Memorial Sloan Kettering Cancer Center

Relevant endpoints for checkpoint inhibitor trials

Management of the patient with prolonged progression-free survival

Is there a role for stopping therapy?

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T-Cell Checkpoint Inhibitors in Lung Cancers

My Patient

- 65 y/o woman, a never smoker
- Stage IV squamous cell lung cancer (PIK3CA E542Q) with metastases to supraclavicular lymph nodes and brain (initial SRS)
- Treated with ipilimumab and nivolumab
- Month 3, new cervical lymph nodes. Bx: Polymorphous Lymphoid Population
- All nodes disappear
- Side Effects: Rash, hypophysitis (hydocortisone)
- Month 26, After ipilimumab 4 and nivolumab 70, residual lung lesion resected. No tumor. Drugs stop
- Month 33, remains NED

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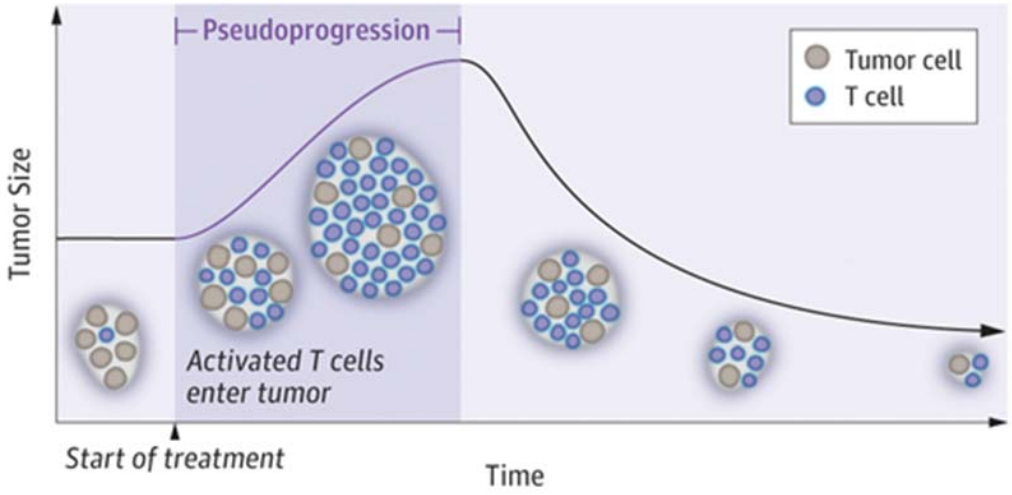
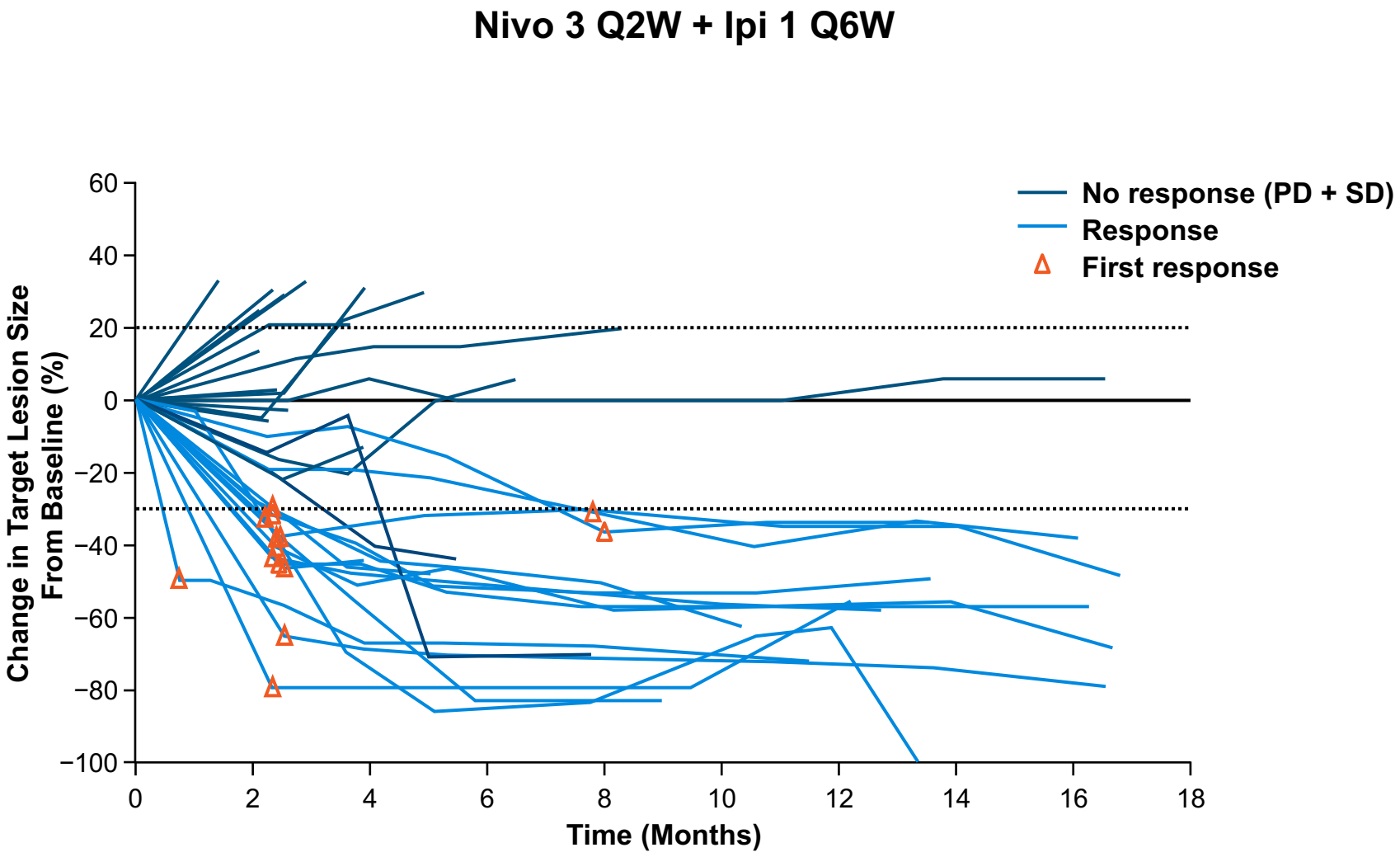
Assessing Response to Immunotherapy Is it Different?

Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)



New, measurable lesions (≥ 5 × 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (<5 × 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
SD	Neither a 50% decrease in tumor burden compared with baseline nor a 25% increase compared with nadir can be established
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

Initial Nivolumab + Ipilimumab in Lung Cancer Kinetics of Response- Is it Different?”

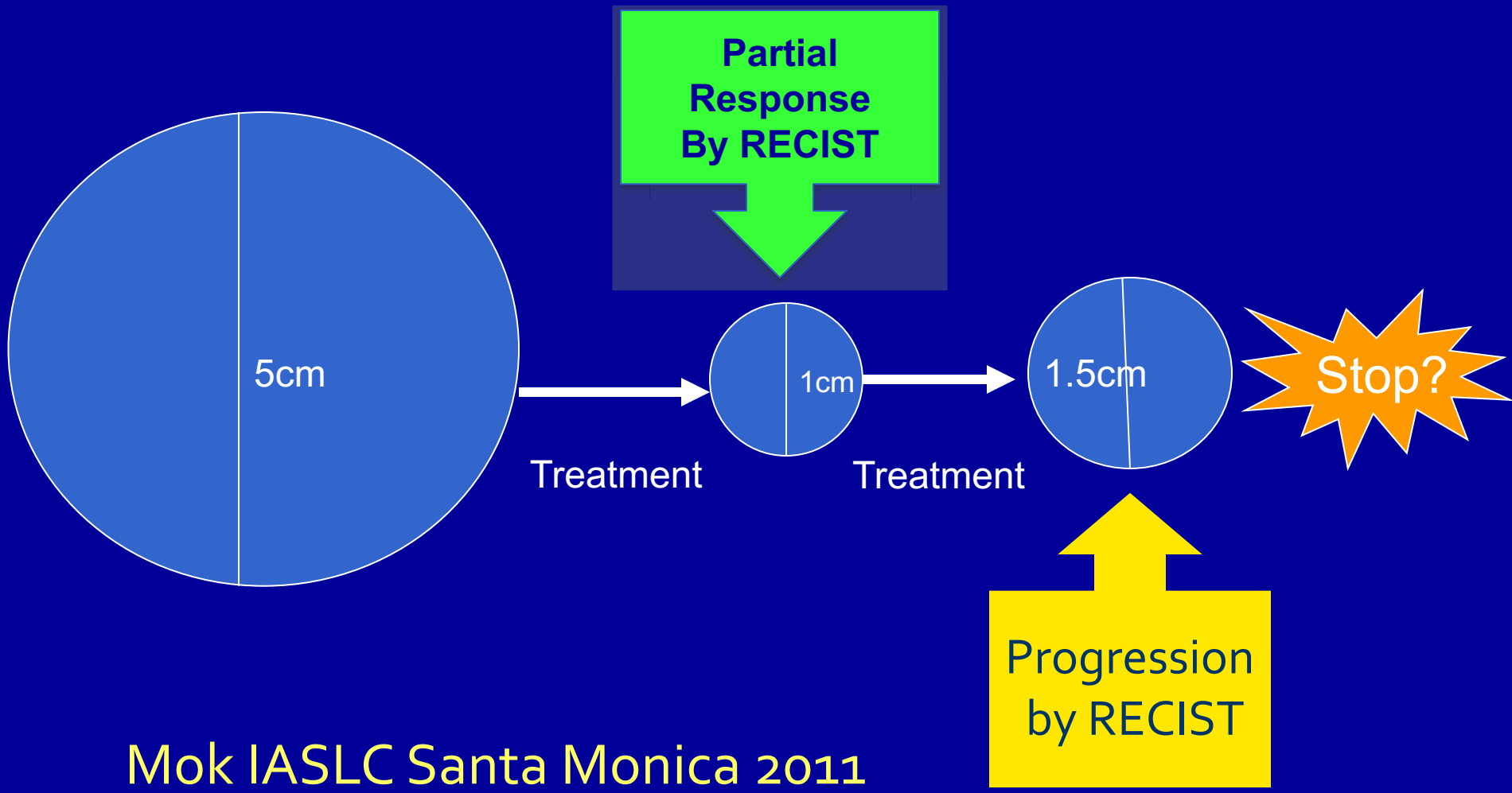


T-Cell Checkpoint Inhibitors in Lung Cancers

Endpoints for Trials

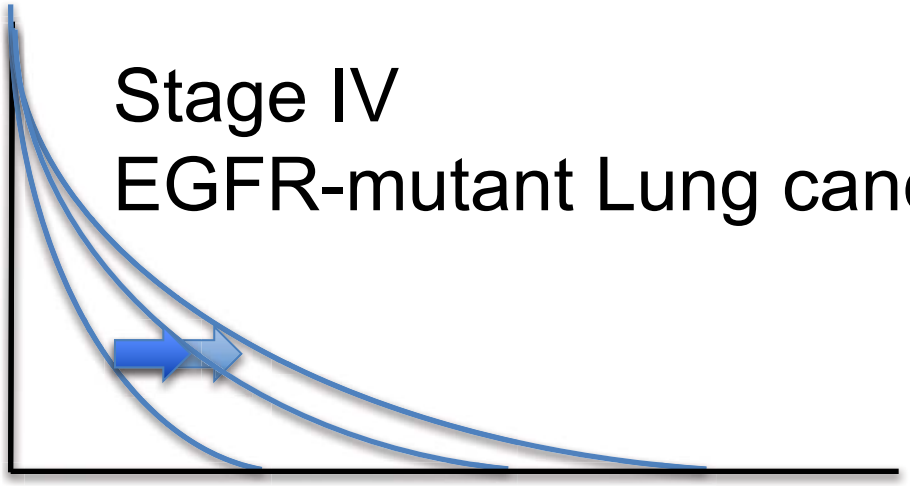
