Immunotherapy in Lung Cancer

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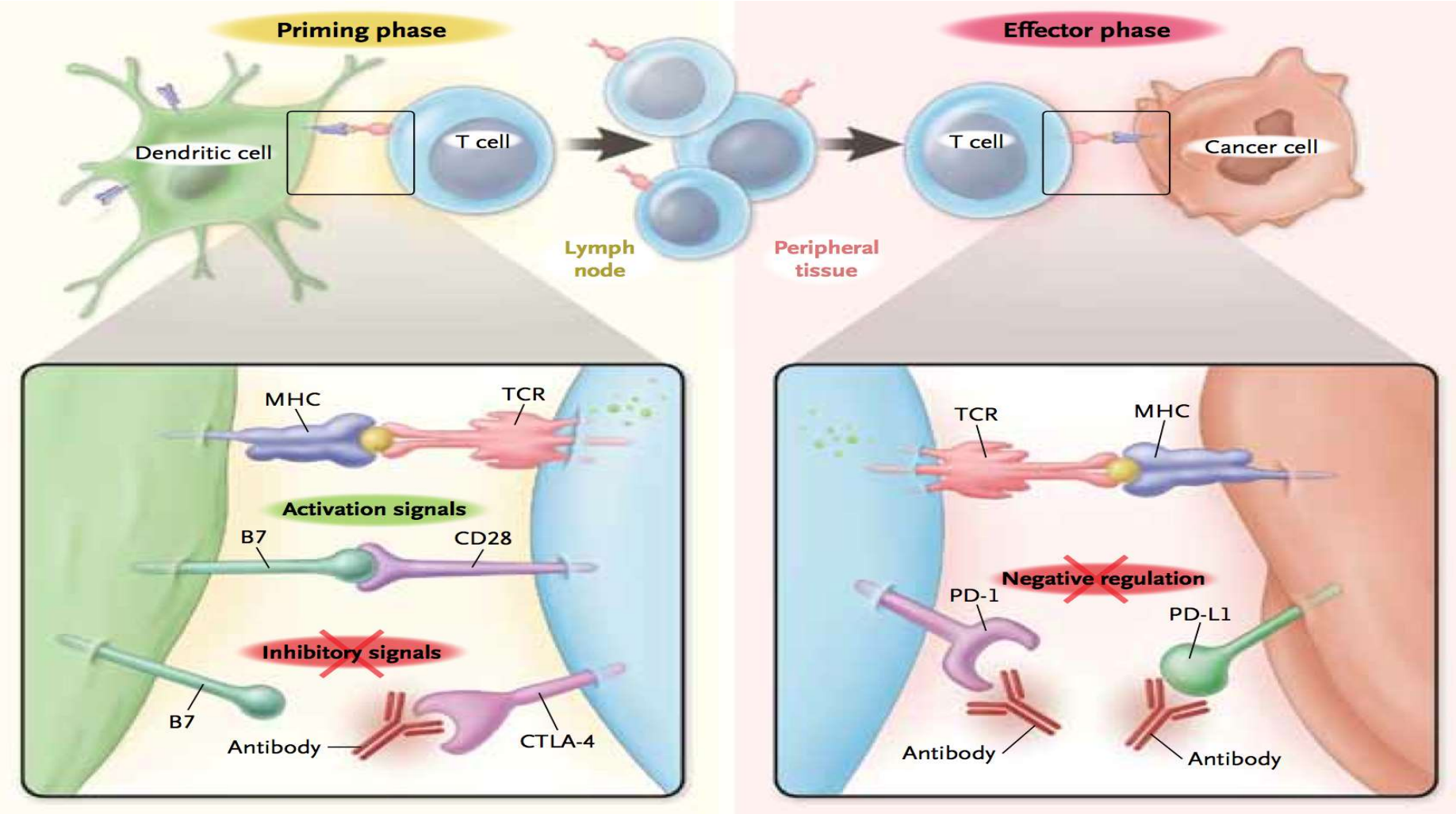
Disclosures

- Research Funding: Genentech, BMS, BI, AstraZeneca, Merck, Array

- Advisor/Consultant/Honoraria: AstraZeneca, Inivata, Takeda

Overview

- Single Agent Immunotherapy
- Immunotherapy plus Chemotherapy
- Duration of Therapy and QOL
- Stage III NSCLC
- Future Directions



Ribas, NEJM 2012

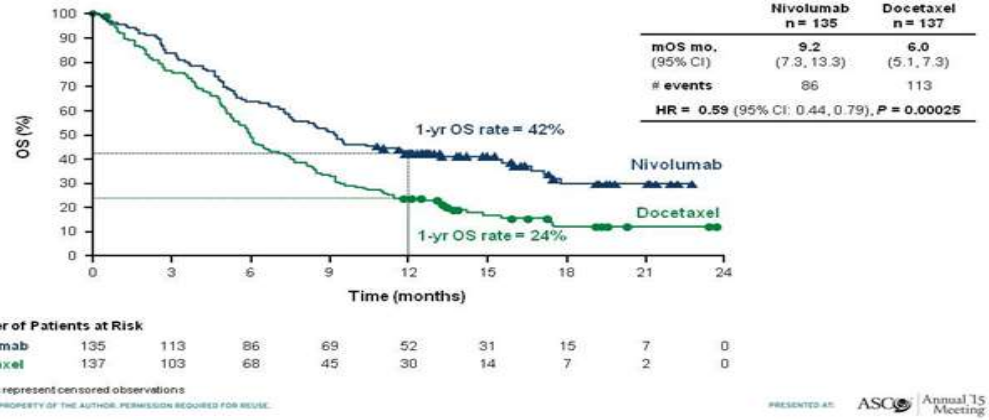
PD-1/PDL-1/CTLA-4 inhibitors

COMPANY	AGENT	TARGET
BMS	Nivolumab	PD-1
Genentech	Atezolizumab	PDL-1
Merck	Pembrolizumab	PD-1
AstraZeneca	Durvalumab	PDL-1
AstraZeneca	MEDI0680	PD-1
Pfizer	Avelumab	PD-L1
Regeneron	Cemiplimab	PD-1
Novartis	Spartalizumab	PD-1
BMS	Ipilimumab	CTLA-4
Medimmune	Tremelimumab	CTLA-4

*Not a complete list

Single Agent – Previously Treated

SQCLC: CheckMate 017
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

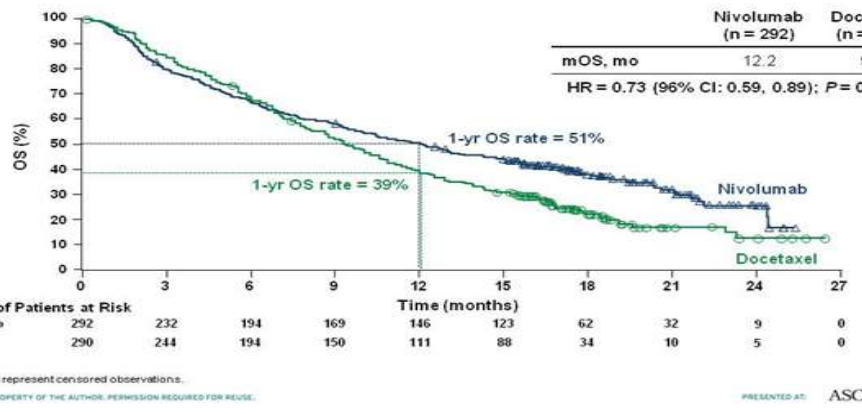
Number of Patients at Risk									
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

PRESENTED AT: ASCO Annual '15 Meeting

Presented by David Spigel, ASCO 2015. Abstract # 8009

Non-SQCLC: CheckMate 057
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

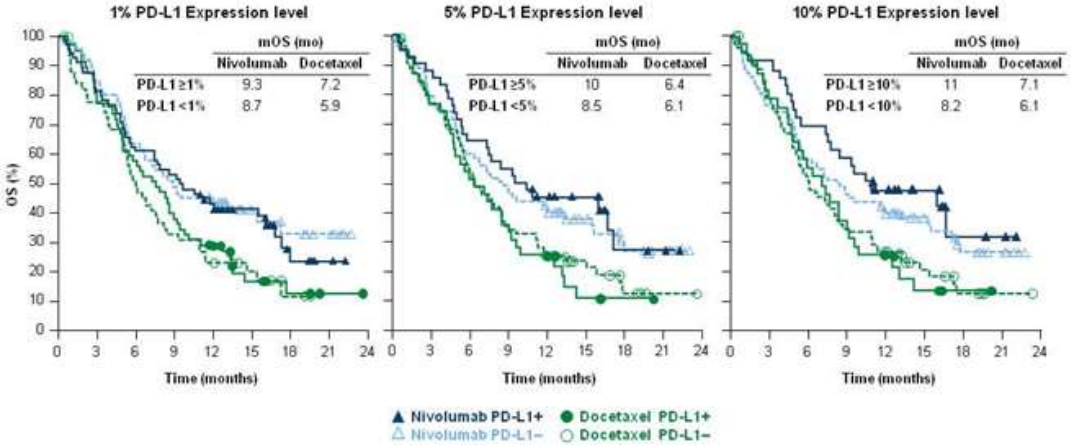
Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

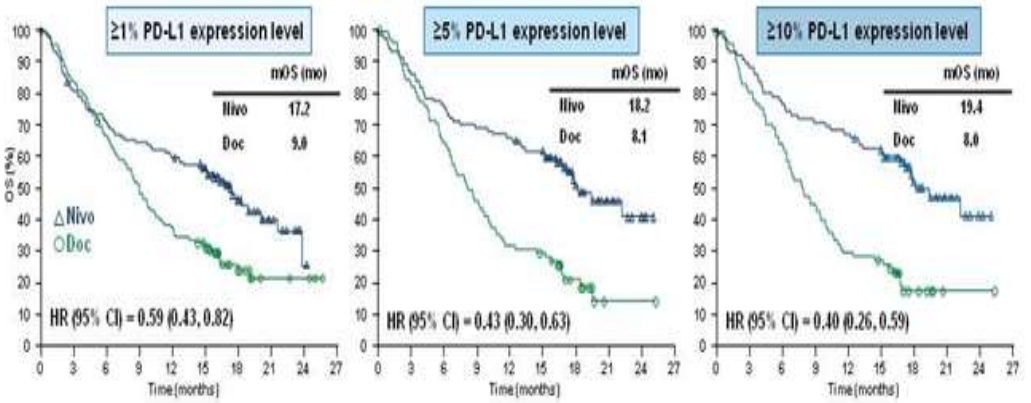
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting

SQCLC: CheckMate 017
OS by PD-L1 Expression

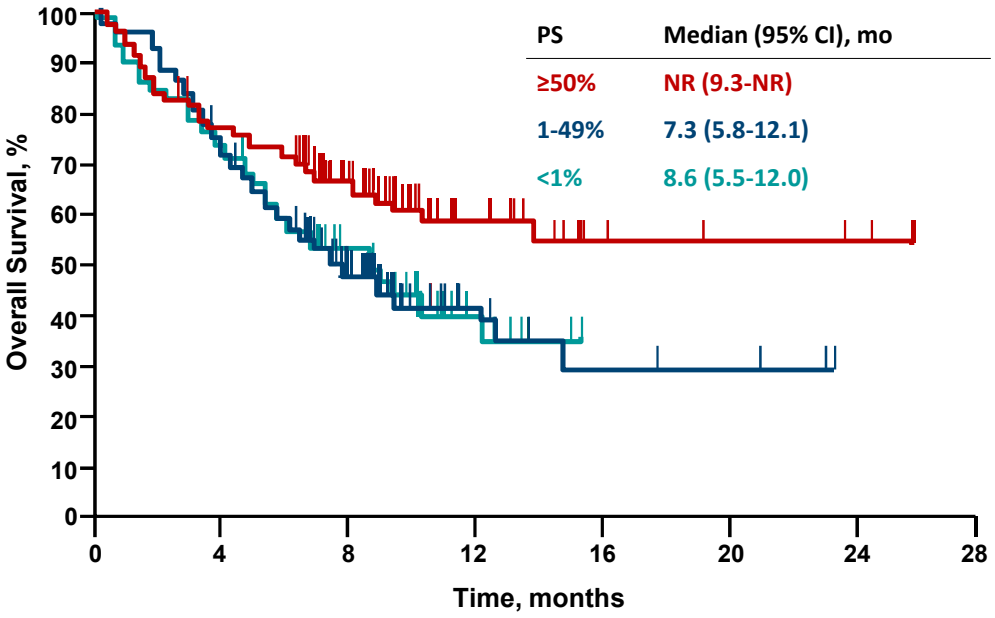


Non-SQCLC: CheckMate 057
OS by PD-L1 Expression



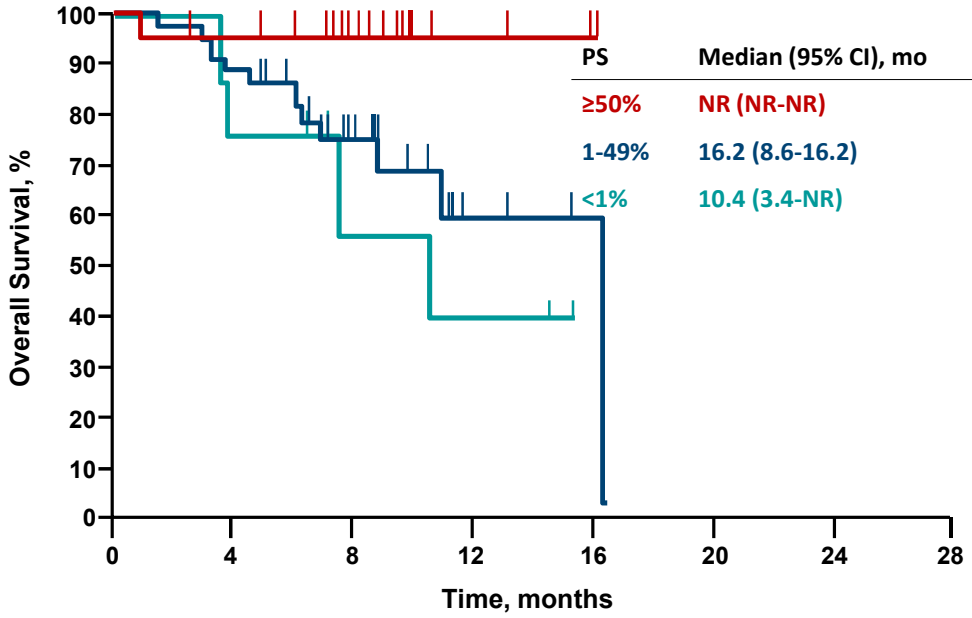
KEYNOTE 001: OS by PD-L1 Expression, Pembrolizumab: CTA-Evaluable Patients by Prior Treatment

Previously Treated



n at risk							
99	74	45	18	5	4	3	0
127	89	43	12	5	4	0	0
68	49	30	6	0	0	0	0

Treatment Naive

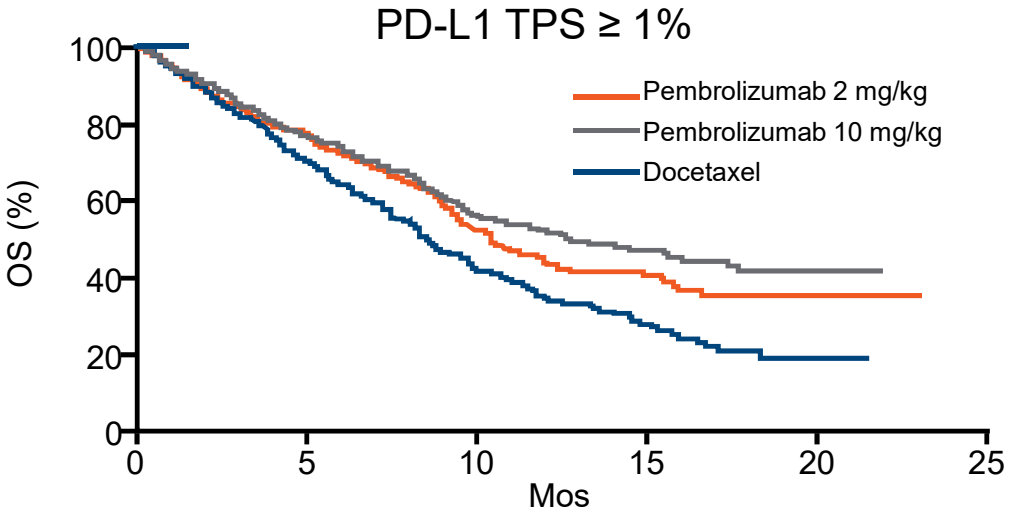


n at risk							
20	18	11	4	0	0	0	0
34	30	15	3	1	0	0	0
8	6	3	2	0	0	0	0

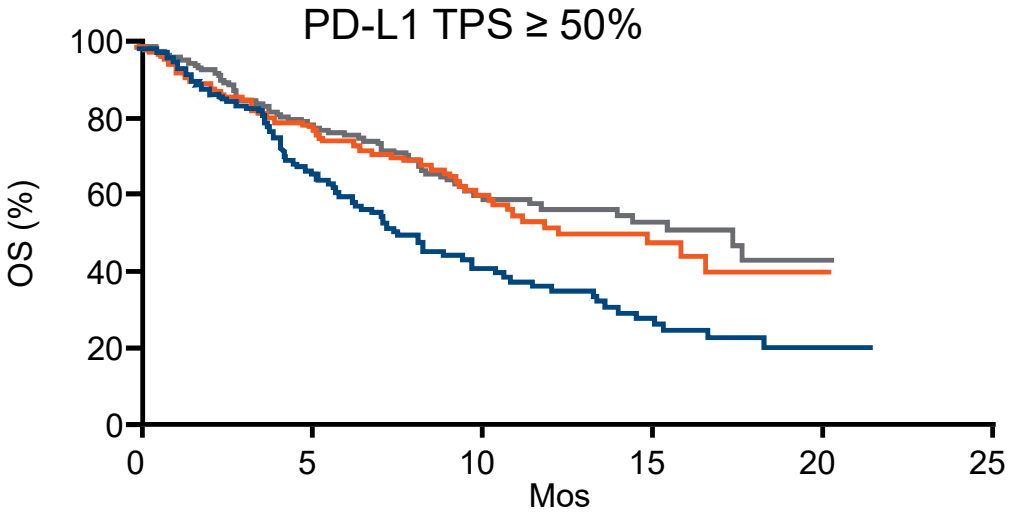
OS was assessed in all patients whose samples were stained within 6 months of cutting.
Analysis cut-off date: August 29, 2014.

Garon EB et al, AACR 2015/NEJM 2015

KEYNOTE 010: Pembrolizumab Randomized Trial Versus Docetaxel in second line



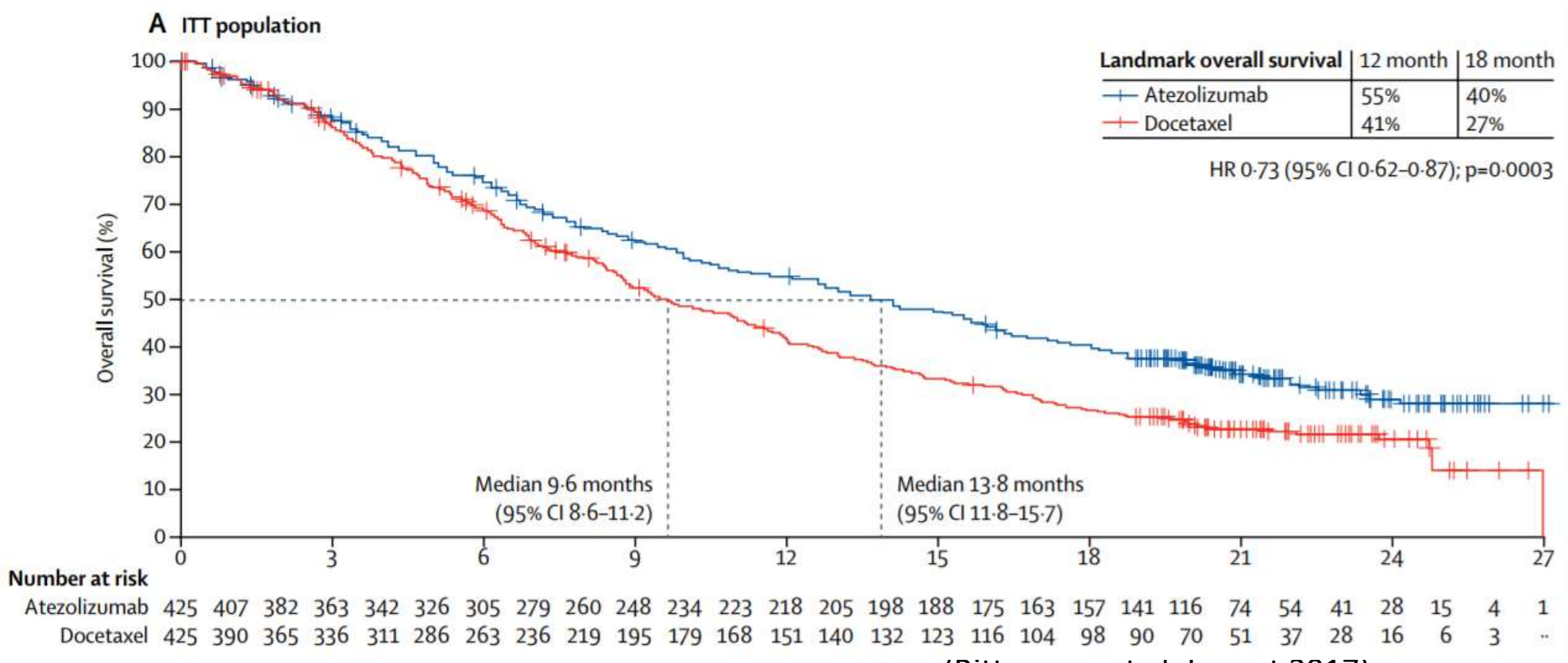
Treatment Arm	Median OS, Mos (95% CI)	1-Yr OS, %	HR vs Docetaxel (95% CI); *P* Value
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2	0.71 (0.58-0.88); .0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3	0.61 (0.49-0.75); < .0001
Docetaxel	8.5 (7.5-9.8)	34.6	–



Treatment Arm	Median OS, Mos (95% CI)	HR vs Docetaxel (95% CI); *P* Value
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77); .0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70); < .0001
Docetaxel	8.2 (6.4-10.7)	–

Herbst RS, et al. Lancet. 2016;387:1540-1550.

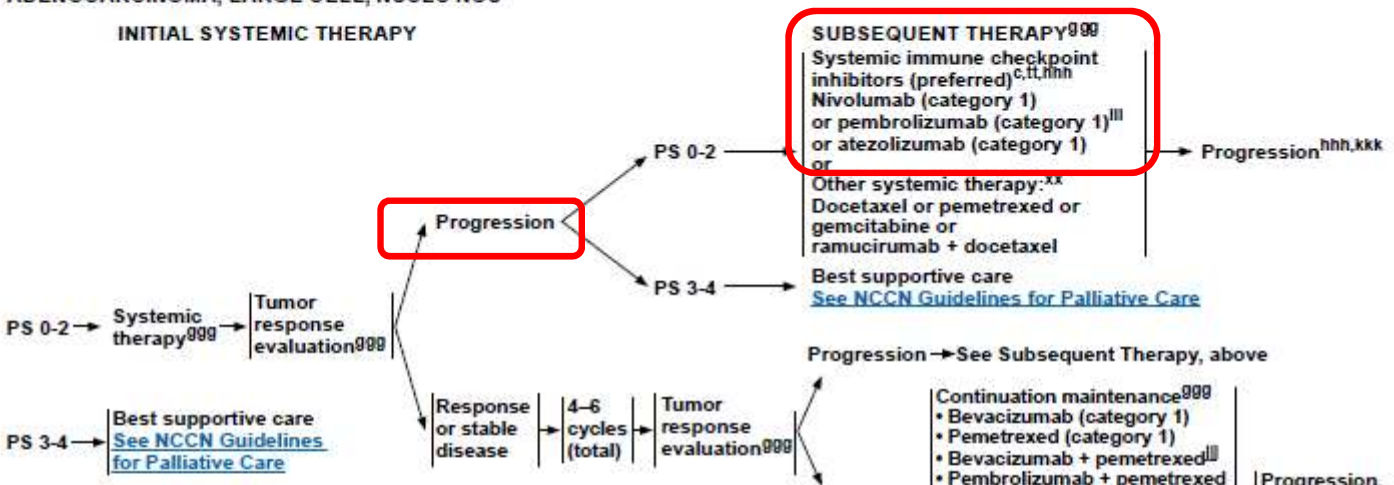
OAK trial: PHASE III, atezolizumab vs. docetaxel for ≥2nd line therapy for *mNSCLC*



(Rittmeyer, et al; Lancet 2017)

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

INITIAL SYSTEMIC THERAPY



[c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 2010;363:733-742.

[tt]The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR+/ALK+* NSCLC.

[xx]If not previously given.

[ccc]If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.

[ddd]If atezolizumab/carboplatin/paclitaxel/bevacizumab given.

