

A New Era: Immunotherapy in Non-Small Cell Lung Cancer



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UNC Cancer Network Lecture
February 21st, 2018

2/20/18

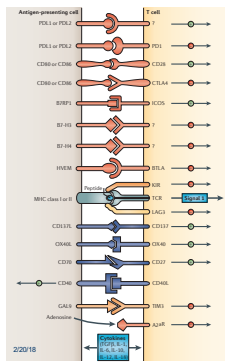


Brief Primer on Tumor Immunology

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Current Therapies very “T-cell” Centric



CTLA-4 = cytotoxic T-lymphocyte antigen 4
PD-1 = programmed cell death protein 1
LAG-3 = lymphocyte activation gene 3;
TIM-3 = T-cell immunoglobulin and mucin protein 3.

Pardoll, Nature Reviews Cancer, 2012

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Action Item: Kill!!!

Cancer cell Lethal holes

Cytotoxic T cell

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Cancer Immunotherapy


- Cancer cells have mutations that make them recognizable by the immune system


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Cancer Immunotherapy


- Cancer cells have mutations that make them recognizable by the immune system
- However, cancer cells can evade the immune surveillance by expressing proteins such as PD-L1
- Inhibiting the PD-L1/PD-1 interaction can restore anti-tumor T-cell activity, potentially leading to long-lasting responses

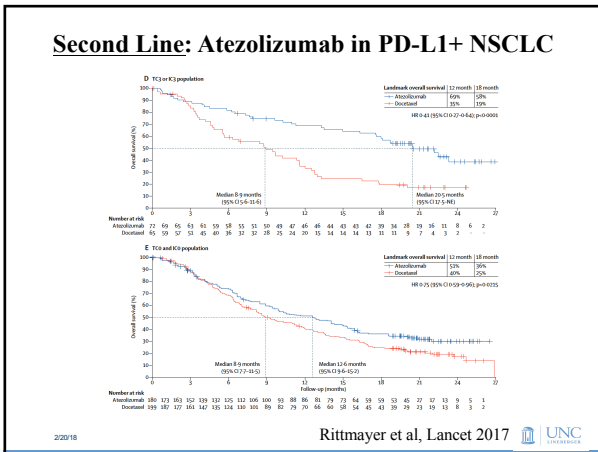
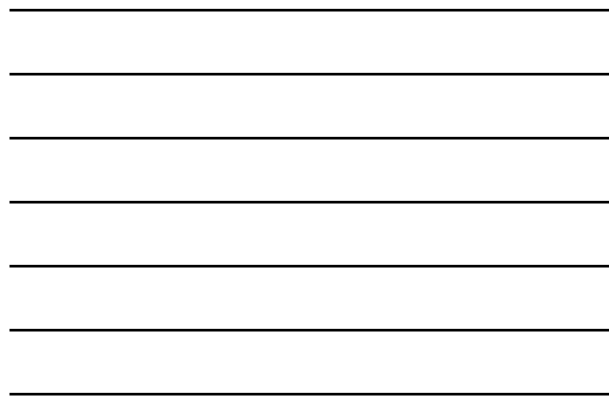
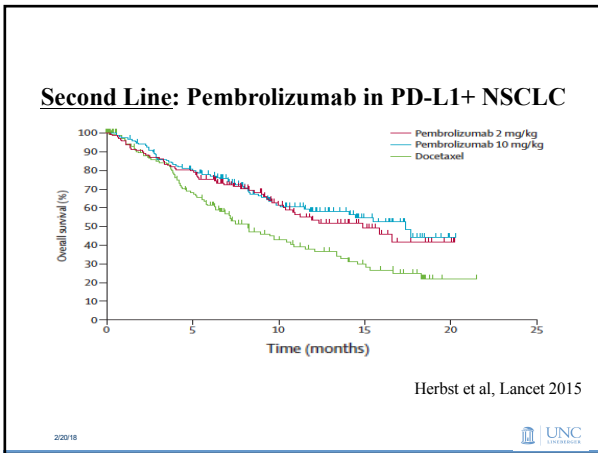
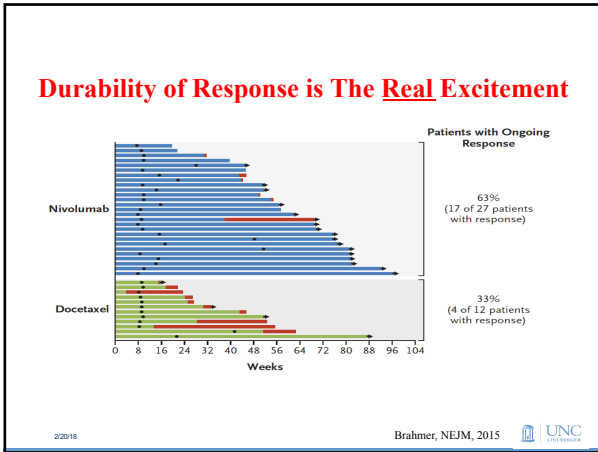
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BP-SIY	BPC-SIY
Green YFP+ tumor cells Red activated 2C T cells	Green YFP+ tumor cells Red activated 2C T cells
Spranger, Cancer Cell, 2017	
<small>2018</small> 	