- In pivotal trials, time to response is the same for chemotherapy as for atezolizumab, nivolumab, and pembrolizumab
- Pseudoprogression is very uncommon (estimate 1%) in trials; frequent in discussions among oncologists
- Virtually all progression with symptoms is "pseudoprogression"
- Single site progression after response seen: Consider local therapy and treatment continuation
- #1 challenge is to identify progression as early as possible to initiate alternative therapies

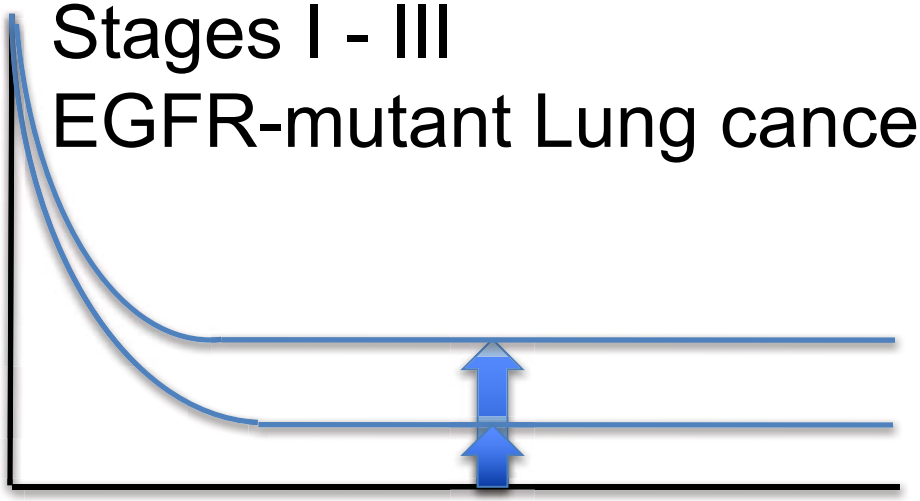
RECIST Criteria for Progression A Signal to Stop the Treatment?



