New Therapies for Lung Cancer

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Disclosures

- **Consultant*: Abbvie, Adaptimmune, Agenus, Amgen, Ariad, AstraZeneca, Biocept, Boehringer Ingelheim, Bristol Myers-Squibb (BMS), Celgene, Foundation Medicine, Genentech/Roche, Gritstone, Guardant Health, Inovio, Merck, MSD, Novartis, Palobiofarma, Pfizer, prIME Oncology, Stemcentrx, Takeda**
- **Grant Funding: Bristol Myers-Squibb (BMS)**

***Includes receipt of consulting fees.**

Top Ten Leading Causes of Cancer-related Deaths

Estimated Deaths

Male		
Lung & bronchus	83,550	26%
Prostate	29,430	9%
Colon & rectum	27,390	8%
Pancreas	23,020	7%
Liver & intrahepatic bile duct	20,540	6%
Leukemia	14,270	4%
Esophagus	12,850	4%
Urinary bladder	12,520	4%
Non-Hodgkin lymphoma	11,510	4%
Kidney & renal pelvis	10,010	3%
All sites	323,630	100%

Female		
Lung & bronchus	70,500	25%
Breast	40,920	14%
Colon & rectum	23,240	8%
Pancreas	21,310	7%
Ovary	14,070	5%
Uterine corpus	11,350	4%
Leukemia	10,100	4%
Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,340	3%
All sites	286,010	100%

Most patients present with unresectable disease

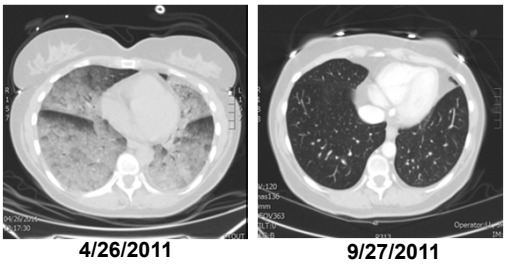
American Cancer Society. *Cancer Facts & Figures*. 2018.

Goals today

- **Discuss major new therapeutic approaches for advanced lung cancer, and present data on solving major issues for each of these approaches**
- **Therapy targeting "driver oncogenes"**
  - **Improving the depth and duration of response to these therapies**
- **Therapy designed to overcome tumor immune escape mechanisms**
  - **Defining novel escape mechanisms and biomarkers for patient selection markers**

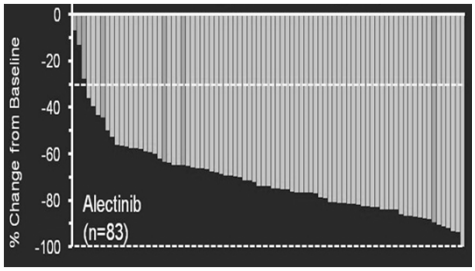
56 year old female never smoker increasingly short of breath

Response to crizotinib (Xalkori)



4/26/2011 9/27/2011

When you match drug and target – alectinib and ALK fusion



Presented By Hiroshi Nokihara at 2016 ASCO Annual Meeting

New, improved drugs against these targets now available

- New drugs are now available that work when the old ones stop working
  - Target mechanisms of resistance to older drugs
  - Effective brain penetration that prevents and more effectively treats brain metastases
    - Some patients with brain metastases can be effectively medically treated and may never need brain radiation
  - E.g. osimertinib, alectinib, and brigatinib
- Drugs with less toxicity
- More selective, more effective drugs against old drivers, e.g. RET, HER2
  - Vandetinib vs. LOXO292
  - Poziotinib and TAK-788

Thus, it is now standard of care to get a tumor genetic analysis <u>before</u> starting any therapy in non-small cell lung cancer

Documented efficacy for: BRAF, MET, TrkA, ROS, RET, HER2, and others…

But even with driver-mutant lung cancer, much remains to be done

- We have extended survivals from 6-8 months to 3 or more years with modern targeted therapies
  - When you are 50 years old 3 years does not sound very good.
- But all patients eventually relapse
  - Some have targetable mechanisms of relapse, but most do not.
- We need to convert responses to cures
  - Target drug persistence rather than resistance
- Universal, reflex genomic testing

Example: data on molecular testing

Proportion of Stage IV Patients Who Received Genetic Alteration Tests

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
Squamous cell carcinoma	24%	20%	25%	29%	3%	28%	15%	25%	23%
Adenocarcinoma	87%	81%	96%	84%	94%	94%	88%	91%	62%
Large cell	68%	77%	71%	50%	70%	74%	44%	71%	78%
NSCLC not otherwise specified (NOS)	75%	75%	87%	43%	94%	85%	85%	67%	59%

Friends of Cancer Research and the Deerfield Institute whitepaper, 2017

However, if you look at the details….

Proportion of Newly-Diagnosed Patients who were Screened for the Following Genetic Alterations

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
EGFR mutations	72%	76%	72%	68%	31%	79%	66%	67%	79%
ALK rearrangement	69%	71%	70%	67%	31%	75%	66%	63%	78%
BRAF V600E mutation	18%	8%	36%	12%	1%	11%	18%	25%	13%
MET amplification	17%	13%	31%	6%	1%	11%	19%	24%	11%
ROS1 rearrangements	38%	36%	45%	32%	4%	29%	39%	36%	57%
HER2 mutations	16%	7%	33%	9%	1%	14%	15%	20%	11%
RET rearrangements	14%	7%	28%	8%	0%	12%	15%	17%	11%
Other	2%	0%	5%	0%	0%	0%	10%	0%	0%

Friends of Cancer Research and the Deerfield Institute whitepaper, 2017

And it gets worse….

- These are survey data of 157 <u>medical oncologists</u> selected for having a <u>high volume</u> of lung cancer patients
- 2017 Flatiron <u>oncology clinic</u> data by Rughani showed 22% of non-squamous metastatic patients had no evidence of EGFR or ALK testing
- 1/3 of patients had results that took more than 4 weeks to come back to the ordering physician
  - < 4 weeks: ~80% got appropriate TKIs
  - > 4 weeks: ~40% got appropriate TKIs

Lung Cancer outcomes are impacted by late detection and low treatment rates

- Only about 20% of lung cancer is localized when found
- Less than 2% of eligible people in the USA are getting lung cancer screening CTs (Pham et al, JCO 2018 (abstr 6504)
- Using the SEER cancer registry of Medicare claims from 2007-2013:
  - 43,165 patients had a new diagnosis of stage IIIB/IV NSCLC
  - 29,720 had any treatment at all (69%)
  - 13,742 (32%) received any systemic therapy
  - Only 8,542 (20%) received "standard", guidelines recommended first line therapy.

