ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Daniel P. Petro, MD

University of Pittsburgh

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Celgene, Consulting Fees; Juno Therapeutics, Immunomedics, Ownership Interest
- I may be discussing non-FDA approved indications during my presentation.

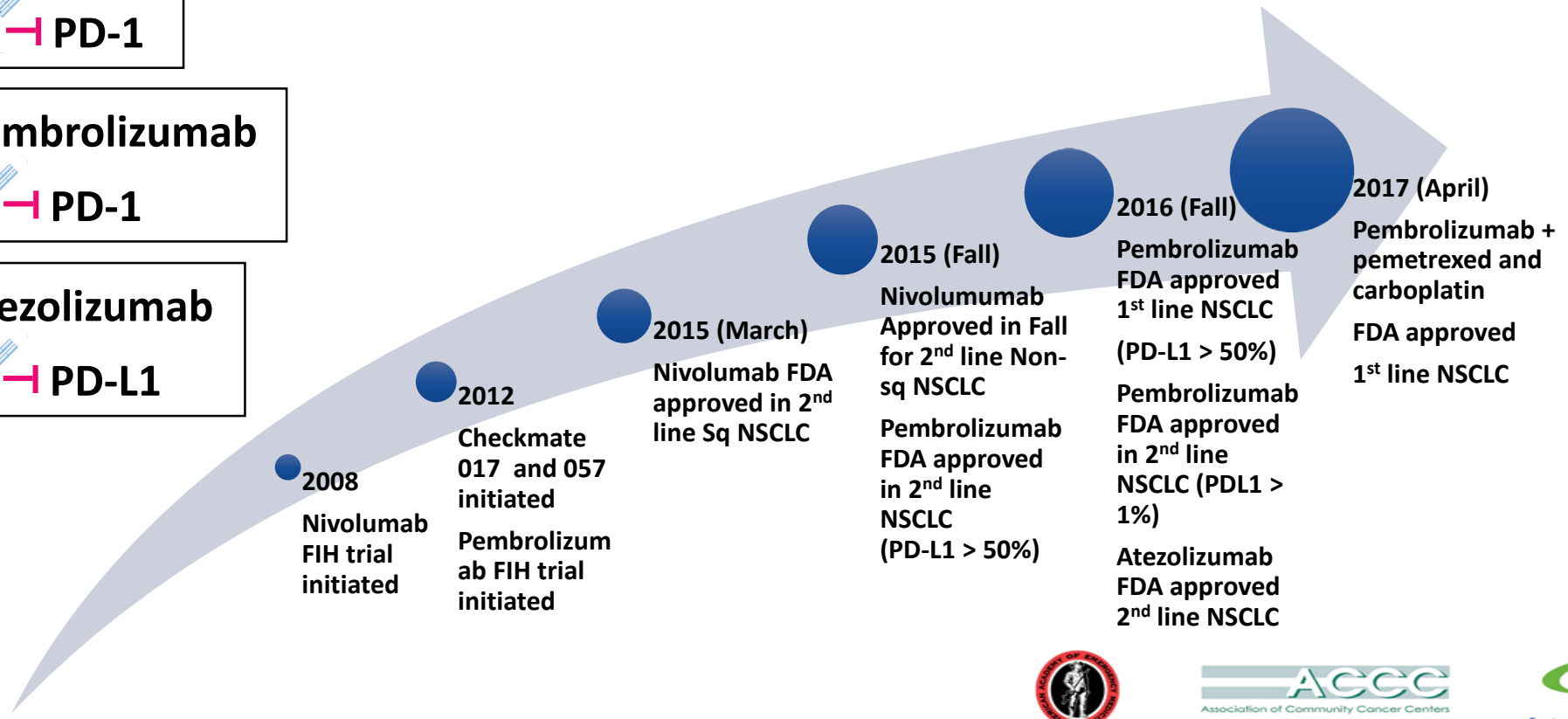
ADVANCES IN Cancer IMMUNOTHERAPY™

Immune checkpoint inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

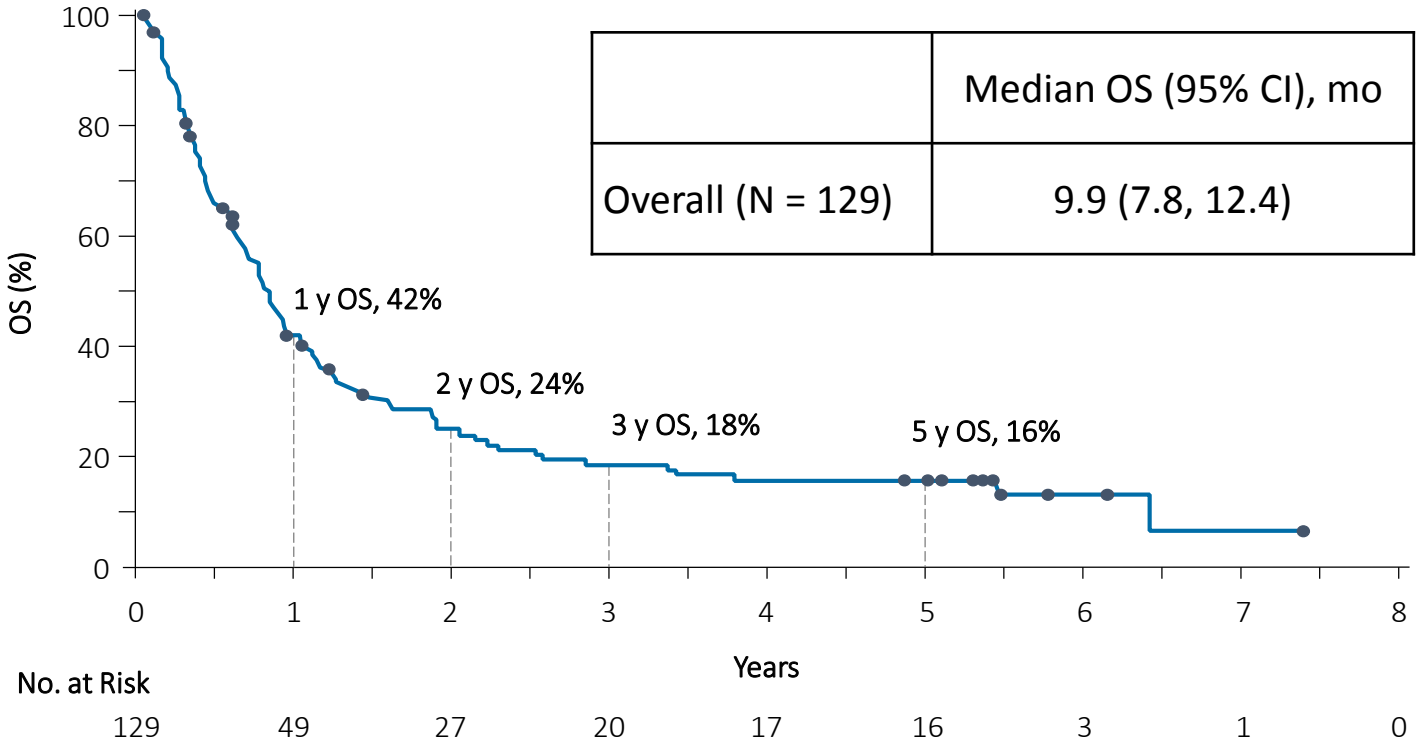


Association of Community Cancer Centers

Society for Immunotherapy of Cancer

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

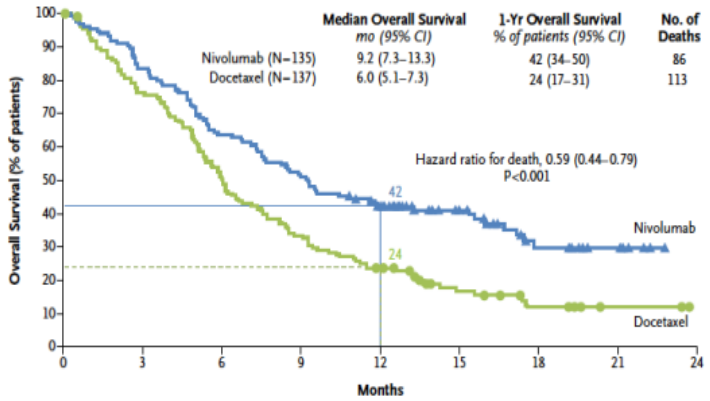
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)



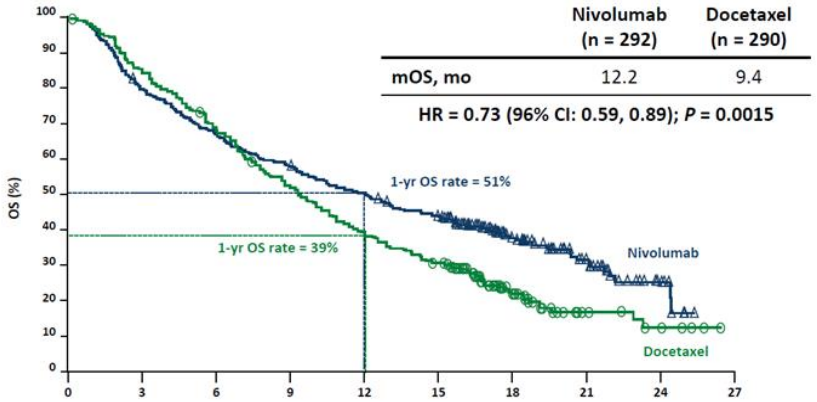
Brahmer et al, AACR 2017

PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

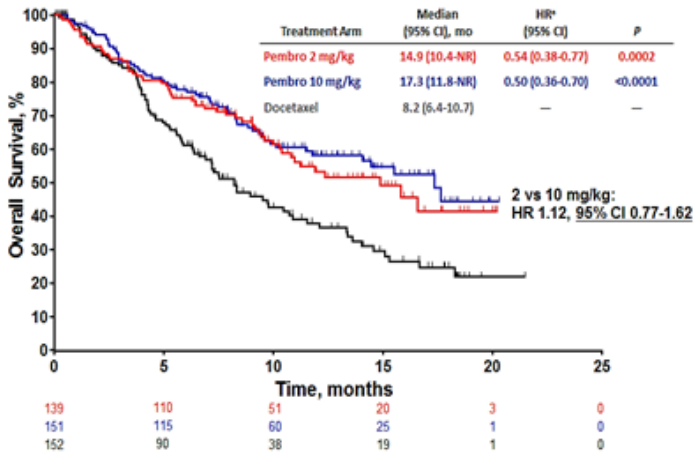
CHECKMATE 017



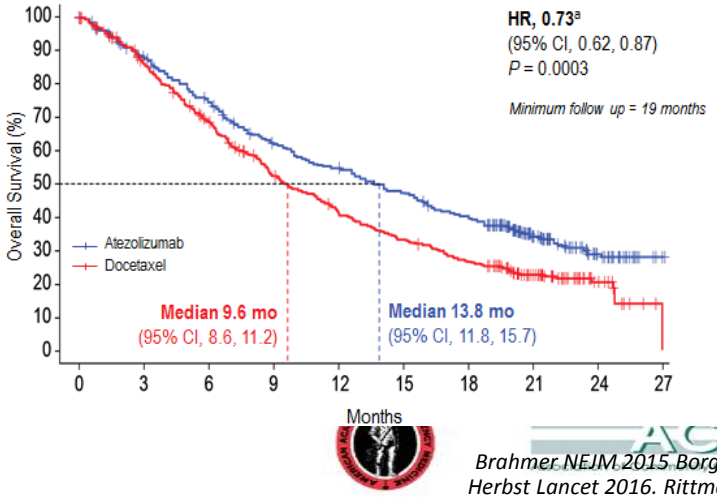
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)