[ggg]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-J).

[hhh]If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.

[lll]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

[lll]If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

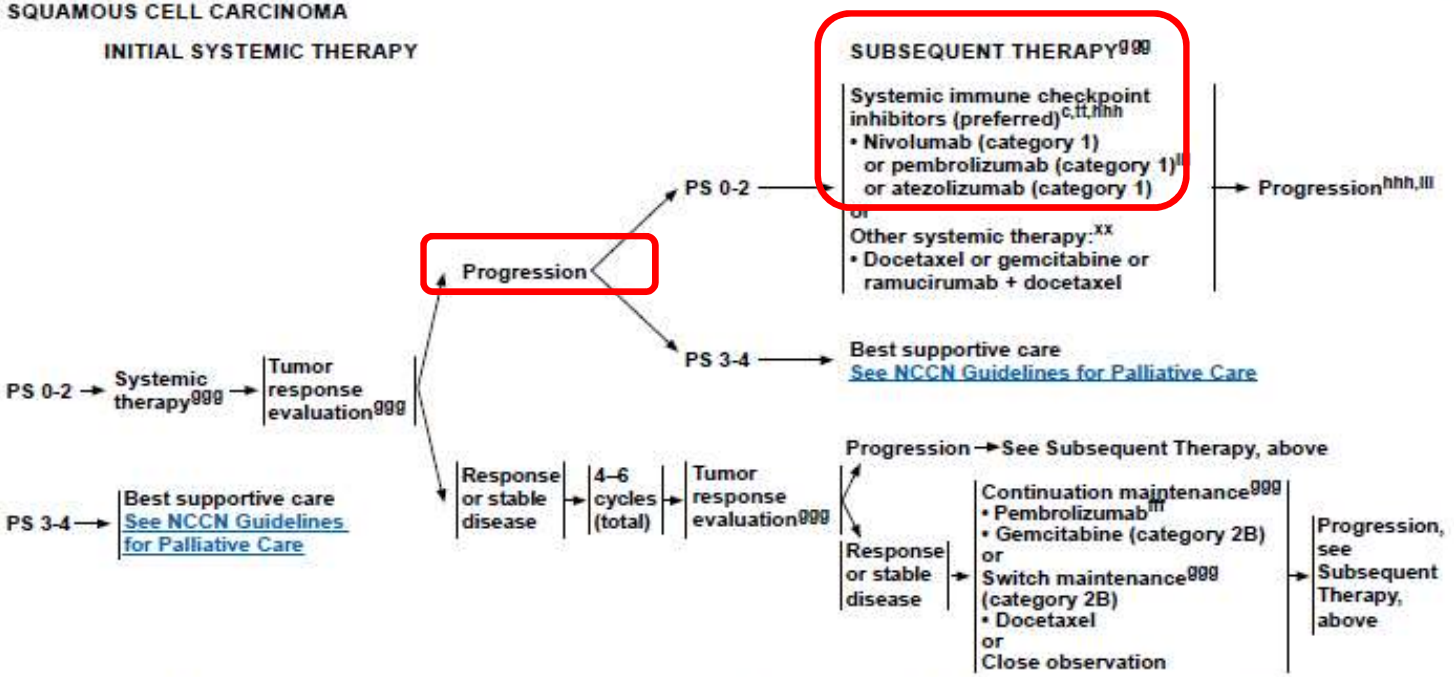
[kkk]If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

SQUAMOUS CELL CARCINOMA

INITIAL SYSTEMATIC THERAPY



[c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 2010;363:733-742.

[tt]The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR*+/*ALK*+ NSCLC.

[xx]If not previously given.

[ff]If pembrolizumab/(cisplatin or carboplatin)/(paclitaxel or albumin-bound paclitaxel) given.

[ggg]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-J).

[hhh]If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.

[ii]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

[iii]If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
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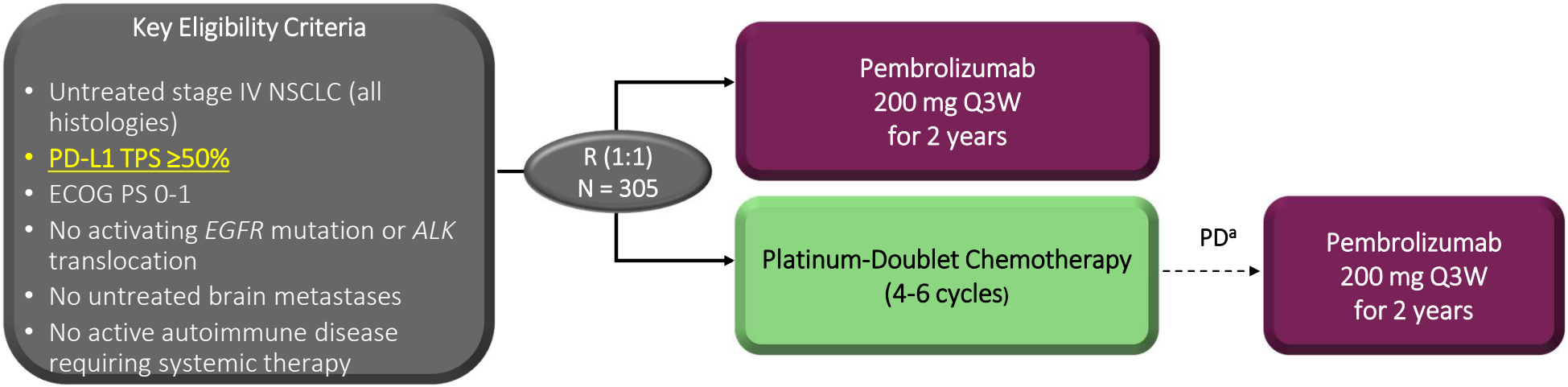
Single Agent - First Line Metastatic

KEYNOTE-024 Study Design

NCT02142738



Key End Points

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

Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met

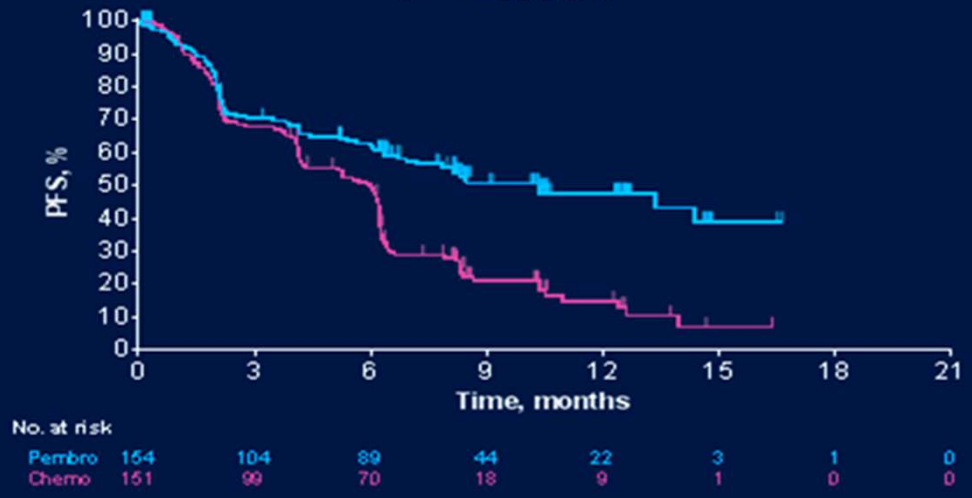
Reck M et al. *N Engl J Med.* 2016;375:1823-1833.

KEYNOTE-024: Primary Analysis

Median Follow-up 11.2 Months

Progression-Free Survival[a]

HR 0.50 (95% CI 0.37-0.68)
***P* < 0.001**

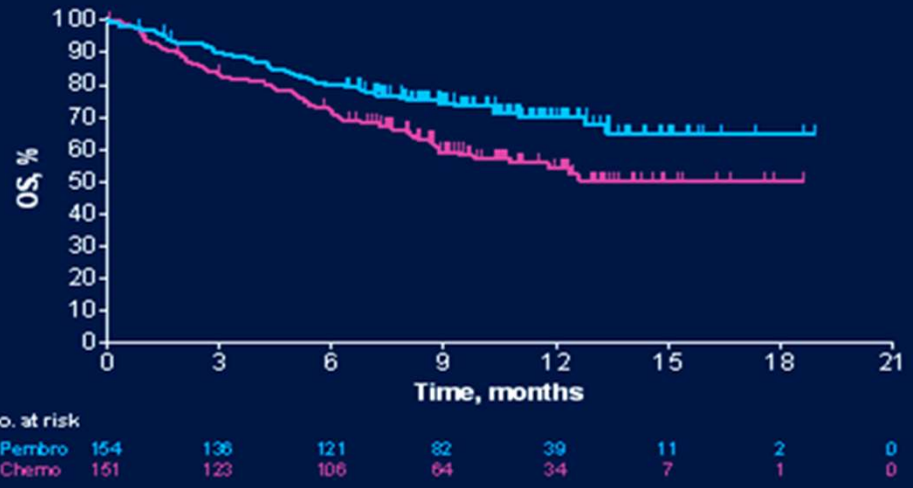


No. at risk

Pembro	154	104	89	44	22	3	1	0
Chemo	151	99	70	18	9	1	0	0

Overall Survival

HR 0.60 (95% CI 0.41-0.89)
***P* = 0.005**



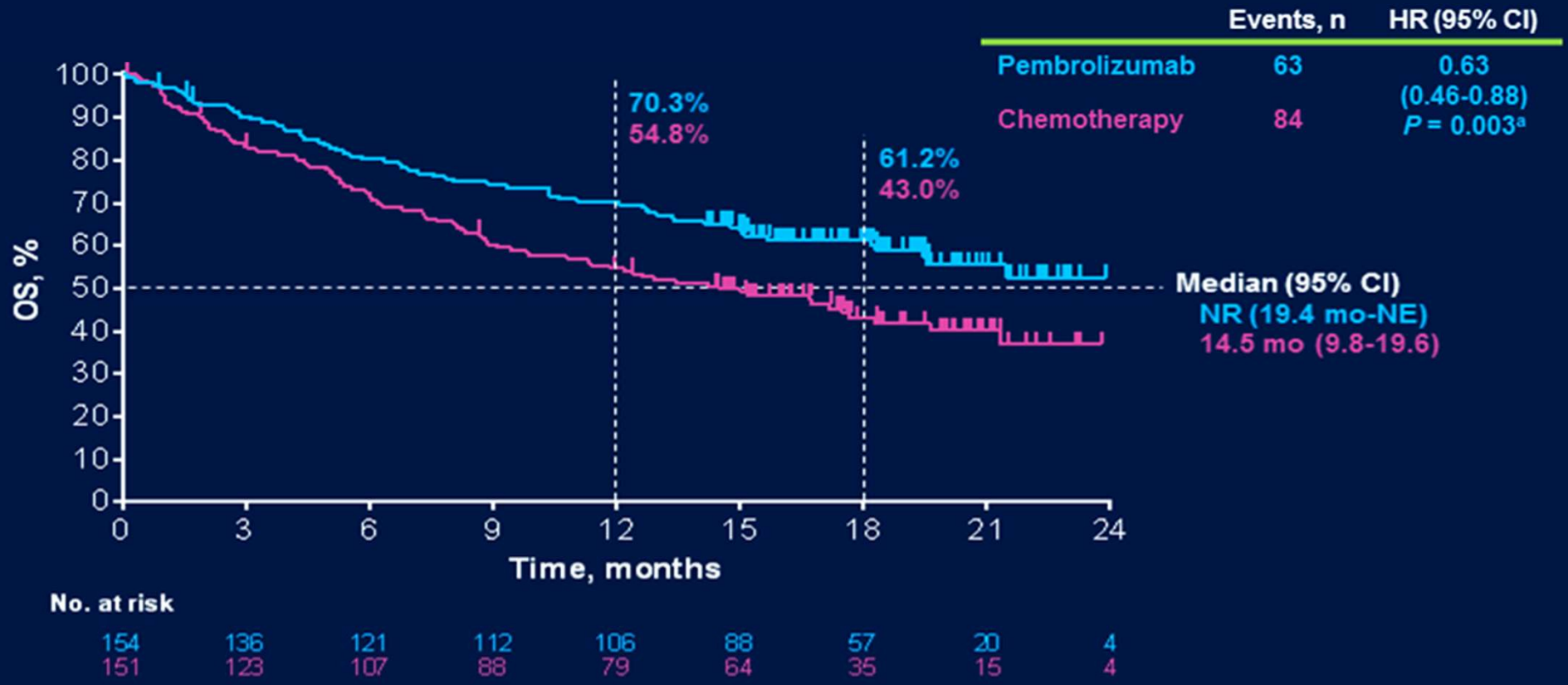
No. at risk

Pembro	154	136	121	82	39	11	2	0
Chemo	151	123	106	64	34	7	1	0

Brahmer J. Presented at: ASCO 2017.

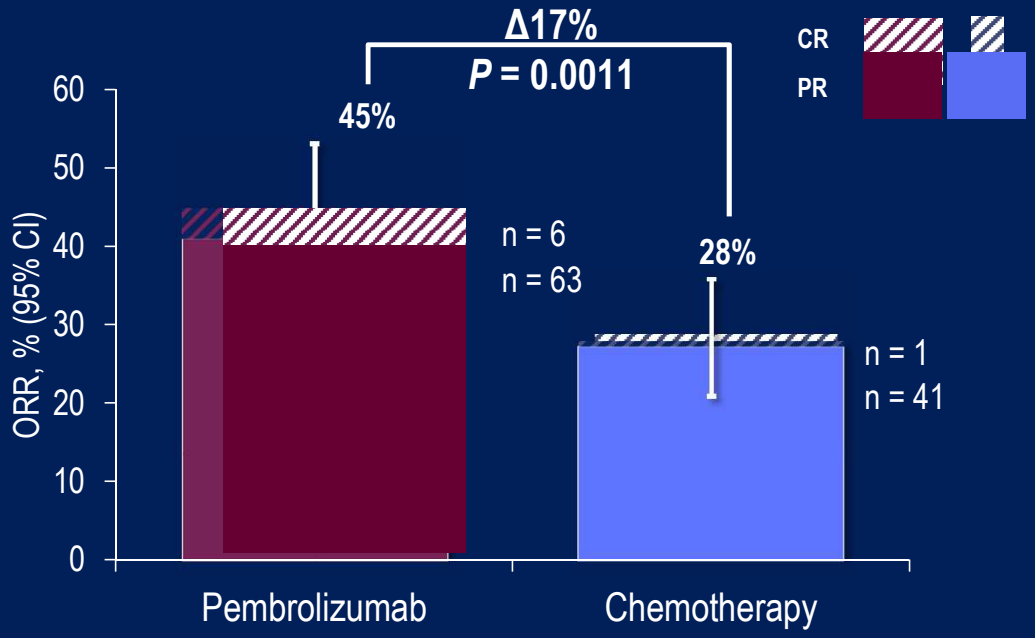
Kaplan-Meier Estimate of OS

Updated Analysis



Brahmer J. Presented at: ASCO 2017.

Confirmed Objective Response Rate

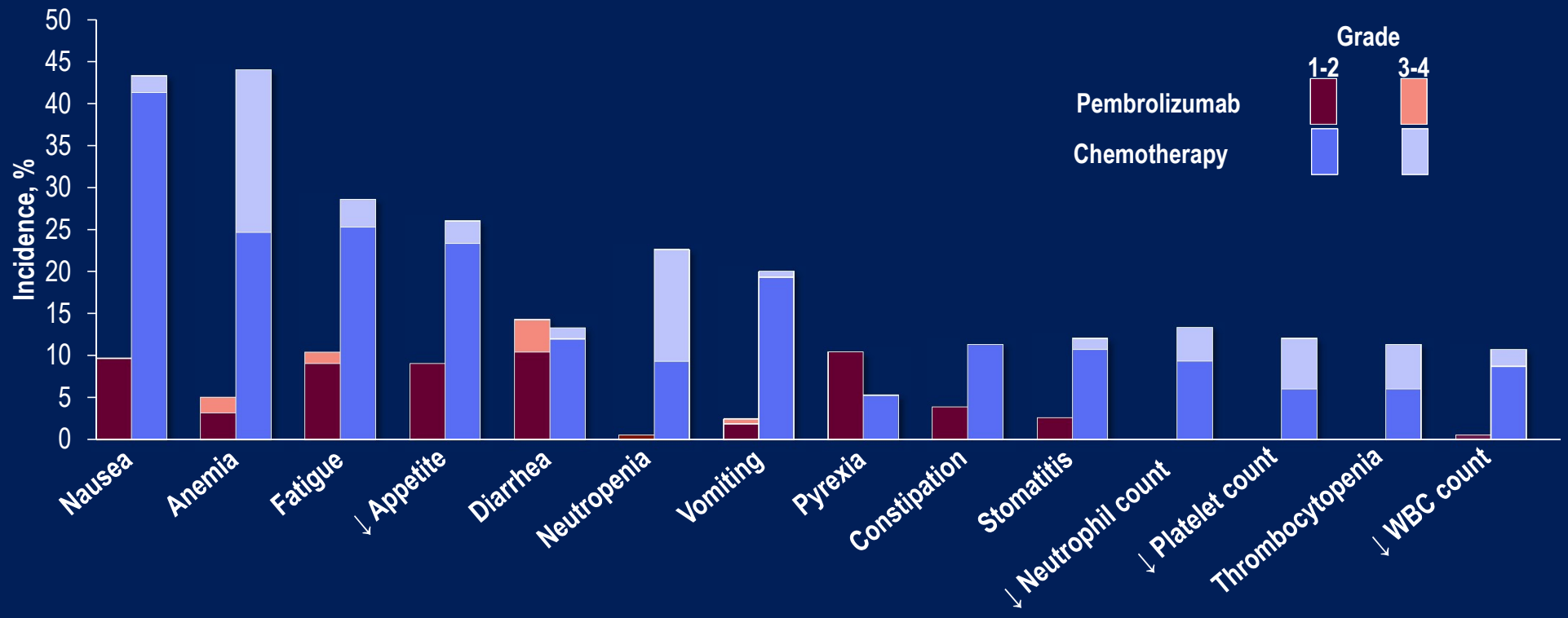


	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.

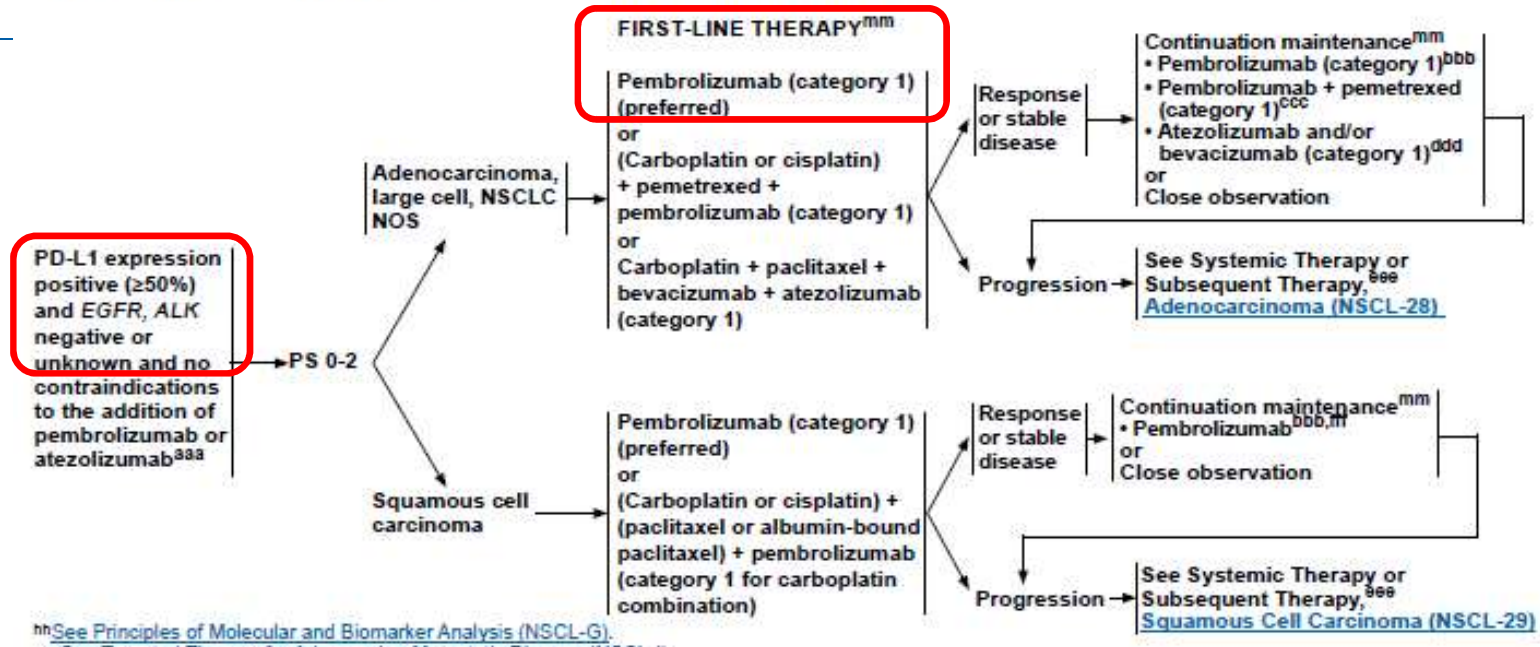
Data cut-off: May 9, 2016.

Treatment-Related AEs With Incidence >10%



Data cut-off: May 9, 2016.