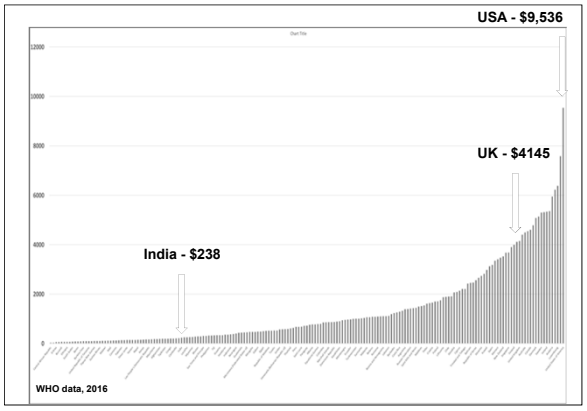
Bittoni and Carbone, Clinical Lung Cancer 2018

In the United Kingdom

- Of 176,225 lung cancer patients:
  - Only 13% got surgery
  - 8% got any radiation
  - 28% got any chemo…

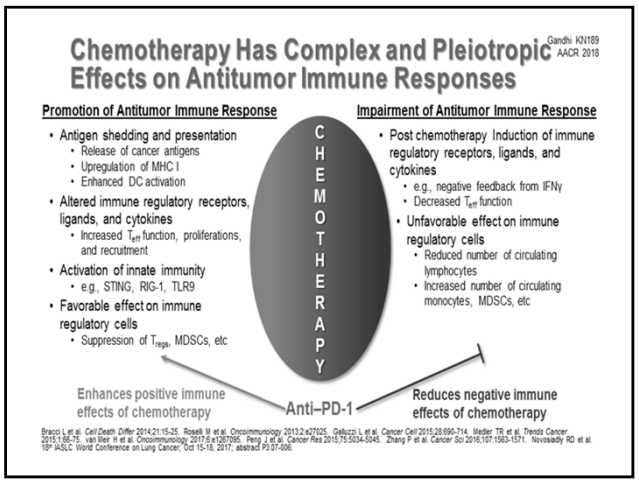
Moller et al, Thorax 2018

Per capita health care expenditures, 2015



Immunotherapy

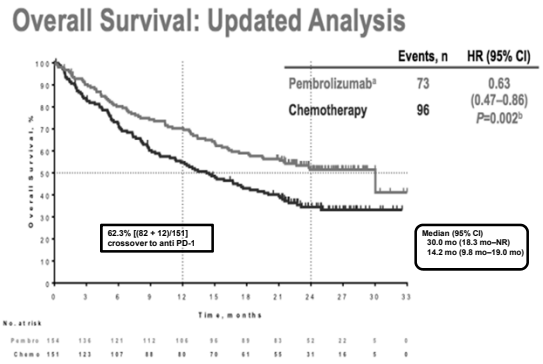
Targeting normal regulatory mechanisms subverted by cancers to avoid immune clearance



PD-1 and PDL-1 signaling is a major mechanism of immune down-regulation

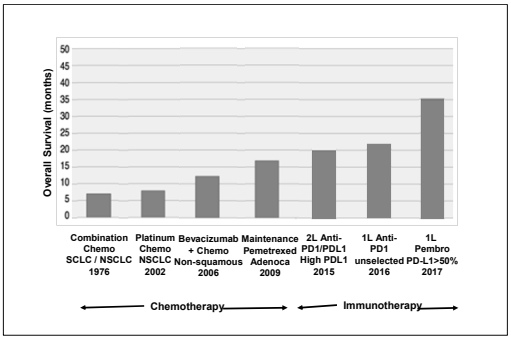
- About 1/3 of tumors have high PD-L1 expression
- About 1/3 have low expression
- About 1/3 have no expression

KN024: PD-L1 >50% NSCLC



Brahmer et.al., *WCLC*, 2017, with permission

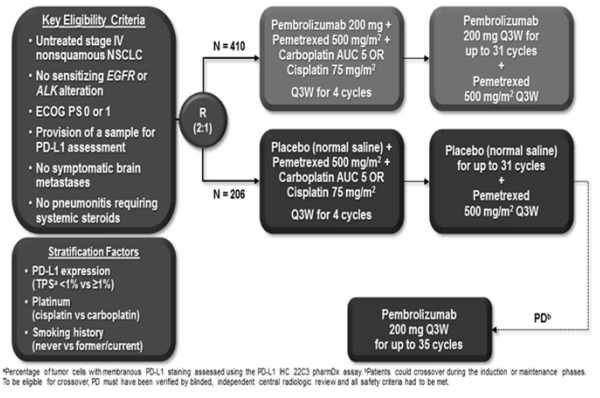
Survival of NSCLC Patients Over Time



Adapted from Pao et al., *Nat Rev Cancer*, 2010; Borghaei et al, *NEJM*, 2015; Rittmeyer et al, *Lancet,* 2017; Hui et al, Ann Oncol, 2017; Leighl et al, ASCO, 2017

Gandhi KN189
AACR 2018

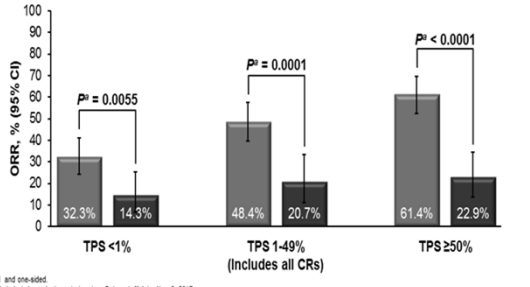
Chemotherapy with IO – KN189 (NCT02578680)



[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Gandhi KN189
AACR 2018

Response Rate by PD-L1 TPS (RECIST v1.1, BICR)