Mok IASLC Santa Monica 2011

Bending the survival curve in lung cancers



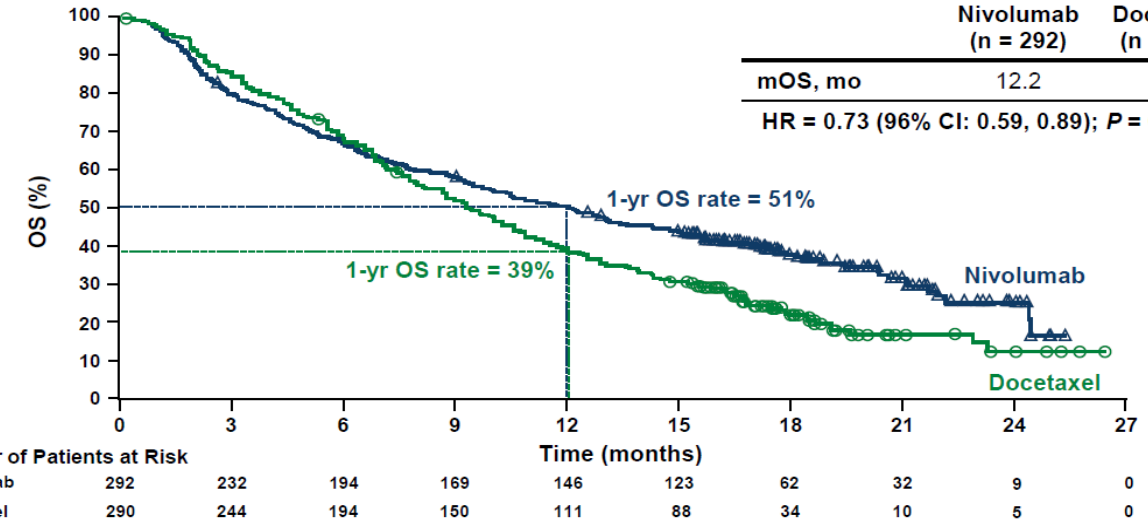


Hellmann
JAMA
Oncology
2015

Nivolumab vs Docetaxel

Adenocarcinoma

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

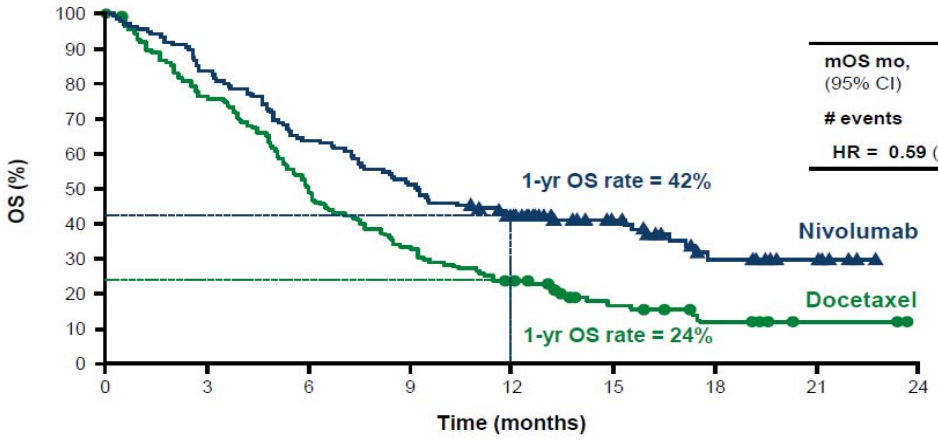
Number of Patients at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Squamous

Median Improvement
1.7 months

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), *P* = 0.00025

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Paz-Ares NEJM 2015,Brahmer, NEJM 2015

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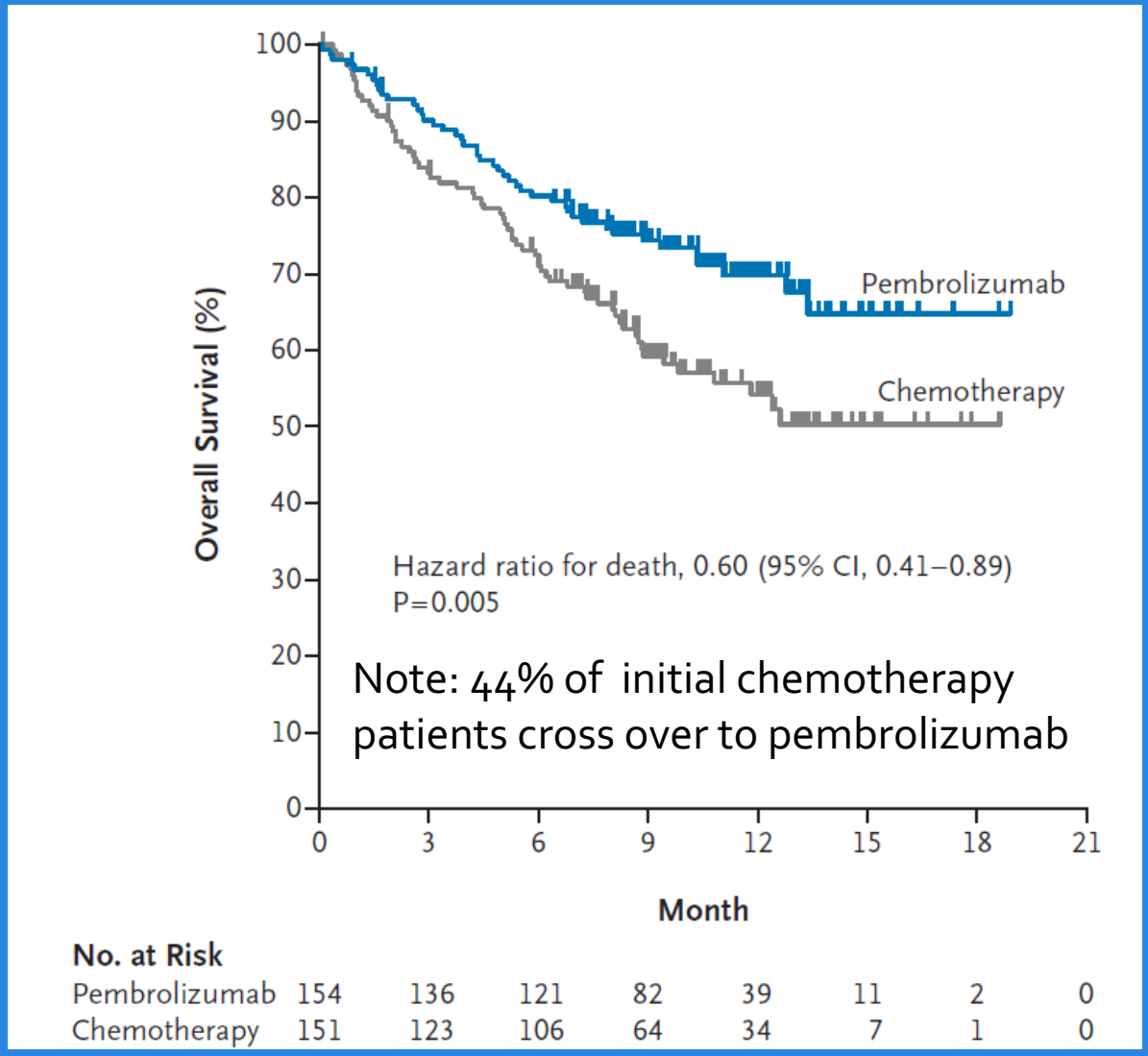
Initial Pembrolizumab vs Chemotherapy Lung Cancers with for PD-L1 >50%



