JADPRO CE Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

The Role of Immune Checkpoint Inhibitors With and Without Combination Therapy for Nonmutated Metastatic NSCLC

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Faculty Financial Disclosures

- **Ms. Eaby-Sandy** has served as a consultant and on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda.
- **Dr. Beardslee** has served as a consultant for AstraZeneca and Herron, and on the speakers bureau for AstraZeneca.
- **Dr. Davies** has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Genentech, and Merck.
- **Ms. Gilbert** has no conflicts of interest to disclose.
- **Ms. Persinger** has served on speakers bureaus for Genentech and Guardant Health, and on the advisory board for AstraZeneca.

Planning Committee Financial Disclosures

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Learning Objective

- Evaluate efficacy and safety data supporting the use of targeted and immune checkpoint inhibitor therapy used to treat NSCLC

Outline

- Review role of chemotherapy in metastatic NSCLC
- The advent of immunotherapy in past 5 years
  - Role in the first-line setting with or without chemotherapy
  - Role in the second-line setting
- Second-line and beyond chemotherapy or immunotherapy in metastatic NSCLC

Audience Response Question

A 68-year-old male presents with metastatic NSCLC with adenocarcinoma histology. He is fit, has a good performance status, and is ready to start first-line treatment. He would like to learn more about which treatment offers the longest survival. Based on this goal, which treatment would you offer as best positioned to meet his goal?

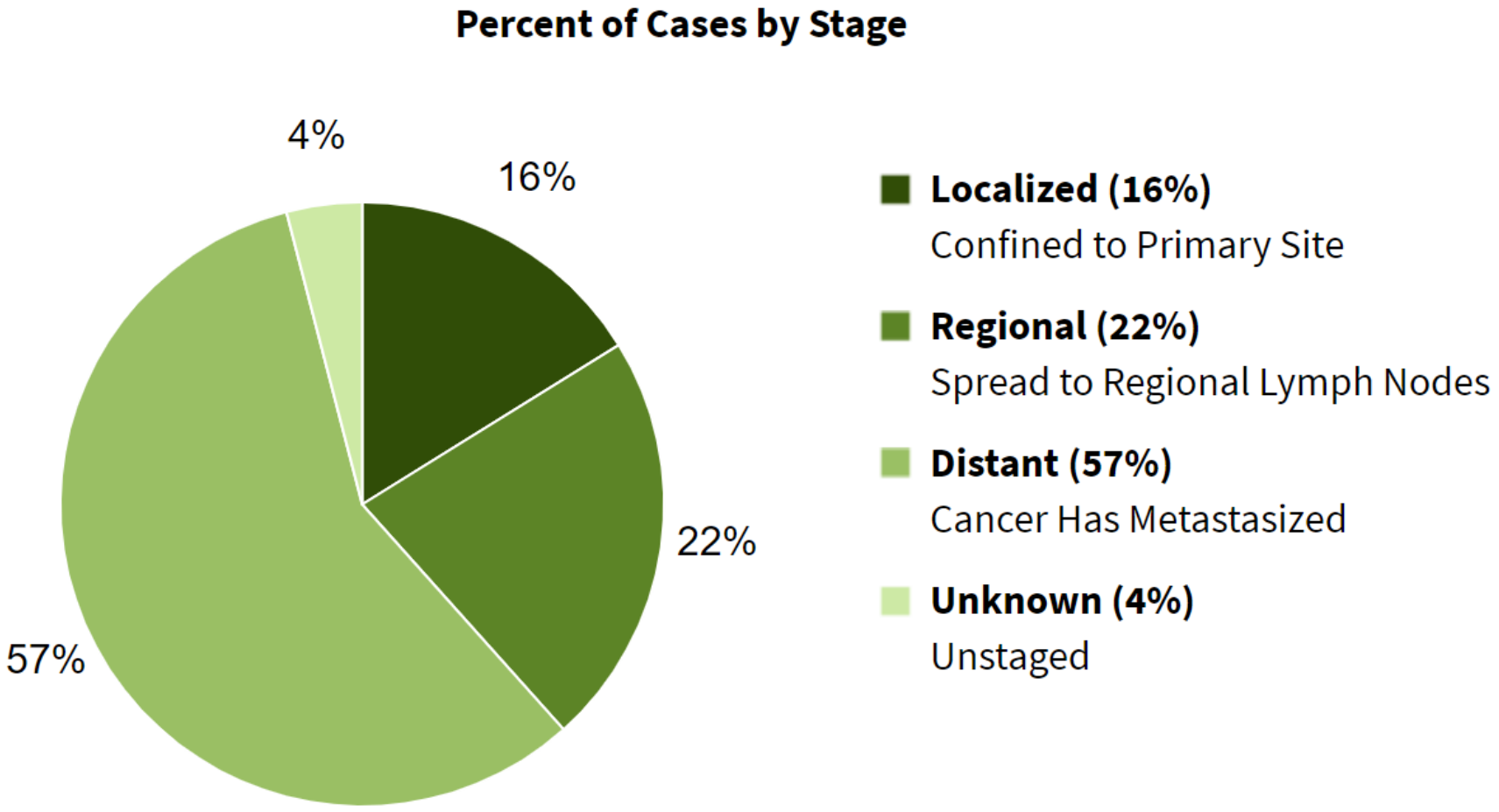
A. Pemetrexed/carboplatin/nivolumab
B. Pemetrexed/carboplatin/pembrolizumab
C. Taxane/carboplatin/bevacizumab/atezolizumab
D. Taxane/carboplatin/pembrolizumab
E. Unsure