BP-SIY	BP-SIY
Green YFP+ tumor cells Red 2C T cells	Green YFP+ tumor cells Red 2C T cells
48h post T cell transfer	120h post T cell transfer
Spranger, Cancer Cell, 2017	
<small>2018</small> 	

Single Agent Efficacy on anti-PD1 or anti-PDL1 in Non-Small Cell Lung Cancer

2018 



Clinical Activity in NSCLC (Squamous)

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First Line: KEYNOTE 024 Pembrolizumab in NSCLC

- Randomized, open label, phase 3.
- 305 untreated stage IV NSCLC. 1934 patients initially screened.
- **PD-L1 > 50% (500 of 1653, ~30% had PD-L1>50%), DAKO 22C3**
- No EGFR or ALK mutation
- No untreated CNS metastases or active autoimmune disease
- Assigned 1:1 to Pembrolizumab 200mg every 3 weeks x35 cycles vs. Platinum based chemotherapy x4-6 cycles n=154 vs. n=151. Crossover to Pembrolizumab permitted if PD in chemotherapy arm.
- Primary endpoints : PFS
- Secondary endpoints : OS, ORR, safety

Reck et al, NEJM, 2016

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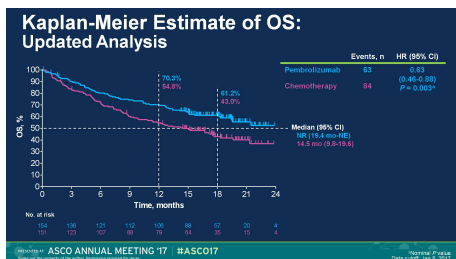
First Line: KEYNOTE 024 Pembrolizumab in NSCLC

PKC	Events (n)	Median (mo)	HR (95% CI)	P-value
Pembro	73	10.3	0.50	<0.001
Chemo	116	6.0	(0.37 - 0.68)	

Reck et al, NEJM, 2016

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First Line: KEYNOTE 024 Pembrolizumab in NSCLC

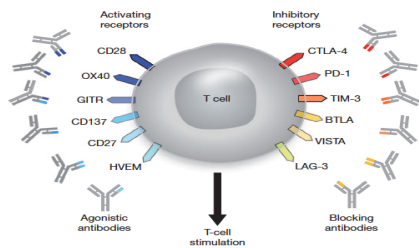


Brahmer, ASCO 2017

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Current Targets of Immuno-Regulatory Antibody Therapy