PD-L1 EXPRESSION POSITIVE (≥50%)[hh]

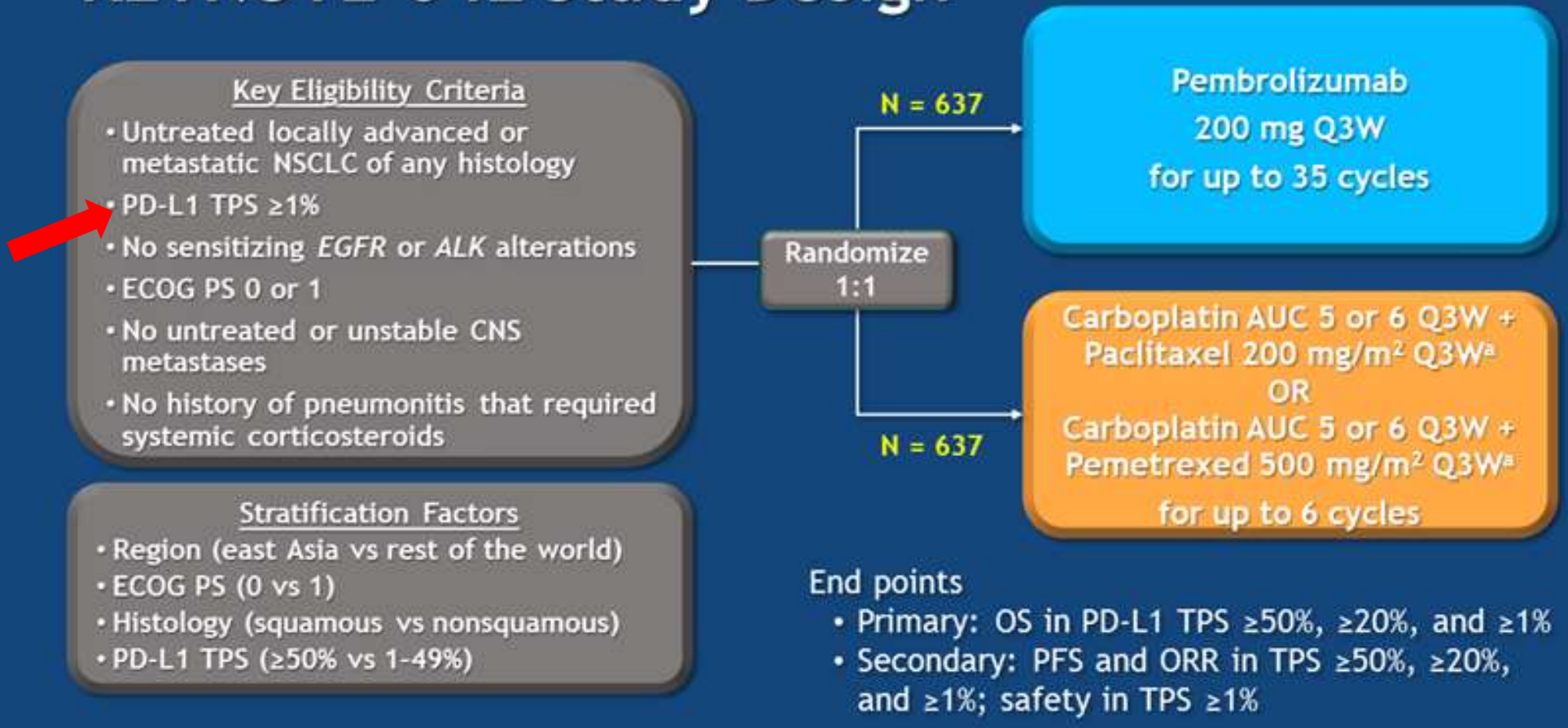


[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[aaa]Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-28 (adenocarcinoma) or NSCL-29 (squamous cell carcinoma).
[bbb]If pembrolizumab monotherapy given.
[ccc]If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[ddd]If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[eee]If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."
[fff]If pembrolizumab/(cisplatin or carboplatin)/(paclitaxel or albumin-bound paclitaxel) given.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Lopes KN042 ASCO 2018

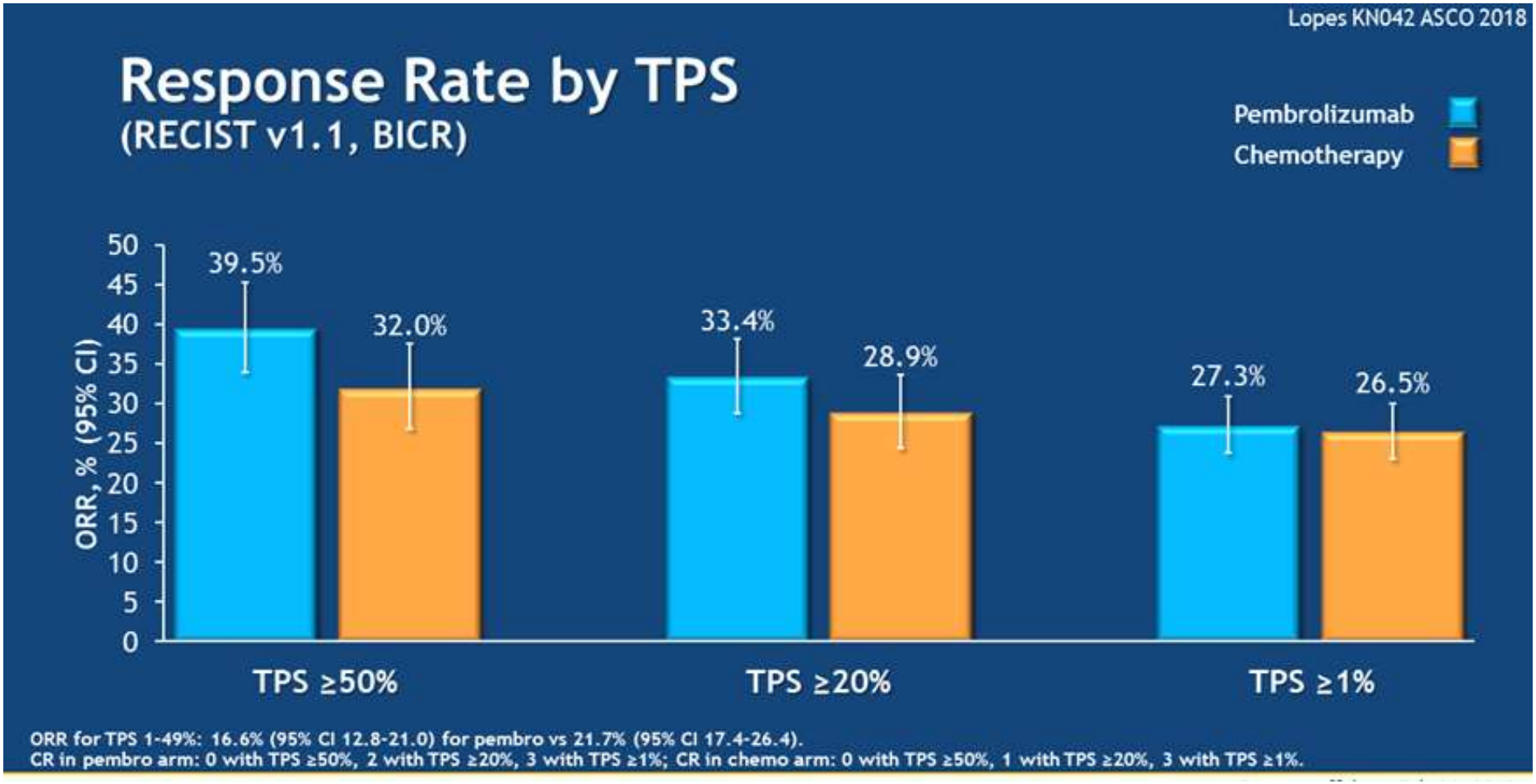
KEYNOTE-042 Study Design



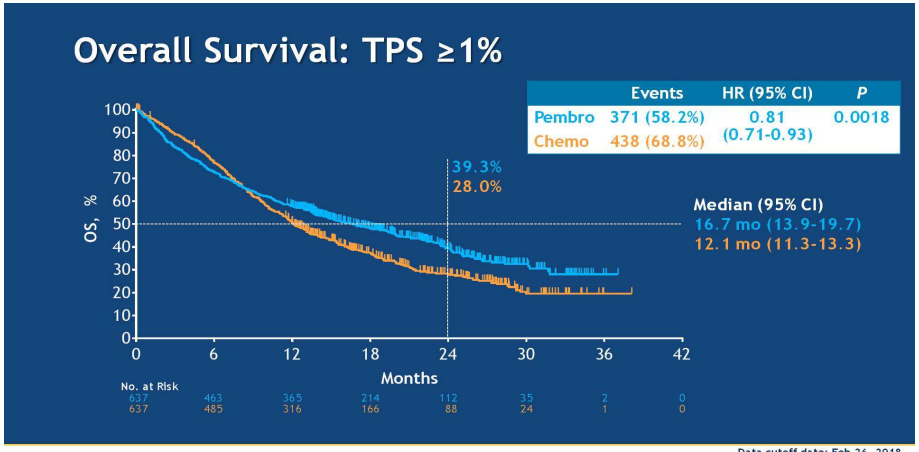
End points
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

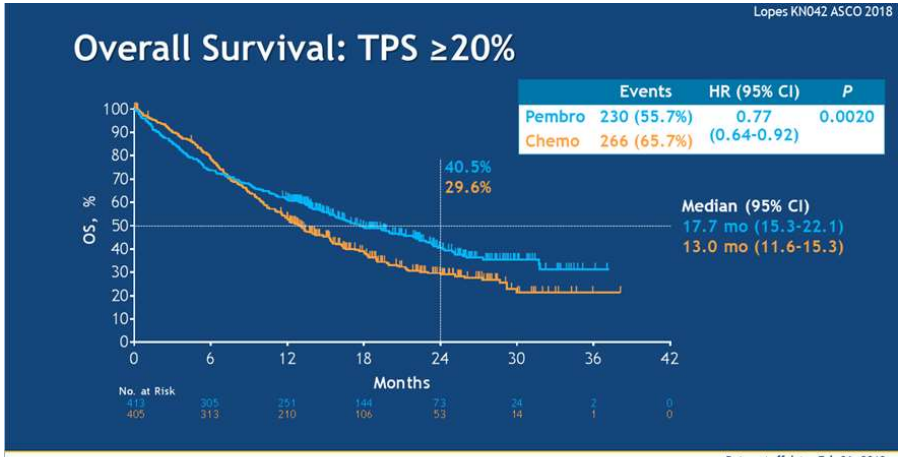
[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

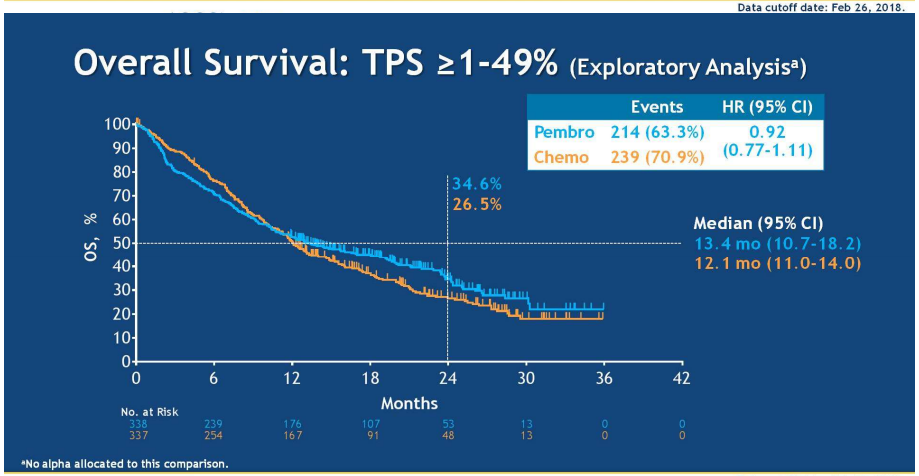
KEYNOTE 042: RESPONSE RATE

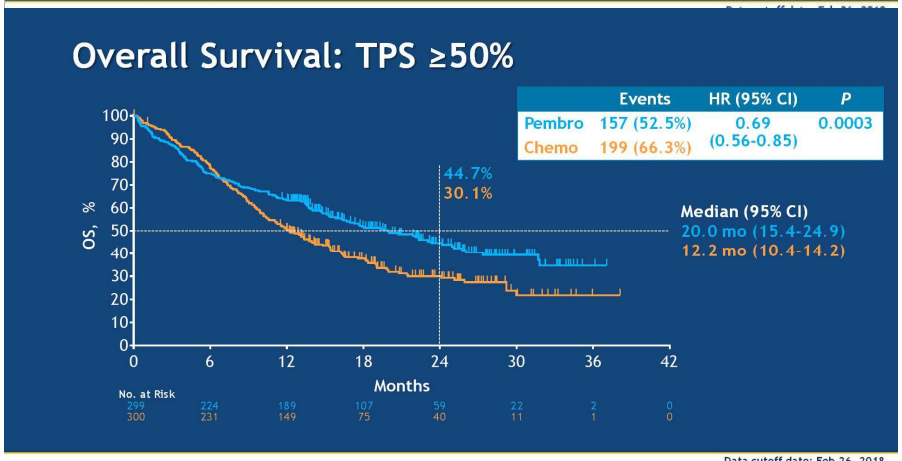


KEYNOTE 042: *Phase III: PEMBRO VS INVESTIGATORS CHOICE PLATINUM BASED THERAPY FOR TREATMENT NAÏVE NSCLC WITH PD-L1 ≥ 1%*



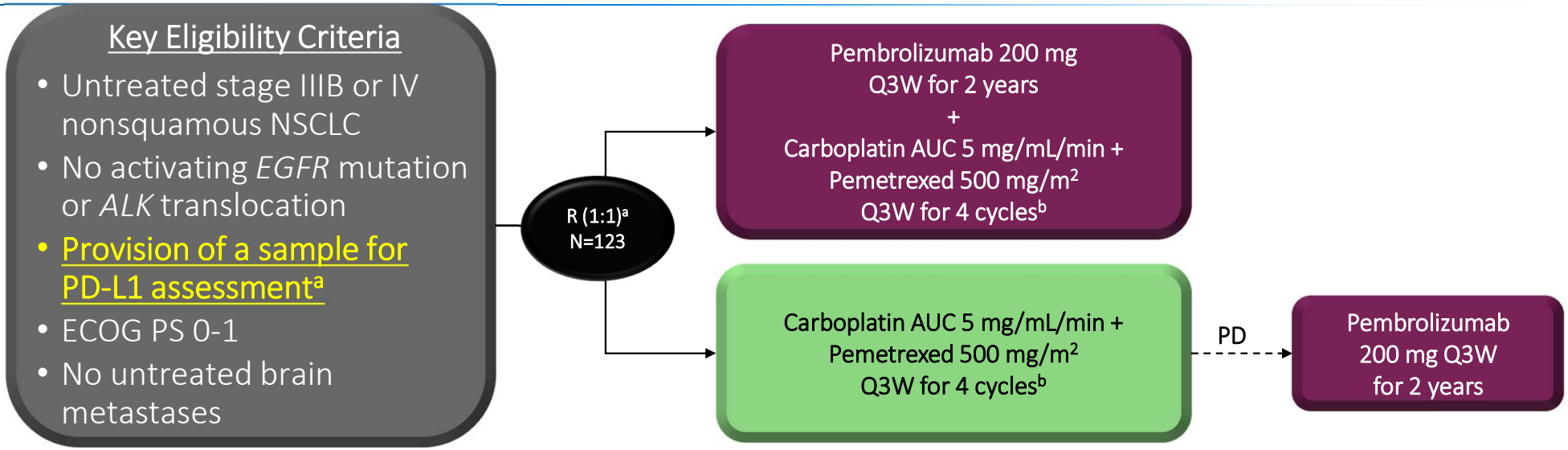






Immunotherapy with Chemotherapy: First Line

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

PD=progressive disease.

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

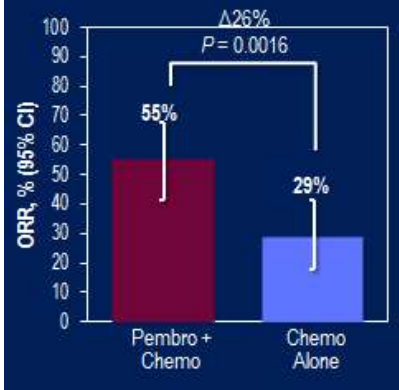
[b]Indefinite maintenance therapy with pemetrexed 500 mg/m^2 Q3W permitted.

Langer CJ et al. *Lancet Oncol.* 2016;17:1497-1508.

KEYNOTE-21G RESULTS

Confirmed Objective Response Rate

RECIST v1.1 by Blinded, Independent Central Review



	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.

Data cut-off: August 8, 2016.

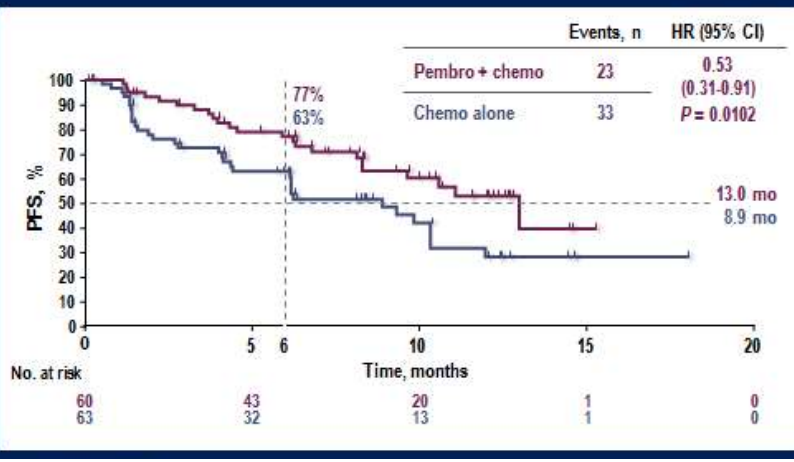
FDA Approves Pembrolizumab as First-Line Combination Therapy With Pemetrexed and Carboplatin for Metastatic Nonsquamous NSCLC

By The ASCO Post

Posted: 5/11/2017 11:00:52 AM

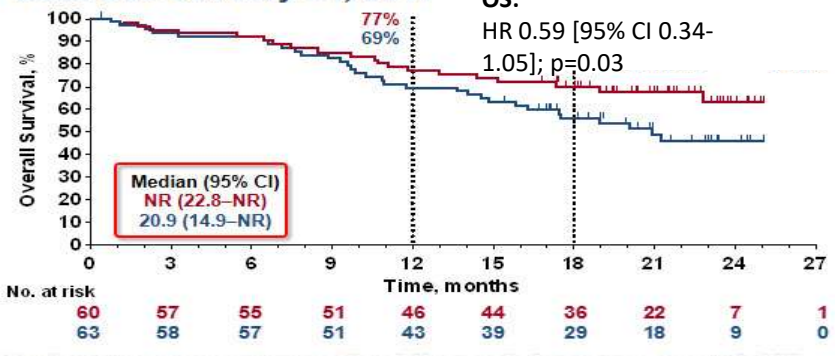
Progression-Free Survival

RECIST v1.1 by Blinded, Independent Central Review



Overall Survival

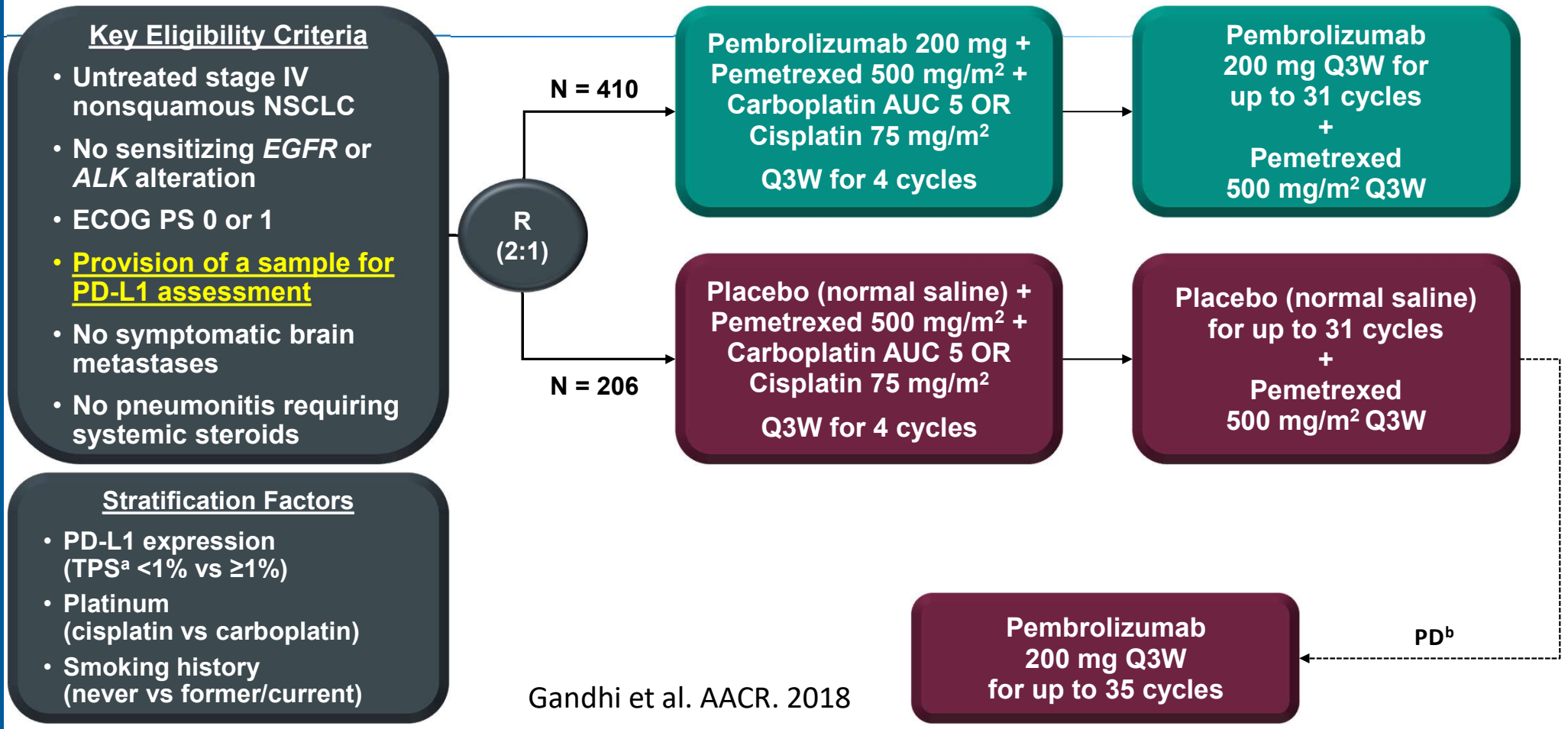
Data Cut-Off: May 31, 2017



OS:
HR 0.59 [95% CI 0.34-1.05]; p=0.03

Updated data from WCLC 2017
Langer & Borghaei

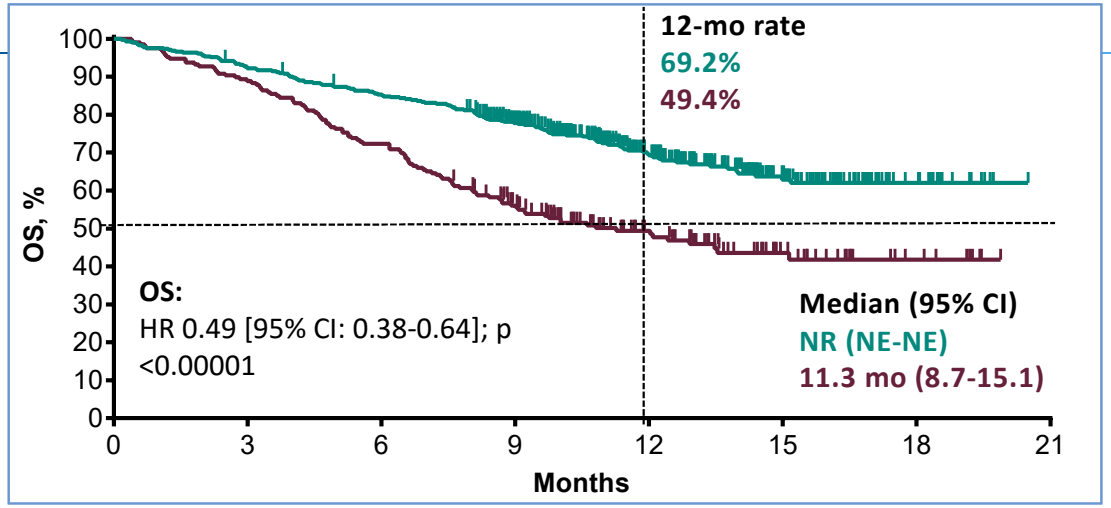
KEYNOTE-189 Study Design (NCT02578680)

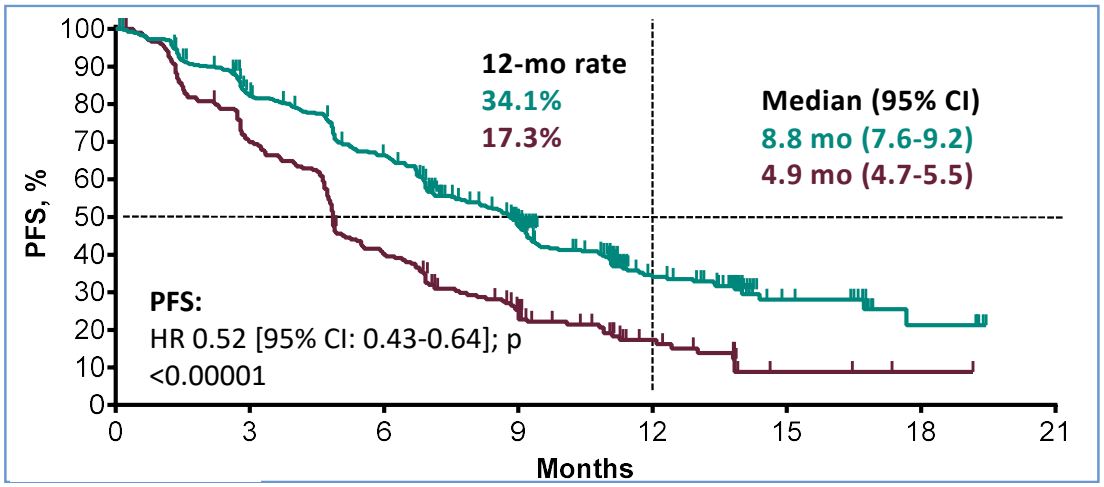


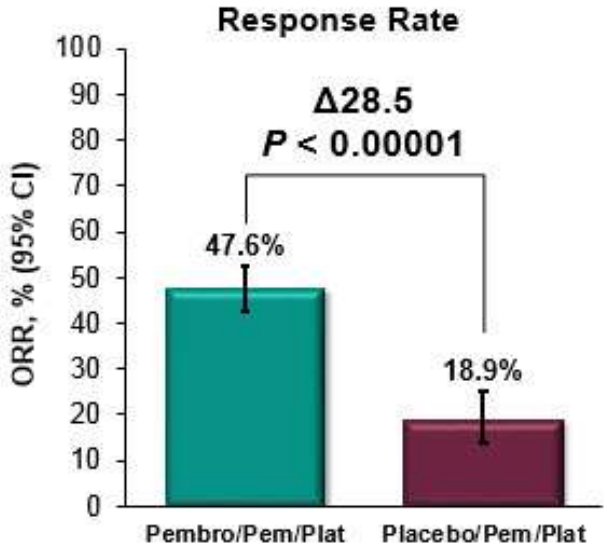
Gandhi et al. AACR. 2018

[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.