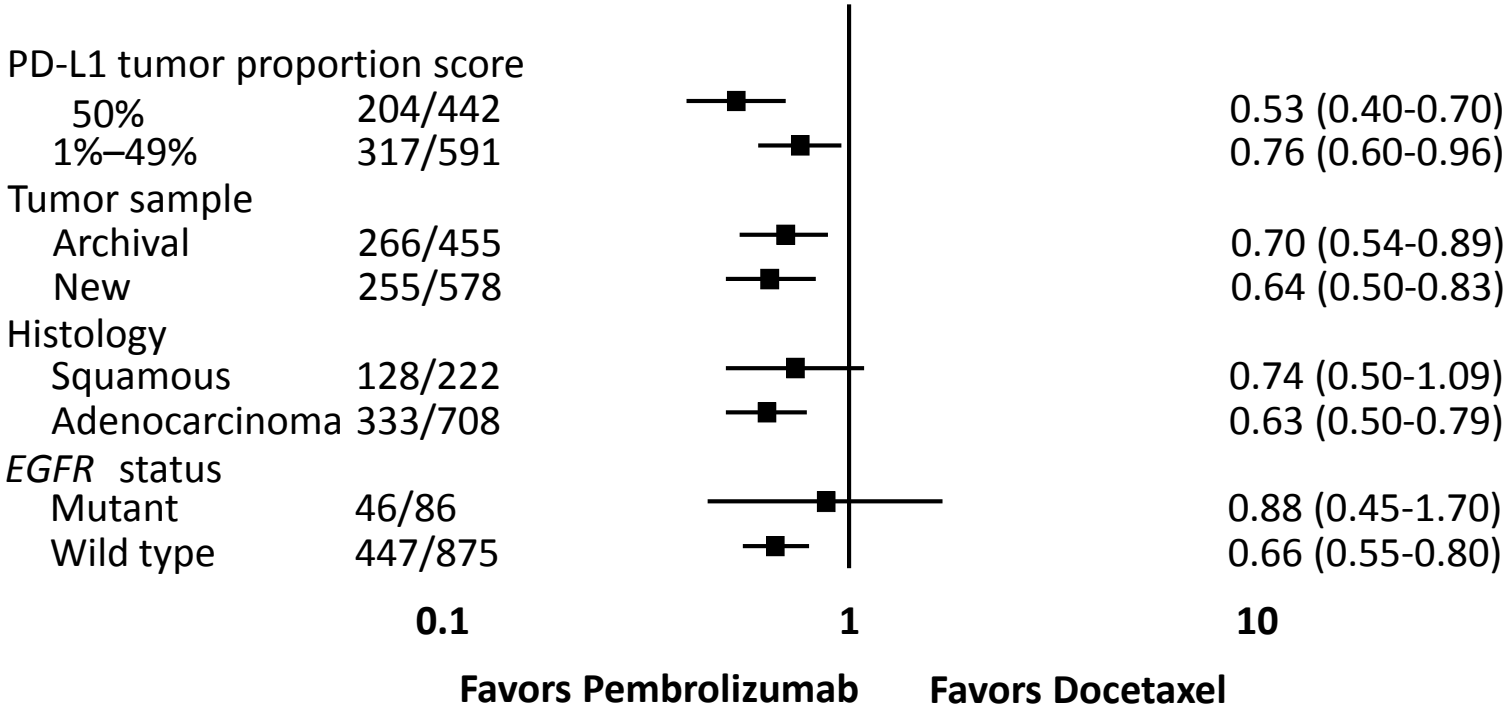


OAK



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

KEYNOTE 010: Pembrolizumab approval ≥ 2nd line (PD-L1 ≥ 1%)

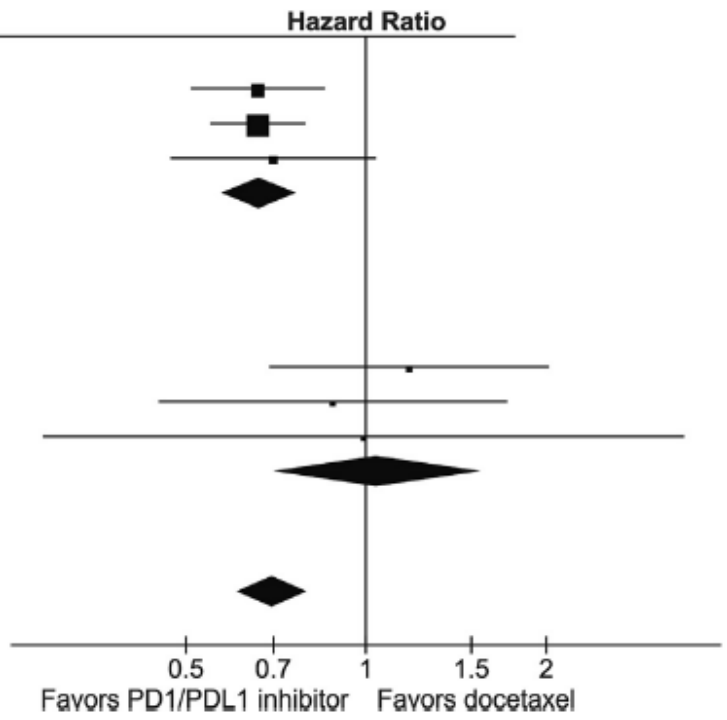


Herbst et al, Lancet 2015

ADVANCES IN Cancer IMMUNOTHERAPY™

EGFRm PD-(L)-1 meta-analysis

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



CK Lee et al., *JTO* 2016

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicities in 2/3L Randomized trials

	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Keynote 010
Related Grade 3-5 AEs	15%	8%	11%	13-16%
Discontinuation due to related AEs	5%	6%	6%	4-5%
Pneumonitis AEs	1%	5%	3%	4-5%

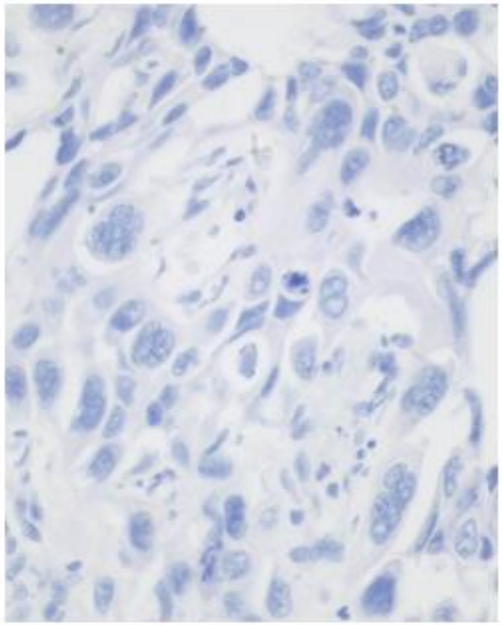
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

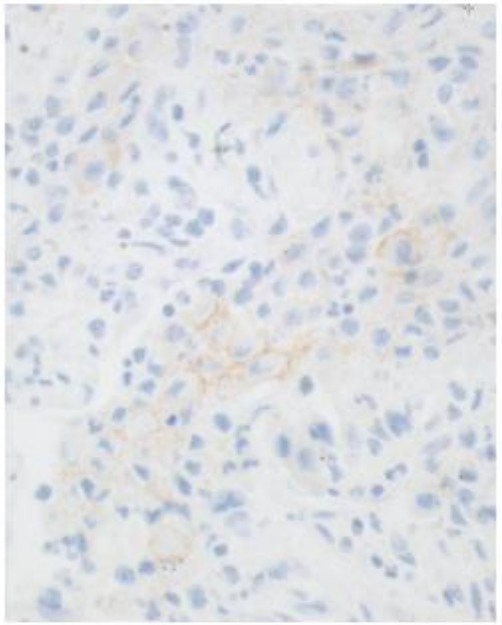
ADVANCES IN Cancer IMMUNOTHERAPY™

PD-L1 selection to bridge the gap?



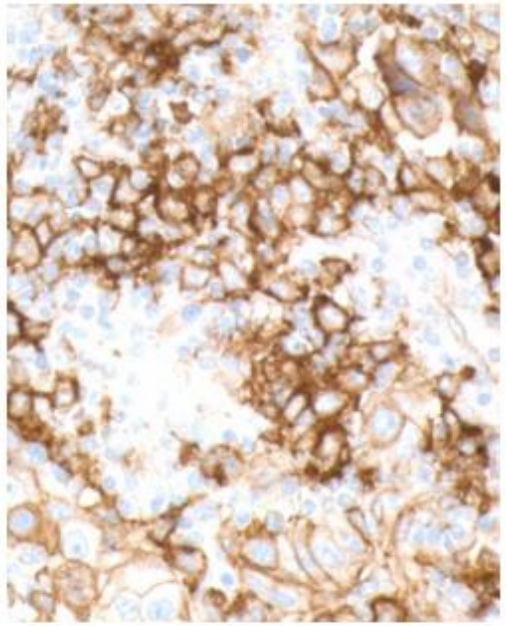
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



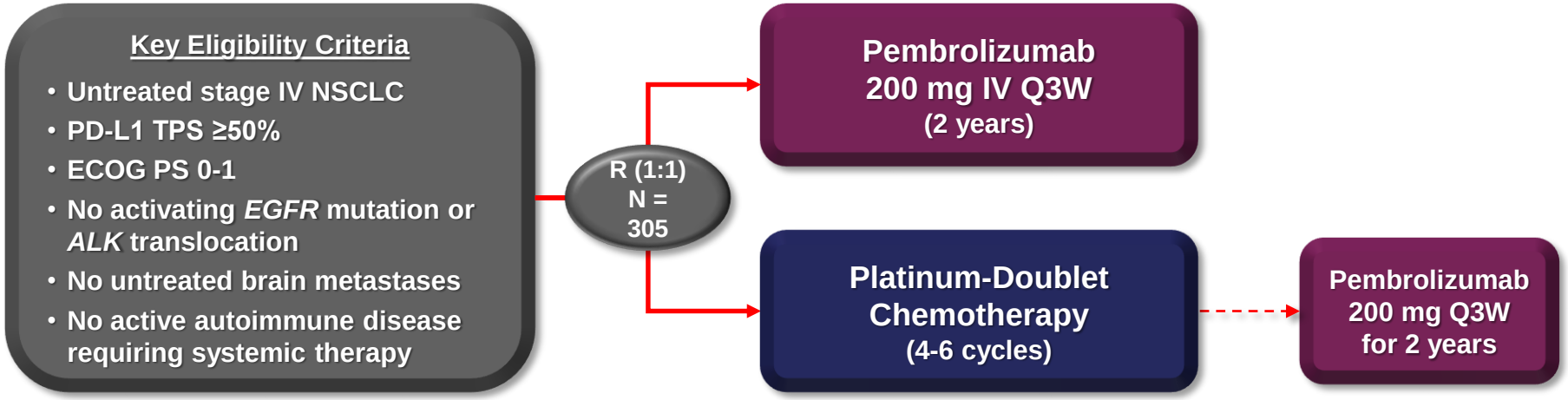
PD-L1 = 100% positive

Strong Positive (50%-100%)