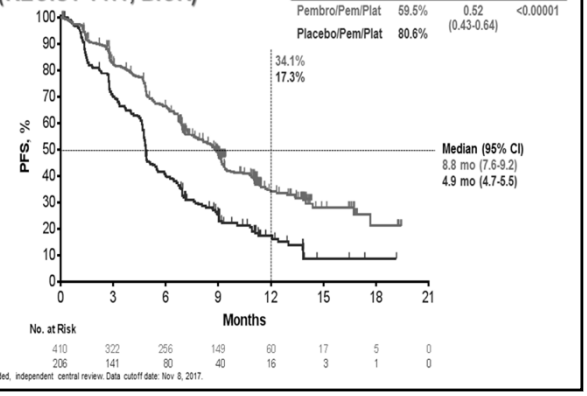


[a]Nominal and one-sided.
BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

Gandhi KN189
AACR 2018

Progression-Free Survival, ITT (RECIST v1.1, BICR)

	Events	HR (95% CI)	P
Pembro/Pem/Plat	59.5%	0.52 (0.43-0.64)	<0.00001
Placebo/Pem/Plat	80.6%		

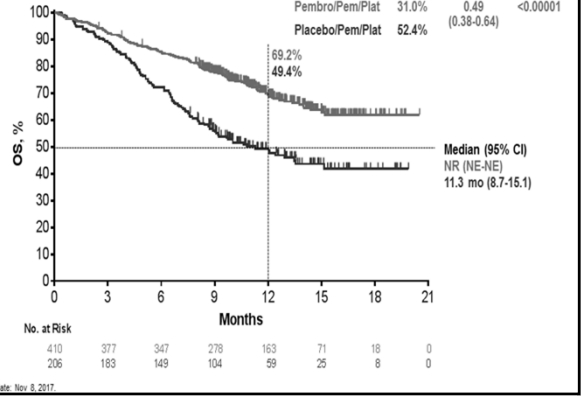


BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

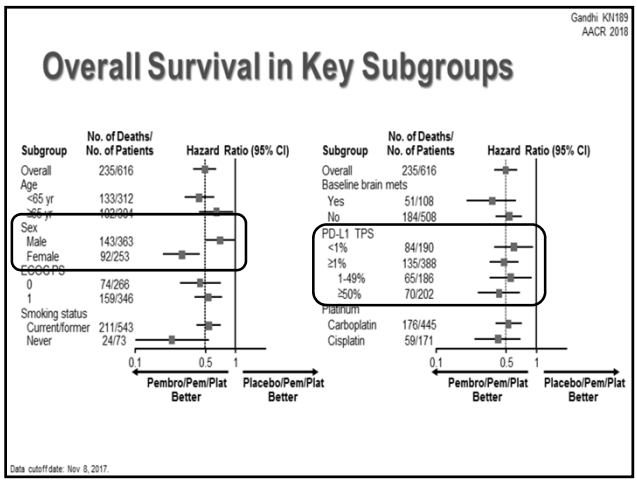
Gandhi KN189
AACR 2018

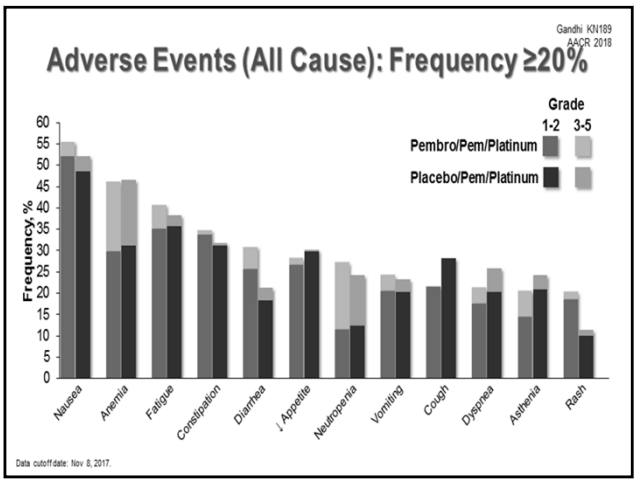
Overall Survival, ITT

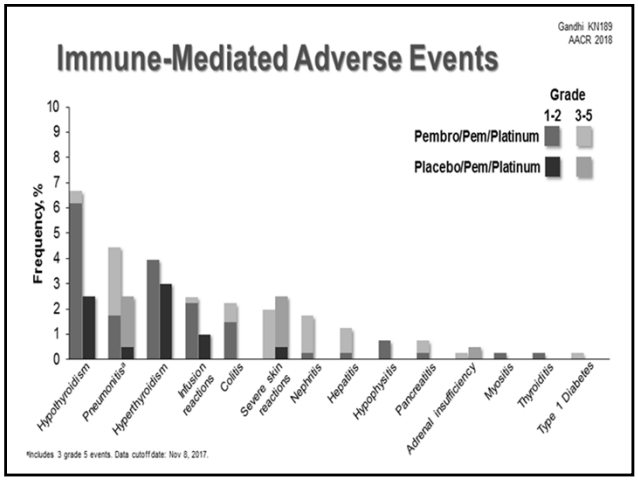
	Events	HR (95% CI)	P
Pembro/Pem/Plat	31.0%	0.49 (0.38-0.64)	<0.00001
Placebo/Pem/Plat	52.4%		

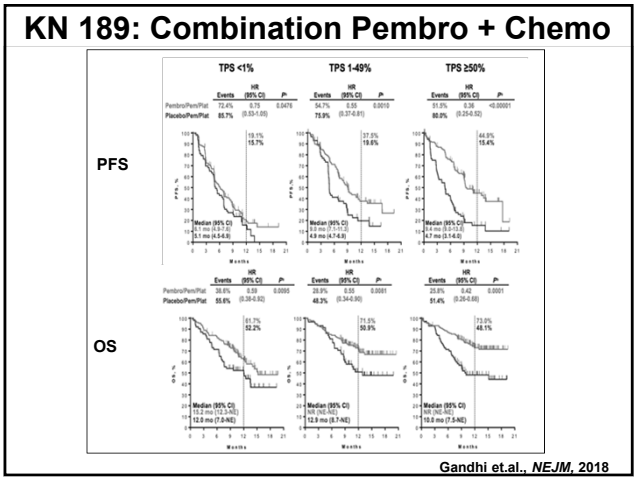


Data cutoff date: Nov 8, 2017.