Keynote 189: Met All Primary Endpoints





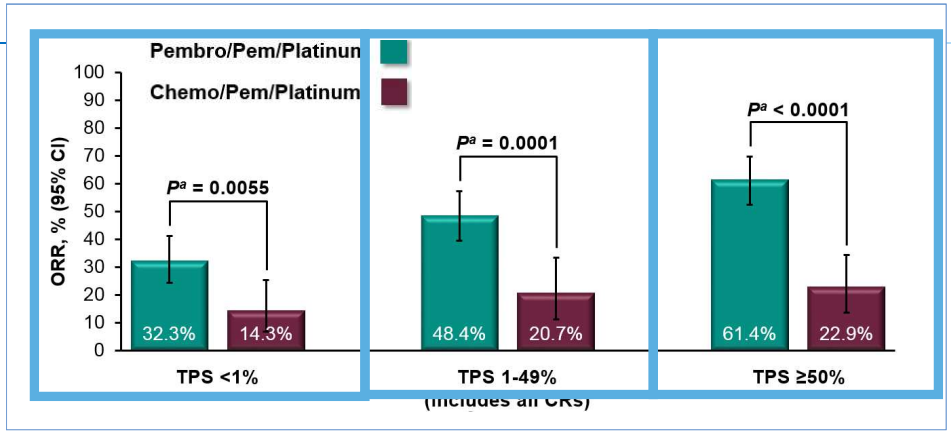


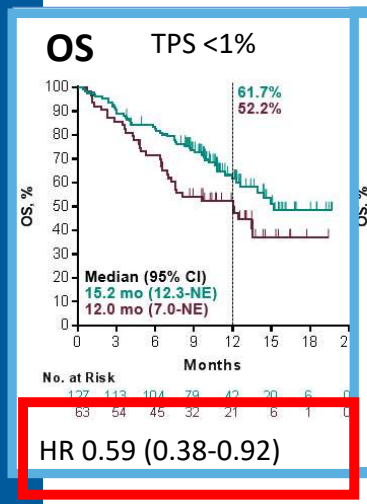
Subgroup Analyses

OS: Positive across all subgroups

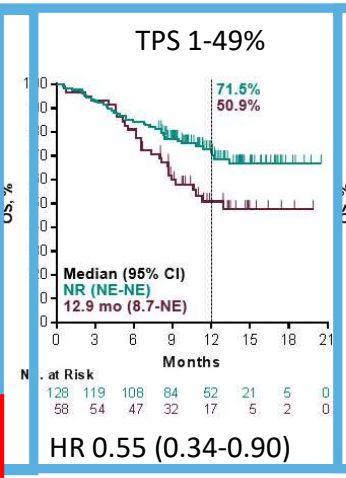
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Keynote 189: Results by PD-L1 status (Exploratory)

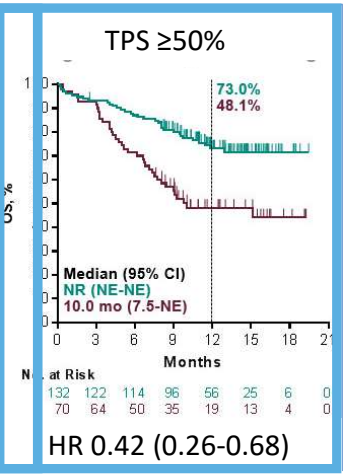




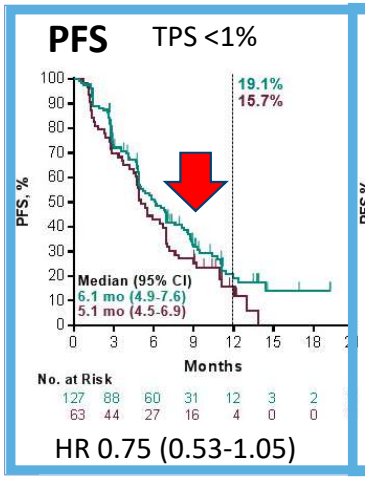
HR 0.59 (0.38-0.92)



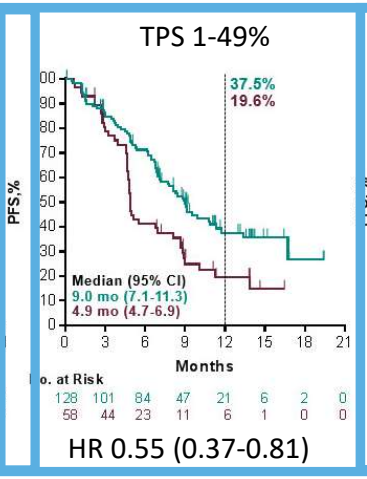
HR 0.55 (0.34-0.90)



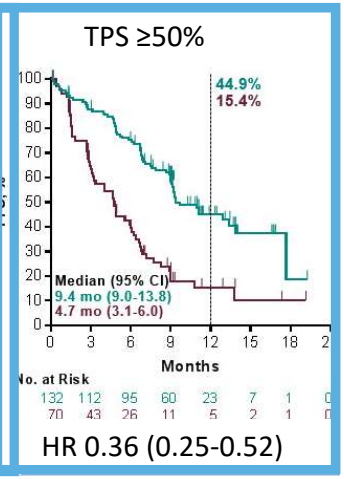
HR 0.42 (0.26-0.68)



HR 0.75 (0.53-1.05)

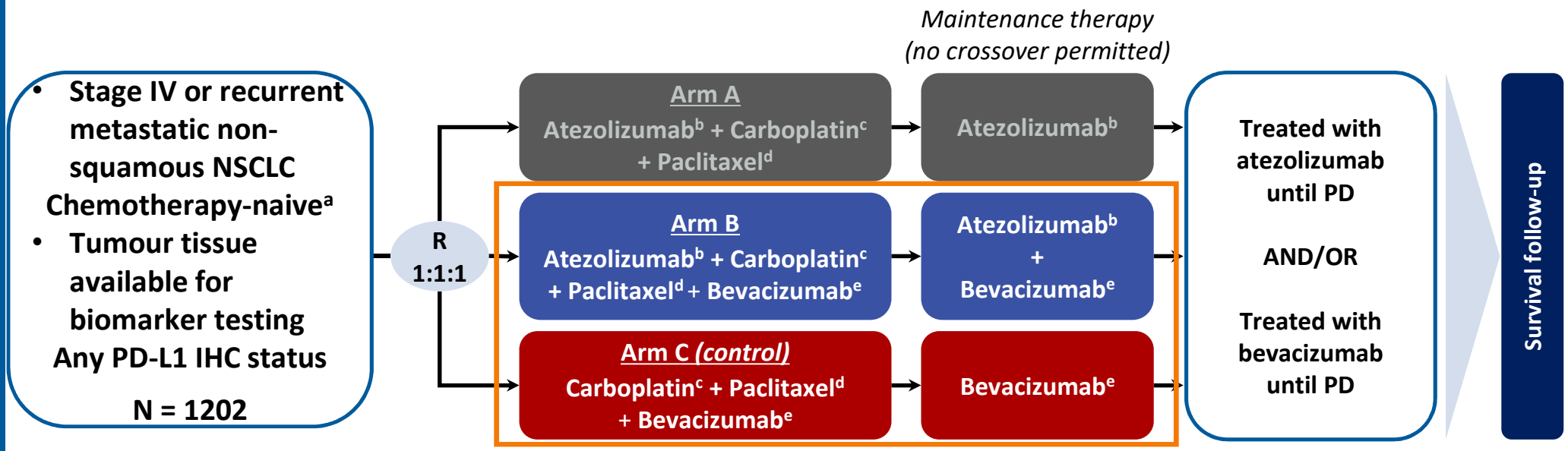


HR 0.55 (0.37-0.81)



HR 0.36 (0.25-0.52)

IMpower150 Study Design



The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

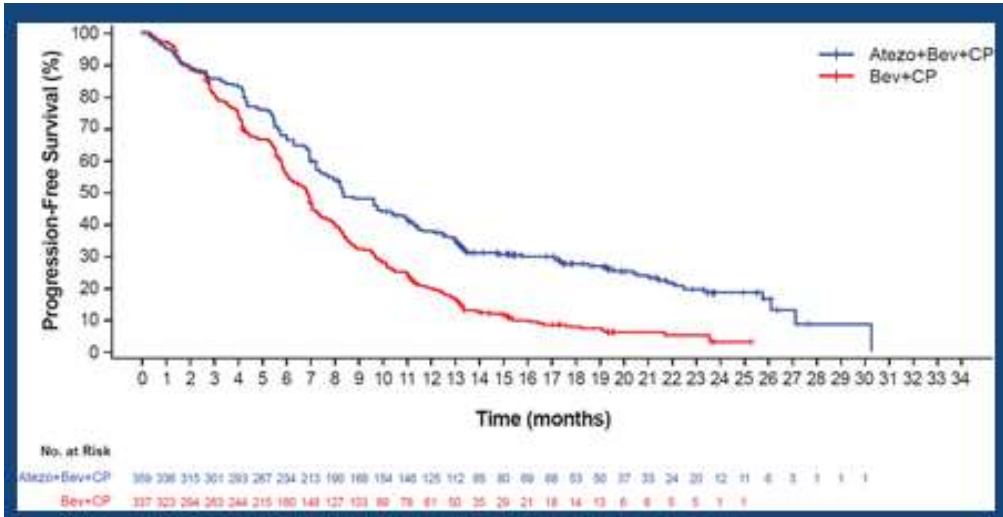
Stratification factors:
- Sex
- PD-L1 IHC expression
- Liver metastases

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w.
[d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

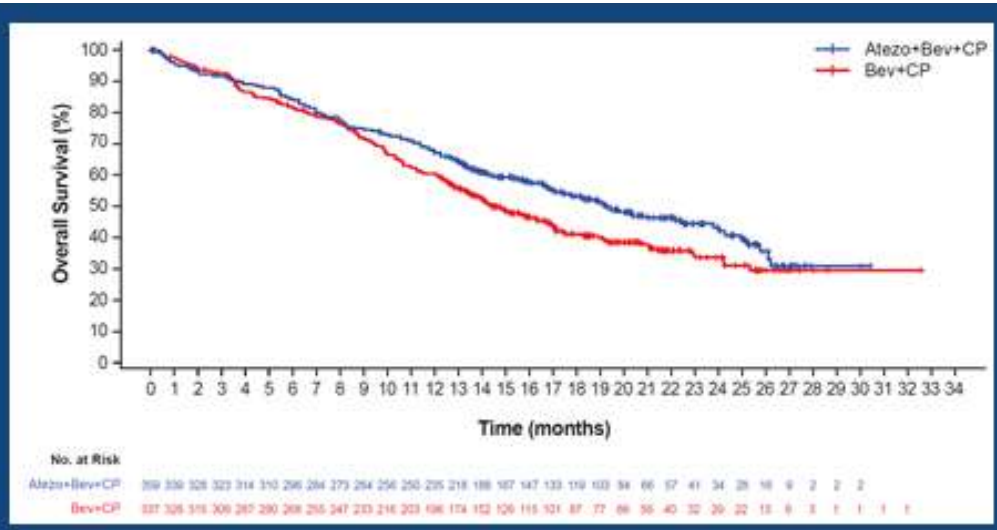
IMPOWER 150 RESULTS

PFS



HR, 0.59
(95% CI: 0.50, 0.70)
P < 0.0001

OS

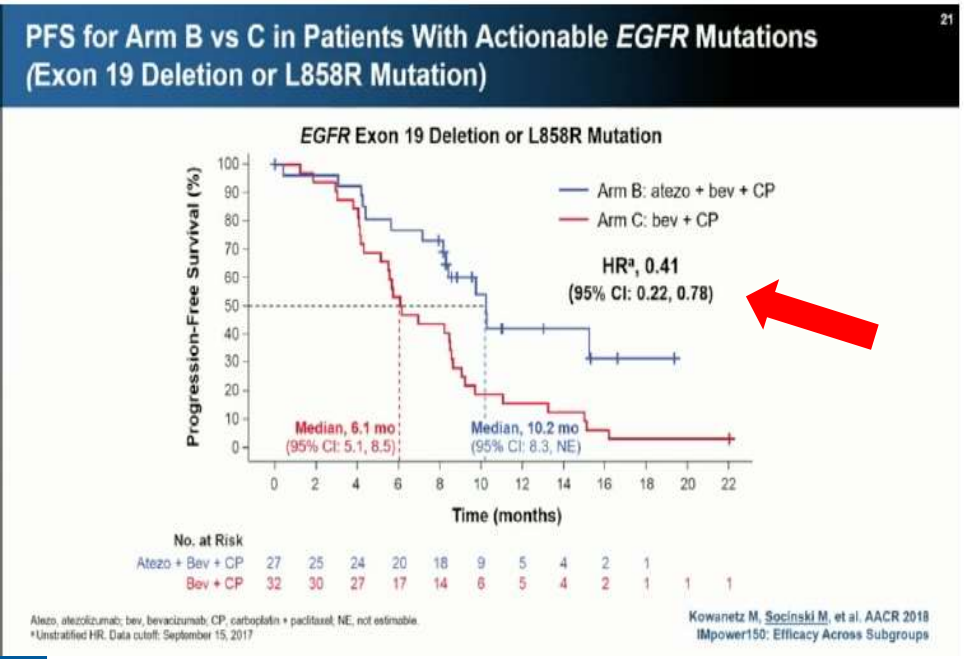


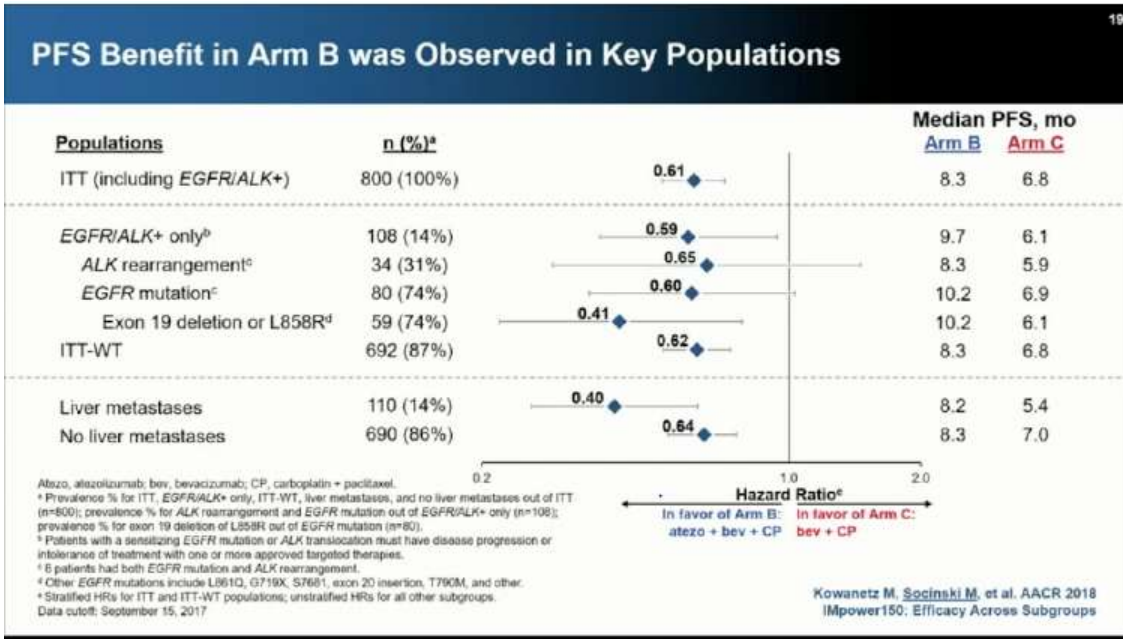
HR, 0.78
(95% CI: 0.64, 0.96)
P = 0.0164

Median follow-up: ~20 mo

Socinksi et al. ASCO 2018.

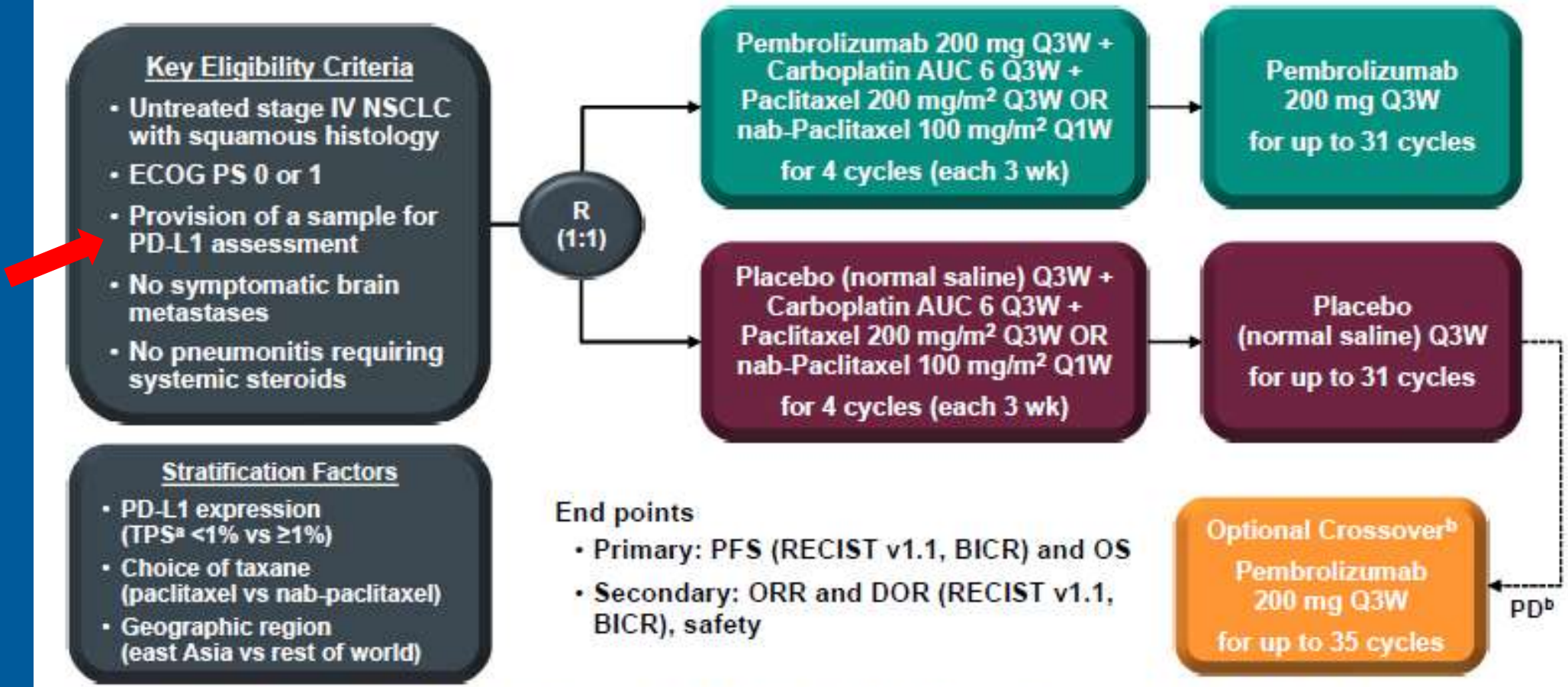
IMPOWER 150 SHOWED BENEFIT IN EGFR MUTANT NSCLC





Paz-Ares KN407 ASCO 2018

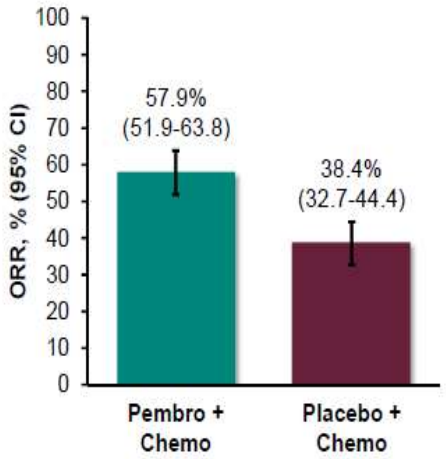
KEYNOTE-407 Study Design (NCT02775435)



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

KN407- RESULTS

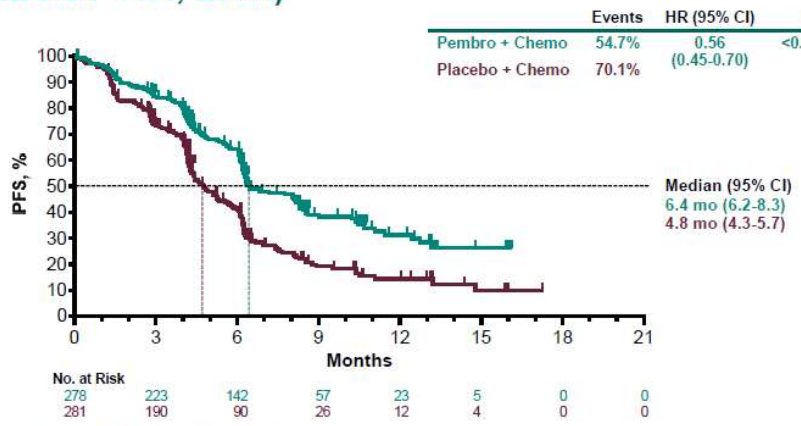
Objective Response Rate at IA2
(RECIST v1.1 by BICR)



Best Response	Pembro + Chemo (N = 278)	Placebo + Chemo (N = 281)
Complete response	4 (1.4%)	6 (2.1%)
Partial response	157 (56.5%)	102 (36.3%)
Stable disease	78 (28.1%)	104 (37.0%)
Progressive disease	17 (6.1%)	39 (13.9%)
Not evaluable[a]	6 (2.2%)	7 (2.5%)
Not assessed[b]	16 (5.8%)	23 (8.2%)

Paz-Ares KN407 ASCO 2018

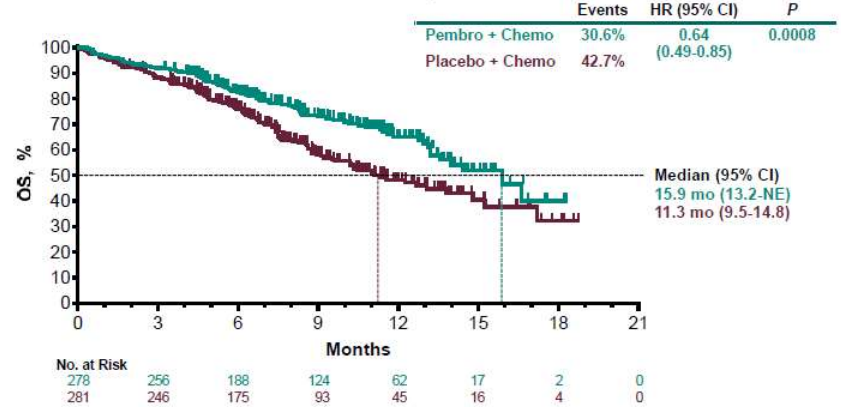
Progression-Free Survival at IA2, ITT
(RECIST v1.1, BICR)



BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Paz-Ares KN407 ASCO 2018

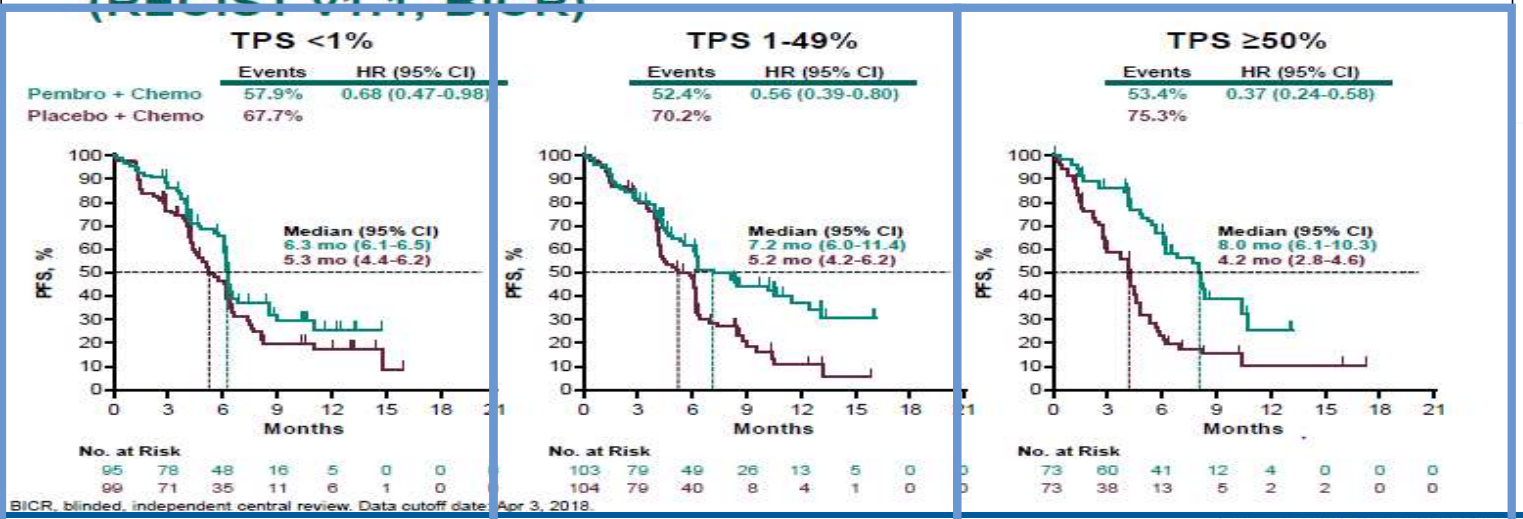
Overall Survival at IA2, ITT



Data cutoff date: Apr 3, 2018.