Reck N Engl J Med 2016

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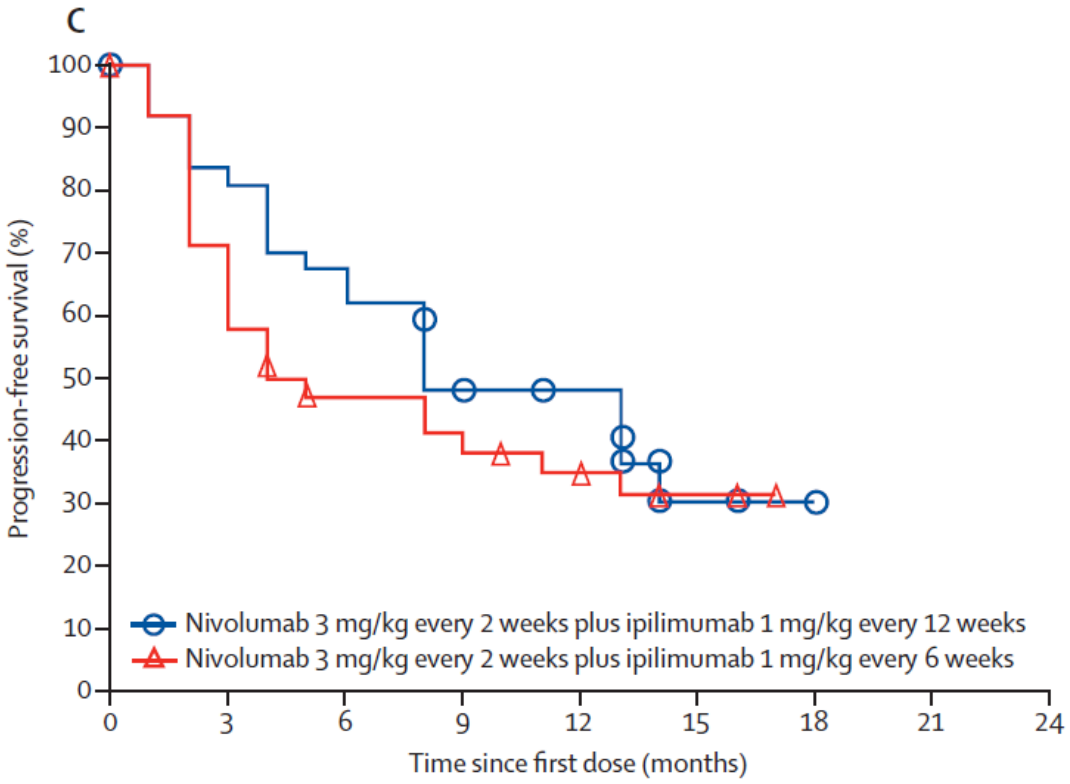
Initial Ipilimumab and Nivolumab Progression-Free Survival



Number at risk (censored)									
Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks	38 (0)	30 (1)	24 (1)	16 (3)	13 (6)	4 (11)	0 (15)	0 (0)	0 (0)
Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks	39 (0)	22 (1)	16 (3)	14 (3)	10 (5)	6 (8)	0 (14)	0 (0)	0 (0)

Hellmann Lancet Oncol 2017

T-Cell Checkpoint Inhibitors in Lung Cancers

Caring for patients with long disease control

- Constant assessment of benefits and side-effects
- Scant data. Reality Check: median time on drugs X mo as initial therapy, 4 mo after chemotherapy
- Duration of therapy empirically defined today
  - One year (atezolizumab)
  - Two years (nivo, pembro)
  - Treatment until progression
- Resist RECIST; Never designed for use in care
- Local therapy of residual disease
- Local therapy of isolated metastases