Audience Response Question

The 5-year survival rate for patients with metastatic NSCLC who had a PD-L1 score of 50% or greater and were treated with single-agent first-line pembrolizumab was approximately:

A. 5%
B. 10%
C. 20%
D. 30%
E. Unsure

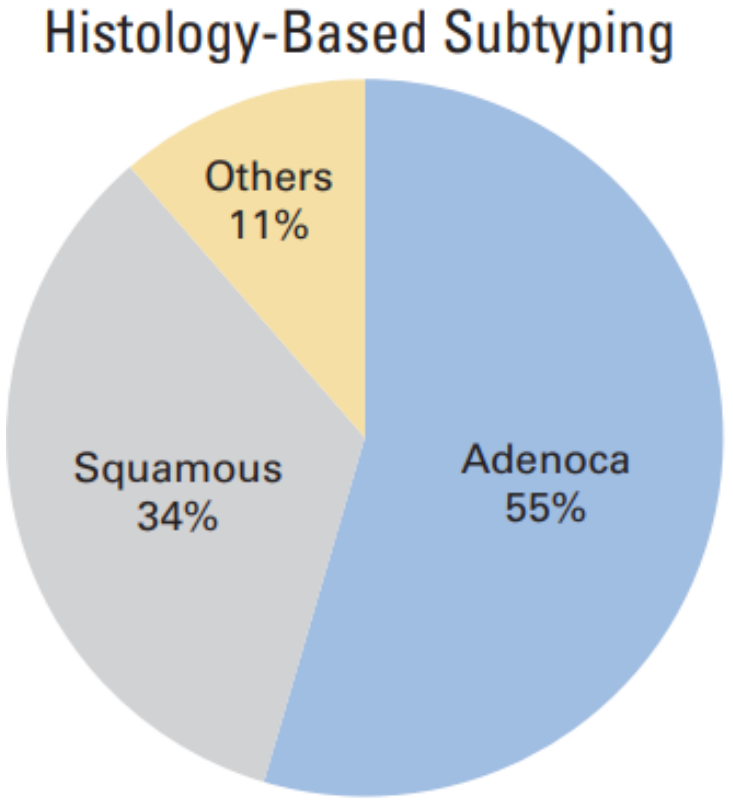
Lung Cancer Stages and Survival



https://seer.cancer.gov/statfacts/html/ungb.html

First-Line Treatment: Chemotherapy and Immunotherapy

Nonsquamous
(predominantly adenocarcinoma)



Case Study: Adenocarcinoma

- Mrs. Adeno is 69 years old and comes to you for treatment consideration for her stage IV NSCLC with adenocarcinoma histology.
- She has smoked for 45 years and has just quit in the past 6 months when she started having symptoms of her lung cancer.
- She has a good PS, some SOB and cough from cancer, and some weight loss and generalized fatigue.
- Her DNA sequencing panel has not come back yet; however, her PD-L1 and FISH tests have
  - PD-L1 is 65%, FISH or IHC: negative for *ROS1* or *ALK*

PS = performance score; SOB = shortness of breath

First-Line Chemotherapy Treatment of Nonsquamous NSCLC: Regimens Used in Past 10 Years

- Cisplatin or carboplatin + any of drugs below
- Bevacizumab added in eligible patients (but what about IO?)
- Pemetrexed added to platinum is superior to gemcitabine + platinum
- Other drugs can combine with platinum in PS 0–1
  - Docetaxel
  - Etoposide
  - Gemcitabine
  - Nab-paclitaxel
  - Paclitaxel
  - Vinorelbine

NCCN Guidelines. Non-Small Cell Lung Cancer. Version 4.2016.