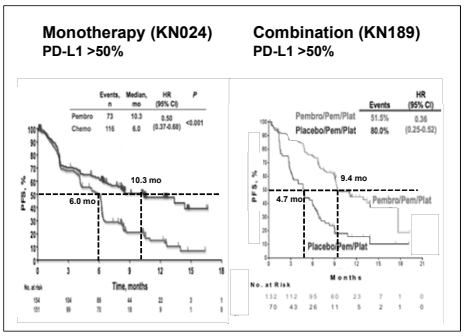

Gandhi KN189
AACR 2018
Overall Survival in Key Subgroups
Subgroup
No. of Deaths/ No. of Patients
Hazard Ratio (95% CI)
Overall 235/616
Age
<65 yr 133/312
≥65 yr 102/304
Sex
Male 143/363
Female 92/253
ECOG PS
0 74/266
1 159/346
Smoking status
Current/former 211/543
Never 24/73
Overall 235/616
Baseline brain mets
Yes 51/108
No 184/508
PD-L1 TPS
<1% 84/190
≥1% 135/388
1-49% 65/186
≥50% 70/202
Platinum
Carboplatin 176/445
Cisplatin 59/171
0.1
0.5
1
Pembro/Pem/Plat Better
Placebo/Pem/Plat Better
Data cutoff date: Nov 8, 2017.


Gandhi KN189
AACR 2018
Adverse Events (All Cause): Frequency ≥20%
Grade
1-2
3-5
Pembro/Pem/Platinum
Placebo/Pem/Platinum
Frequency, %
Nausea
Anemia
Fatigue
Constipation
Diarrhea
↓ Appetite
Neutropenia
Vomiting
Cough
Dyspnea
Asthenia
Rash
Data cutoff date: Nov 8, 2017.


Gandhi KN189
AACR 2018
Immune-Mediated Adverse Events
Grade
1-2
3-5
Pembro/Pem/Platinum
Placebo/Pem/Platinum
Frequency, %
Hypothyroidism
Pneumonitis[a]
Hyperthyroidism
Infusion reactions
Colitis
Severe skin reactions
Nephritis
Hepatitis
Hypophysitis
Pancreatitis
Adrenal insufficiency
Myositis
Thyroiditis
Type 1 Diabetes
[a]Includes 3 grade 5 events. Data cutoff date: Nov 8, 2017.

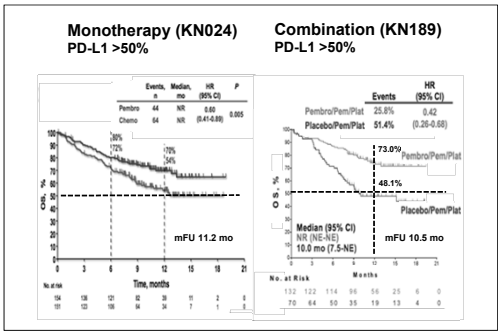

KN 189: Combination Pembro + Chemo
TPS <1%
TPS 1-49%
TPS ≥50%
PFS
OS
Gandhi et.al., NEJM, 2018

Pembro vs Combination Pembro + Chemo PD-L1 >50%: PFS



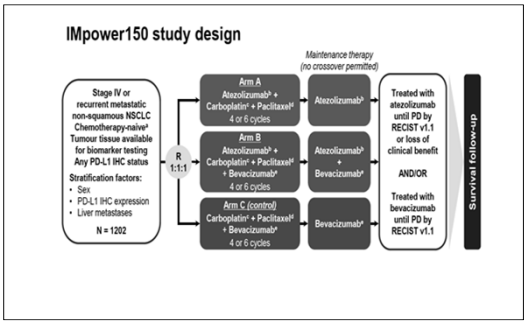
Reck et.al., *ESMO*, *NEJM,* 2016; Gandhi et.al., *AACR*, *NEJM,* 2018

Pembro vs Combination Pembro + Chemo: PD-L1 >50%: OS



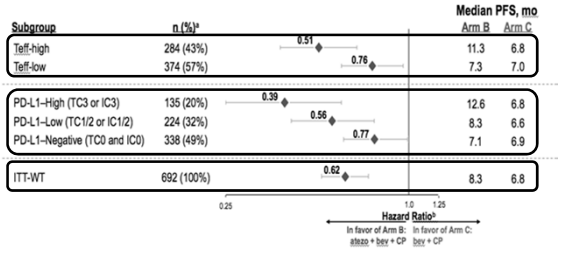
Reck et.al., *ESMO*, *NEJM,* 2016; Gandhi et.al., *AACR*, *NEJM,* 2018

IMPOWER 150: First-Line Carbo/Taxol + Bevacizumab +/- Atezolizumab



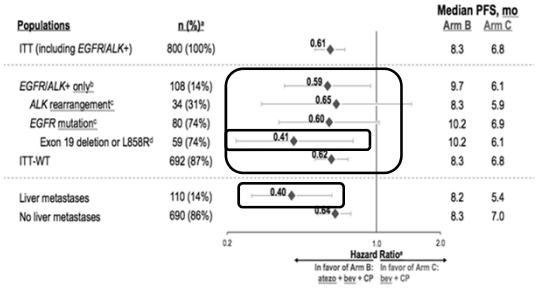
Reck et.al.,*ESMO Immuno-Oncology Congress,* 2017

IMPOWER 150: First-Line Carbo/Taxol + Bevacizumab +/- Atezolizumab Subgroup Analyses: Teff & PD-L1



Kowanetz et.al., *AACR*, 2018

IMPOWER 150: First-Line Carbo/Taxol + Bevacizumab +/- Atezolizumab Subgroup Analyses



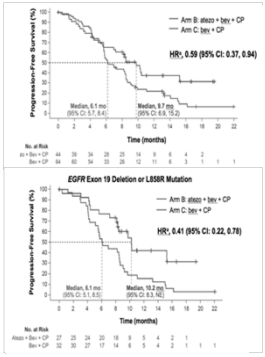
Kowanetz et.al., *AACR*, 2018

OS For EGFR Mutant Tumors In Previously Treated NSCLC

- **Nivolumab (CheckMate 057)**
  - **OS HR 1.18 (0.69 – 2.0)**
- **Pembrolizumab (KEYNOTE 010)**
  - **OS HR 0.88 (0.45 – 1.70)**
- **Atezolizumab (OAK)**
  - **OS HR 1.24**