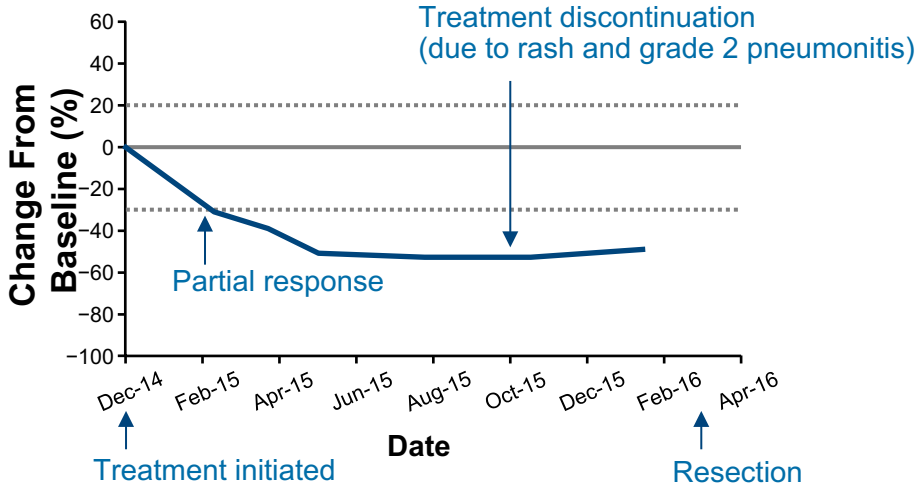
T-Cell Checkpoint Inhibitors in Lung Cancers

Stopping T-cell checkpoint inhibitors

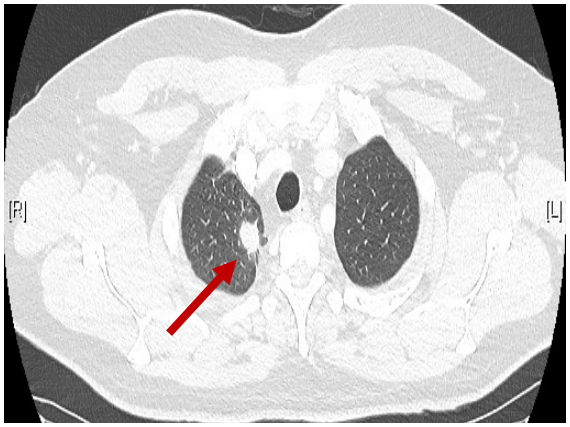
- Constant assessment of benefits and side-effects. Severe toxicity possible after months or years
- In theory: additional treatment of marginal benefit if sensitive clone eradicated or T cells "educated"
- Scant data
- In rare cases, resected residual lesions show no cancer
- Outcomes after stopping therapy are variable
- No data to support "rechallenge"
- No data to support switching to another agent in the class either at best response or at relapse

Case Study
Pathological CR (Nivo 3 Q2W + Ipi 1 Q6W)

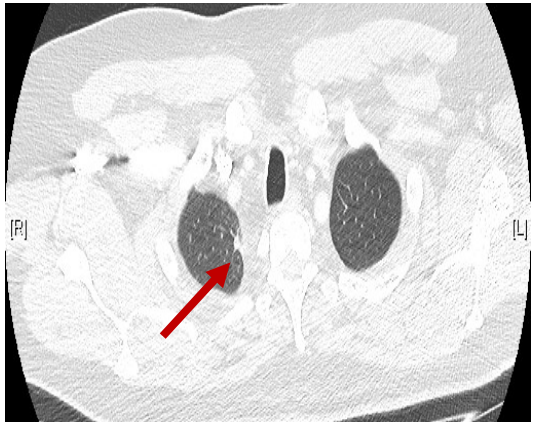
- 54-yr-old male (former smoker, 52 pack-yr) with metastatic large-cell lung cancer (PD-L1 <1%[a])
  - 53% total tumor size reduction by RECIST
  - Radiographic residual lesions in the lung and mediastinal lymph nodes, without distant disease