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

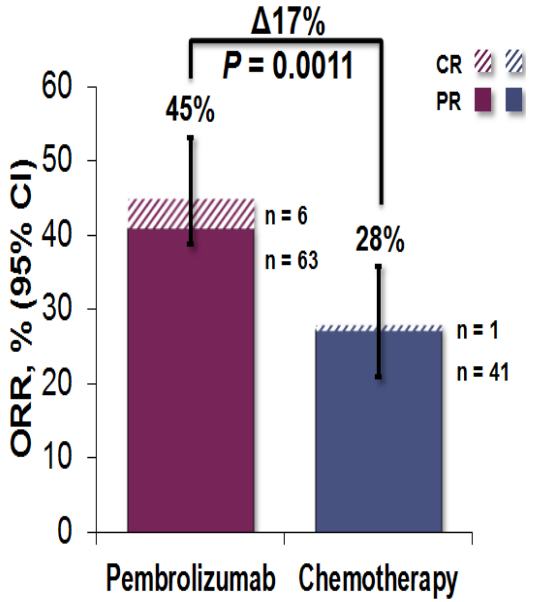
Primary: PFS (RECIST v1.1 per blinded, independent central review)

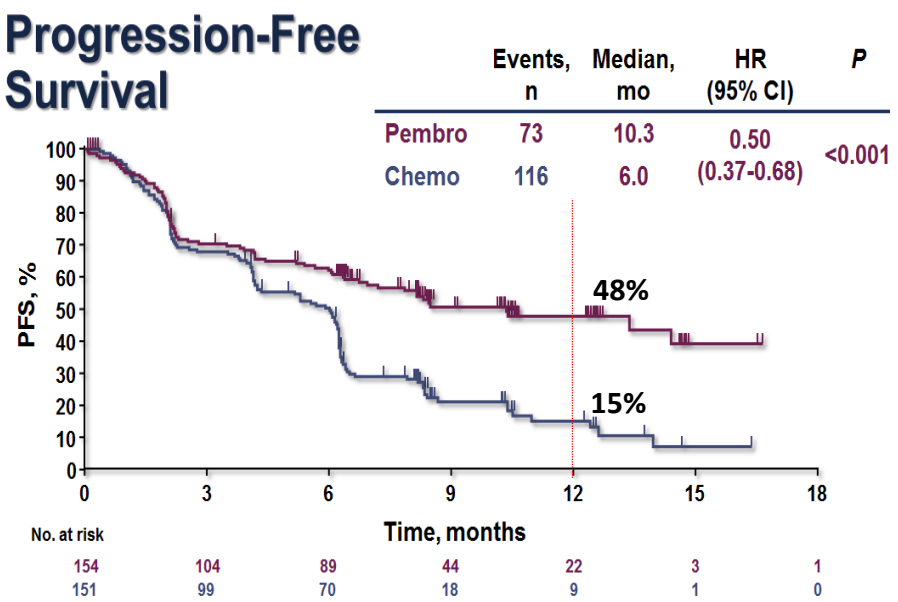
Secondary: OS, ORR, safety

Exploratory: DOR

Reck M et al, ESMO 2016, NEJM 10/16

Efficacy data: Keynote 24



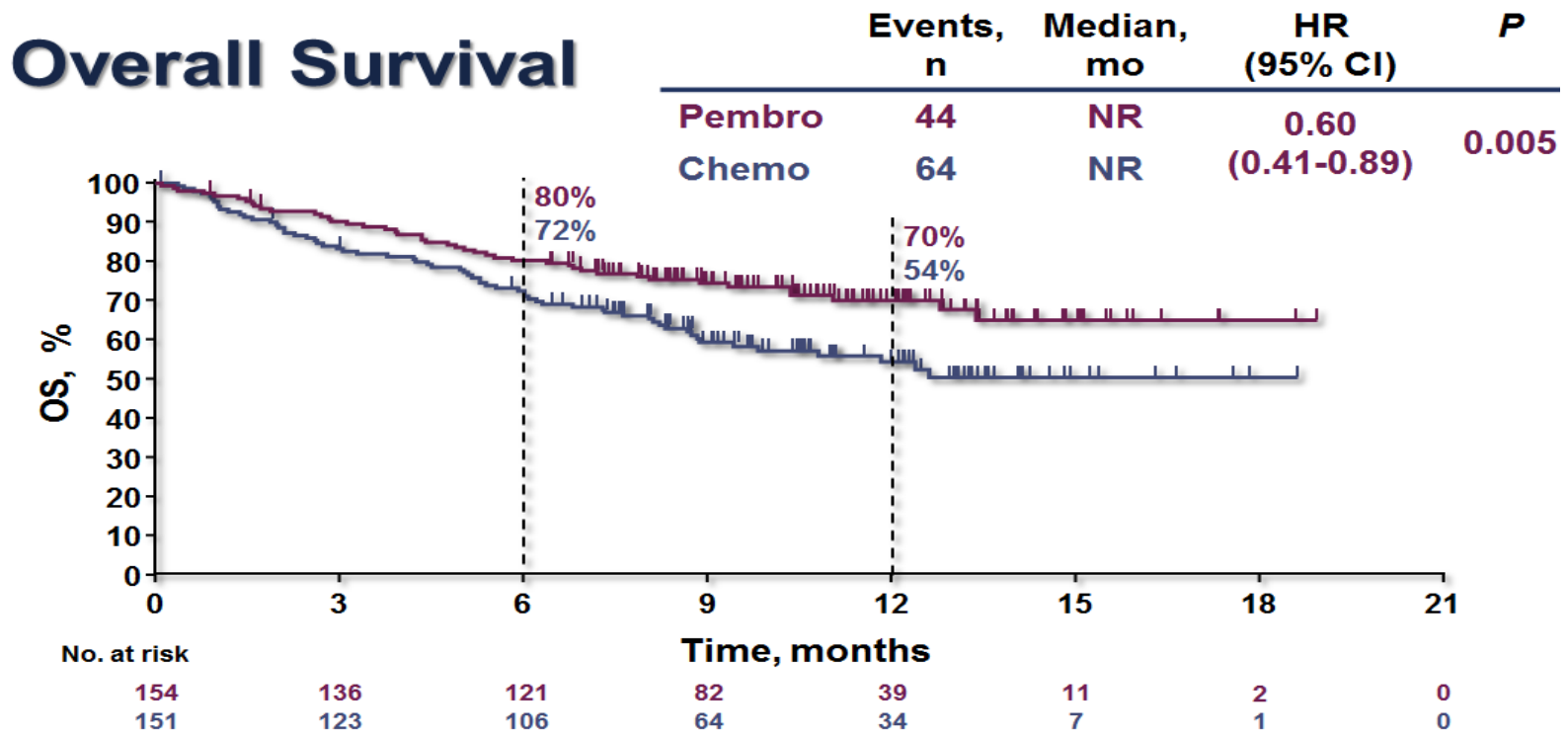


imaging every 9 weeks

- Clear and strong signal of activity
  - → ORR is improved, with a control arm that performs as expected (based on other phase III trials)
  - → 45% ORR is the one of best RRs ever reported in 1st line setting (and with monotherapy!)
  - → Time to Response is identical between Pembro and Chemo
  - → PFS is improved by 4.3 months (HR of 0.50)
  - → Improvement of PFS in all subgroups (except female/never smokers => lower mutational load ?)
  - → Strongest signal of PFS benefit observed in SqCC (HR of 0.35)

Reck M et al, ESMO 2016, NEJM 10/16

Keynote 24: Survival data



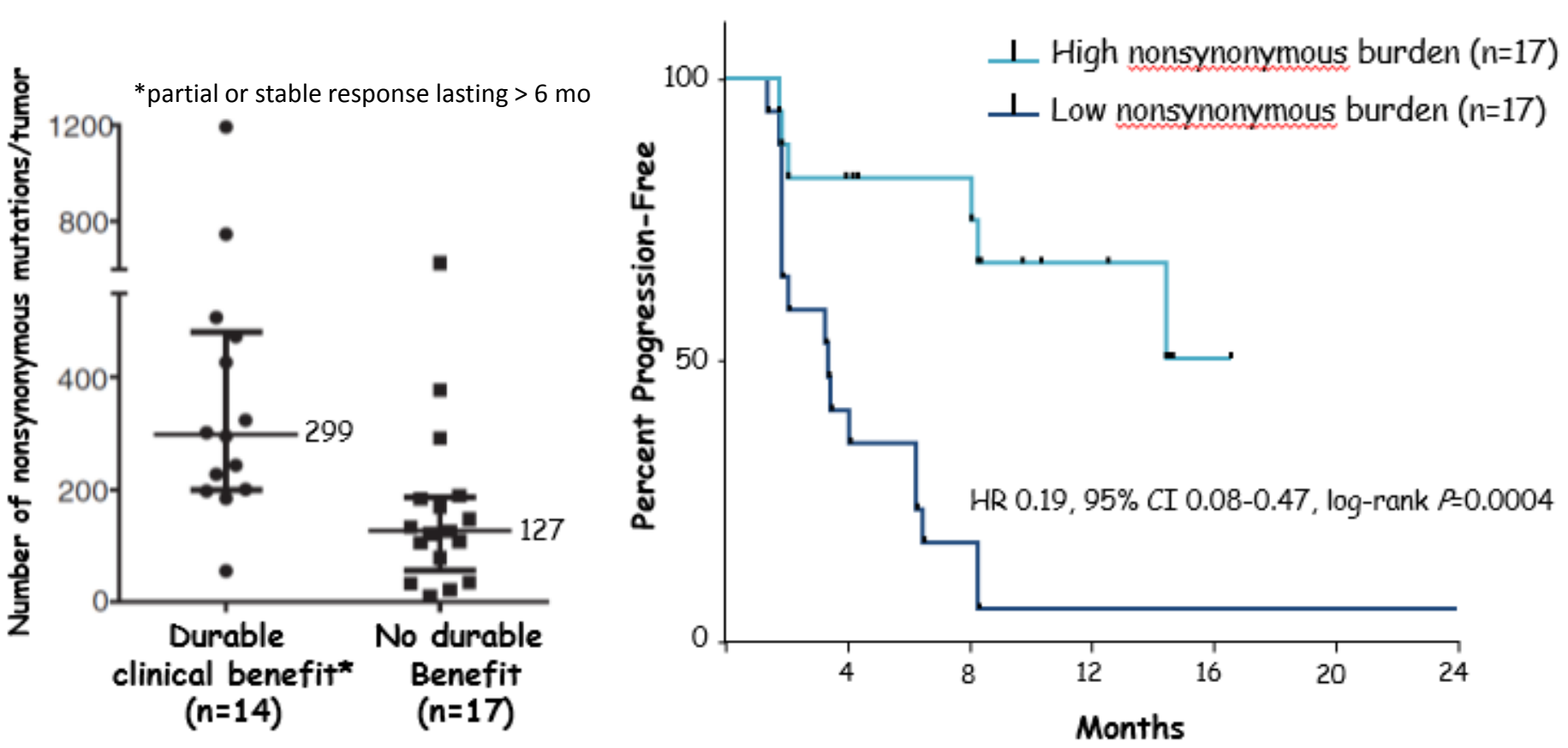
Clearcut survival benefit

- **Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)**
- **HR for death: 0.60**
- **Despite cross-over in 50% of patients on the control arm**