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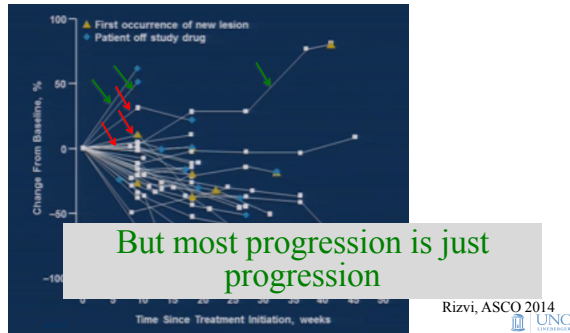


PD-L1 As a Biomarker

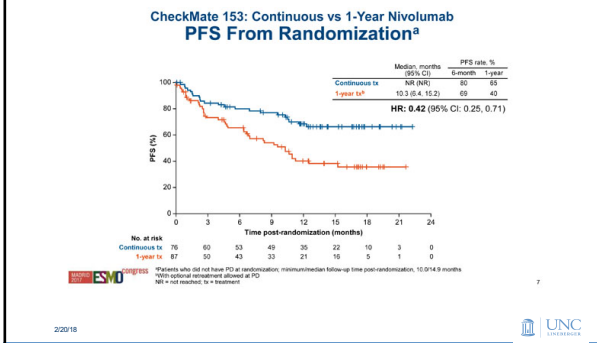
Drug	Antibody	Definition of Positive	Best information on utility of PDL1
Nivolumab	Dako 28-8	Variable by study: • ≥ 5 in >100 cells in 1L lung study • $\geq 5, \geq 1$ in >100 cells in 2L lung study	In squamous 2L lung study, seemed predictive; not predictive in nonsquamous 2L study
Pembrolizumab	22C3	$\geq 50\%$ expression in tumor cells	Predictive in phase III study
Atezolizumab	SP142	Combined tumor cell and/or infiltrating T cell	Seemed predictive in POPLAR+OAK
MEDI-4736	SP263	Membrane positivity of $\geq 25\%$ of tumor cells	Responses in both PDL1 and PDL1 positive

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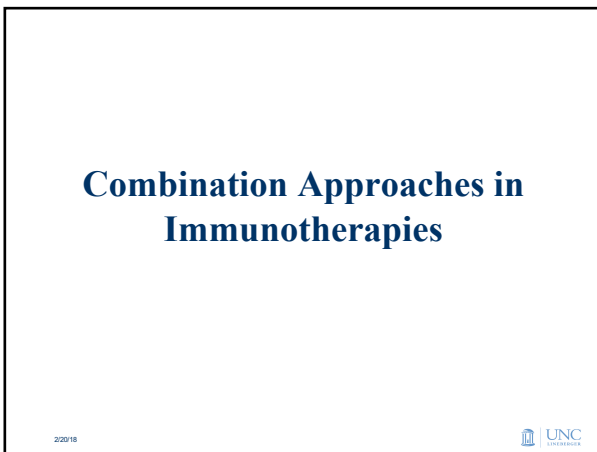
Some progression is really pseudo-progression