Paz-Ares KN407 ASCO 2018

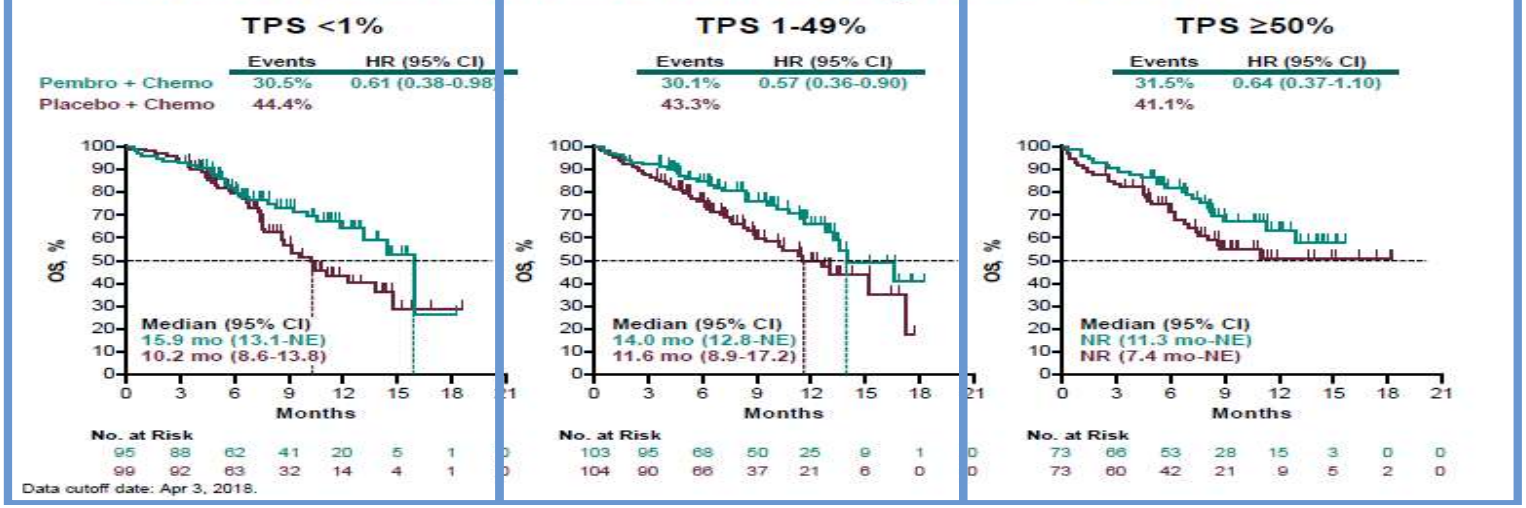
Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)



BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Paz-Ares KN407 ASCO 2018

Overall Survival at IA2 by PD-L1 TPS



Data cutoff date: Apr 3, 2018.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

Initial Systemic Therapy Options

Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)

No contraindications to the addition of pembrolizumab or atezolizumab[c]

- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d] (preferred)**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d] (preferred)**
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1)[3,d,e,f,g]**

Contraindications to the addition of pembrolizumab or atezolizumab[c]

- **Bevacizumab/carboplatin/paclitaxel (category 1)[4,e,f,g]**
- **Bevacizumab/carboplatin/pemetrexed[4,e,f,g]**
- **Bevacizumab/cisplatin/pemetrexed[6,e,f,g]**
- **Carboplatin/albumin-bound paclitaxel (category 1)[7]**
- **Carboplatin/docetaxel (category 1)[8]**
- **Carboplatin/etoposide (category 1)[9,10]**
- **Carboplatin/gemcitabine (category 1)[11]**
- **Carboplatin/paclitaxel (category 1)[12]**
- **Carboplatin/pemetrexed (category 1)[13]**
- **Cisplatin/docetaxel (category 1)[8]**
- **Cisplatin/etoposide (category 1)[14]**
- **Cisplatin/gemcitabine (category 1)[12,15]**
- **Cisplatin/paclitaxel (category 1)[16]**
- **Cisplatin/pemetrexed (category 1)[15]**
- **Gemcitabine/docetaxel (category 1)[17]**
- **Gemcitabine/vinorelbine (category 1)[18]**

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- **Albumin-bound paclitaxel[19]**
- **Carboplatin/albumin-bound paclitaxel[20,21]**
- **Carboplatin/docetaxel[8]**
- **Carboplatin/etoposide[9,10]**
- **Carboplatin/gemcitabine[11]**
- **Carboplatin/paclitaxel[12]**
- **Carboplatin/pemetrexed[13]**
- **Docetaxel[22,23]**
- **Gemcitabine[24-26]**
- **Gemcitabine/docetaxel[17]**
- **Gemcitabine/vinorelbine[18]**
- **Paclitaxel[27-29]**
- **Pemetrexed[30]**

[a]Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b]Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c]Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d]If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.
[e]Bevacizumab should be given until progression.
[f]Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[g]Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,h]

Initial Systemic Therapy Options

Squamous Cell Carcinoma (PS 0-1)

No contraindications to the addition of pembrolizumab[c]

- Pembrolizumab/carboplatin/paclitaxel[31,d] (category 1) (preferred)
- Pembrolizumab/carboplatin/albumin-bound paclitaxel[31,d] (category 1) (preferred)
- Pembrolizumab/cisplatin/paclitaxel[d]
- Pembrolizumab/cisplatin/albumin-bound paclitaxel[d]

Contraindications to the addition of pembrolizumab[c]

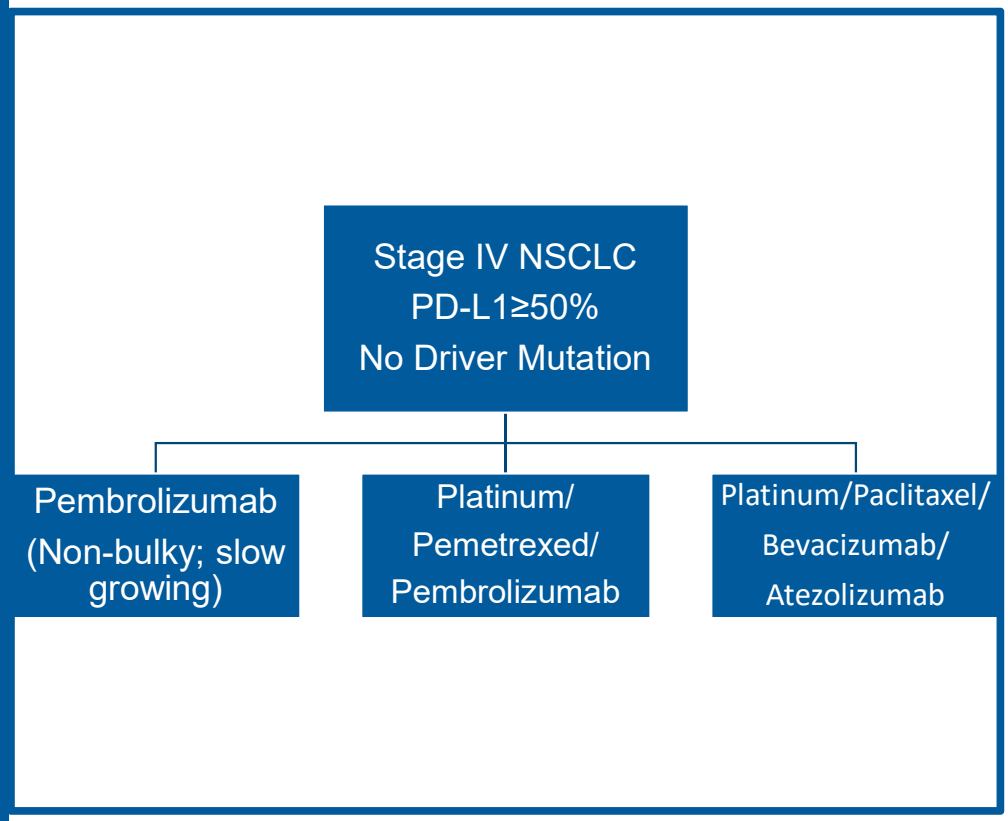
- Carboplatin/albumin-bound paclitaxel (category 1)[7]
- Carboplatin/docetaxel (category 1)[8]
- Carboplatin/gemcitabine (category 1)[11]
- Carboplatin/paclitaxel (category 1)[12]
- Cisplatin/docetaxel (category 1)[8]
- Cisplatin/etoposide (category 1)[14]
- Cisplatin/gemcitabine (category 1)[12,15]
- Cisplatin/paclitaxel (category 1)[16]
- Gemcitabine/docetaxel (category 1)[17]
- Gemcitabine/vinorelbine (category 1)[18]

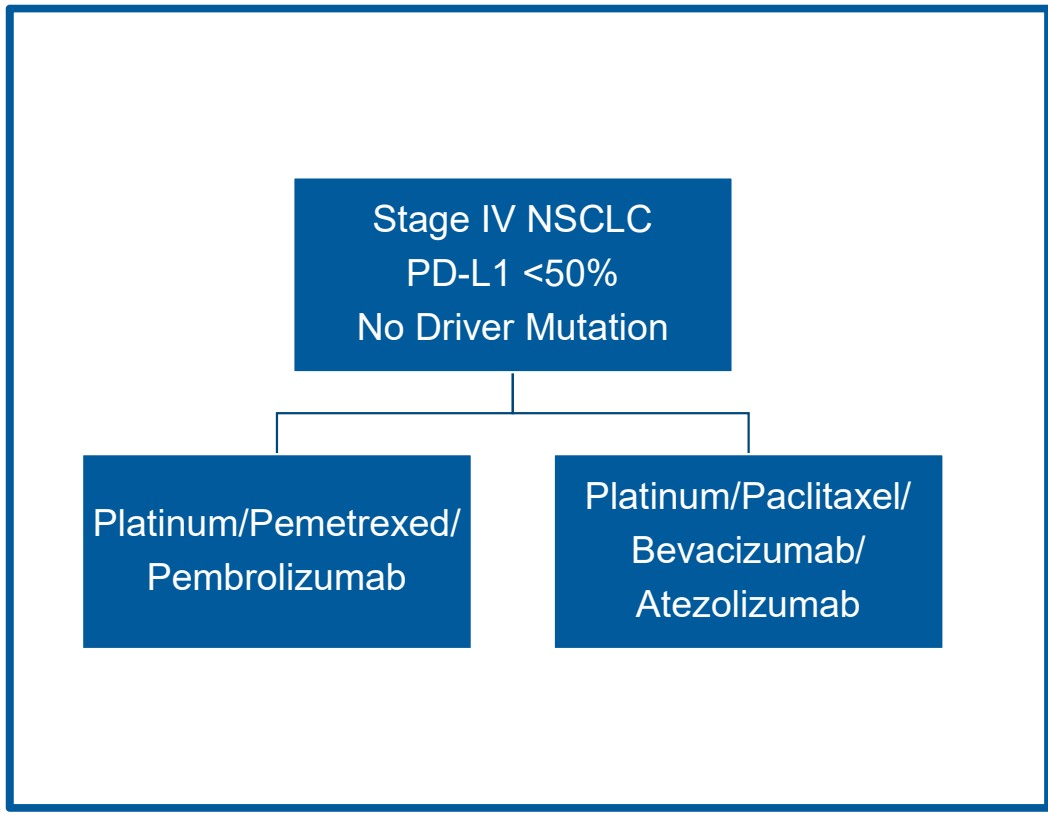
Squamous Cell Carcinoma (PS 2)

- Albumin-bound paclitaxel[19]
- Carboplatin/albumin-bound paclitaxel[20,21]
- Carboplatin/docetaxel[8]
- Carboplatin/etoposide[9,10]
- Carboplatin/gemcitabine[11]
- Carboplatin/paclitaxel[12]
- Docetaxel[22,23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[17]
- Gemcitabine/vinorelbine[18]
- Paclitaxel[27-29]

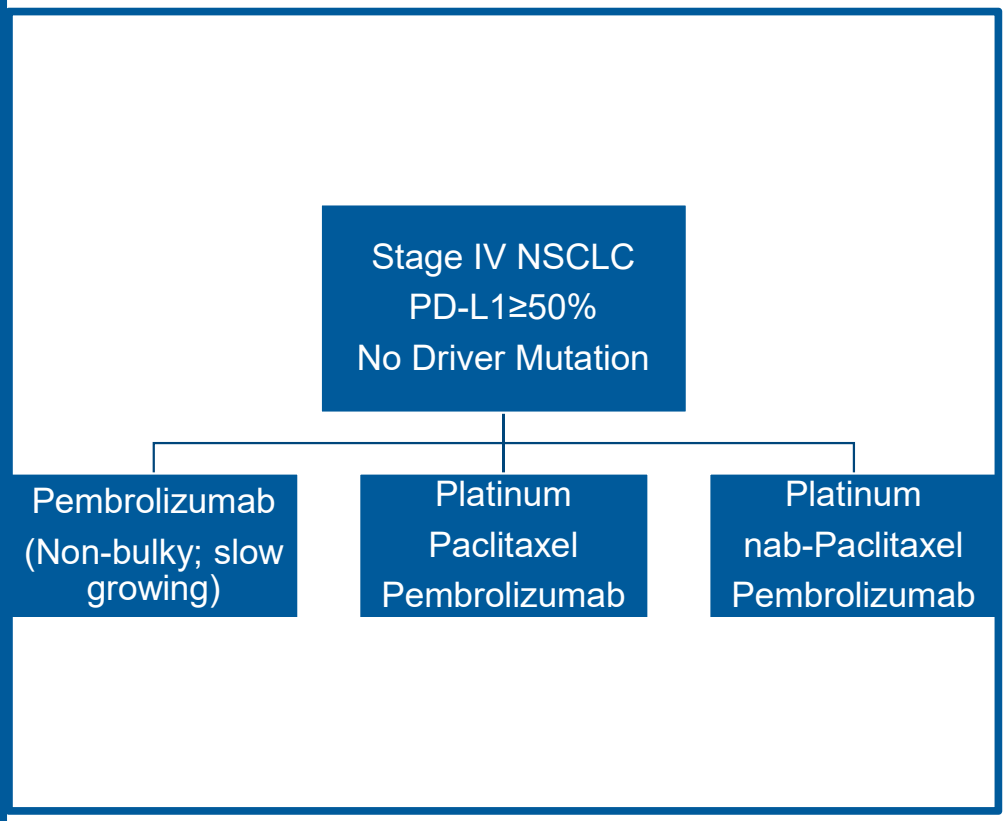
[a]Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b]Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c]Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive

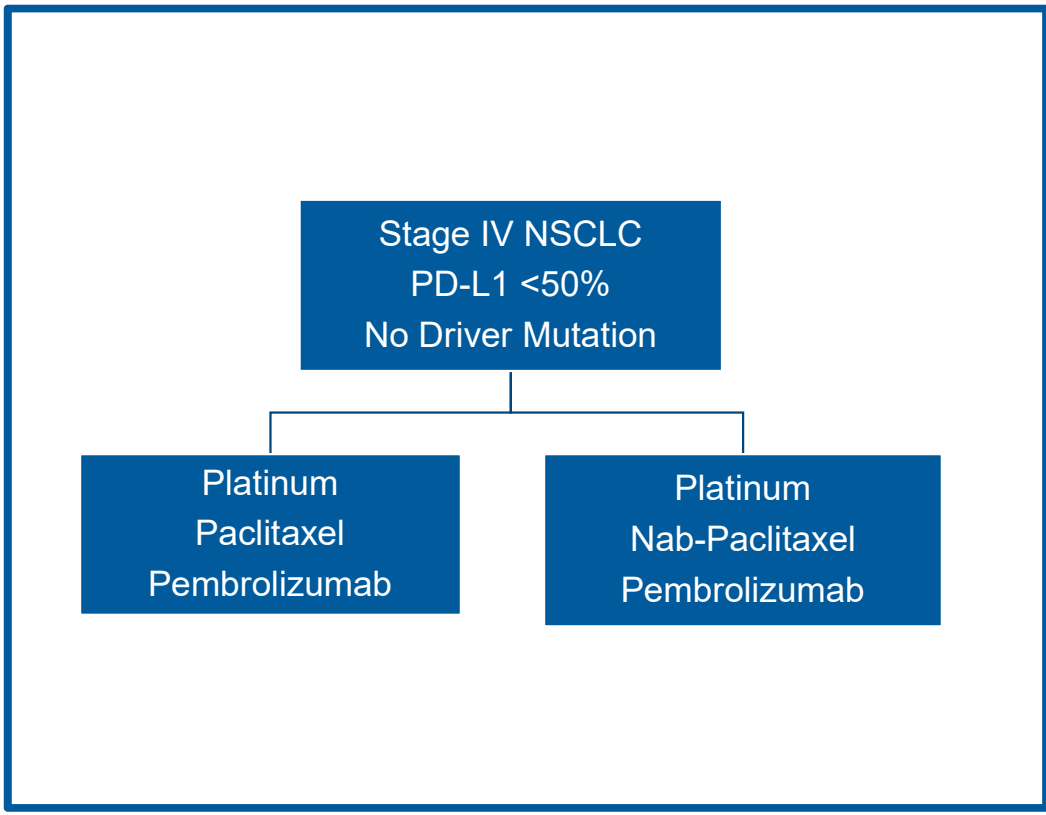
Non-Squamous Cell NSCLC: First Line



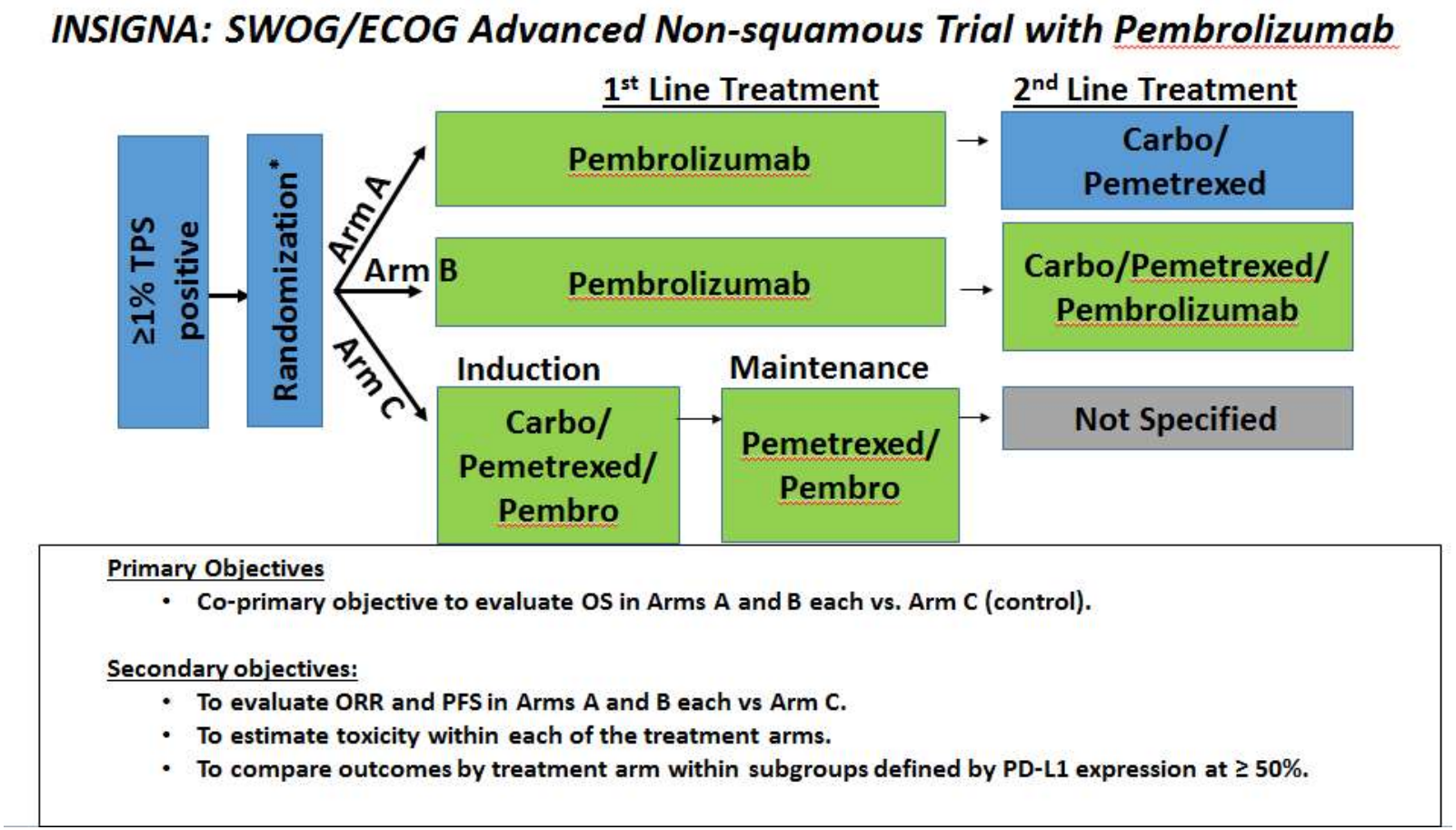


Squamous Cell NSCLC: First Line



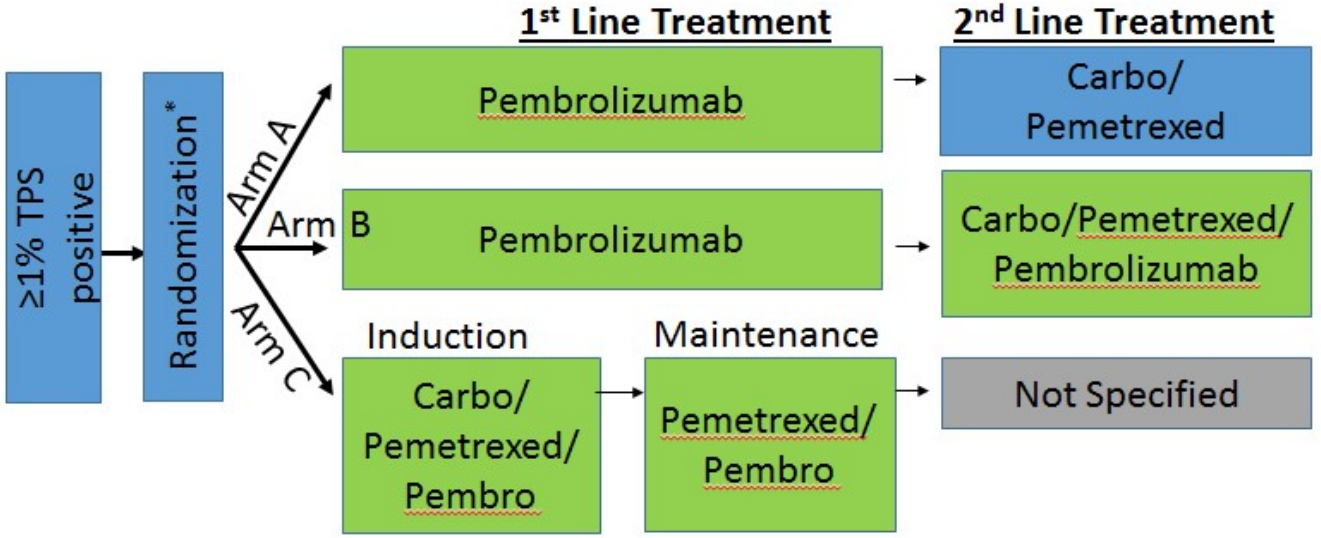


S1709/EA5163: INSIGNA—A Randomized, Phase III Study of First line Immunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker SIGNature-driven Analysis



S1709/EA5163: INSIGNA—A Randomized, Phase III Study of First line Immunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker SIGNature-driven Analysis

INSIGNA: SWOG/ECOG Advanced Non-squamous Trial with Pembrolizumab



Integrated Biomarker Objective:

- To establish a ***predictive signature*** for clinical benefit (OS), to treatment with chemo combined with pembrolizumab versus pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50%).
- To establish a ***prognostic signature*** associated with better outcome (OS) to 1st line treatment with pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50% TPS).