Reck M et al, ESMO 2016, NEJM 10/16

ADVANCES IN Cancer IMMUNOTHERAPY™

Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



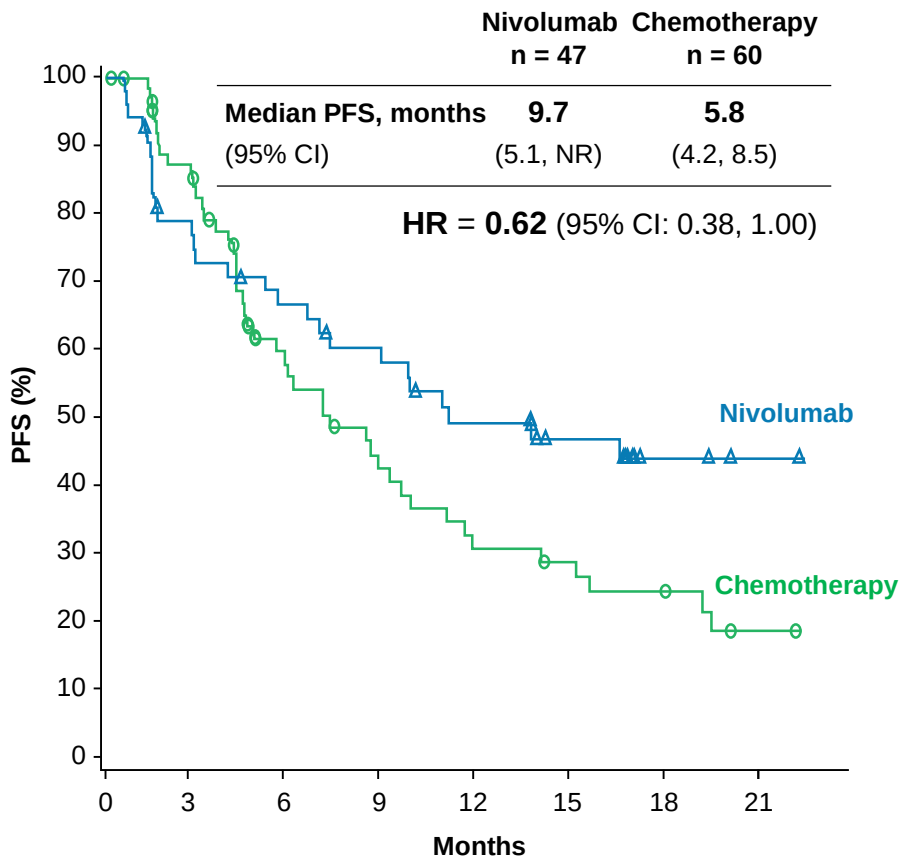
Rizvi N et al, Science 2015:348(6230):124-128

sitc or Immunotherapy of Cancer

PFS by Tumor Mutation Burden Subgroup CheckMate 026 TMB Analysis

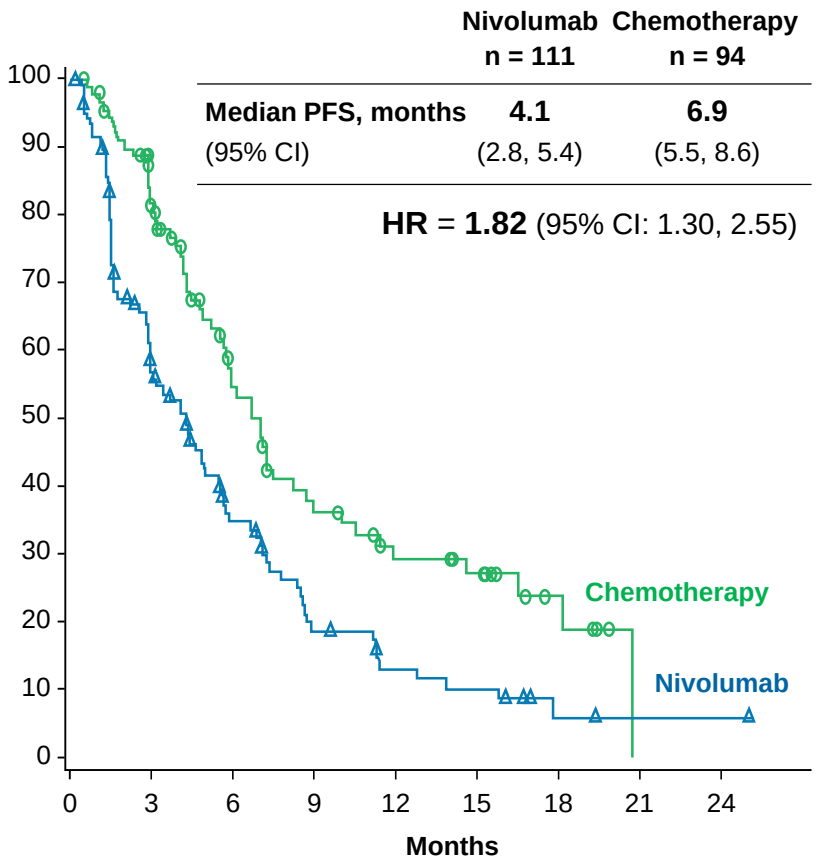
Nivolumab in First-line NSCLC

High TMB



No. at Risk								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB

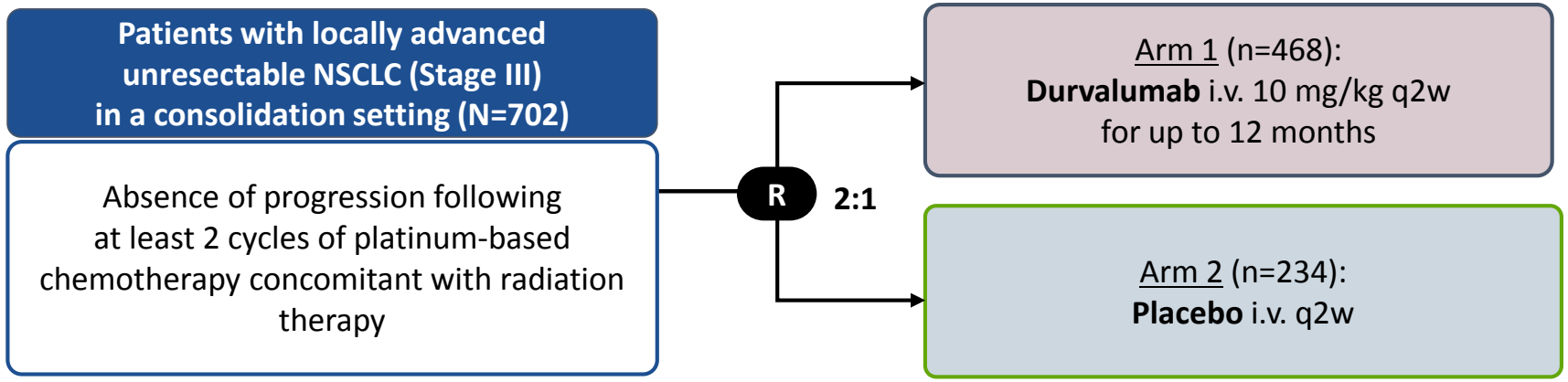


111	54	30	15	9	7	2	1	1	
94	65	37	23	15	12	5	0	0	

Peters, et al., AACR 2017

PACIFIC (NCT02125461/D4191C00001): Study Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)



Primary endpoints
- PFS, OS

Secondary endpoints
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

Est. completion: 2017
FPD[4] Q2 14
LPCD: Q2 16

DoR = duration of response; DSR = deep sustained response; FPD, first patient dosed; i.v. = intravenous; LPCD = last patient commenced dosing; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; q2w = every 2 weeks; QoL = quality of life.

PACIFIC (NCT02125461/D41[illegible]001): Study Design

- Phase 3, randomized, double-blind, placebo-co[illegible], global study (26 countries)

Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting (N=702)

Absence of progression followi[illegible] at least 2 cycles of platinum[illegible] chemotherapy concomitant[illegible] therap[illegible]

Arm 1 (n=468): **[illegible]valumab** i.v. 10 mg/kg q2w for up to 12 months

Arm 2 (n=234): **Placebo** i.v. q2w

Primary endpoi[illegible]
- PFS, OS

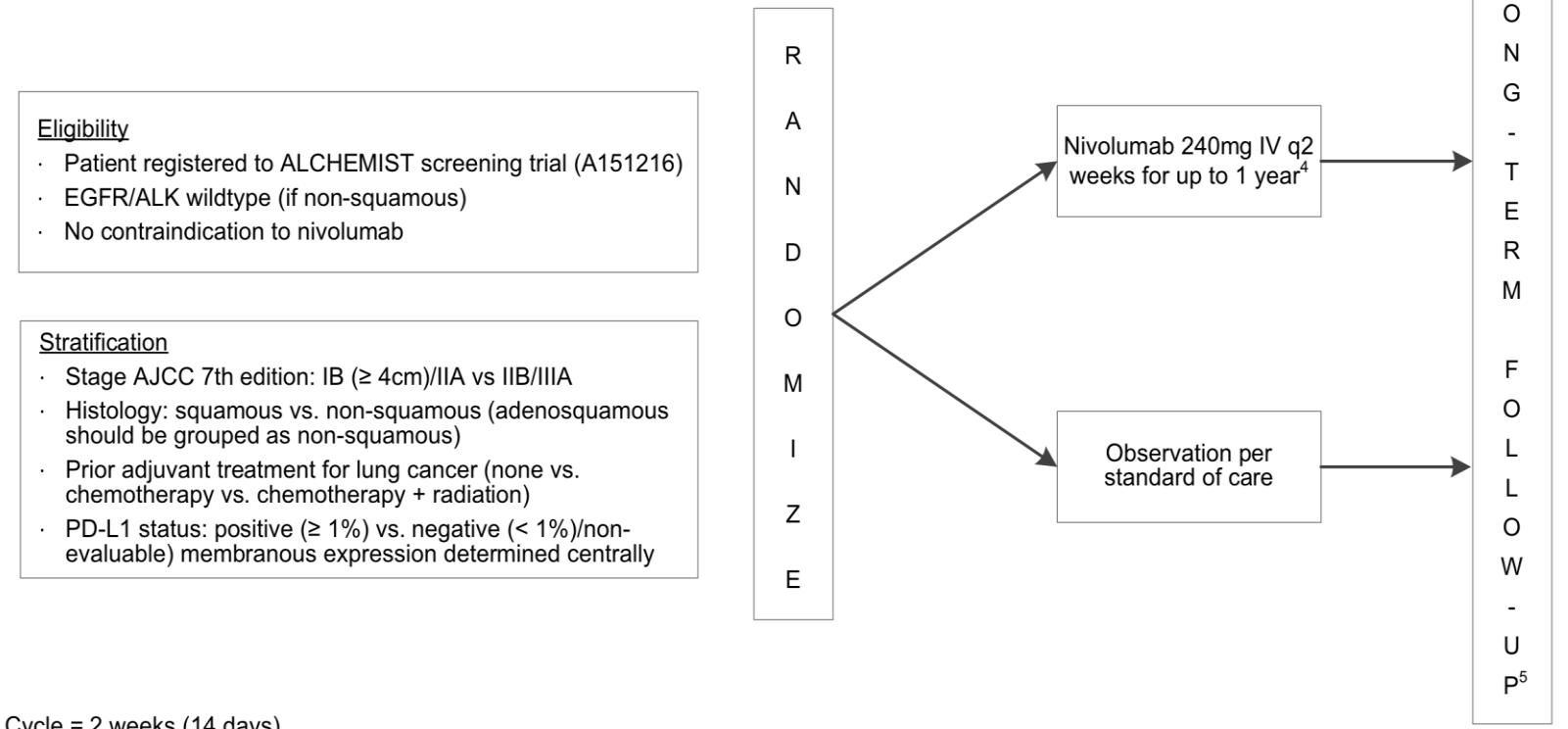
Second[illegible]
- [illegible]
- [illegible]
- PK[illegible]

Est. completion: 2017
FPD[4] Q2 14
LPCD: Q2 16

Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

DoR = duration of [illegible] = deep sustained response; FPD, first patient dosed; i.v. = intravenous; LPCD [illegible]tient commenced dosing; NSCLC = non-s[illegible]ll cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; q2w = every 2 weeks; QoL = quality of life.