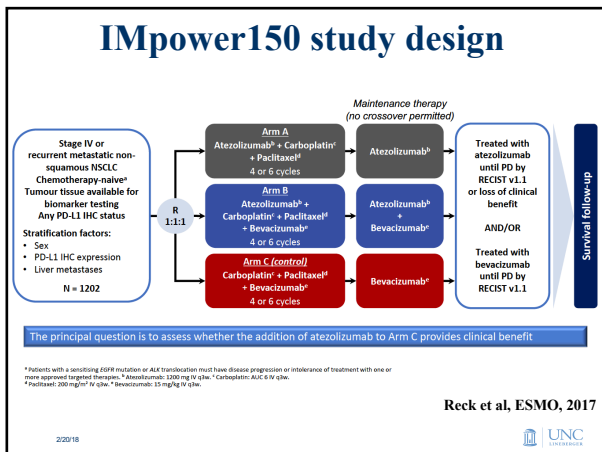
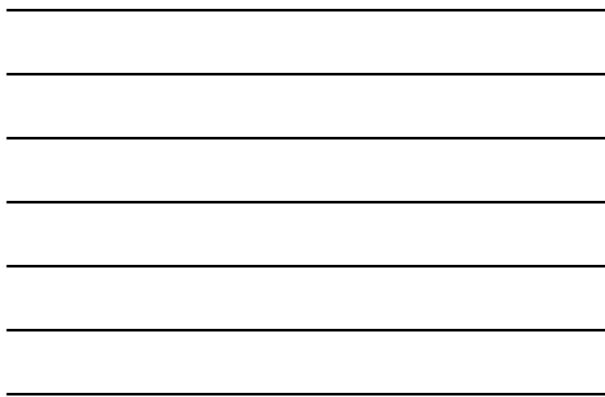
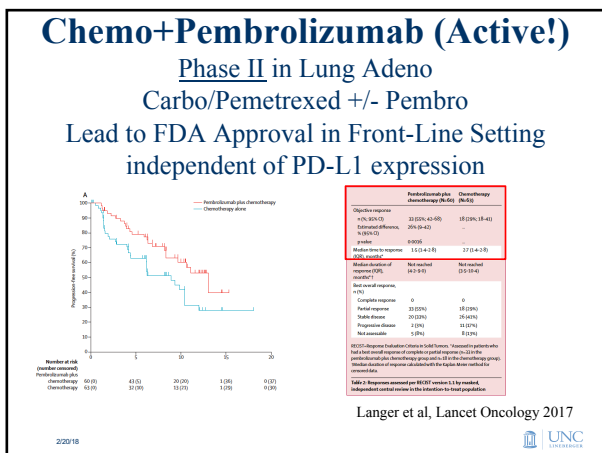
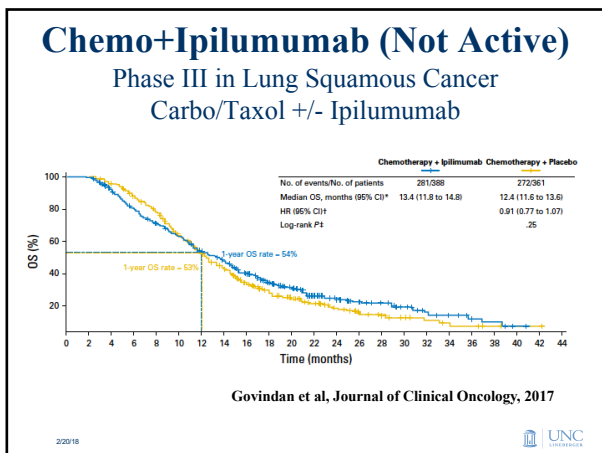


After 1 year of stable disease on Nivolumab, stay on treatment!



Combination Approaches in Immunotherapies




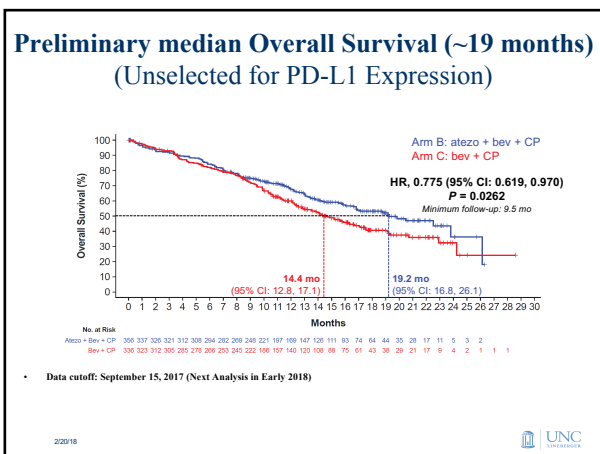
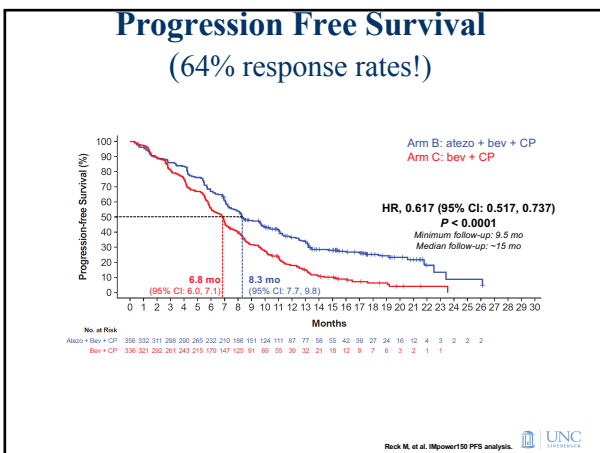