Approved Immunotherapy Drugs in Metastatic NSCLC

Drug	Indications	MOA Dosing
Nivolumab	Metastatic NSCLC: 1. After failure of platinum-based chemotherapy regimen, independent of PD-L1 status.	• PD-1 inhibitor • 240 mg IV every 2 weeks OR 480 mg IV every 4 weeks
Pembrolizumab	Metastatic NSCLC: 1. First-line single agent if PD-L1 TPS score ≥ 1% 2. First line in combination with platinum-based chemotherapy independent PD-L1 3. Second line after failure of platinum-based chemotherapy regimen, if TPS score ≥ 1% 4. Locally advanced for TPS score ≥ 1% if not candidate or refused concurrent chemo/radiation therapy	• PD-1 inhibitor • 200 mg IV every 3 weeks

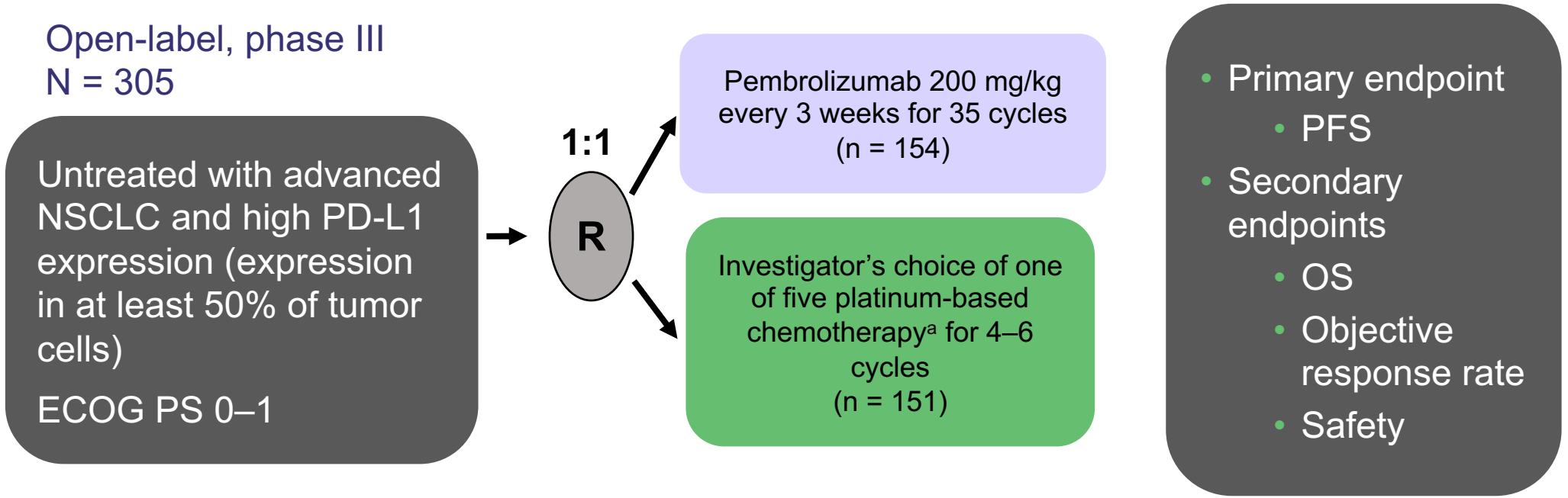
Atezolizumab	Metastatic NSCLC:
	1. After failure of platinum-based chemotherapy regimen, independent of PD-L1 status
	2. In nonsquamous combination with taxane plus carboplatin plus bevacizumab
		• PD-L1 inhibitor
		• 1200 mg IV every 3 weeks
		• In maintenance or single agent after chemo:
		  • 840 mg q2 weeks OR
		  • 1200 mg q3 weeks OR
		  • 1680 mg q4 weeks

Nivolumab Package Insert, 2019. Pembrolizumab Package Insert, 2019; Atezolizumab Package Insert, 2019

Case Study (cont.)

- For Mrs. Adeno 69 y/o, adenocarcinoma, PD-L1 65%, ALK/ROS1 neg, molecular pending
  - How would you manage this patient?
  - Would you wait for molecular to start systemic tx?
  - In addition, Mrs. Adeno has rheumatoid arthritis and is on weekly MTX and hydroxychloroquine and 10 mg prednisone daily, which controls her symptoms