EA5142: ANVIL – Adjuvant Nivolumab in Resected NSCLC



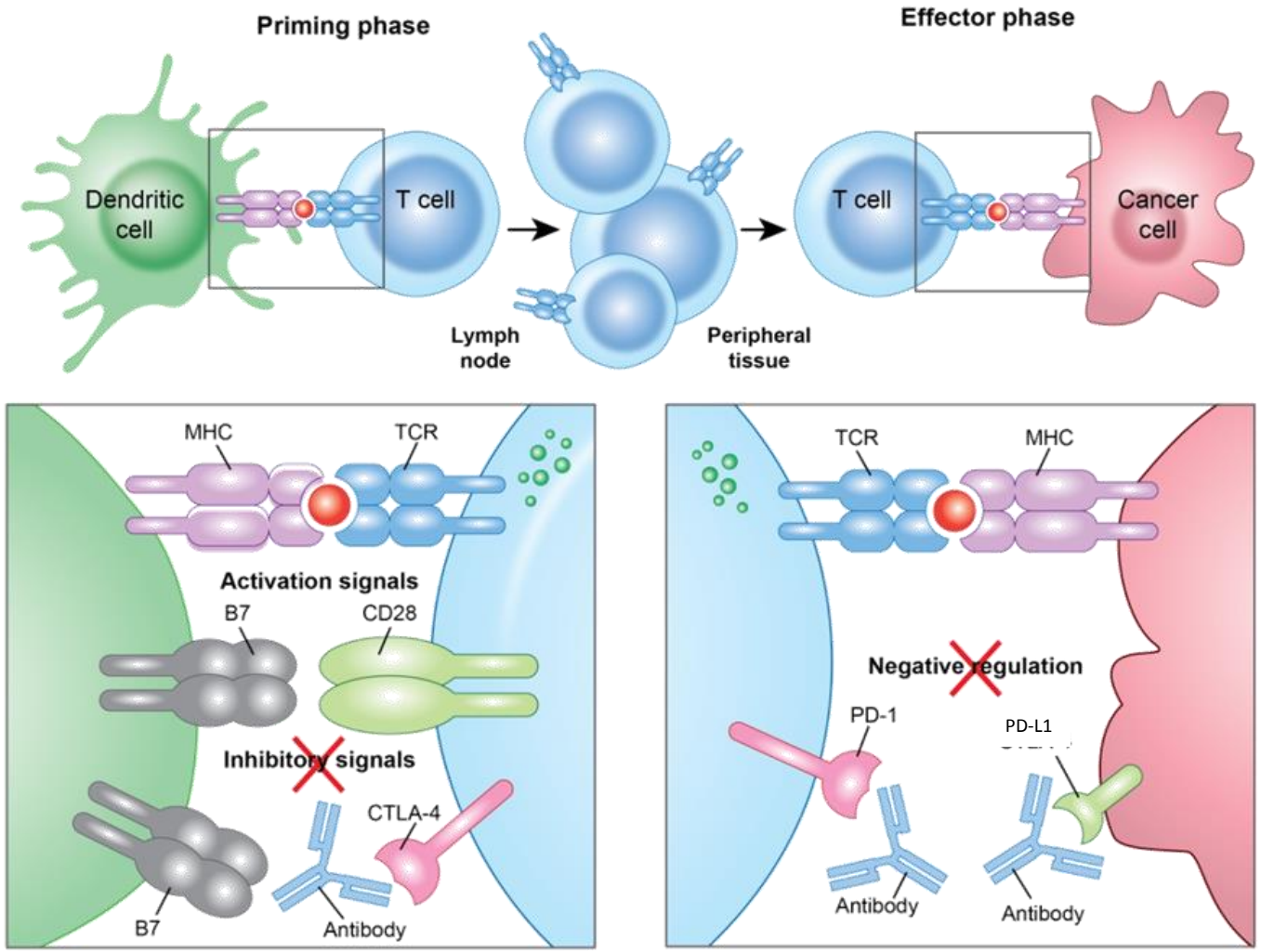
Cycle = 2 weeks (14 days)
Accrual Goal = 714 patients

1. If Stage 1B, then tumor must be ≥ 4cm
2. Adenosquamous should be grouped as non-squamous
3. PD-L1+ is defined as ≥ 1% by IHC
4. Maximum number of doses is 26
5. Patients will be followed for recurrence and survival for 10 years

Co-primary endpoints: DFS and OS in all patients

ADVANCES IN Cancer IMMUNOTHERAPY™

Combination
Immune checkpoint blockade



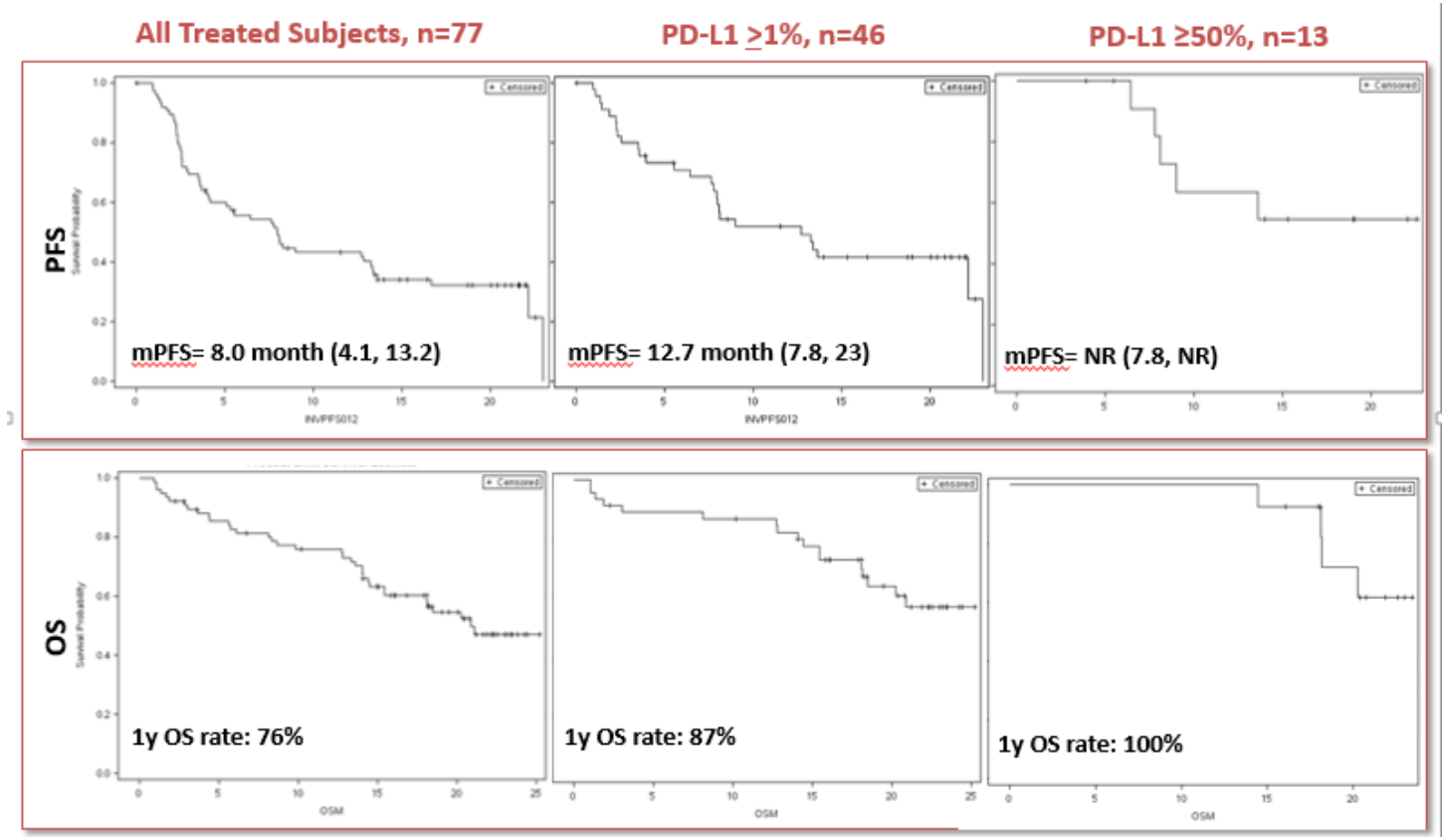
Ribas A, N Engl J Med 2012; 366:2517-2519.

ADVANCES IN Cancer IMMUNOTHERAPY™

Ipilimumab: CTLA-4

Nivolumab: PD-1

Combination I-O (IPI/NIVO) potential in first line ?