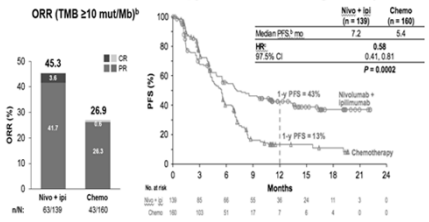
Borghaei et.al. *NEJM*, 2015; Herbst et.al., *Lancet*, 2015; Barlesi et.al., *ESMO*, 2016

IMPOWER 150: EGFR/ALK+ Cohort



Kowanetz et.al., *AACR*, 2018

CheckMate 227: First-Line Nivolumab+ Ipilimumab vs Chemotherapy in TMB high

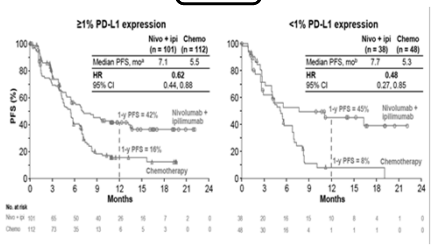


- **Median time to response was 2.7 months with nivolumab + ipilimumab and 1.5 months with chemotherapy**

Hellmann et.al., *AACR (with permission)*

CheckMate 227: First-Line Nivolumab+ Ipilimumab vs Chemotherapy

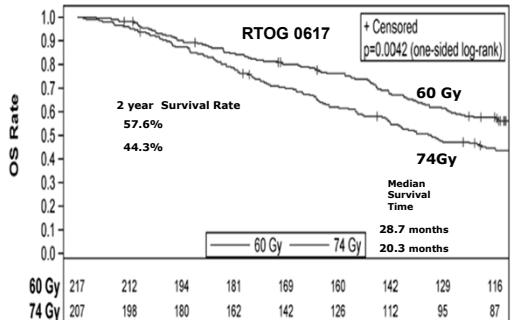
TMB ≥10



Hellmann et.al., *AACR (with permission),* 2018

Combinations of targeted and immunotherapies for locally advanced NSCLC

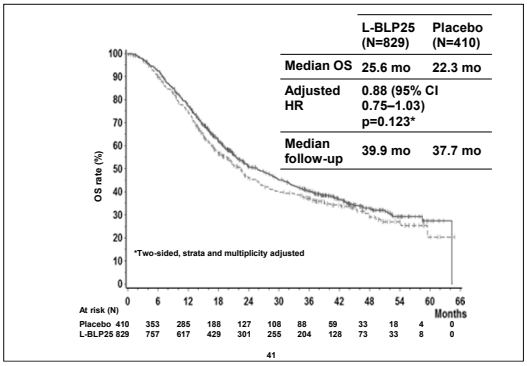
More Radiation Therapy isn't the Answer



More Radiation Therapy isn't the Answer

- In RTOG 0617
  - 60 Gy
    - 28.7 months median survival
    - 57.6% 2 year survival
  - 74 Gy
    - 20.3 month median survival
    - 44.3% 2 year survival

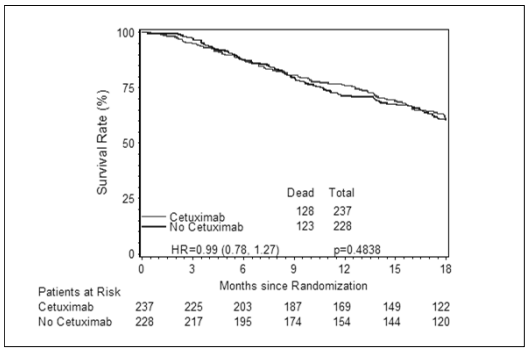
START Trial: Chemoradiation + vaccine



	L-BLP25 (N=829)	Placebo (N=410)
Median OS	25.6 mo	22.3 mo
Adjusted HR	0.88 (95% CI 0.75–1.03) p=0.123*	
Median follow-up	39.9 mo	37.7 mo

Presented by: Charles Butts, M.D., with permission

RTOG 0617, NCCTG N0628,CALGB 30609 Cetuximab vs. no Cetuximab



WCLC 2013 Sydney

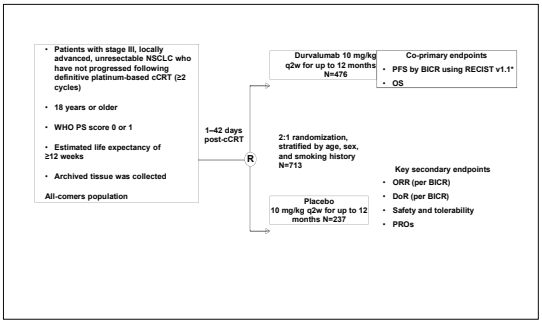
SWOG 0023 - EGFR TKI after chemo/RT

- **Patients treated with EGFR TKIs after chemo/RT for stage III NSCLC**
  - **Have statistically significantly shorter survival**
    - **23 month median survival for gefitinib**
    - **35 month median survival for placebo**

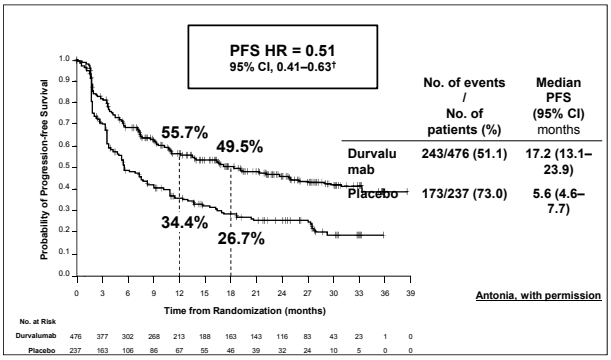
Kelly et al, *J Clin Oncol 26:2450-2456. © 2008*

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study



Updated Progression-free Survival by BICR* (ITT)