Baseline characteristics in ITT

Baseline characteristics	Arm A: atezo + CP (N = 402)	Arm B: atezo + bev + CP (N = 400)	Arm C (control): bev + CP (N = 400)
Median age (range), years	63 (32-85)	63 (31-89)	63 (31-90)
Sex, male, n (%)	241 (60%)	240 (60%)	239 (60%)
ECOG PS, 0, n (%)	180 (45%)	159 (40%)	179 (45%)
Tobacco use history, n (%)			
Current smoker Previous smoker	98 (24%) 227 (57%)	90 (23%) 228 (57%)	92 (23%) 231 (58%)
Never smoker	77 (19%)	82 (21%)	77 (19%)
Liver metastases, yes, n (%)	53 (13%)	53 (13%)	57 (14%)
EGFR mutation, positive, n (%)	46 (11%)	35 (9%)	45 (11%)
ALK rearrangement, positive, n (%)	9 (2%)	13 (3%)	21 (5%)
Teff gene signature expression, high, n (%) ^a	177 (44%)	166 (42%)	148 (37%)
Of those tested	124	106	115
PD-L1 expression, n (%) ^b			
TC2/3 or IC2/3	137 (34%)	140 (35%)	133 (33%)
TC1/2/3 or IC1/2/3	213 (53%)	209 (52%)	195 (49%)
TC0 and IC0	188 (47%)	191 (48%)	205 (51%)

IC, tumour-infiltrating immune cells; TC, tumour cells.
^a The Teff gene signature high value of 2 - 1.51 was used. * 1 patient in Arm A had unknown PD-L1 9HC expression.
^b TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.
 Data cutoff: September 15, 2017.

Rick M. et al. IMpower150 PFS analysis. 



Some caution about immune therapy combinations...

6/12/2017: FDA places hold on two phase III trials of pembrolizumab + IMiD in Multiple Myeloma

KEYNOTE-183 (randomized phase III, Multiple Myeloma)

- pomalidomide/dexamethasone ± pembrolizumab
- ≥2 prior lines of therapy, refractory to last line of therapy

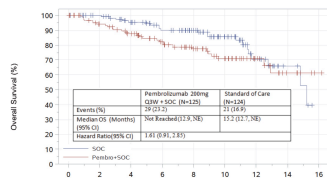
KEYNOTE-185 (randomized phase III, newly diagnosed MM)

- lenalidomide/dexamethasone ± pembrolizumab
- Treatment-naïve, newly diagnosed MM

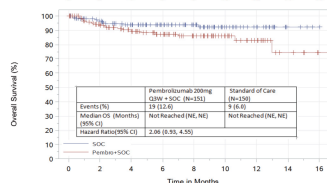
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In two Phase III studies, Pembro lead to worse overall survival with IMiD combinations