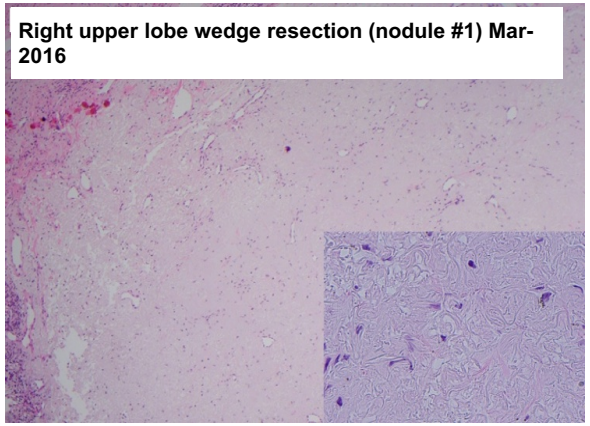
Before nivo + ipi therapy



Following nivo + ipi therapy



No viable tumor in resected residual lesions



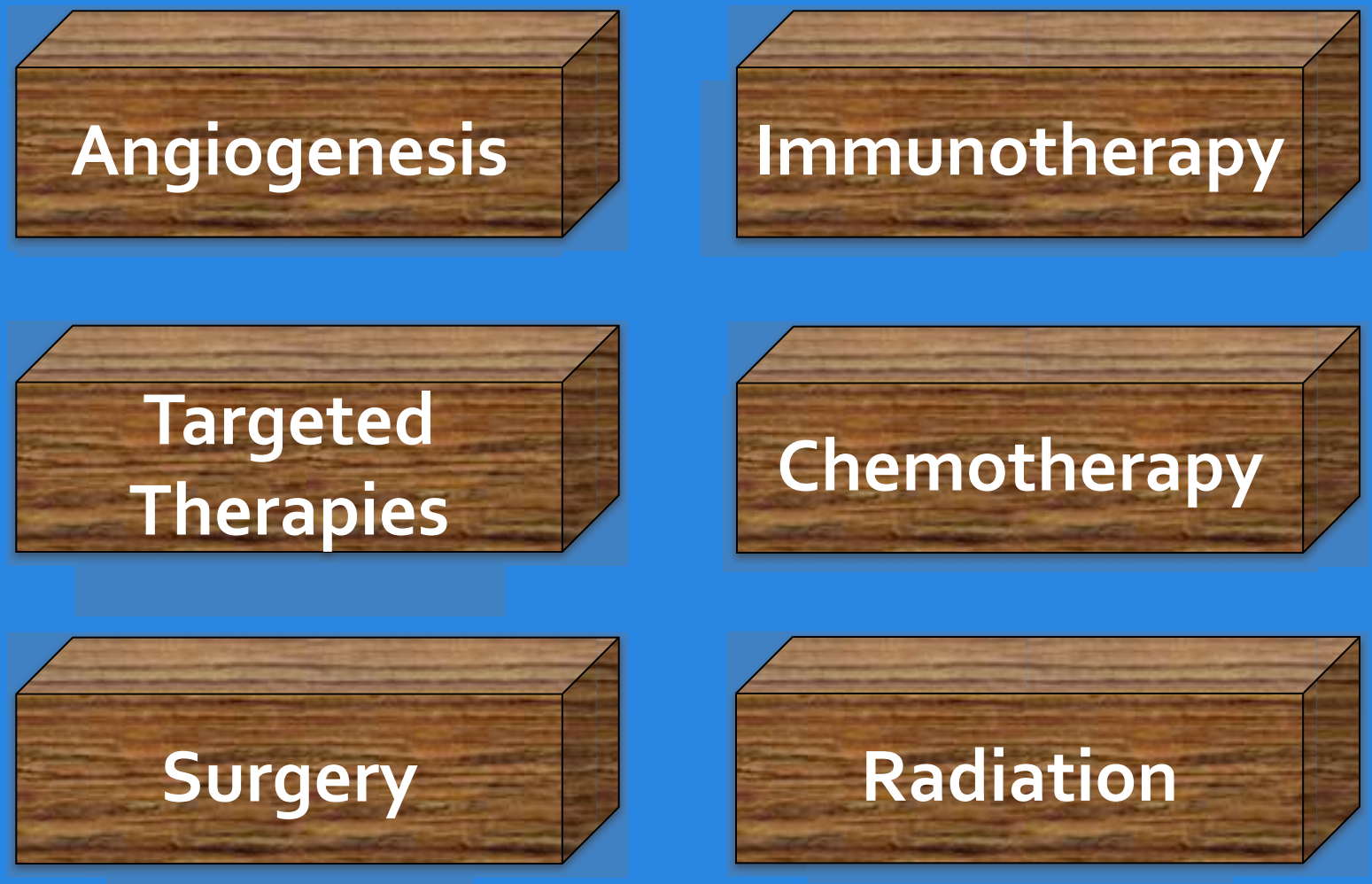
Courtesy of Dr. William Travis, MSKCC

T-Cell Checkpoint Inhibitors in Lung Cancers

Conclusions

- Anti CTLA4 and anti-PD-1 and PD-L1 strategies work
- Benefits and risks must be assessed at *every visit*
- No specific time on treatment guarantees ongoing benefit or freedom from fron severe side-effects
- Concepts for management of solitary sites of progression and oligometastases are the same here

Components of Care for Lung Cancers



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Components of Care for Lung Cancers