KEYNOTE-024 Pembrolizumab vs. Platinum-Based Chemotherapy



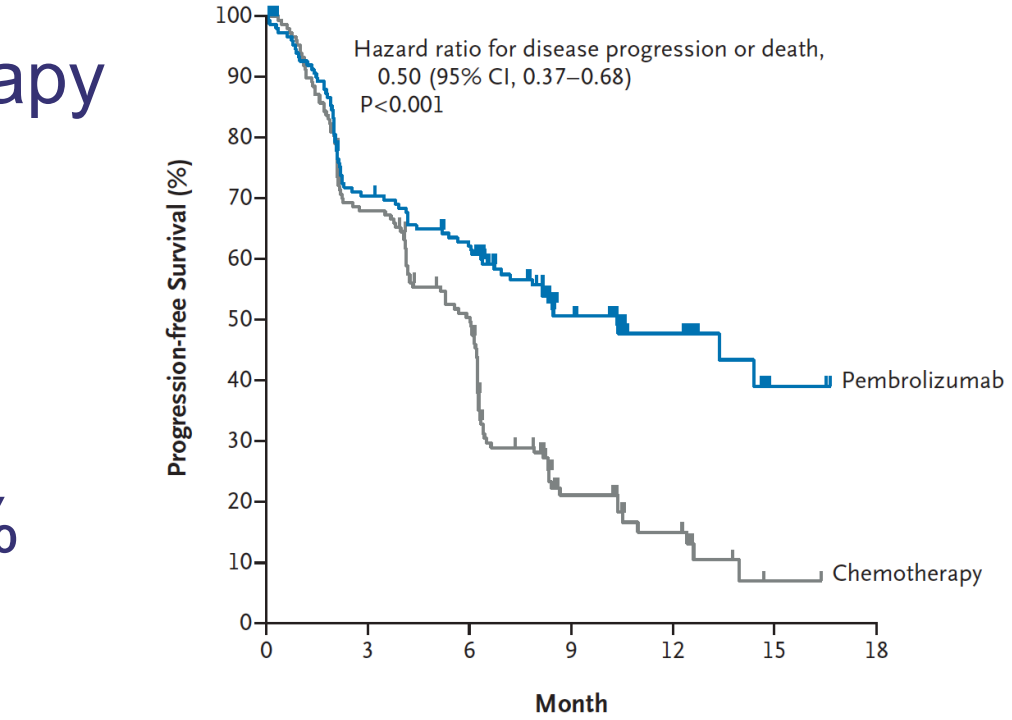
- 23%–28% patients with advanced NSCLC have high level of programmed death ligand 1 (PD-L1) expression; defined as 50% of tumor cells.

[a]carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel.

Reck M, et al. *N Engl J Med.* 2016;375:1823–33.

Pembrolizumab vs. Platinum-Based Chemotherapy: PFS

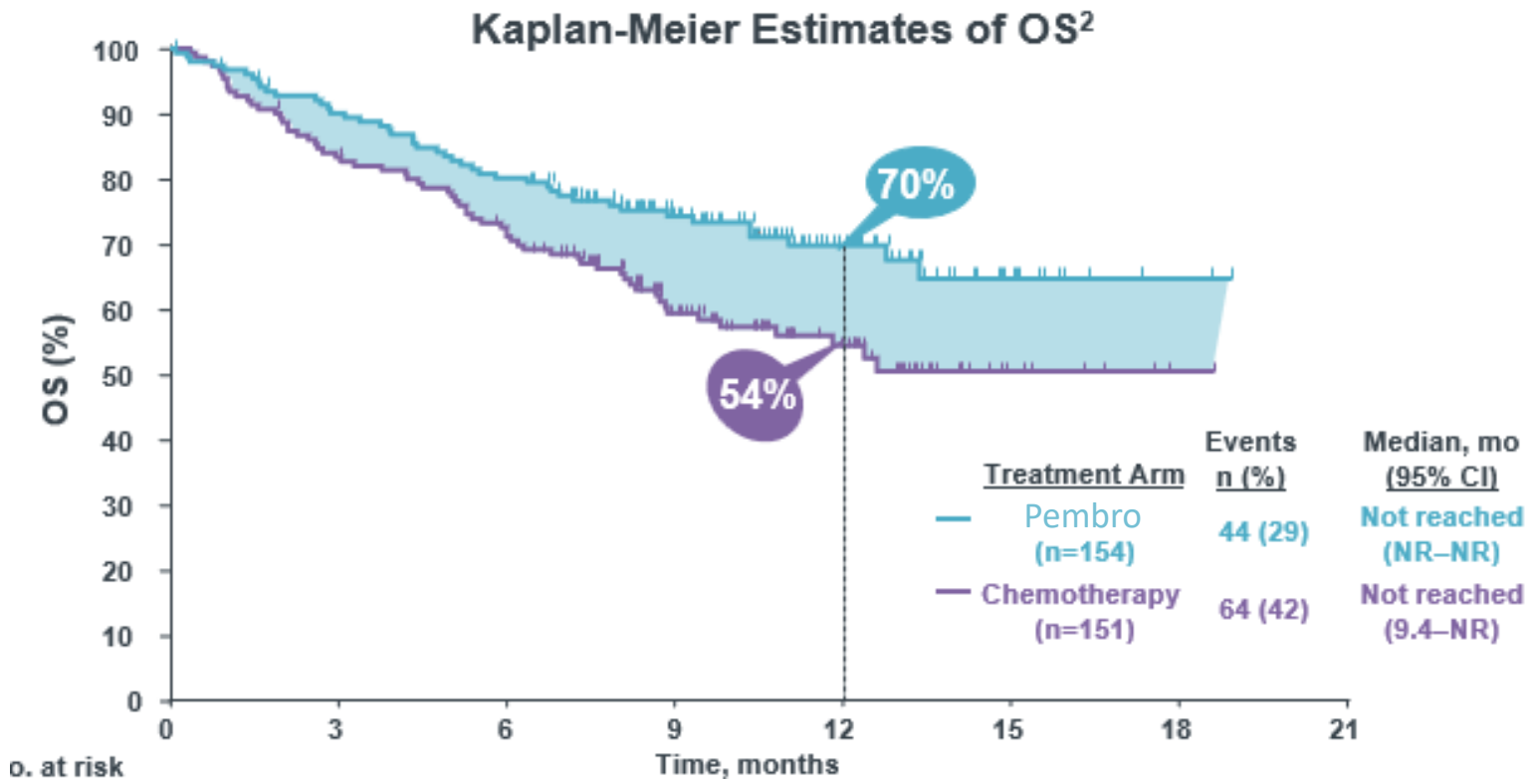
- First time single-agent immunotherapy better than platinum-based chemotherapy
- Generally less toxic than chemotherapy
- This benefit is seen in PD-L1 ≥ 50% expression