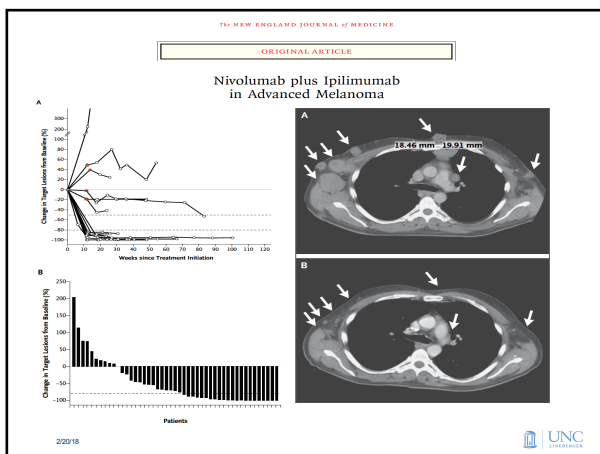


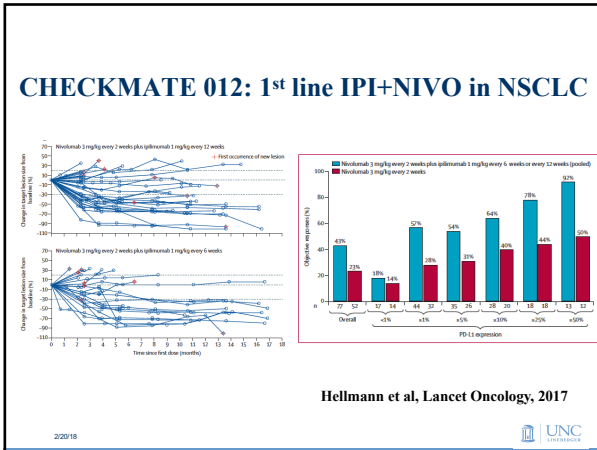
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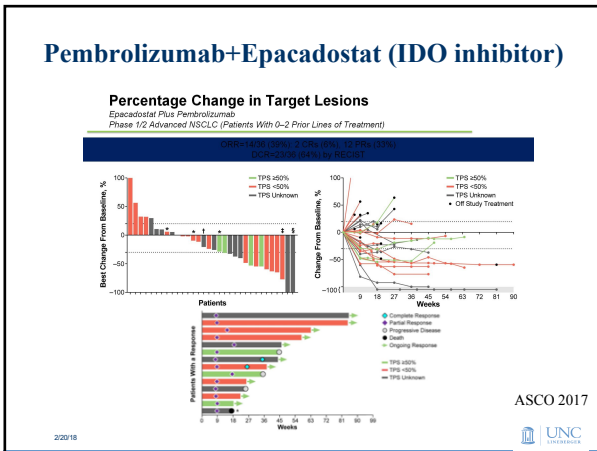


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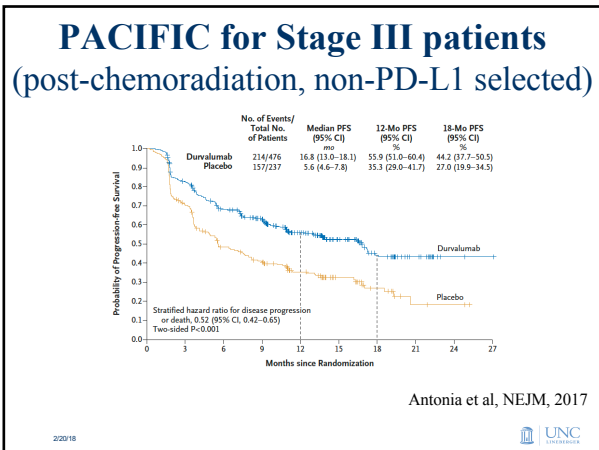






Reasons to be excited about immunotherapies in earlier Stage disease...

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- ### Take Home Points
- FDA approved immune therapies block the PD1/PDL1 axis
 - Toxicities are different from chemo, however anti-PD1/PDL1 therapies are usually well tolerated (sometimes zero side effects)
 - Pembro approved in 1st line (PD-L1>50%, ~30% of patients)
 - 3 agents approved in 2nd line setting (2 anti-PD1, 1 anti-PDL1)
 - Promising chemo combinations, especially in combination with anti-angiogenesis approaches
 - Other immunotherapy combinations are showing early promise, however caution is warranted (better preclinical data needed)
 - Likely a massive wave of new combos to come (~3,000 combo trials underway)
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