TUMOR MUTATION BURDEN

CheckMate 568 Study Design[a]

Key Eligibility Criteria
- Stage IV or recurrent stage IIIb NSCLC
- No prior systemic therapy
- No known sensitizing *EGFR/ALK* alterations
- ECOG PS 0–1
- PD-L1 all comers

→ **Nivolumab 3 mg/kg Q2W**
Ipilimumab 1 mg/kg Q6W
N = 288 →

Until disease progression or unacceptable toxicity or maximum of 2 years

Primary endpoints[b]:
- ORR[b] in PD-L1 ≥1% and <1% populations[c]

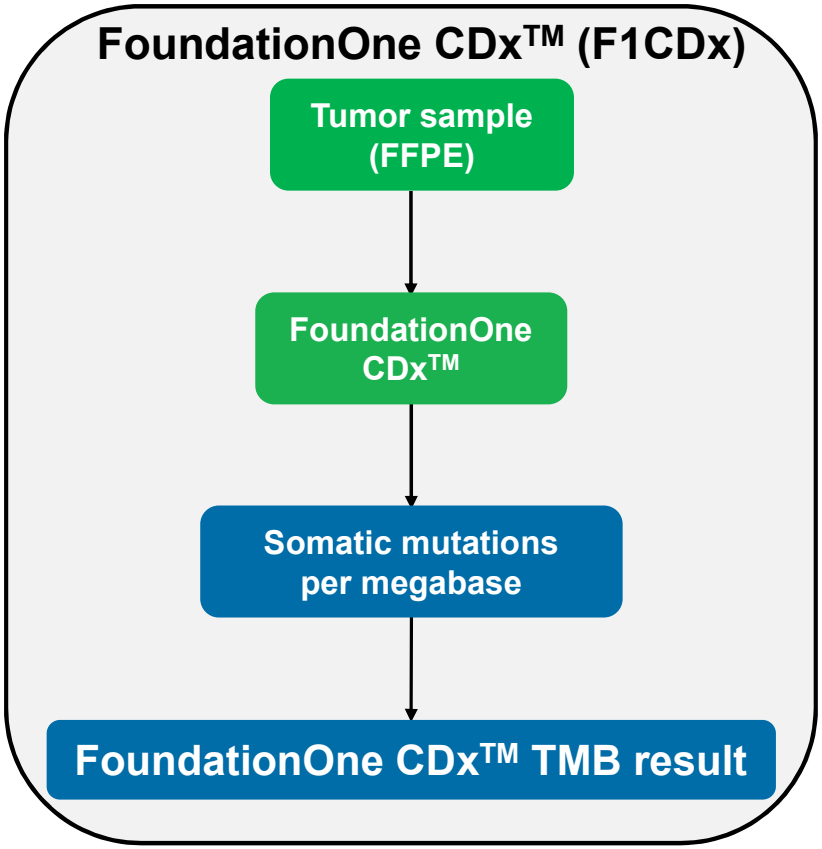
Select secondary endpoints[b]:
- PFS and OS
- ORR, PFS, and OS by TMB

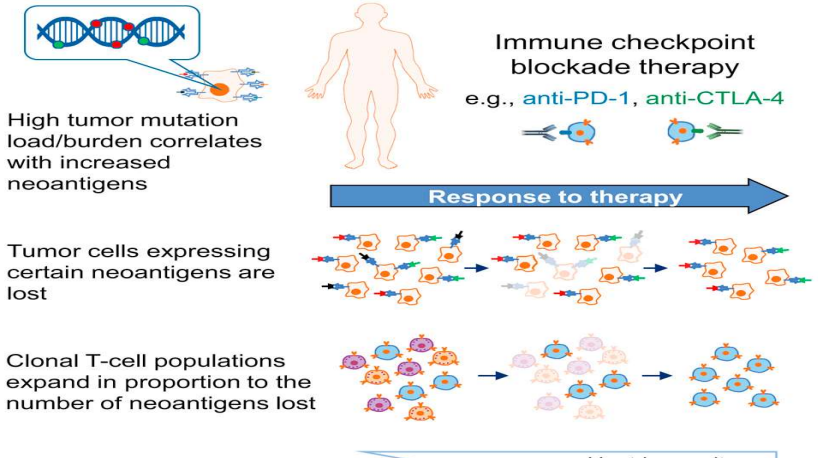
Database lock: August 24, 2017; minimum follow-up: 6 months; median follow-up: 8.8 months

Ramalingam et al. AACR 2018

[a]NCT02659059; [b]Efficacy analyses by blinded independent central review (BICR); [c]PD-L1 status determined by Dako PD-L1 IHC 28-8 pharmDx immunohistochemical test

TMB Analysis With FoundationOne CDx™ Assay

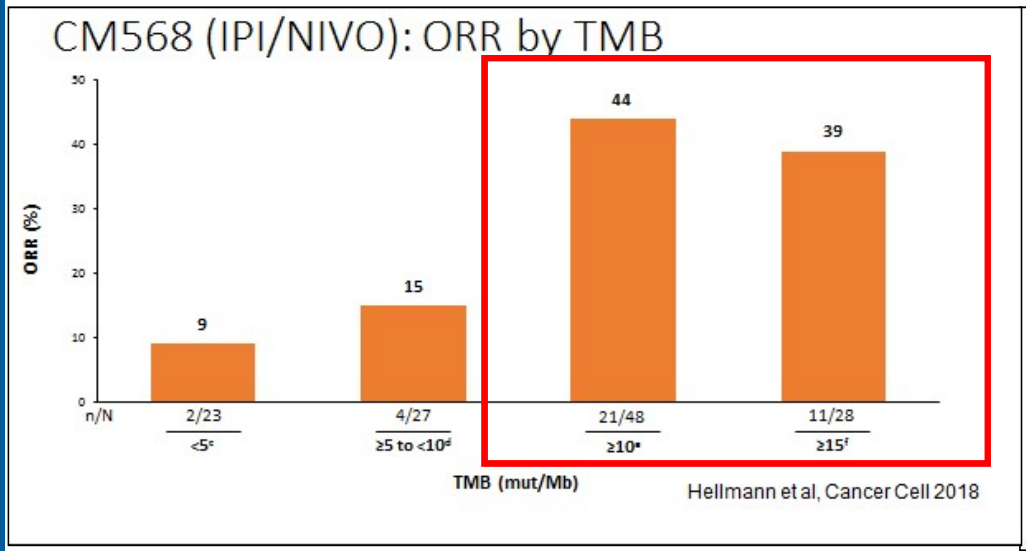


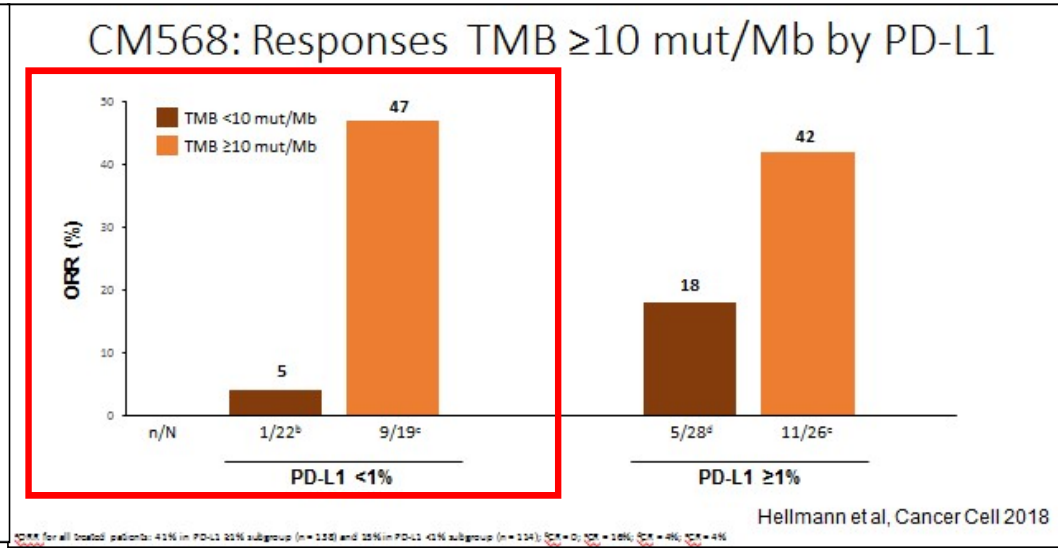


- FoundationOne CDx™ uses next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements
  - TMB: total number of synonymous and non-synonymous variants (≥5% allele frequency) after filtering germline mutations

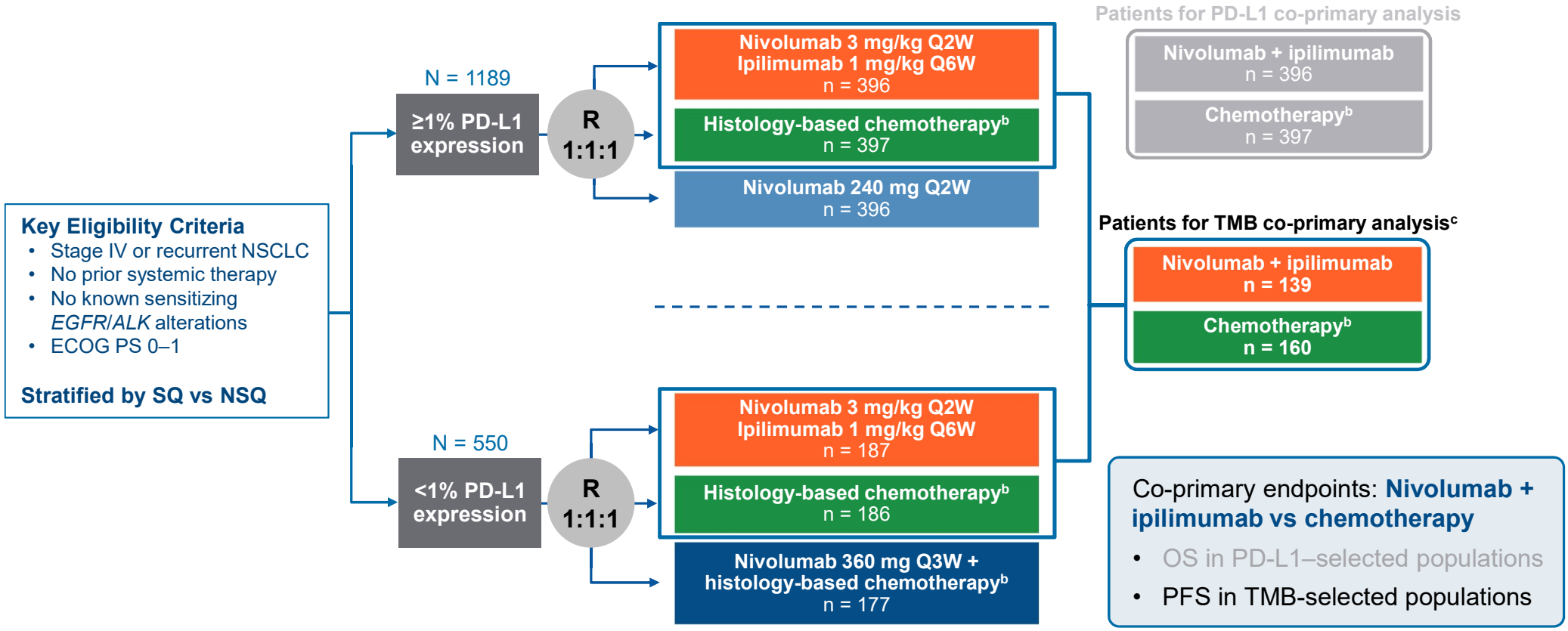
FoundationOne CDx™ Technical Information. Cambridge, MA: Foundation Medicine Inc; 2018.

CHECKMATE 568 DATA





CheckMate 227 Part 1 Study Design[a]

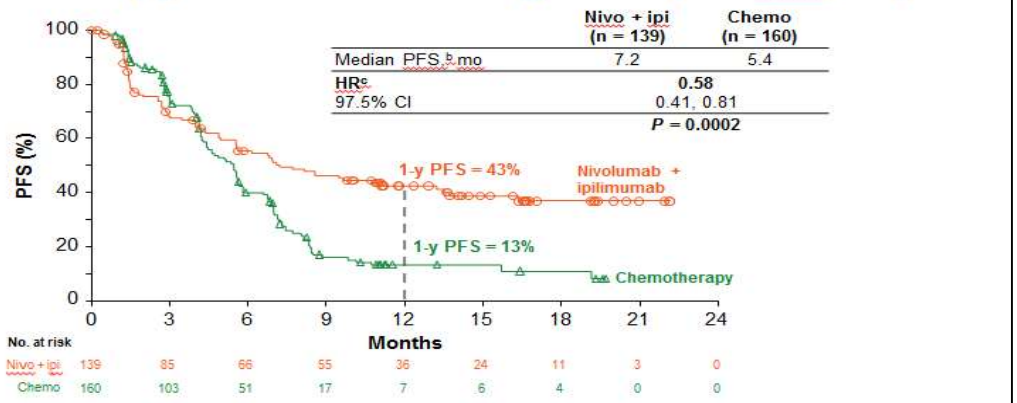


Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

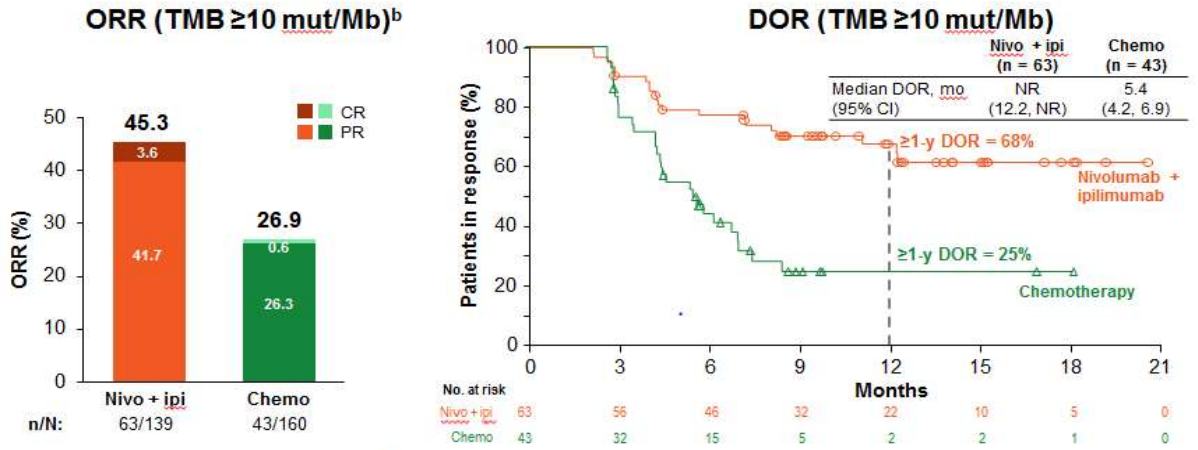
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

ORR and DOR in Patients With High TMB (≥10 mut/Mb)[a]



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

	OS (Mos)	HR	95% CI
TMB ≥10 Mut/Mb			
Ipi/Nivo	23.03	0.77	0.56 - 1.06
Chemo	16.72		
TMB <10 Mut/Mb			
Ipi/Nivo	16.20	0.78	0.61- 1.00
Chemo	12.42		

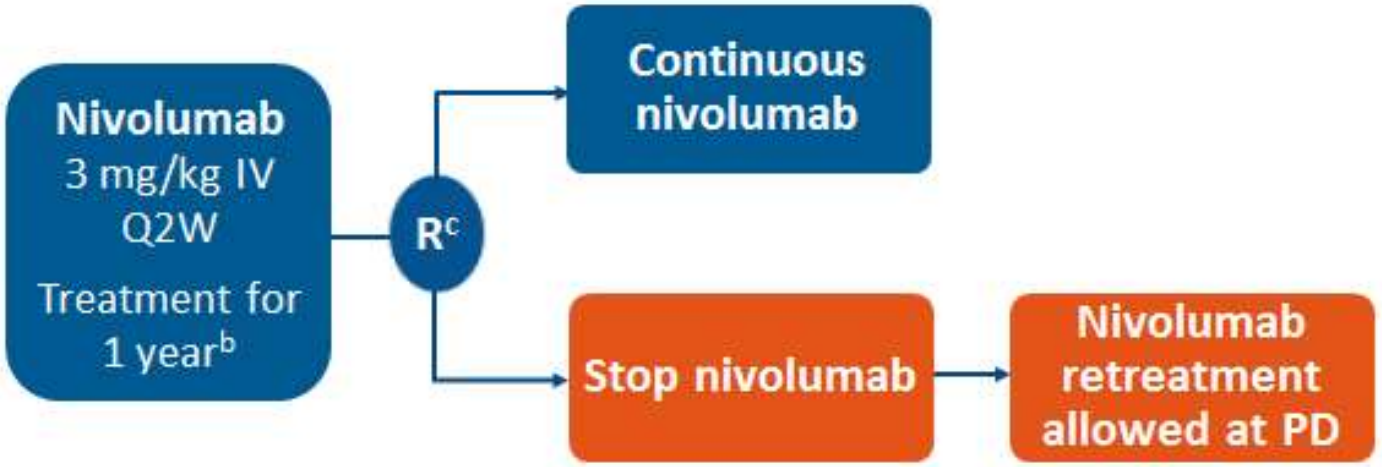
Duration of Therapy and QOL

Checkmate 153

Continuous vs 1-Year Fixed-Duration

Key eligibility criteria

- Advanced/ metastatic NSCLC
- ≥1 prior systemic therapy[a]
- ECOG PS 0–2
- Treated CNS metastases allowed



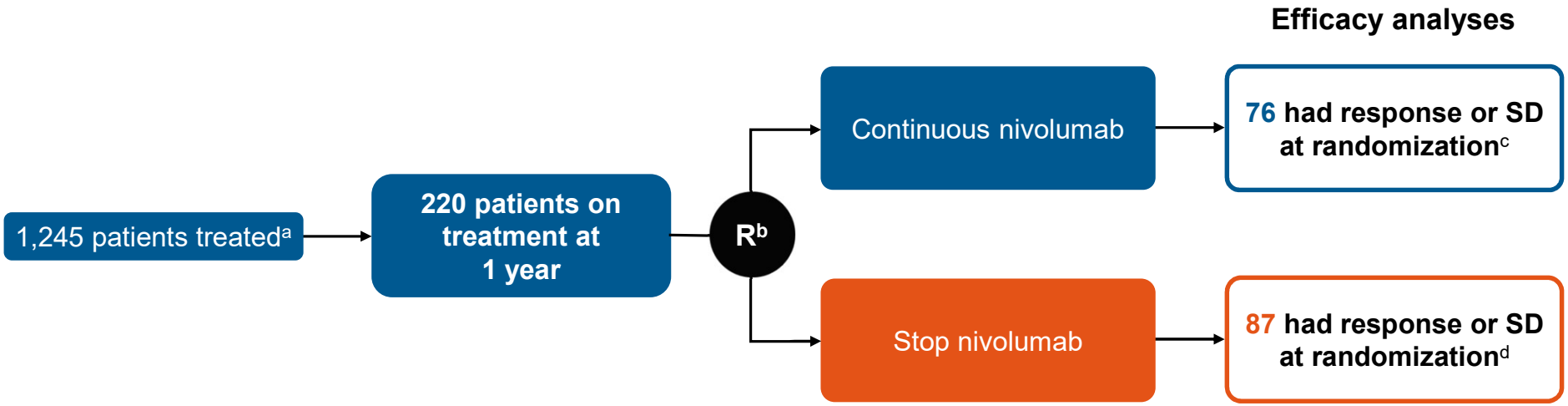
Exploratory endpoints[d]: safety/efficacy with continuous vs 1-year treatment, efficacy, other (eg, biomarkers, PK)

[a]Conventional systemic therapies, excluding immuno-oncology therapies; [b]Treatment until PD, unacceptable toxicity or withdrawal of consent; treatment beyond investigator-assessed PD permitted; [c]All patients on treatment at 1 year were randomized regardless of response status; [d]Primary endpoint was incidence of high-grade select treatment-related AEs[1,2]

Spigel, ESMO 2017

CheckMate 153: Continuous vs 1-Year Nivolumab

Patient Flow and Analysis Populations



MADRID 2017 ESMO congress

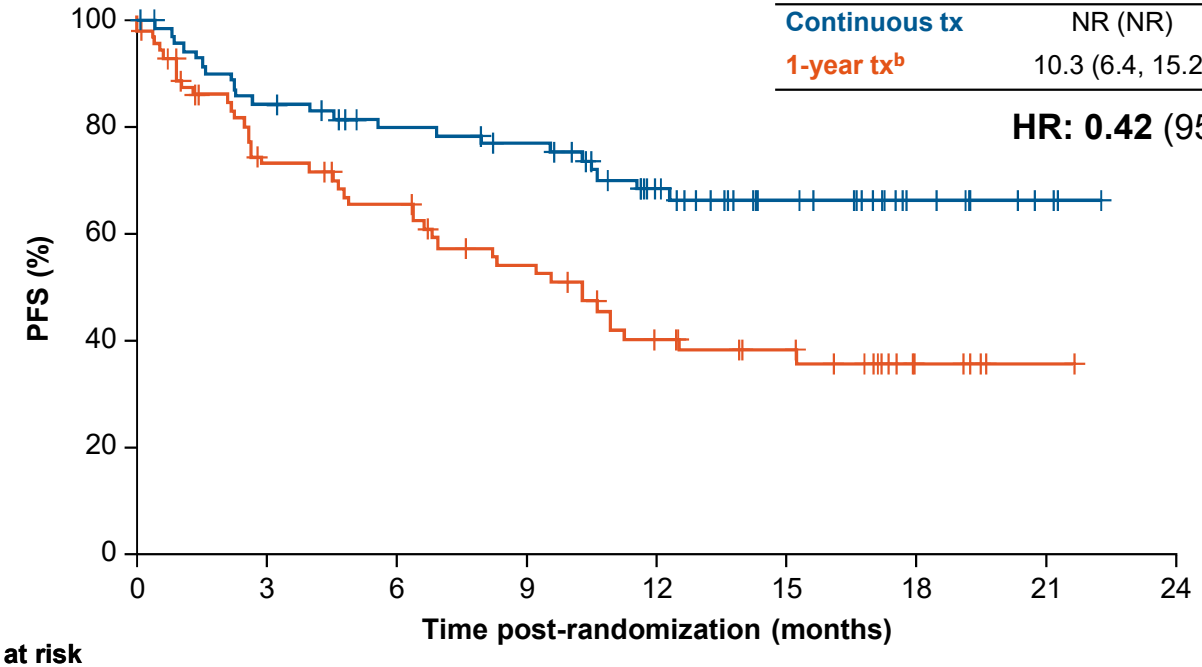
[a]Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;
[b]All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; [c]8 patients discontinued treatment due to patient request or withdrawal of consent; [d]12 patients discontinued treatment due to patient request or withdrawal of consent

CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization[a]

	Median, months (95% CI)	PFS rate, %	
		6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)



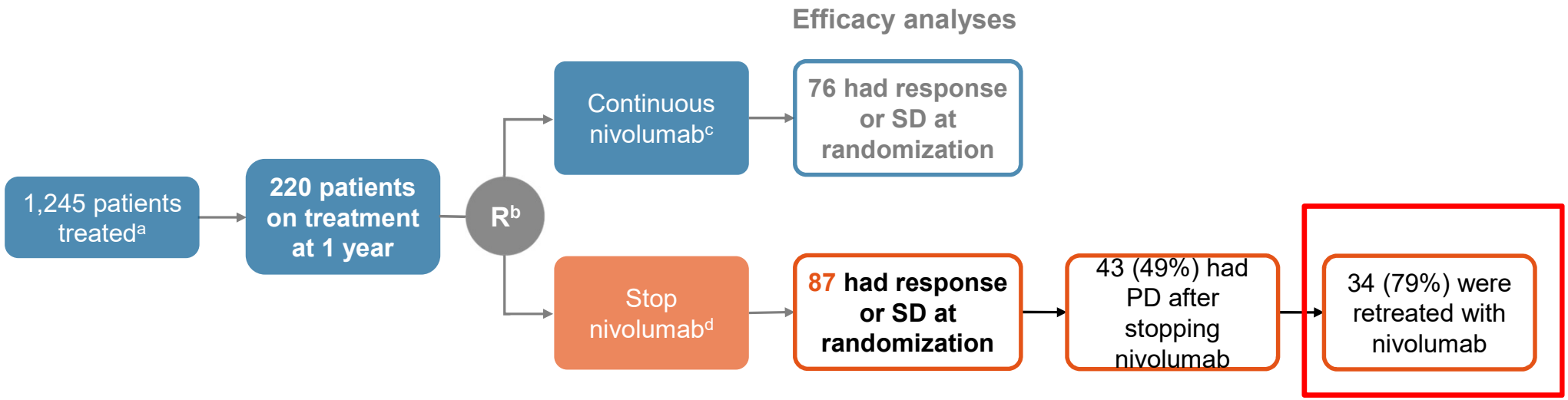
No. at risk									
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