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

Reck M, et al. *N Engl J Med.* 2016;375:1823–33.

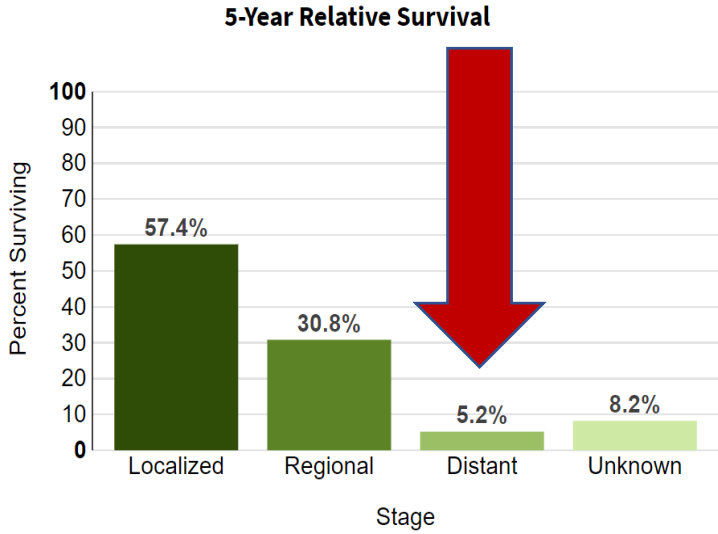
Pembrolizumab vs. Platinum-Based Chemotherapy: Overall Survival (OS)



Reck M, et al. *N Engl J Med.* 2016;375:1823–33.