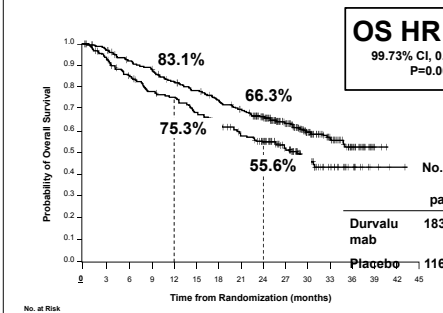


	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

Antonia, with permission

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)

Overall Survival* (ITT)



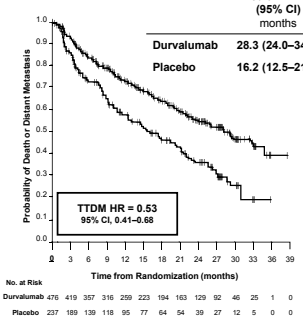
	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

Antonia, with permission

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached

Updated Time to Death or Distant Metastasis (TTDM) by BICR* (ITT)



	Median TTDM (95% CI) months
Durvalumab	28.3 (24.0–34.9)
Placebo	16.2 (12.5–21.1)

Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Antonia, with permission

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†A patient may have had more than one new lesion site

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
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IMpower133: Primary PFS, OS, and safety in a Ph1/3 study of 1L atezolizumab + carboplatin + etoposide in extensive-stage SCLC

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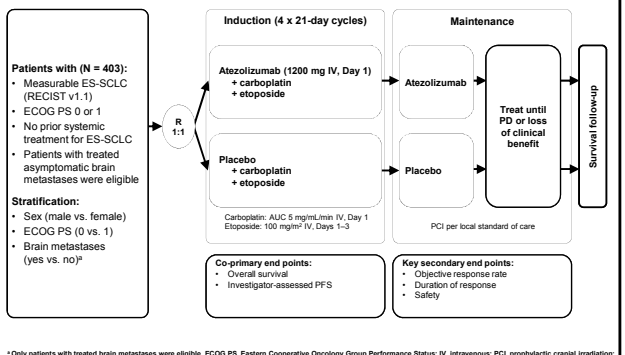
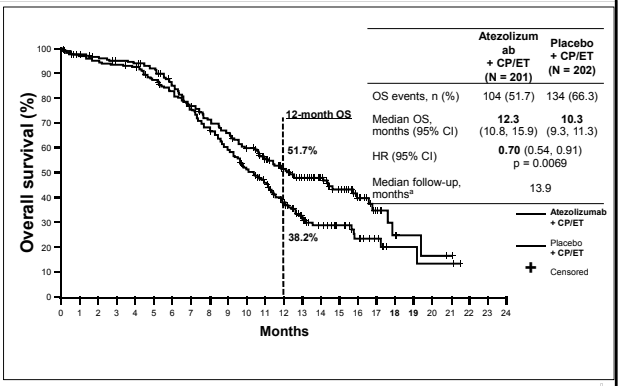
IMpower133

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Overall survival



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

WCLC 2018, with permission

LOTS of progress with IO, BUT: Response rates in unselected patients with single agent IO are ~ 20%

- For driver-targeted therapies, we have learned to expect nearly universal clinical benefit with appropriate patient selection
- With IO, we either use no biomarker or accept modest enrichment for effect.
- How can we best select patients for current and future immunotherapies?

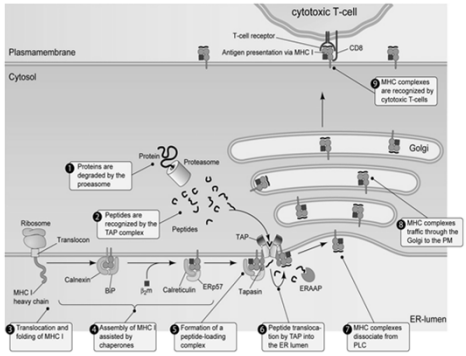
PD-L1 enriches for benefit, but is an imperfect marker

Response rates in enriched cohorts about doubled, but still less than 50%.

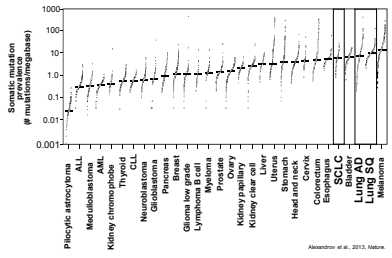
Patients with PD-L1 negative tumors still sometimes respond.

Other selection markers: Tumor Mutation Burden

Class I MHC presentation



Lung Cancer Has a High Frequency of Mutations



Alexandrov et al., 2013, Nature.

Lung cancers are associated with particularly high tumor mutation burden (TMB)*

*Analyzed using an algorithm developed to extract mutational signatures from catalogues of somatic mutations in 7,042 primary cancers. AD=adenocarcinoma; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; SCLC=small cell lung cancer; SQ=squamous.

Alexandrov LB et al. *Nature* 2013;500(7463):415-421.

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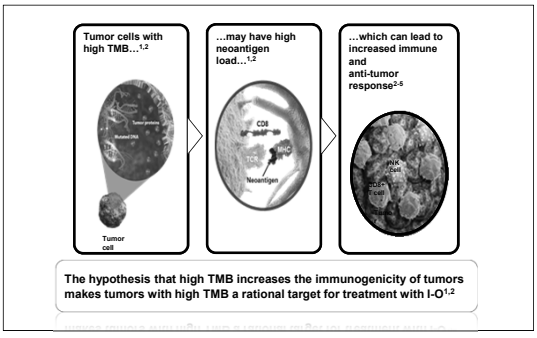
High Tumor Mutation Burden May Influence the Immune-Mediated Anti-Tumor Response

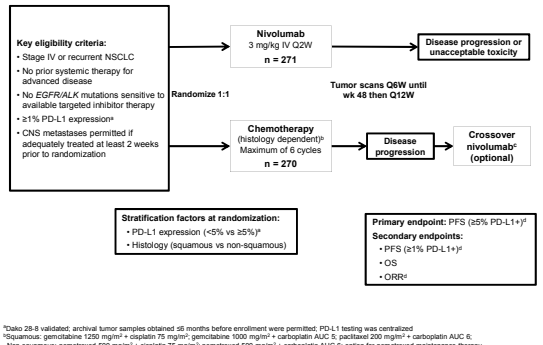


The hypothesis that high TMB increases the immunogenicity of tumors makes tumors with high TMB a rational target for treatment with I-O[1,2]

MHC=major histocompatibility complex; NK=natural killer; TCR=T-cell receptor; TMB=tumor mutation burden.