MADRID 2017 ESMO congress

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

CheckMate 153: Continuous vs 1-Year Nivolumab

Retreatment in 1-Year Treatment Arm



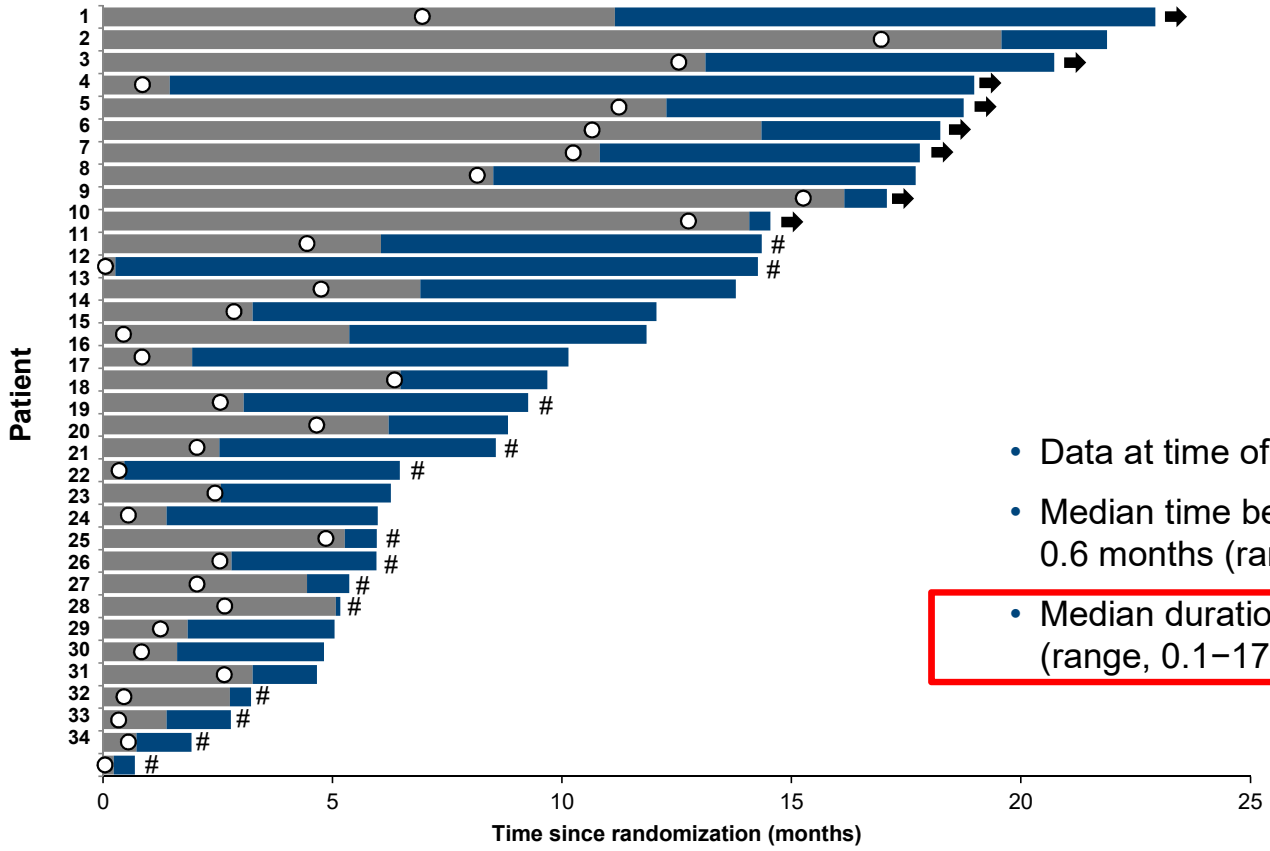
Data at time of analysis (database lock May 15, 2017)

MADRID 2017 ESMO congress

[a]Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;
[b]All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; [c]8 patients discontinued treatment due to patient request or withdrawal of consent; [d]12 patients discontinued treatment due to patient request or withdrawal of consent

CheckMate 153: Continuous vs 1-Year Nivolumab

Initiation and Duration of Retreatment



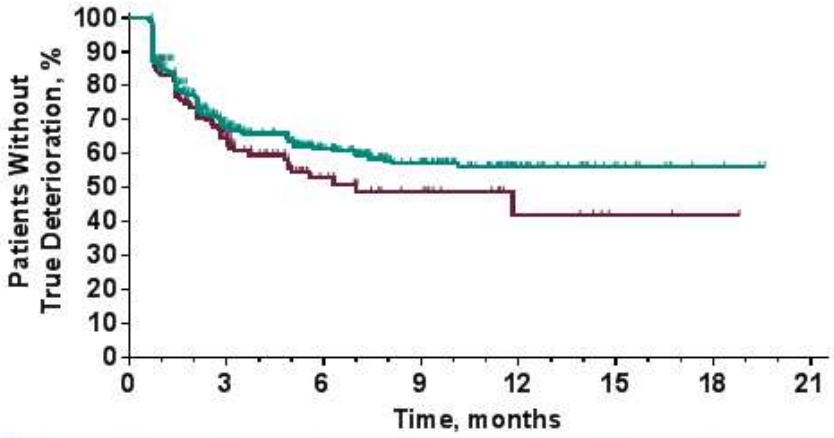
Off nivolumab treatment
Nivolumab retreatment
PD
Retreatment ongoing
Patient died

- Data at time of analysis (database lock May 15, 2017)
- Median time between progression and retreatment: 0.6 months (range, 0.1–4.9)
- Median duration of retreatment: 3.8 months (range, 0.1−17.5)

MADRID 2017 ESMO congress

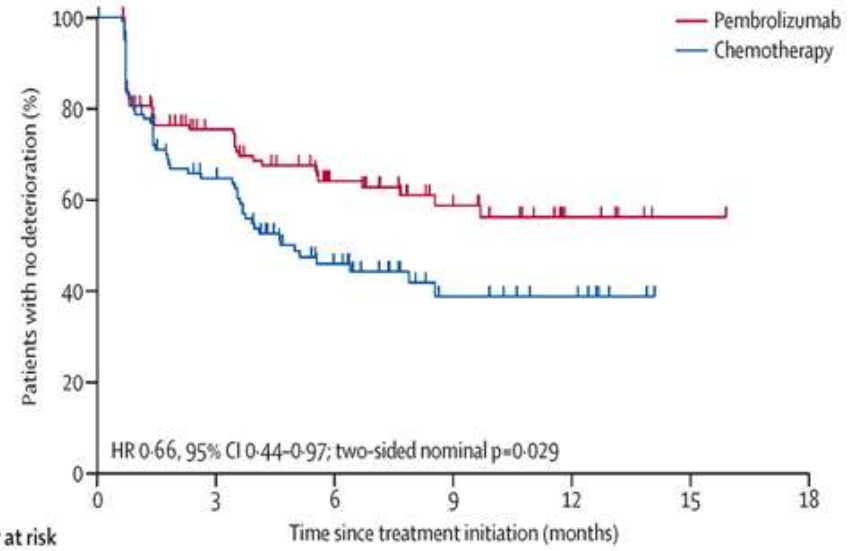
Patients who had not died and were not continuing retreatment were in follow-up and alive as of database lock

Time to True Deterioration in Composite of Cough, Chest Pain, and Dyspnea[a]



No. at risk[b]								
Pembro/Pem/Plat	402	189	128	72	32	11	3	0
Placebo/Pem/Plat	200	68	29	17	6	2	1	0

Keynote 189. All PDL1.



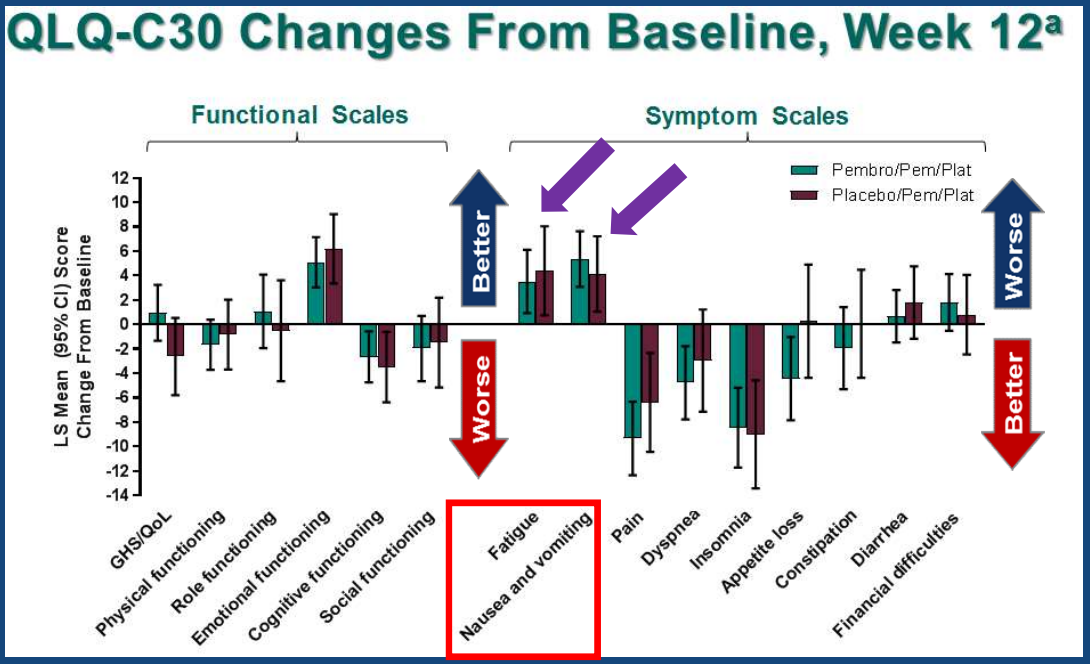
Number at risk (number censored)							
Pembrolizumab	151 (0)	78 (42)	47 (62)	26 (80)	7 (98)	1 (104)	0 (105)
Chemotherapy	148 (0)	60 (49)	30 (63)	11 (79)	7 (83)	0 (90)	0 (90)

Keynote 024. PDL1 ≥50%

Brahmer, J. et al. Lancet Oncology 2017.

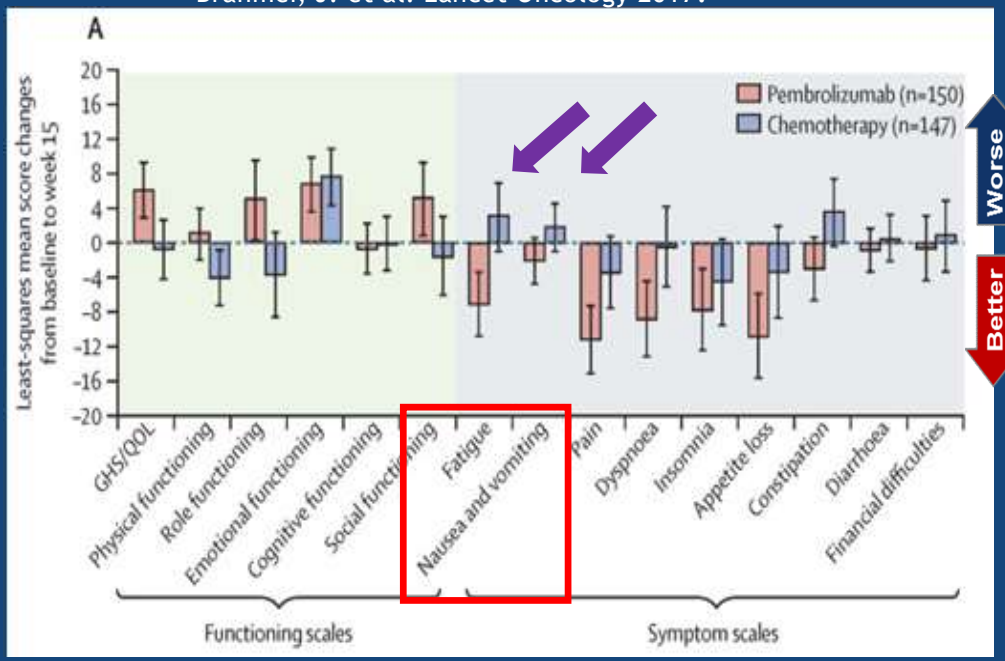
Keynote 189. Carboplatin/Pemetrexed/Pembrolizumab All PDL1. Week 12

Garissano et al. ASCO 2018.



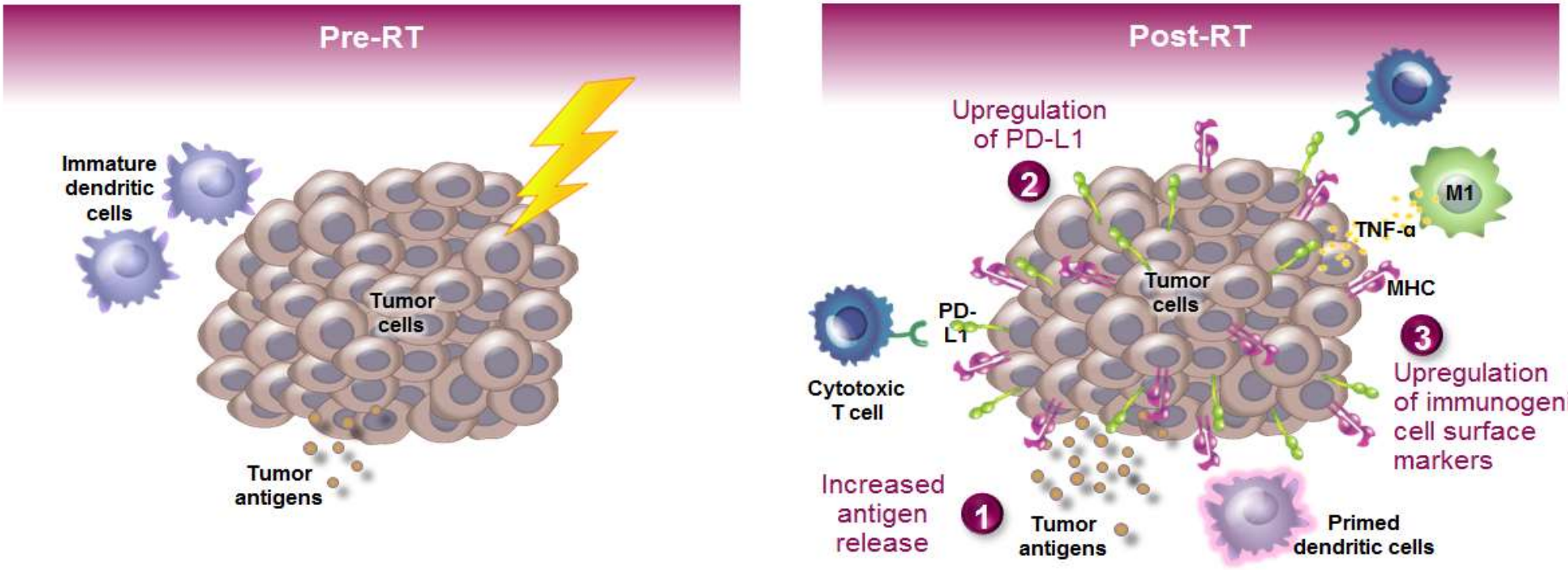
Keynote 024. Pembrolizumab Single Agent PDL1 ≥50%. Week 15.

Brahmer, J. et al. Lancet Oncology 2017.



STAGE III NSCLC

RT Induces Multiple Immunomodulatory Changes That May Influence the Effectiveness of Immunotherapy[1-3]



M1, tumor-associated macrophage; MHC I, major histocompatibility complex I; PD-L1, programmed cell death-ligand 1; TNF-α, tumor necrosis factor alpha.

1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, Asea A. *Frontiers Oncol*. 2012;2:191. 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

PACIFIC Study Design: Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following CRT (≥2 cycles)
  - *Platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane, or pemetrexed)*
  - *Radiation therapy (mean dose to the lung <20 Gy, or the V20 <35%, or both; 54 to 66 Gy)*
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks

All-comers population
(all patients regardless of PD-L1 expression)

1-42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

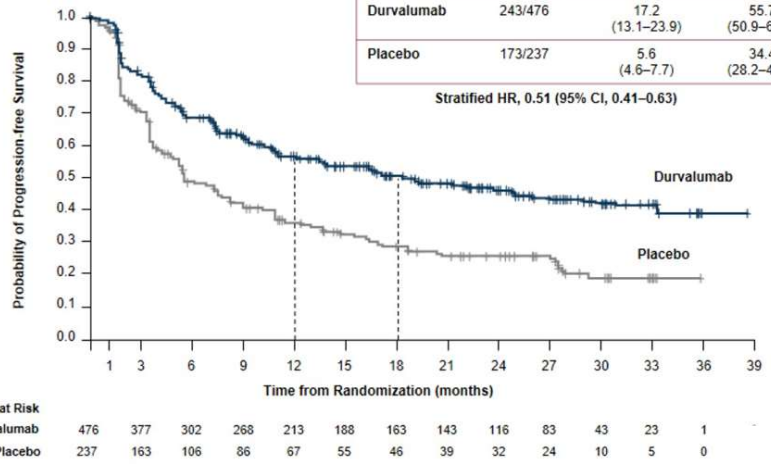
PACIFIC Trial: Updated OS and PFS

PACIFIC: Updated Progression-Free Survival by BICR – ITT

DCO: March 22, 2018

	No. of events / No. of patients	Median PFS (95% CI) months	12-mo PFS (95% CI) %	18-mo PFS (95% CI) %
Durvalumab	243/476	17.2 (13.1–23.9)	55.7 (50.9–60.2)	49.5 (44.6–54.2)
Placebo	173/237	5.6 (4.6–7.7)	34.4 (28.2–40.7)	26.7 (20.9–32.9)

Stratified HR, 0.51 (95% CI, 0.41–0.63)

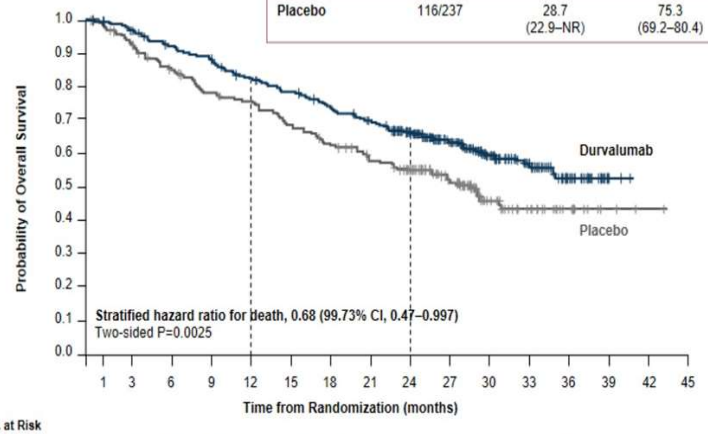


No. at Risk													
Durvalumab	476	377	302	268	213	188	163	143	116	83	43	23	1
Placebo	237	163	106	86	67	55	46	39	32	24	10	5	0

PACIFIC: Overall Survival – in the ITT Population[a]

DCO: March 22, 2018

	No. of events / No. of patients	Median OS (95% CI), months	12-mo OS (95% CI) %	24-mo OS (95% CI) %
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



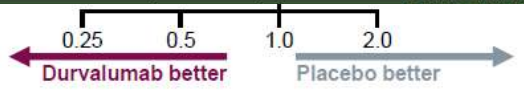
No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Antonia SA…, Gray JE et al. NEJM. 2018.

Progression-free and Overall Survival by Subgroup (ITT)

		PFS (BICR)			OS		
			No. of events / No. of patients (%)			No. of events / No. of patients (%)	
		HR (95% CI)	Durvalumab	Placebo	HR (95% CI)	Durvalumab	Placebo
	All patients		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Sex	Male		155/334 (46.4)	111/166 (66.9)		141/334 (42.2)	80/166 (48.2)
	Female		59/142 (41.5)	46/71 (64.8)		42/142 (29.6)	36/71 (50.7)
Age at randomisation	<65 years		108/261 (41.4)	91/130 (70.0)		89/261 (34.1)	58/130 (44.6)
	≥65 years		106/215 (49.3)	66/107 (61.7)		94/215 (43.7)	58/107 (54.2)
Smoking status	Smoker		197/433 (45.5)	140/216 (64.8)		169/433 (39.0)	103/216 (47.7)
	Non-smoker		17/43 (39.5)	17/21 (81.0)		14/43 (32.6)	13/21 (61.9)
Disease stage	Stage IIIA		108/252 (42.9)	82/125 (65.6)		101/252 (40.1)	70/125 (56.0)
	Stage IIIB		104/212 (49.1)	72/107 (67.3)		79/212 (37.3)	44/107 (41.1)
Tumour histologic type	Squamous		117/224 (52.2)	66/102 (64.7)		103/224 (46.0)	56/102 (54.9)
	Non-squamous		97/252 (38.5)	91/135 (67.4)		80/252 (31.7)	60/135 (44.4)
Prior definitive CT	Cisplatin		115/266 (43.2)	87/129 (67.4)		94/266 (35.3)	64/129 (49.6)
	Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Best response to prior treatment	CR	NA*	2/9 (22.2)	4/7 (57.1)	NA*	2/9 (22.2)	3/7 (42.9)
	PR		99/232 (42.7)	72/111 (64.9)		83/237 (35.0)	50/112 (44.6)
	SD		108/222 (48.6)	77/114 (67.5)		93/223 (41.7)	61/115 (53.0)
***EGFR* status**	Positive		17/29 (58.6)	11/14 (78.6)	NA*	10/29 (34.5)	6/14 (42.9)
	Negative		131/315 (41.6)	112/165 (67.9)		117/317 (36.9)	80/165 (48.5)
	Unknown		66/132 (50.0)	34/58 (58.6)		56/130 (43.1)	30/58 (51.7)
PD-L1 status (pre-specified)	≥25%		48/115 (41.7)	31/44 (70.5)		37/115 (32.2)	23/44 (52.3)
	<25%		85/187 (45.5)	68/105 (64.8)		74/187 (39.6)	41/105 (39.0)
	Unknown		81/174 (46.6)	58/88 (65.9)		72/174 (41.4)	52/88 (59.1)

PFS data based on DCO of Feb 13, 2017.



OS data based on DCO of March 22, 2018.

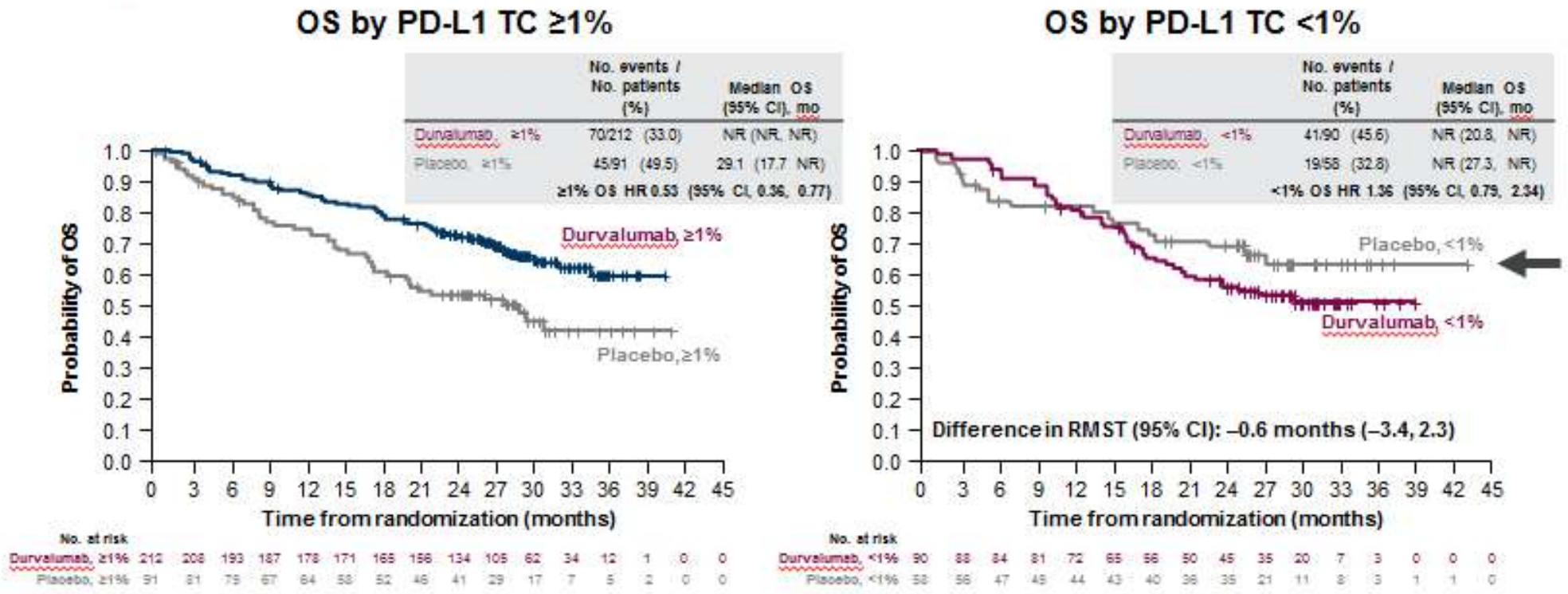
*Not calculated if subgroup has <20 events.

CR, complete response; EGFR, epidermal growth factor receptor; NA, not available; PR, partial response; SD, stable disease.

Faivre-Finn C, et al. Presented at: ESMO 2018 Congress; October 19-23, 2018; Munich, Germany. Abstract 1363O.

MUNICH 2018 ESMO

OS by PD-L1 TC ≥1% and <1%



OS DCO: 22 March 2018

- In the PD-L1 TC <1% subgroup, imbalances exist in baseline the characteristics.
- Placebo arm: > more females, non-SQCLC, and Stage IIIA.

Faivre-Finn C, et al. Presented at: ESMO 2018 Congress; October 19-23, 2018; Munich, Germany. Abstract 1363O.

