steroids is the mainstay of management

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