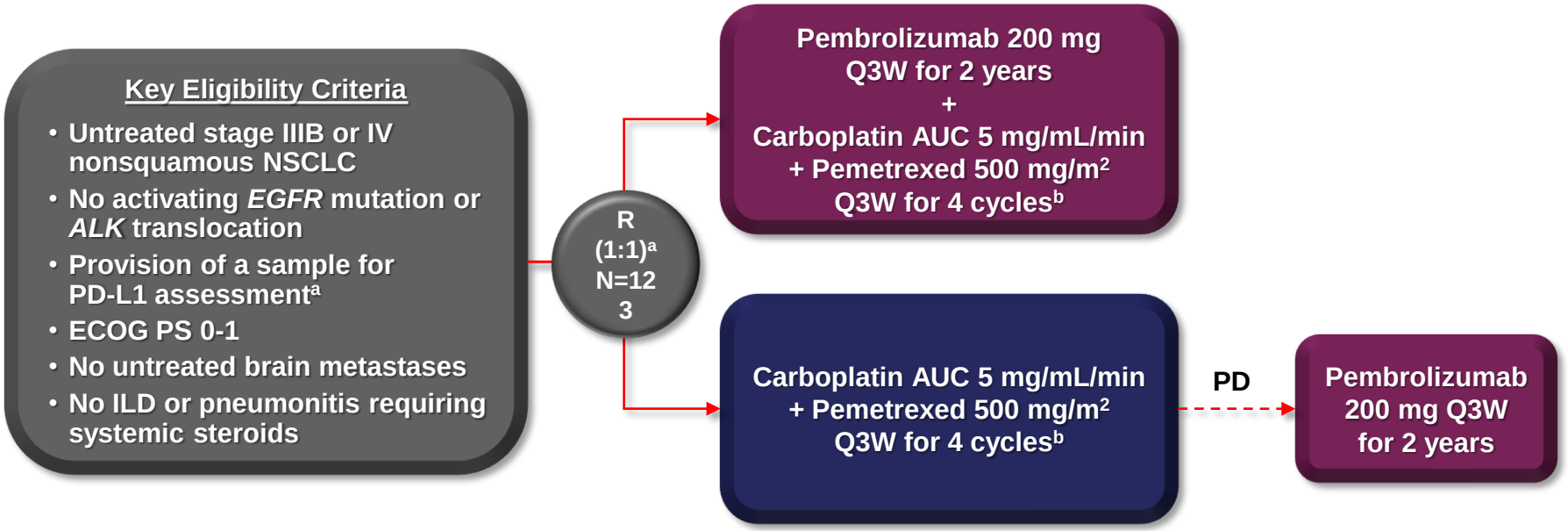


CheckMate 012
Goldman, et al, ASCO Annual Meeting, 2017

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

KEYNOTE-021 Cohort G



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

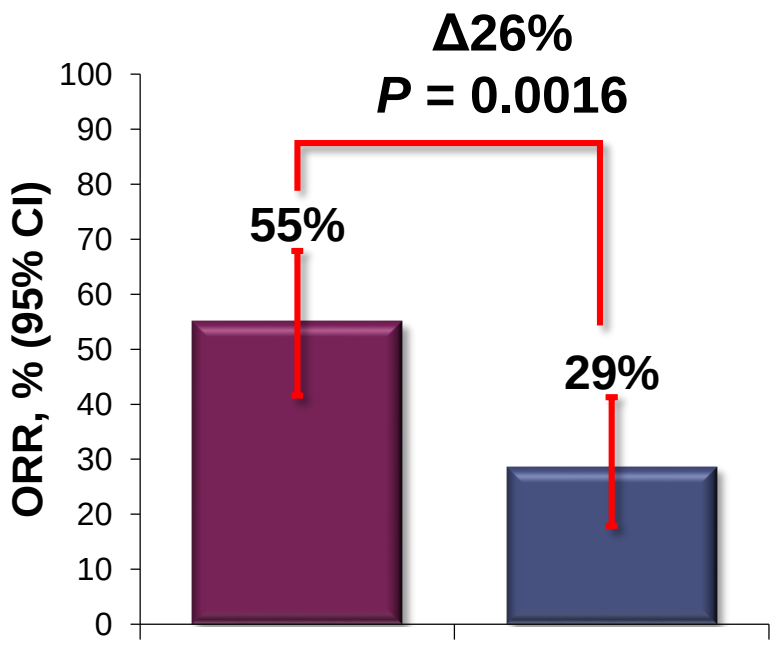
Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer, et al Lancet Oncology 2016

Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



Data cut-off: August 8, 2016.

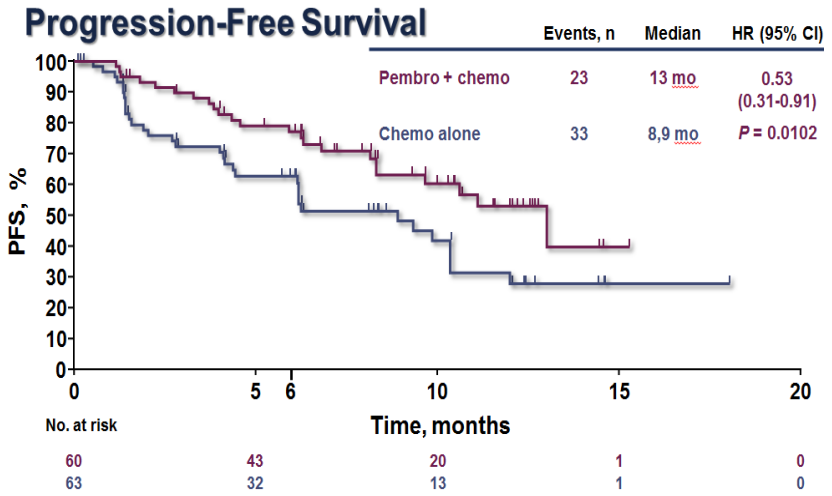
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response, [a] n (%)	29 (88)	14 (78)

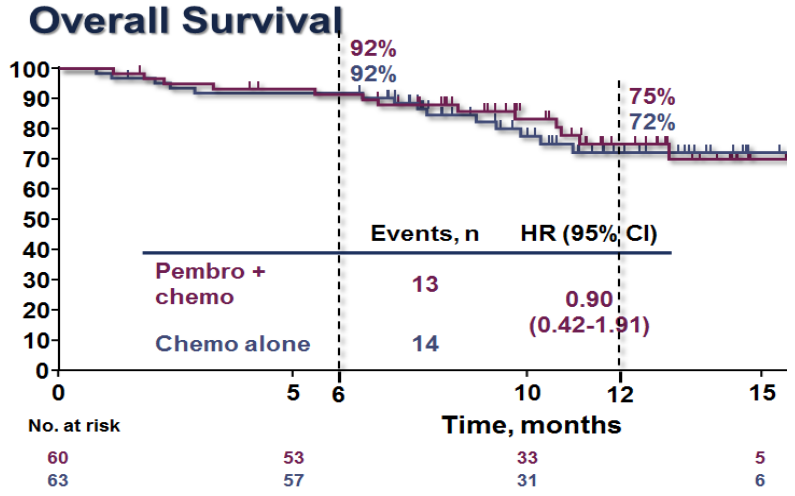
DOR = duration of response; TTR = time to response.

[a]Alive without subsequent disease progression.

Langer, et al Lancet Oncology 2016

PFS and OS Survival data



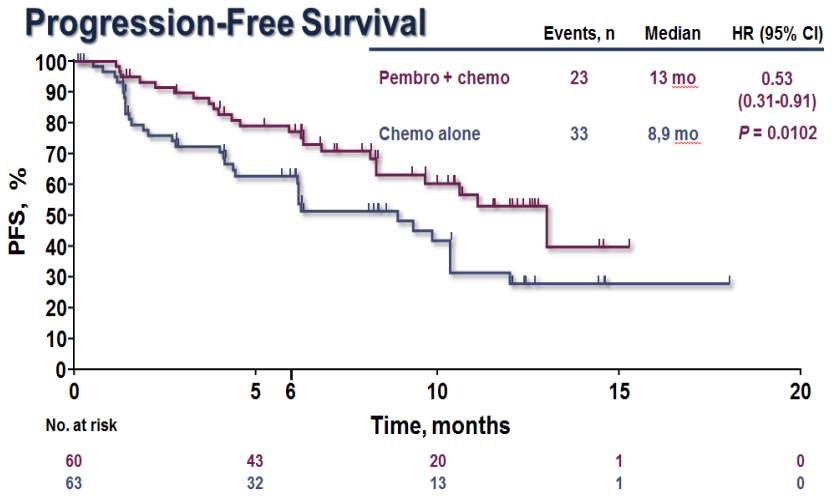


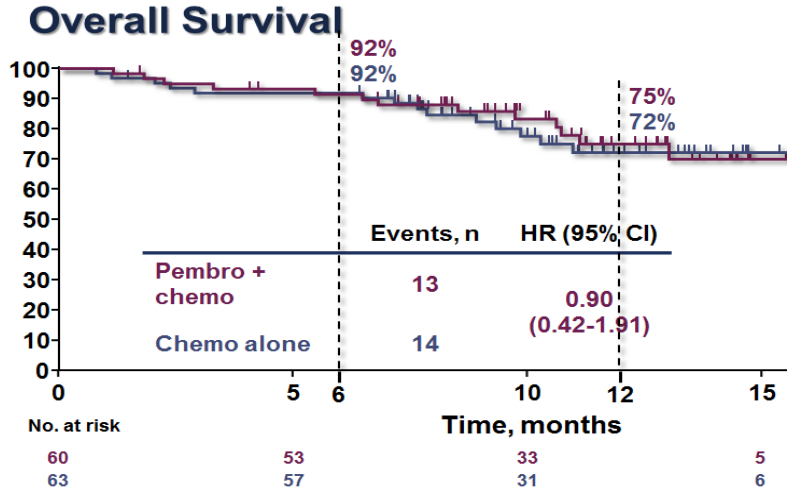
Clear PFS benefit and no OS advantage

- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Langer, et al Lancet Oncology 2016

PFS and OS Survival data





Clear PFS benefit and no OS advantage

- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Updated (ASCO ‘17):

- RR: 57% vs 30.5%
- PFS HR has dropped to 0.5 from 0.53, Median now NR vs 8.9
- OS HR has dropped to 0.69 from 0.9 with dip in p value from 0.37 to 0.13 (1yr OS 76% vs 69%)

Langer, et al Lancet Oncology 2016,
Papadimitrikopolou, ASCO 2017

Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

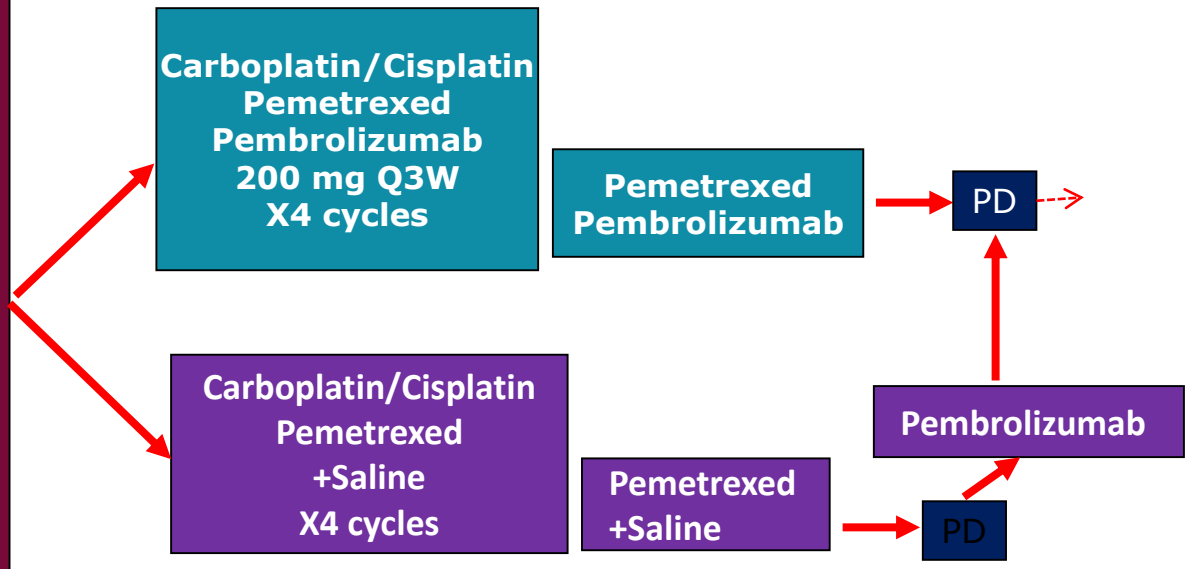
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin

RANDOMIZATION

2:1

N=570



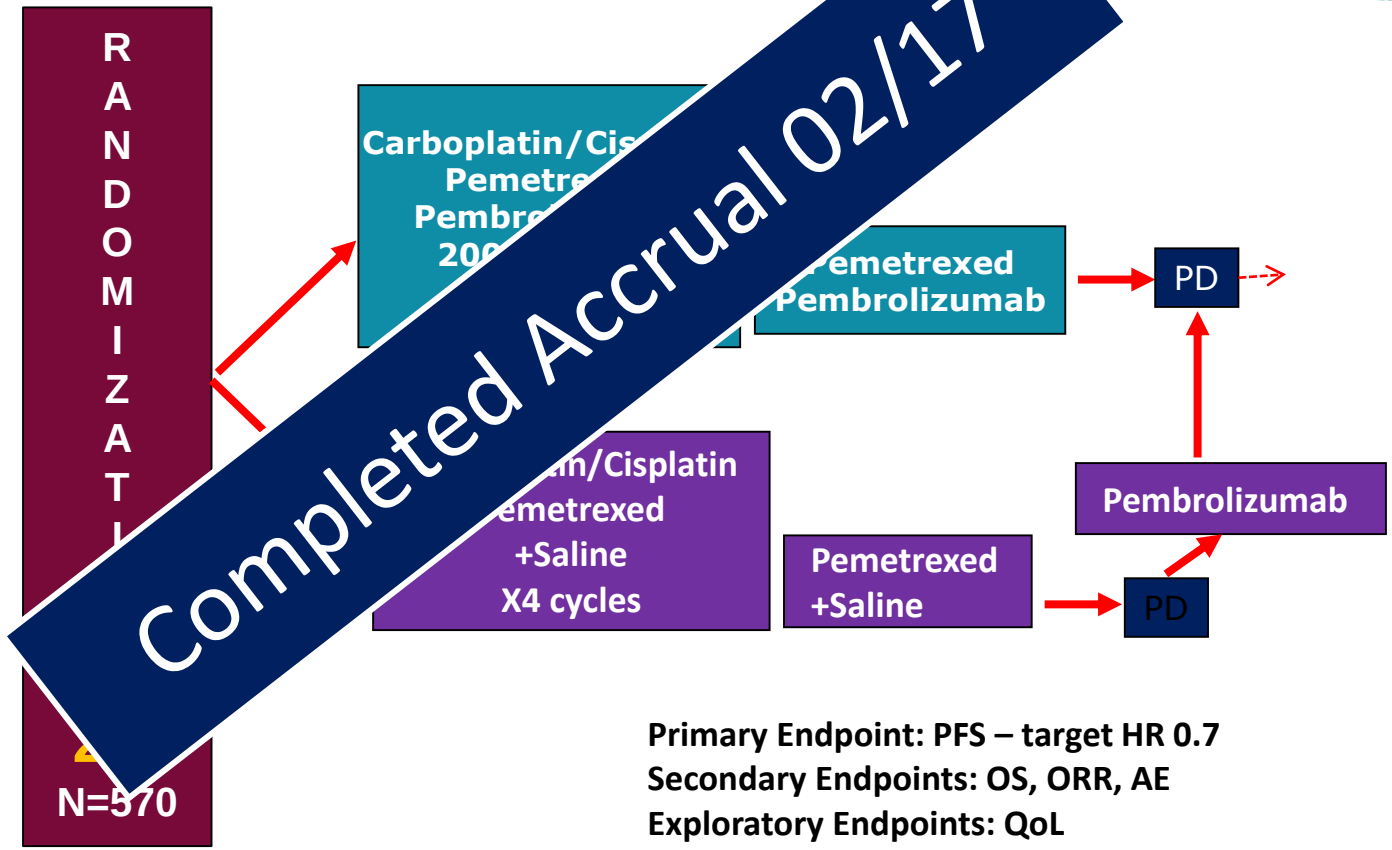
Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratify:
- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin



Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

ADVANCES IN Cancer IMMUNOTHERAPY™

Phase 3 first-line combination trials in advanced NSCLC (all PD-L1 unselected)

Treatment	N*	Arms			Primary endpoint
Checkmate 227[1]	1980	Nivolumab, ipilimumab	Nivolumab	Plt-doublet chemotherapy	OS
MYSTIC[2]	1092	Durvalumab, tremelimumab	Durvalumab	SOC Plt-based chemotherapy	PFS
NEPTUNE[3]	800	Durvalumab, tremelimumab	SOC Plt-based chemotherapy	-	OS
IMpower 130[4]	550	Atezolizumab, nab-paclitaxel/carboplatin	nab-paclitaxel/carboplatin	-	PFS
IMpower 150[5]	1200	Atezolizumab, paclitaxel/carboplatin, bevacizumab	Atezolizumab, paclitaxel/carboplatin	Paclitaxel/ carboplatin, bevacizumab	PFS
IMpower 131[6]	1200	Atezolizumab, nab-paclitaxel/carboplatin	Atezolizumab, paclitaxel/carboplatin	Nab-paclitaxel/carboplatin	PFS

*Estimated enrolment

Plt, platinum; SOC, standard of care

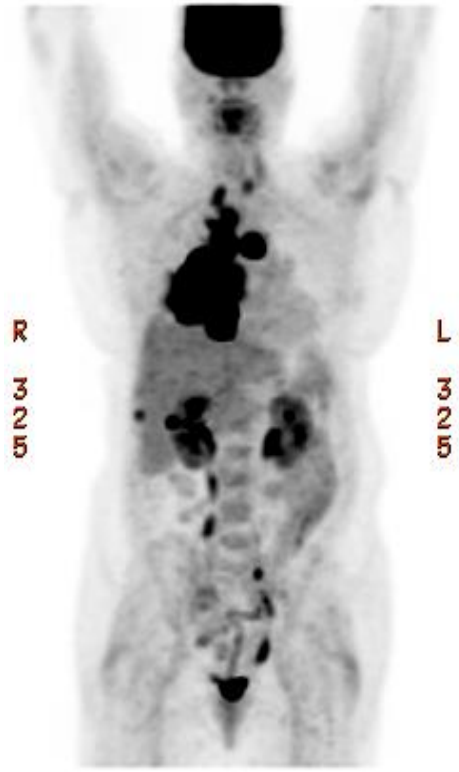
1. NCT02477826; 2. NCT02453282; 3. NCT02542293; 4. NCT02367781; 5. NCT02366143; 6. NCT02367794

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

GS

- GS 65 y.o. tobacco user (20 pack years) presented with persistent cough in 4/2017.
  - CT chest 8.8cm right paraspinal mass causing partial collapse RML, mutistation N2 LAD, right internal mammary LAD and small right pleural effusion.
  - Ultrasound-guided right paraspinal mass biopsy revealed poorly diff squamous cell CA. PD-L1 expression 60% (Dako 22C3 clone).
  - Staging PET/CT scan 5/2017 revealed FDG uptake in the right paraspinal mass, multistation N2 LAD, right internal mammary LAD, right lung nodules and bone mets (right 10th rib, left iliac and left sacrum).



ADVANCES IN Cancer IMMUNOTHERAPY™

GS

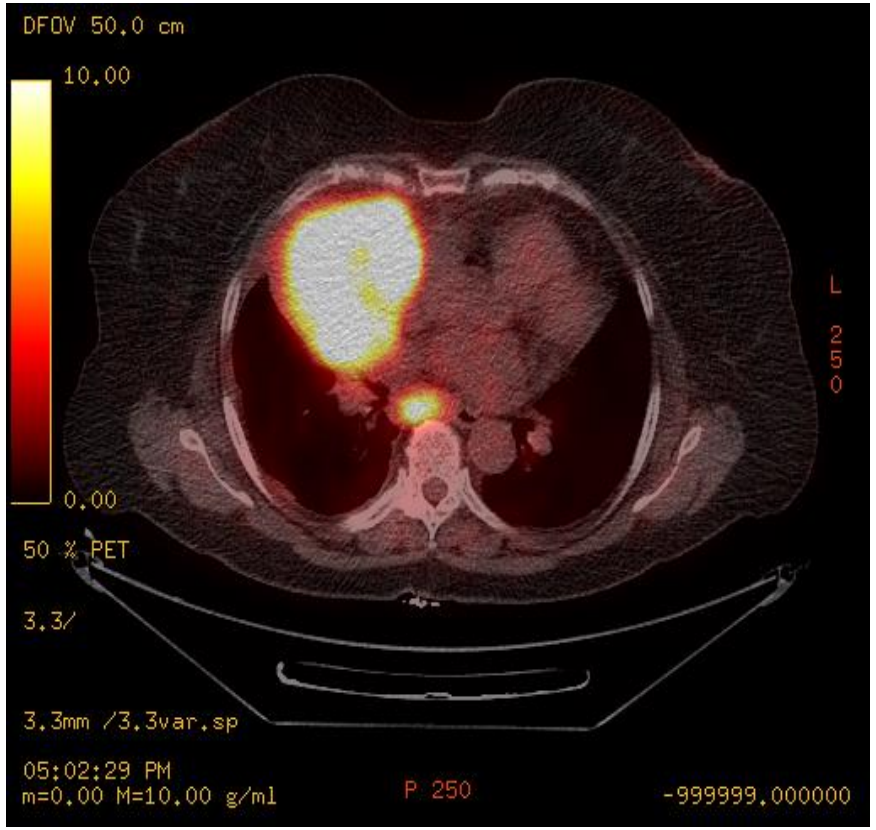
- Which treatment option do you recommend for 1st line therapy in this clinical setting?
  - Carboplatin/Paclitaxel
  - Carbopaltin/nab-Paclitaxel
  - Carboplatin/Gemcitabine
  - PD1 inhibitor

ACCC Association of Community Cancer Centers

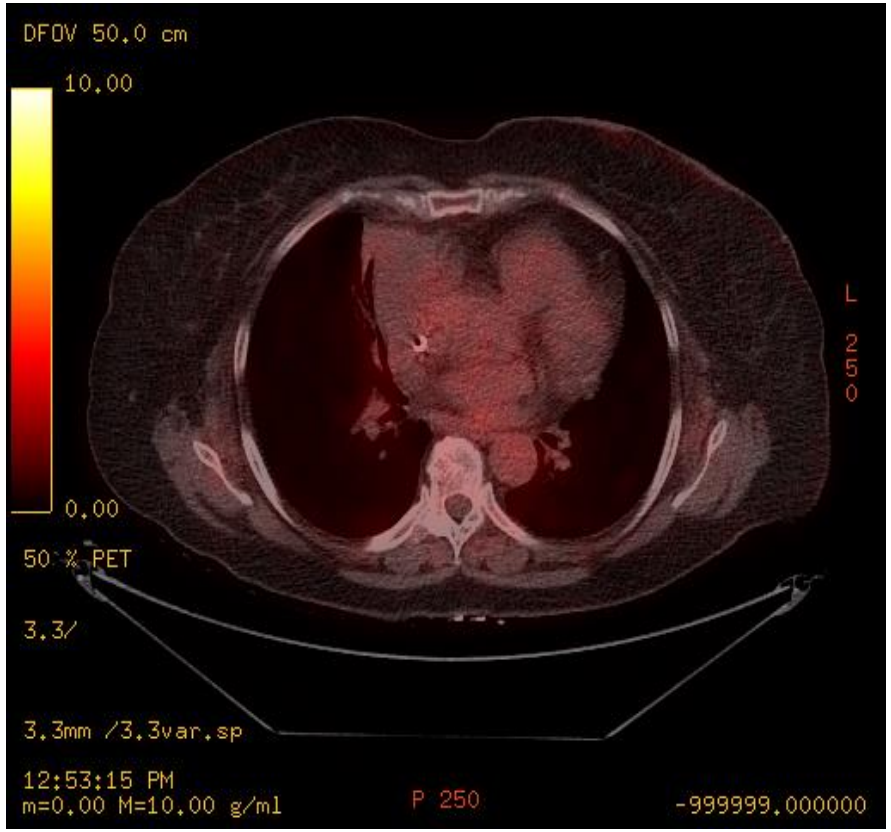
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

For 1st line treatment, GS received single agent Pembrolizumab. After 4 doses of Pembrolizumab, she had a significant response.