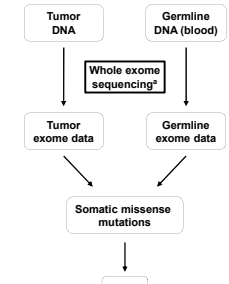
1. Schumacher TN, Schreiber RD. *Science.* 2015;348(6230):69-74. 2. Kim JM, Chen DS. *Ann Oncol.* 2016;27(8):1492-1504.
3. Liontos M et al. *Ann Transl Med.* 2016; 4(14):264. 4. Sharma P, Allison JP. *Science.* 2015;348(6230):56-61.
5. Giannakis M et al. *Cell Rep.* 2016;15:857-865.

Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



[a]Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m² + cisplatin 75 mg/m²; gemcitabine 1000 mg/m² + carboplatin AUC 5; paclitaxel 200 mg/m² + carboplatin AUC 6. Non-squamous: pemetrexed 500 mg/m² + cisplatin 75 mg/m²; pemetrexed 500 mg/m² + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review
[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review

CheckMate 026 Tumor Mutation Burden Analysis: Nivolumab in First-line NSCLC



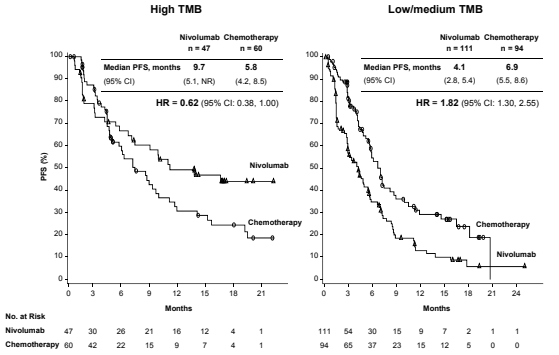
[a]DNA was sequenced on the Illumina HiSeq 2500 using 2 × 100-bp paired-end reads; an average of 84 and 89 million reads were sequenced per tumor and germline sample, respectively (average 84.6 × and 93 × the mean target coverage, respectively)

Sample size throughout TMB determination		
Patients, n (%)	**Tumor DNA**	**Germline DNA**
Randomized	541 (100)	541 (100)
Samples available for DNA extraction[a]	485 (90)	452 (84)
DNA available for sequencing	408 (75)	452 (84)
Successful preparation of next-generation sequencing library	402 (74)	452 (84)
Passed internal quality control[b]	320 (59)	432 (80)
Matched tumor-germline exome sequences for TMB analysis[c]	312 (58)	

[a]Samples were not available for various reasons, including but not limited to lack of patient pharmacogenetic consent, samples exhausted for PD-L1 testing, or poor tissue sampling
[b]Internal quality control failure included factors such as discordance between tumor and germline DNA, too few sequence reads, and low or uneven target region coverage
[c]8 patients with available tumor DNA sequences did not have matched germline DNA sequences

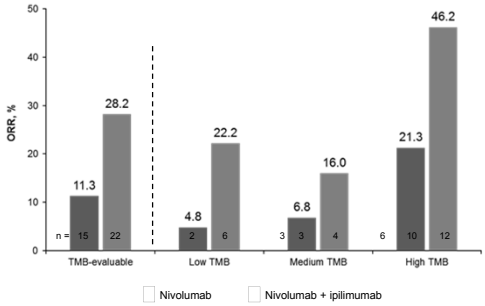
Carbone et al, NEJM 2017

PFS by Tumor Mutation Burden Subgroup
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



Carbone et al, NEJM 2017 59

Checkmate 032 (Nivo ± Ipi): ORR by TMB Subgroup in SCLC



ORR=overall response rate; TMB=tumor mutation burden.

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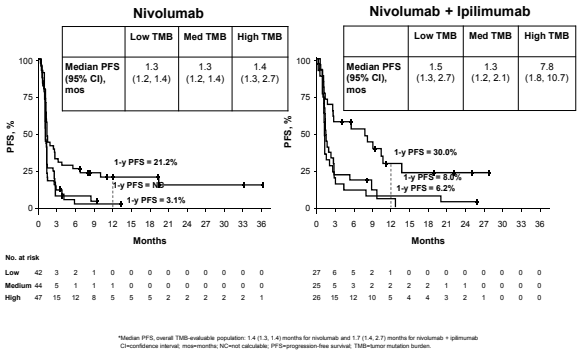
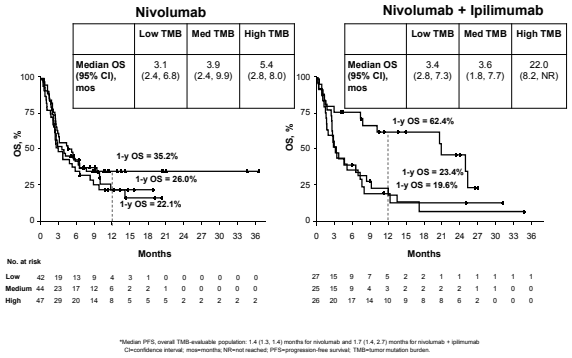
Checkmate 032 (Nivo ± Ipi): PFS by TMB Subgroup in SCLC



*Median PFS, overall TMB-evaluable population: 1.4 (1.3, 1.4) months for nivolumab and 1.7 (1.4, 2.7) months for nivolumab + ipilimumab
CI=confidence interval; mos=months; NC=not calculable; PFS=progression-free survival; TMB=tumor mutation burden.

Antonia, WCLC 2017, with permission

Checkmate 032 (Nivo ± Ipi): OS by TMB Subgroup in SCLC



*Median PFS, overall TMB-evaluable population: 1.4 (1.3, 1.4) months for nivolumab and 1.7 (1.4, 2.7) months for nivolumab + ipilimumab
CI=confidence interval; mos=months; NR=not reached; PFS=progression-free survival; TMB=tumor mutation burden.