Updated 5-Year OS Results of KEYNOTE-001

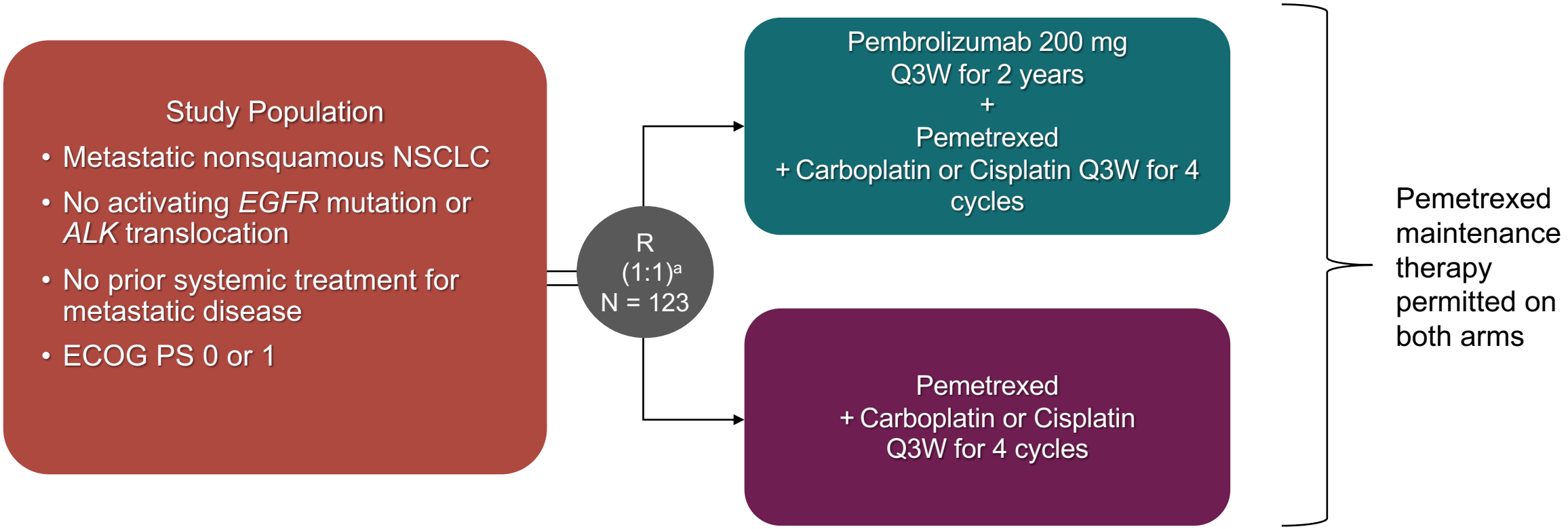
- KEYNOTE-001 original pembrolizumab single-agent study across tumor types, including a NSCLC cohort, in which 101 were treatment naïve
- The median OS was 22.3 months for first-line single agent pembrolizumab
- **However**, the 5-year OS for first line was
  - 23.2% for all-comers of PD-L1 expression
  - 29.6% for ≥ 50% PD-L1 expression!