PACIFIC- SAFETY UPDATE

PACIFIC: Updated Safety Summary

DCO: March 22, 2018

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

Pneumonitis

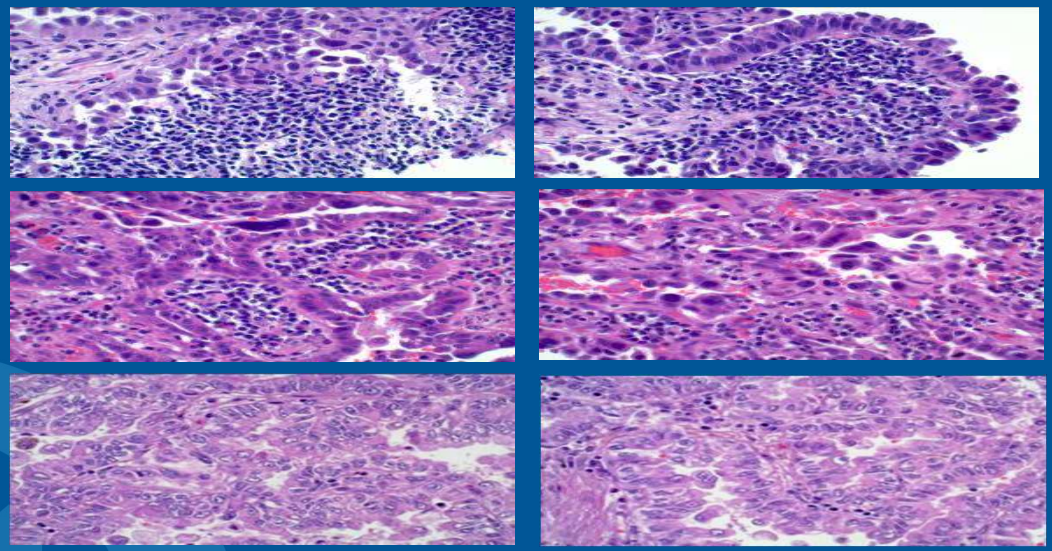
Exploratory Subgroup Analysis in Pneumonitis: Time to Onset (WCLC 2018)

	Durvalumab	Placebo
Time to onset from 1st dose, median days (range) [N]	55.0 (1–406) [161]	55.0 (1–255) [58]
Time to onset from radiotherapy, median days (range) [N]	73.0 (20–433) [161]	76.5 (24–280) [58]
Duration, median days (range) [N]*	64.0 (3–568) [79]	57.0 (5–187) [23]

Antonia SA…, Gray JE et al. NEJM. 2018.
Vansteenkiste JF, et al. WCLC. 2018.

FUTURE DIRECTIONS

Insufficient number of T cells extravasate into the tumor.



High TIL

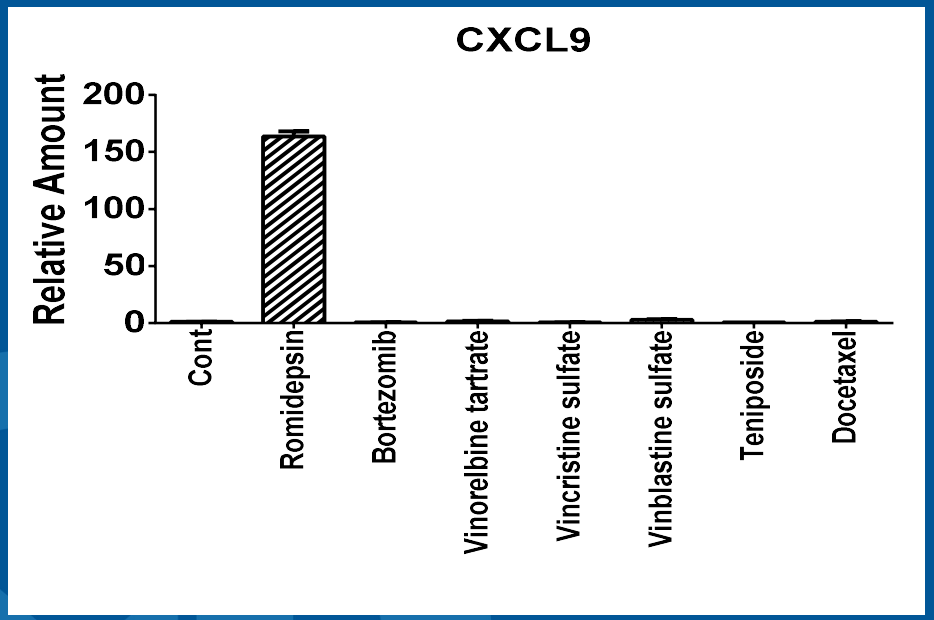
Moderate TIL

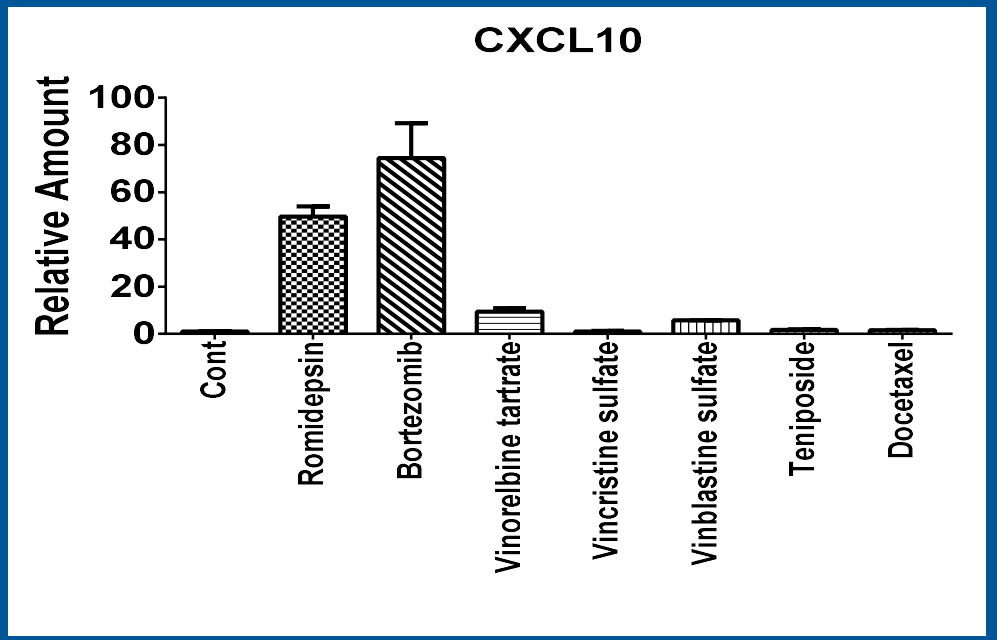
Low TIL

*TIL: Tumor infiltrating Lymphocytes

MOFFITT CANCER CENTER

HDACi Induce the Secretion of T cell Chemokines



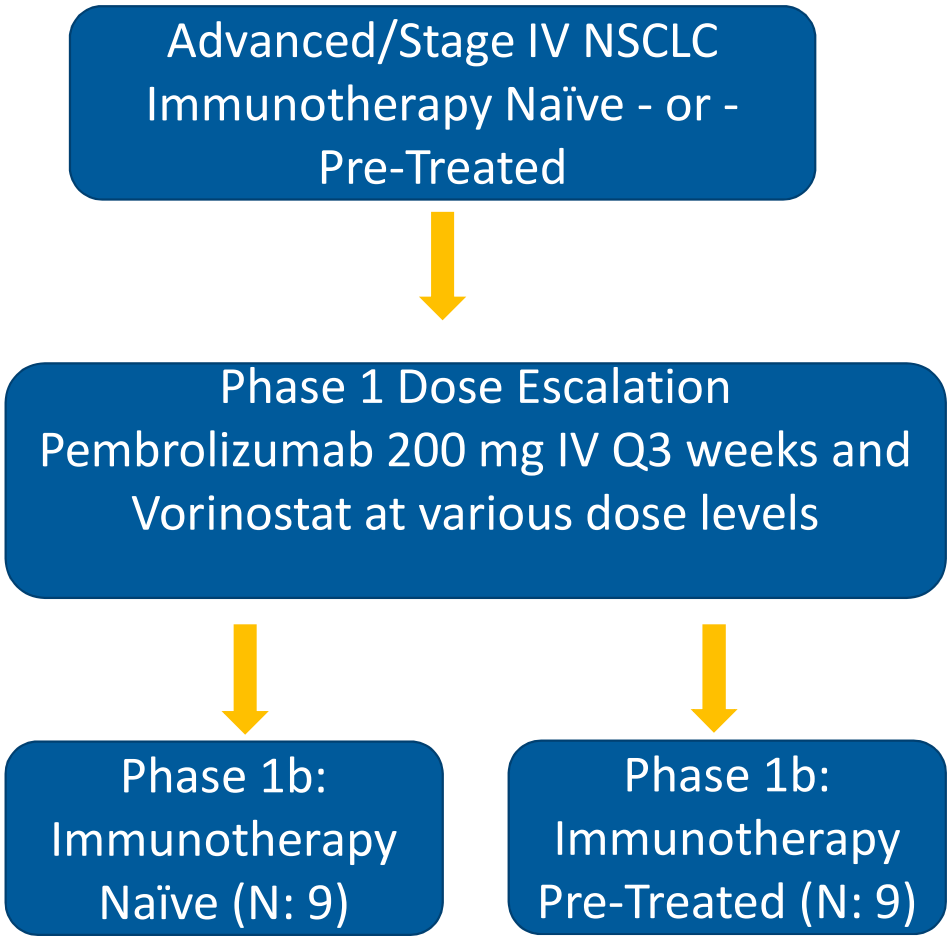


Jhanelle Gray, MD and Amer Beg, PhD

Trial: Pembrolizumab plus vorinostat

MOFFITT CANCER CENTER

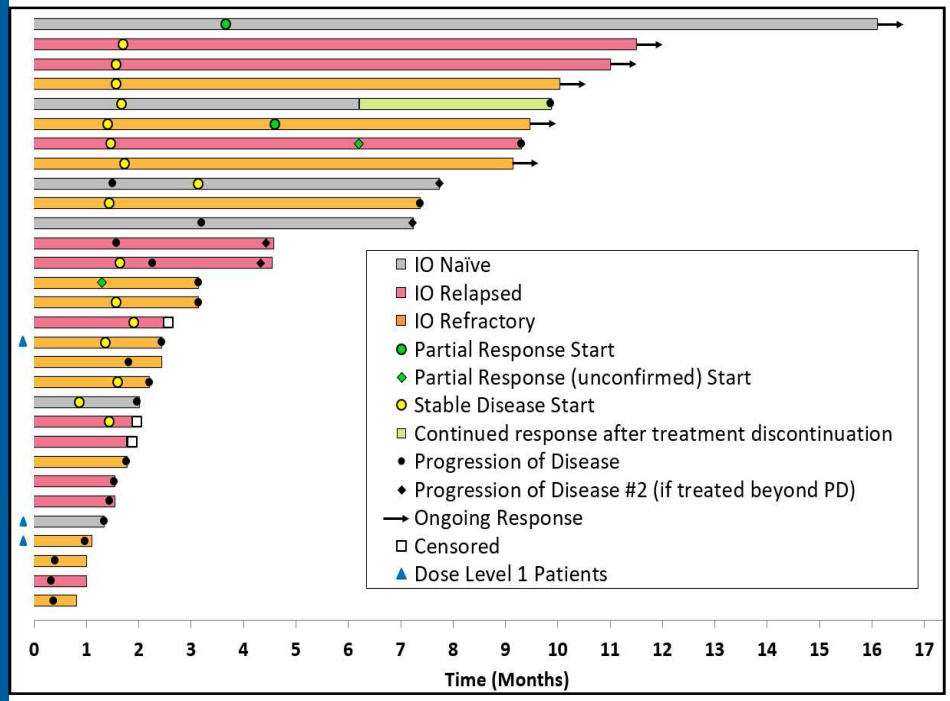
PHASE I: PEMBROLIZUMAB & VORINOSTAT- STUDY DESIGN

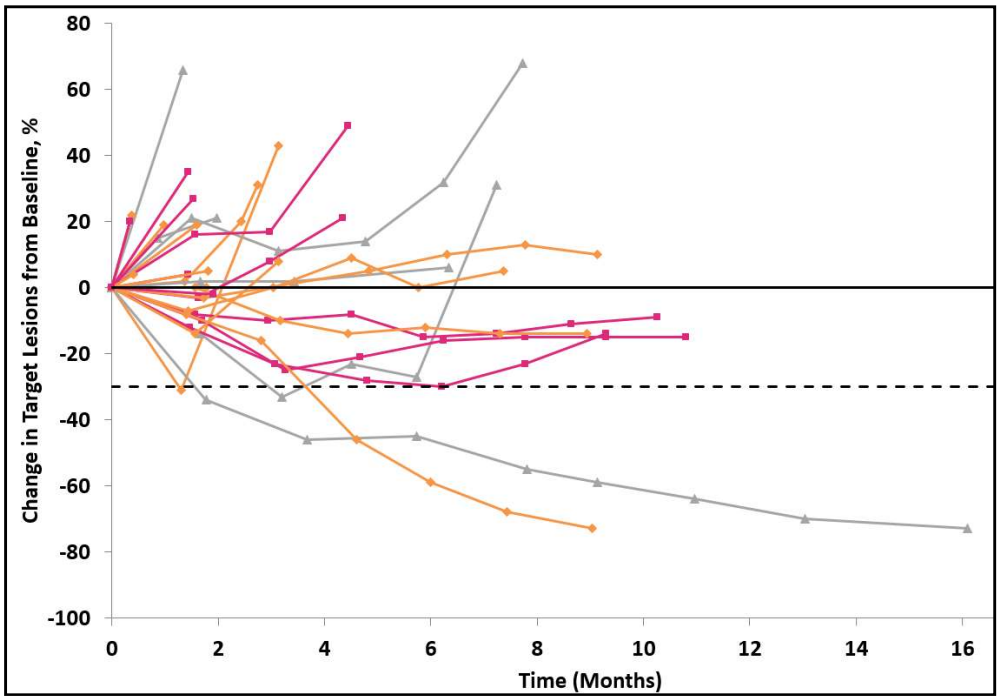


Dose Level	Vorinostat Dose
-1	100mg PO Daily
1	200mg PO Daily
2	400mg PO Daily

Study PI: Jhanelle E. Gray, MD

PEMBROLIZUMAB PLUS VORINOSTAT-RESULTS

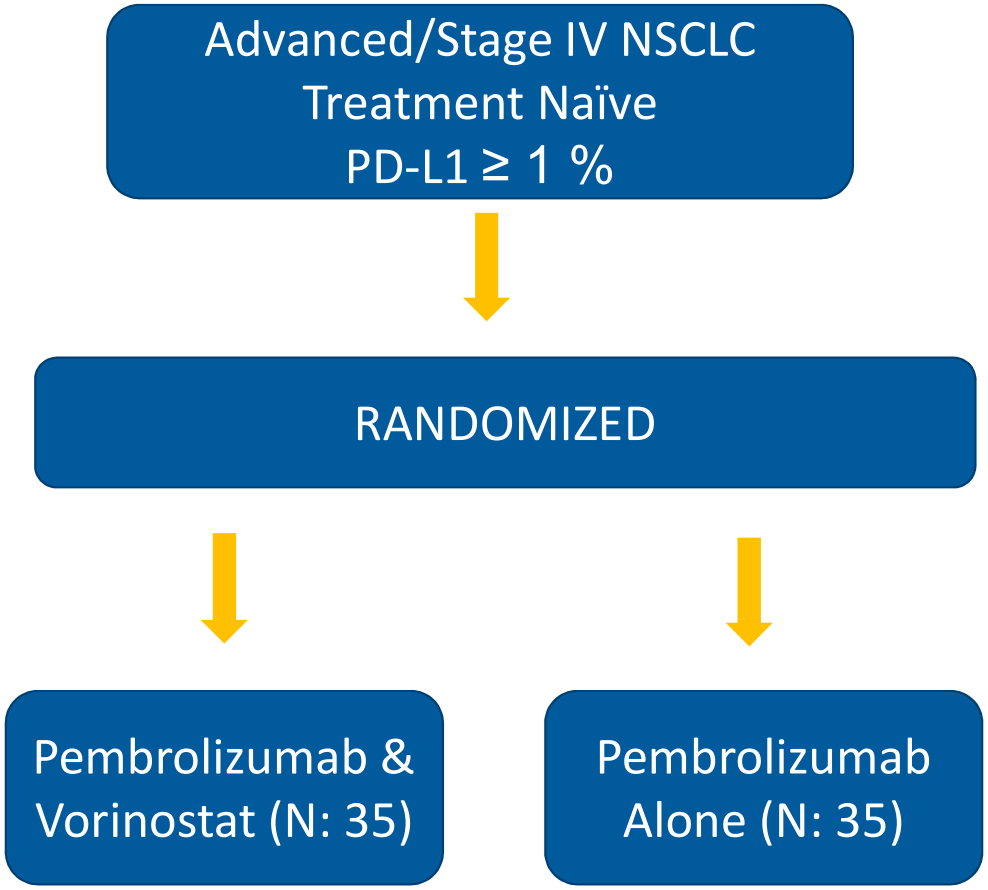




Saltos, Gray et al. ASCO 2018.

Funding: DOD Grant. PIs: Gray & Beg

PHASE II PEMBROLIZUMAB & VORINOSTAT-STUDY DESIGN



-Primary Endpoint: ORR
-Secondary Endpoints: PFS, OS, DOR, Biomarker Correlates

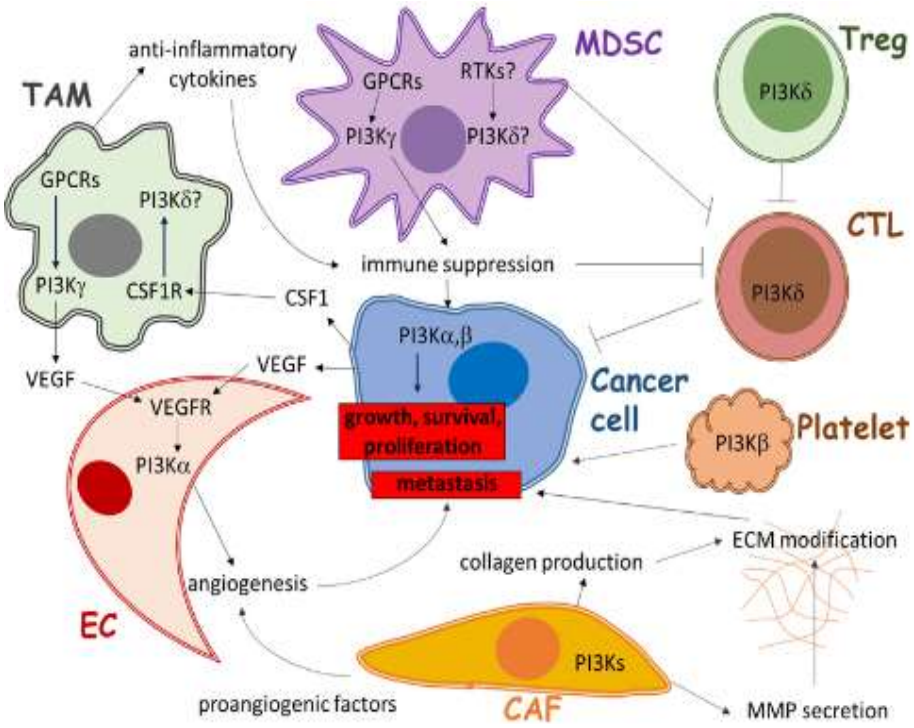
-Pre and On Treatment Biopsies
-Serial Blood Collections

Funding: DOD Grant. PIs: Gray & Beg
Study PI: Jhanelle Gray, MD

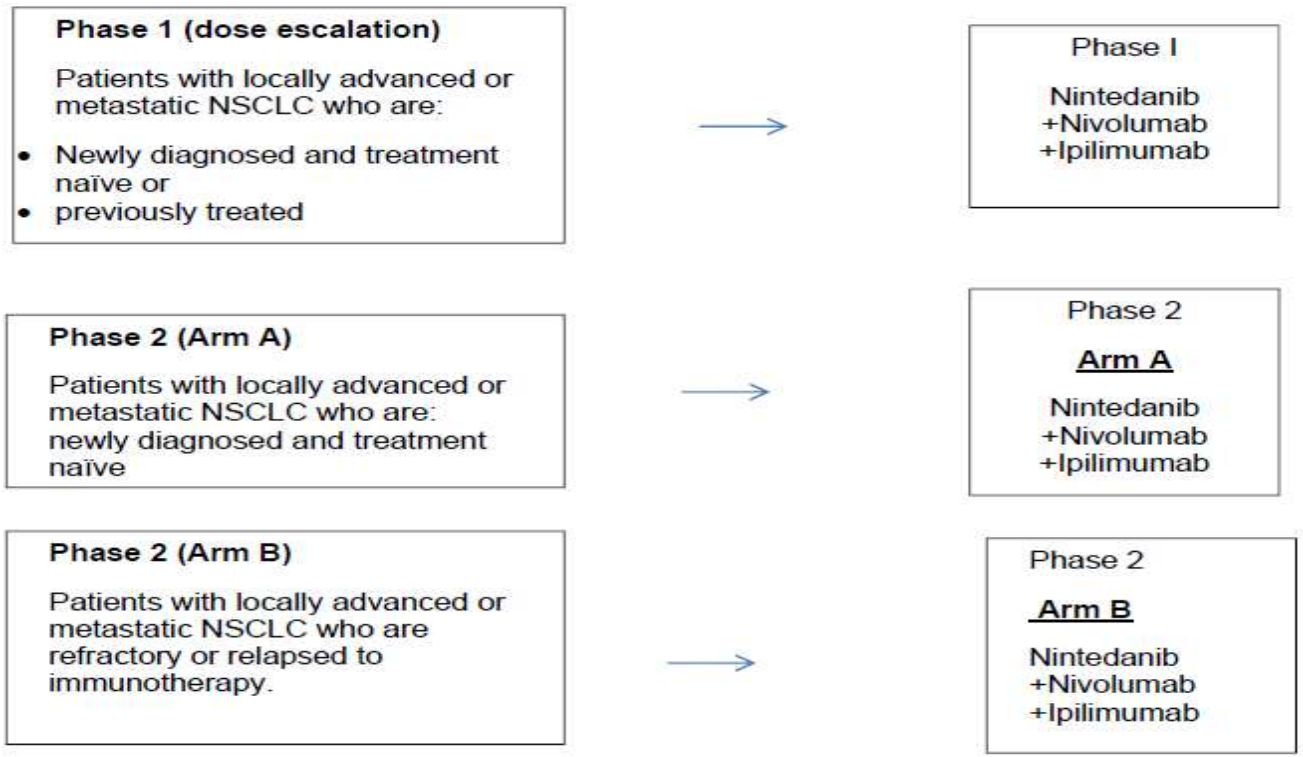
Targeting the Tumor Microenvironment (TME)

- Multiple factors in the TME are immunosuppressive including Cancer Associated Fibroblasts (CAFs).

- Nintedanib, an oral triple inhibitor, blocks three growth factor receptors simultaneously:
  - Vascular endothelial growth factor receptors (VEGFR 1-3),
  - PDGFR alpha and beta
  - Fibroblast growth factor receptors (FGFR 1-3).



Trial Outline



Primary Endpoint Phase 1: MTD/RP2D
Primary Endpoint Phase 2: ORR

Tissue Requirements per Visit

Screening/Pre-treatment	On Treatment (C2D8)	End of Treatment
IHC	IHC	IHC
Immunoscore	Immunoscore	Immunoscore
Nanostring	Nanostring	Nanostring
AQUA FIHC	AQUA FIHC	AQUA FIHC
Mutational Load Analysis by NGS	N/A	N/A

Funding: Funding by Florida Department of Health JEK Grant. BMS and BI for supporting the trial.
PI: Jhanelle E. Gray, MD

Other Clinical Settings Under Evaluation

- Adjuvant/Consolidation for resectable NSCLC
- Neoadjuvant NSCLC
- Consolidation after sequential chemo/rads for unresectable NSCLC
- Concurrent with or Following SBXRT
- CNS disease

SUMMARY

- For advanced stage/metastatic NSCLC, nivolumab, pembrolizumab (PD-L1 ≥ 1%) and atezolizumab are FDA approved for second-line treatment following progression on the platinum-doublet chemotherapy.

- Single agent Pembrolizumab (based on the KN-21G & KN 189 trials) is FDA approved for treatment naïve stage IV NSCLC with a PD-L1 ≥ 50%.

- The KN 042 trial (pembrolizumab, PD-L1 ≥ 1%) is currently under review at the FDA.

SUMMARY

- For patients with treatment naive advanced/metastatic **non-squamous** NSCLC without a driver mutation, regardless of PD-L1 status, carboplatin, pemetrexed & pembrolizumab as well as carboplatin, paclitaxel, bevacizumab & atezolizumab are FDA approved.
- For patients with newly diagnosed advanced/metastatic **squamous** NSCLC without a driver mutation, regardless of PD-L1 status, carboplatin, taxane & pembrolizumab is FDA approved.
- For patients with newly diagnosed advanced/metastatic, driver mutation negative, **PD-L1 ≥ 50%,** non-squamous NSCLC, **without bulky disease or rapid progression**, single agent pembrolizumab is reasonable.
- The INSIGNA trial may help to address questions that remain.

SUMMARY

- The optimal duration of immunotherapy is not yet known.
- Toxicity and QOL should be considered when making treatment decisions.
- For patients with unresectable Stage III NSCLC who have not progressed post 2 cycles of definitive chemoradiation, durvalumab is FDA approved.
- Many trials are underway to evaluate immunotherapy combination trials.

Thank You

- Questions?