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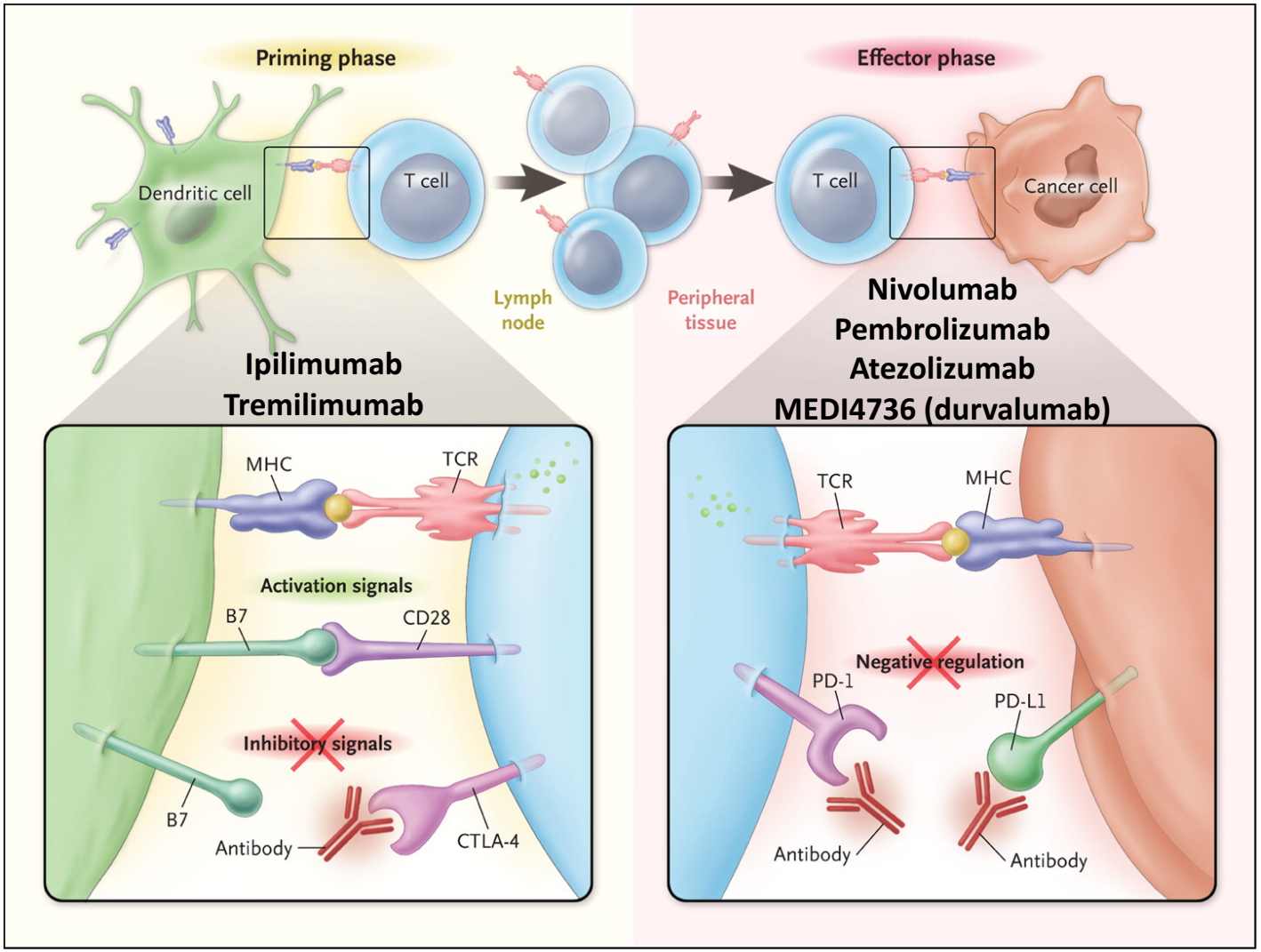
Immune Checkpoint Blockade



Ribas NEJM 2012, 366:2517-2519

Phase III Trial of Nivolumab vs Docetaxel After Initial Therapy in Patients with Squamous Cell Lung Cancers (CheckMate 017)

- Randomized phase III trial in 272 patients
- All had prior therapy for stage IIIB/IV squamous cell lung cancers
- Improved survival over docetaxel with 1%, 5%, and 10% PD-L1 expression

	Nivolumab 3 mg/kg q2wks	Docetaxel 75 mg/m2 q3wks	*p*-value
Entered	**135**	**137**	
CR/PR Rate	20%	9%	0.008
1 Yr Survival	42%	24%	
Median Overall Survival	9 mo	6 mo	0.0016
Median Progression-Free Survival	4 mo	2 mo	0.001
Grade 3-5 Adverse Events	7%	55%	

Brahmer et al. NEJM 2015

Phase III Trial of Nivolumab vs Docetaxel After Initial Therapy in Patients with Lung Adenocarcinomas (CheckMate 057)

- Randomized phase III trial in 582 patients
- All had prior therapy for stage IIIB/IV lung adenocarcinomas
- Improved survival over docetaxel with 1%, 5%, and 10% PD-L1 expression

	Nivolumab 3 mg/kg q2wks	Docetaxel 75 mg/m2 q3wks	*p*-value
Entered	292	290	
CR/PR Rate	19%	12%	0.024
1 Yr Survival	51%	39%	
Median Overall Survival	12 mo	9 mo	0.0016
Median Progression-Free Survival	2 mo	4 mo	0.39
Grade 3-5 Adverse Events	11%	54%	

Borghaei et al. N Engl J Med 2015