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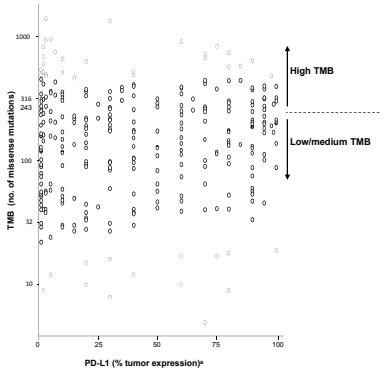
Do PD-L1 and TMB independently predict clinical outcomes?

Tumor Mutation Burden and PD-L1 Expression are independent

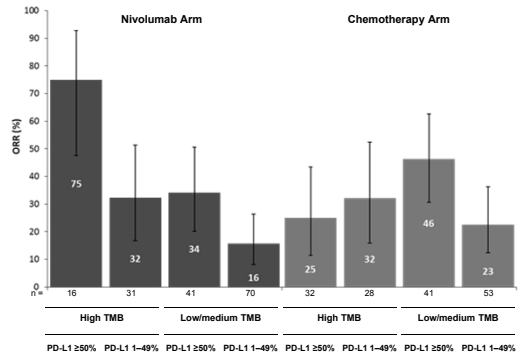
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



aAll patients had ≥1% PD-L1 tumor expression

Carbone et al, NEJM 2017 64

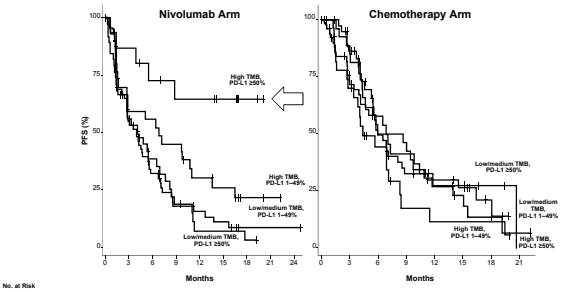
Overall Response Rate by TMB Subgroup and PD-L1 Expression
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



*ORR was 45.6% in patients with ≥50% PD-L1 expression in the nivolumab arm of the TMB-evaluable population

Carbone et al, NEJM 2017 65

Progression-Free Survival by TMB Subgroup and PD-L1 Expression
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



No. at Risk

High TMB, PD-L1 ≥50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1–49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1–49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Carbone et al, NEJM 2017 66

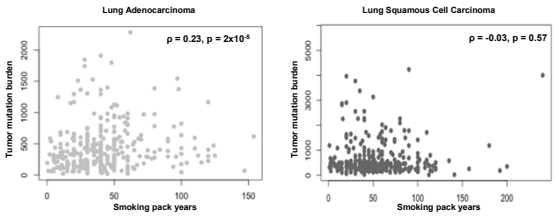
Questions to be answered re: TMB

- Cutoff?
- Platform?
  - WES
  - Targeted panels
  - Blood-based assays?
- Role in IO combinations?
- Role in meso and SCLC?

Can all of the TMB differences be explained by smoking exposure?

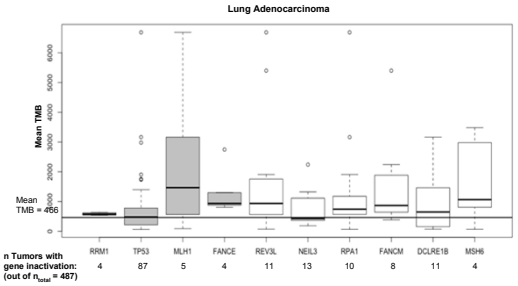
DNA integrity – maintenance genes

Is smoking pack years just as good as tumor mutation burden?



Sharpnack, Carbone, He WCLC 2017

Inactivation of which genes is associated with increased TMB?



Sharpnack, Carbone, He WCLC 2017

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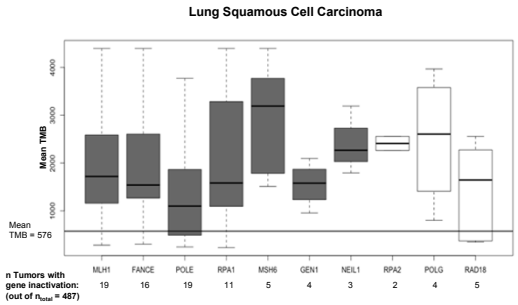
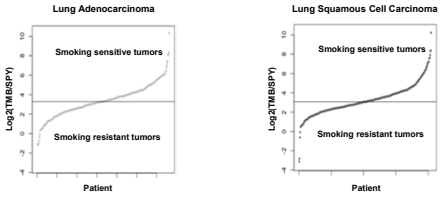


Sharpnack, Carbone, He WCLC 2017

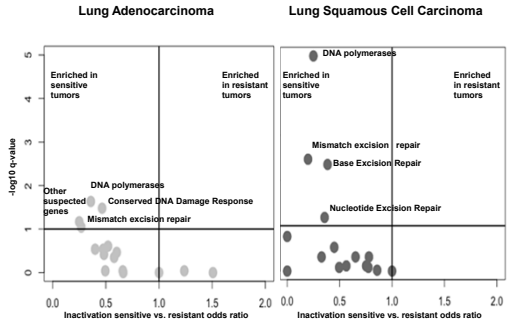
Smoking sensitive vs. resistant tumors



"Smoking sensitive" tumors have >10 mutations per smoking pack year

Sharpnack, Carbone, He WCLC 2017

DNA polymerase and mismatch excision repair pathway inactivation is enriched in smoking sensitive NSCLC



Sharpnack, Carbone, He WCLC 2017

DNA repair mutations - conclusions

1. **MLH1 and FANCE inactivation are associated with increased TMB in both adenocarcinoma and squamous cell carcinoma.**
2. **Smoking is not a sufficient substitute biomarker for TMB.**
3. **DNA repair pathway alterations might be potential therapeutic biomarkers of immune checkpoint inhibition in NSCLC.**

Summary

- **We have made a lot of progress toward improving the quality and quantity of life for lung cancer patients**
- **Virtually all of this progress has been through the application of basic science to medicine and studying medical phenomena to better understand the science**
- **There is still a lot of room for improvement**
  - **In selecting the best therapy for each patient**
  - **For improving the effectiveness of our current therapies**
  - **Defining new targets for therapy.**