Garon E. et al. J Clin Oncol. 2019; 37. doi:10.1200/JCO.19.01207

Or…For Any PD-L1 Expression in Metastatic Adenocarcinoma

KEYNOTE-189 Chemo+Pembro vs. Chemo Alone

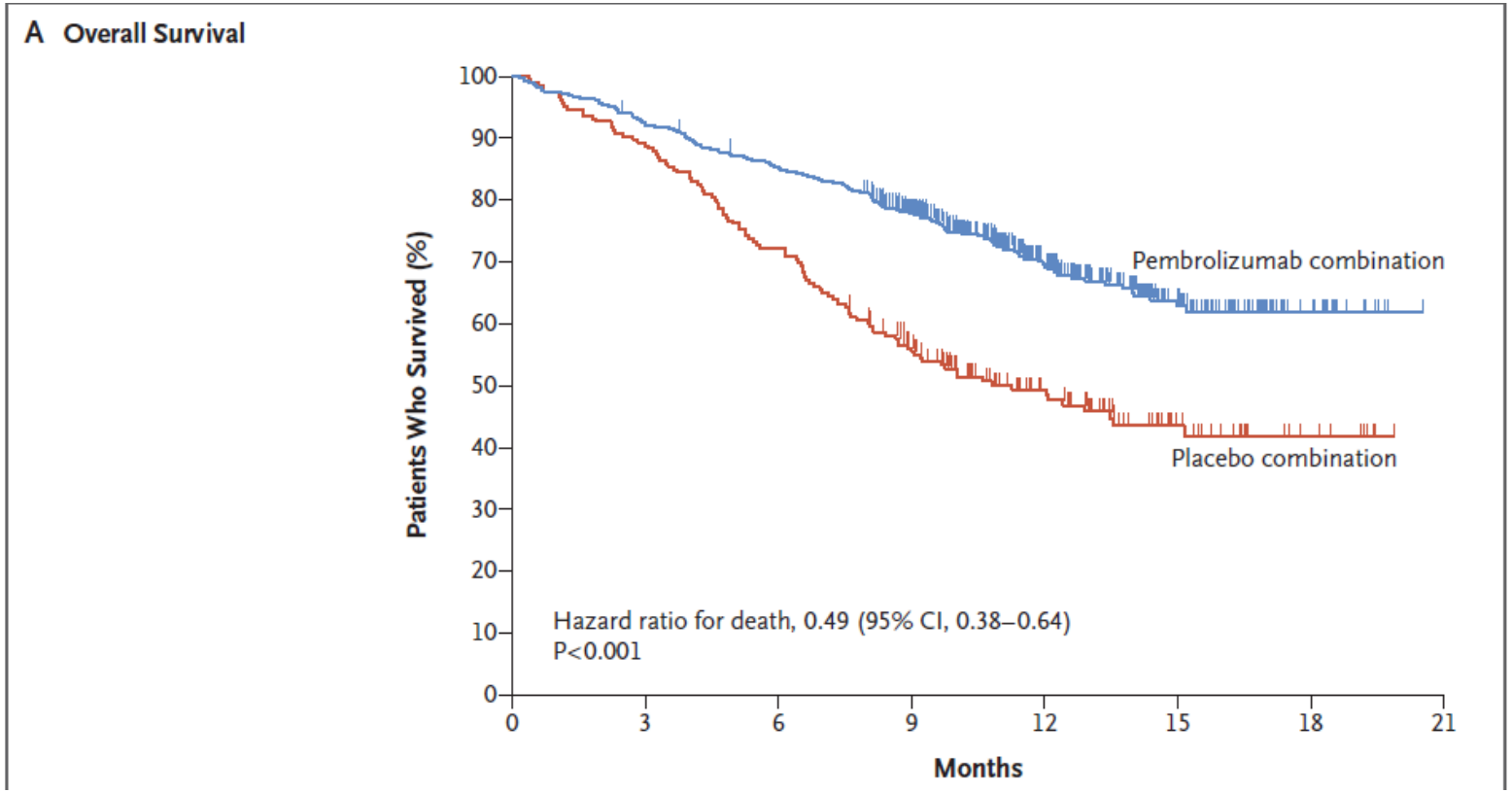


End Points

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

KEYNOTE-189: Chemo+Pembro vs. Chemo Alone: OS Results

- At 12 months, 69% alive in chemo plus pembro arm as opposed to 49% in chemo alone arm
- Median OS was not reached in chemo plus pembro arm, was 11.3 months in chemo alone arm.



Gandhi L, et al. *N Engl J Med*. 2018;378:2078-92.

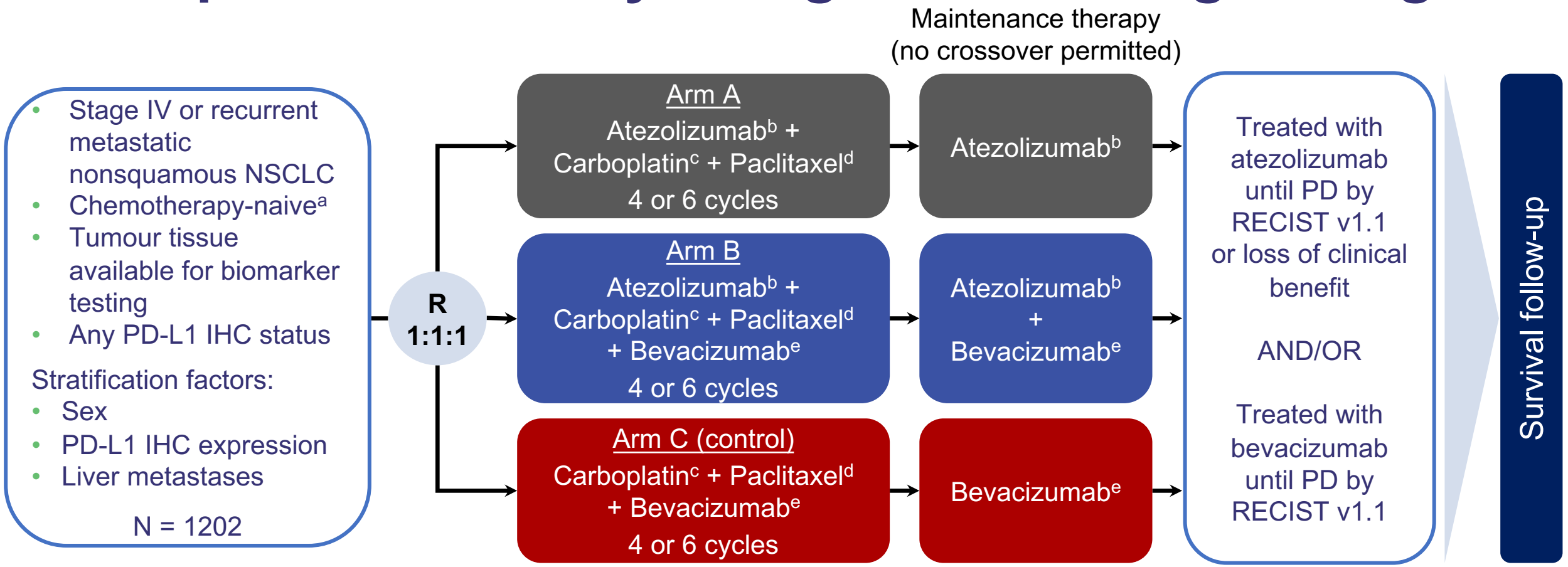
KEYNOTE-189: 2019 Update at ASCO

- Median overall survival reached in both arms:
  - **22 months** for pemetrexed/platinum/pembrolizumab, vs.
  - **10.7 months** for pemetrexed/platinum alone
- Also, interesting stat of PFS2 (PFS from randomization until after second-line therapy):
  - 17 months vs. 9 months (in favor of pembrolizumab arm)
  - Further demonstrates importance of IO given first line