PET/CT scan May 2017



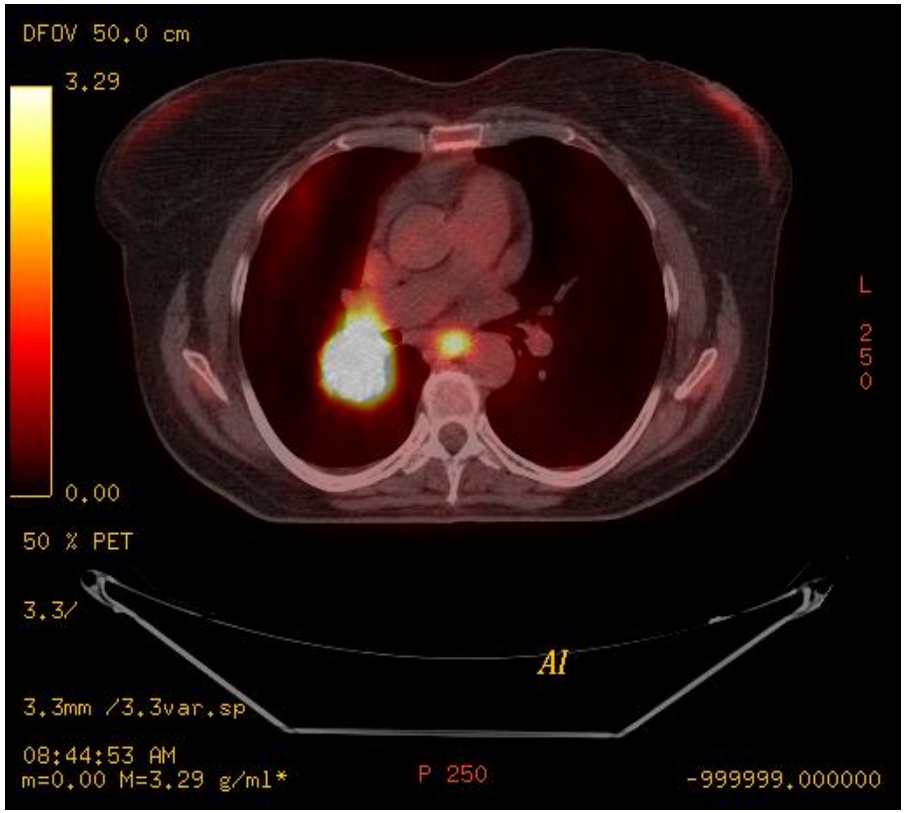
PET/CT scan August 2017

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

KY

- KY 68 y.o. tobacco user (45 pack years) presented in 5/2016 with increasing SOB.
  - CT chest revealed right hilar mass 4.4cm.
  - 6/2017 CT-guided right hilar mass biopsy revealed poorly diff squamous cell CA; insufficient tissue to determine PD-L1 and molecular studies.
  - Staging PET/CT 6/2016 revealed increased FDG uptake in left supraclavicular LAD, 5.0cm right hilar mass, multistation N2 LAD, RUL noduel 2.0cm and left adrenal mass.
  - Staging MRI brain revealed multiple CNS mets. Treated with Gammaknife in 7/2016.



ADVANCES IN Cancer IMMUNOTHERAPY™

KY

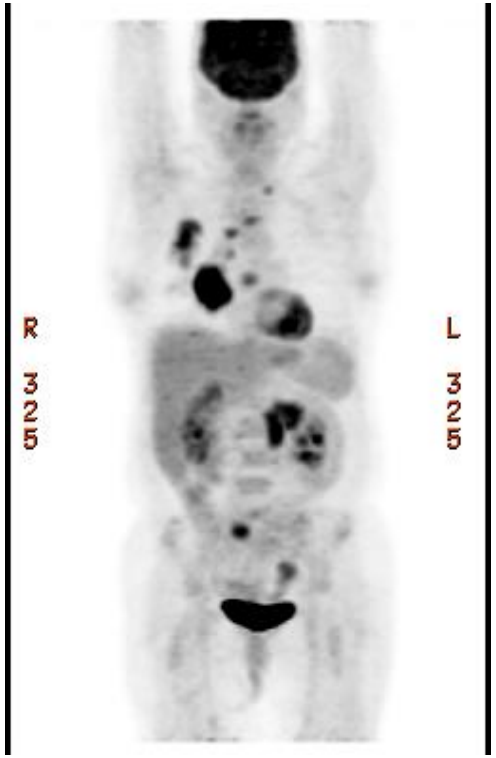
- Which treatment option do you recommend for 1st line therapy in this clinical setting?
  - Carboplatin/Paclitaxel
  - Carbopaltin/nab-Paclitaxel
  - Carboplatin/Gemcitabine
  - PD1 inhibitor

ACCC Association of Community Cancer Centers

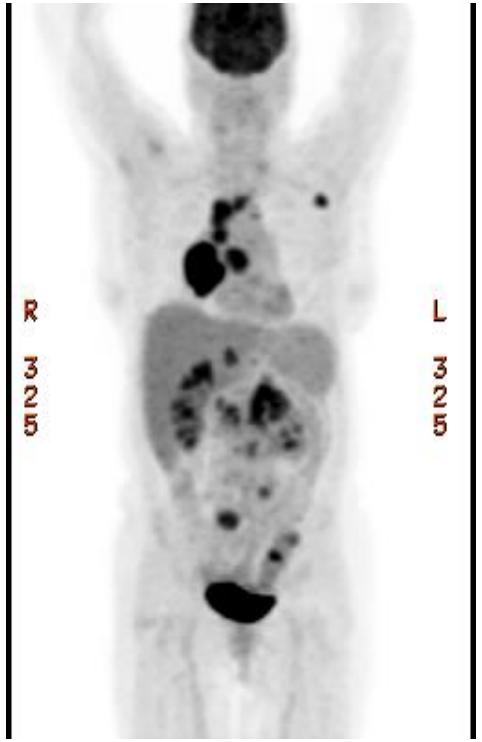
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

For 1st line treatment, KY received Carboplatin and nab-Paclitaxel completing 3 cycles. Unfortunately, her scans revealed progression with new left axillary LAD, increase in right hilar mass, mediastinal LAD, left adrenal met and abdominal LAD.



PET/CT June 2016

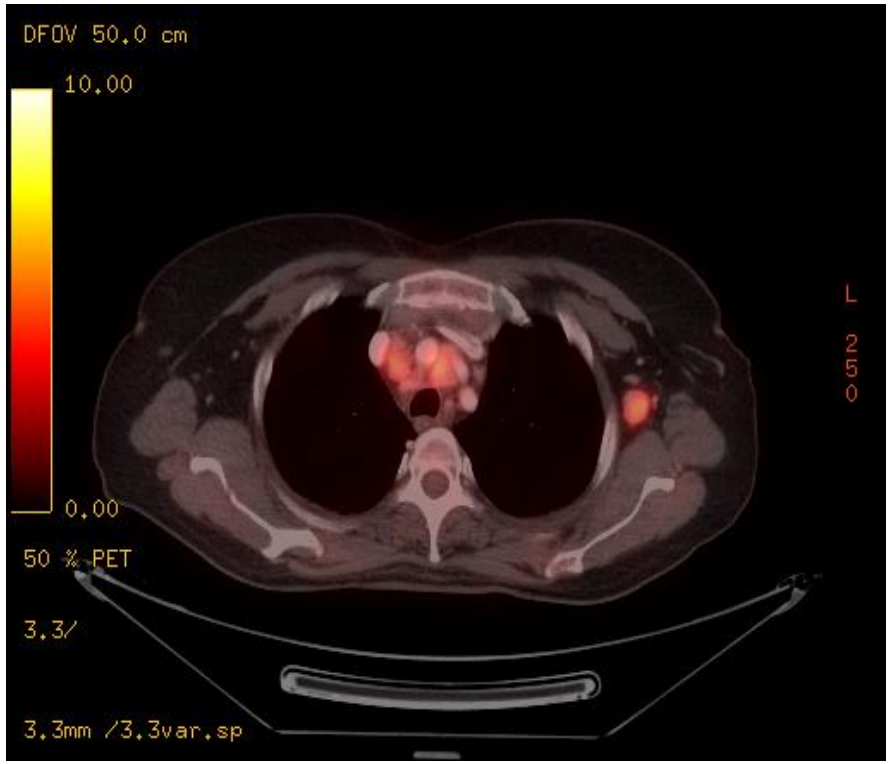


PET/CT Sept 2016

ADVANCES IN Cancer IMMUNOTHERAPY™

KY

- In October 2017, she undergoes u/s-guided left axillary LN biopsy
  - Path revealed poorly diff squamous cell CA
  - PD-L1 negative



ADVANCES IN Cancer IMMUNOTHERAPY™

KY

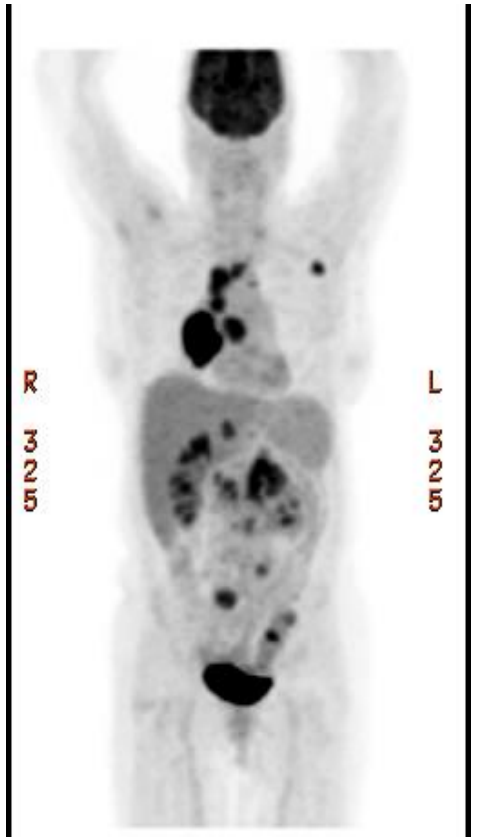
- Which treatment option do you recommend for 2nd line therapy in this clinical setting?
  - Ramucirumab plus Docetaxel
  - Gemcitabine
  - Afatinib
  - PD-1 or PD-L1 inhibitor

ACCC Association of Community Cancer Centers

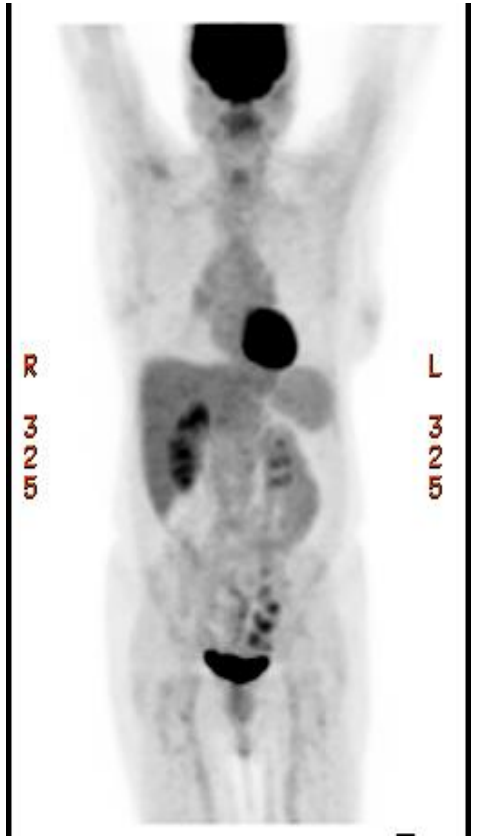
sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

KY received 6 doses of Nivolumab from 11/2016 until 1/2017.
PET/CT scan 2/2017 revealed significant treatment response.
She has now received 19 doses of Nivolumab last on 8/23/17.



PET/CT scan Sept 2016



PET/CT scan Feb 2017

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Association of Community Cancer Centers

Society for Immunotherapy of Cancer