Gadgeel SM et al. *J Clin Oncol* 37, 2019 (suppl; abstr 9013)

If 3 Drugs Are Good, What About Combining 4 Drugs?

IMpower150 Study Design: Combining 4 Drugs



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

Reck M, et al. IMpower150 PFS analysis.

[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.

IMpower150: Combining 4 Drugs!

- Atezolizumab + paclitaxel + carboplatin + bevacizumab (APCB) showed superior PFS to PCB alone in wild-type population (8.3 months vs. 6.8 months, $p < .001$)
- Median OS significantly greater in ABCP group than BCP group (**19.2 months vs. 14.7 months**, $p = .02$)[a]
- Where is this regimen used? For mutation + population after receiving their "targeted therapy" up front? Role of IO in mutated population.
- Do 4 drugs increase both medical and financial toxicity?

Socinski MA, et al. *N Engl J Med*. 2018;378:2288-301.
[a]Patients without EGFR/ALK

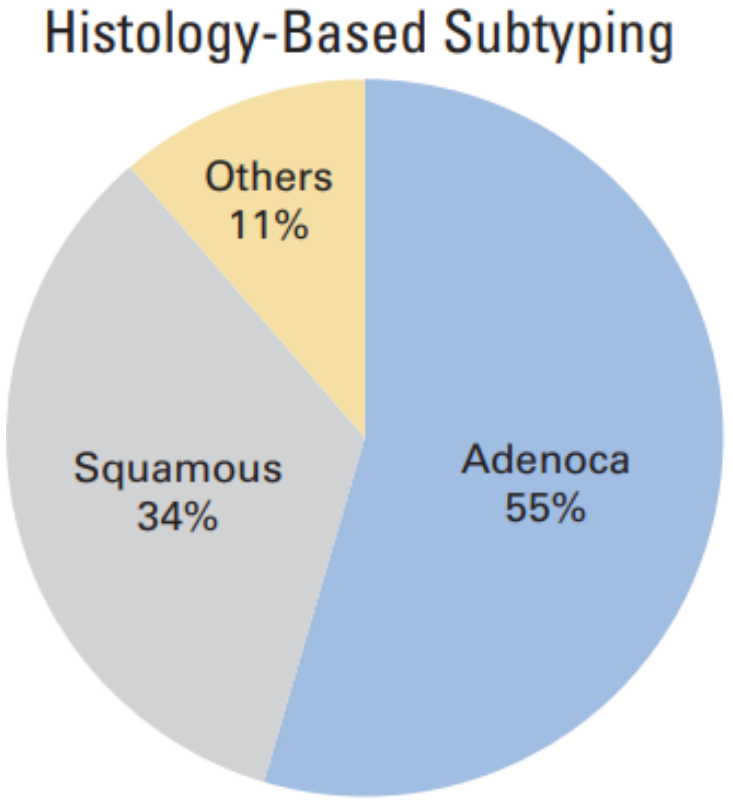
Summary

	Pembrolizumab single agent in ≥ 50% PD-L1	Pemetrexed/platinum/ pembrolizumab in any PD-L1	Taxane/carboplatin/atezolizumab/bevacizumab
Median PFS	10.3 months (2016 data)	8.8 months (2018 data)	8.3 months
Median OS	30 months (2018 data)	22 months (2019 data)	19.2 months

- What about nivolumab?
  - In studies combining chemotherapy and nivolumab vs. chemotherapy alone, nivolumab has not met its primary endpoints of PFS and OS in general populations. Some benefit did appear, but unclear how to delineate.

First-Line Treatment: Chemotherapy and Immunotherapy

Squamous Cell Carcinoma



Case Study: Squamous

- Mr. Squam is a 72 year old with metastatic squamous NSCLC, PD-L1 of 0%
- 2 PPD smoker, and has cut back to 1/2 PPD now, but still smoking
- Bone mets which were radiated. SOB at baseline, significant weight loss.
- Diabetic

Chemotherapy

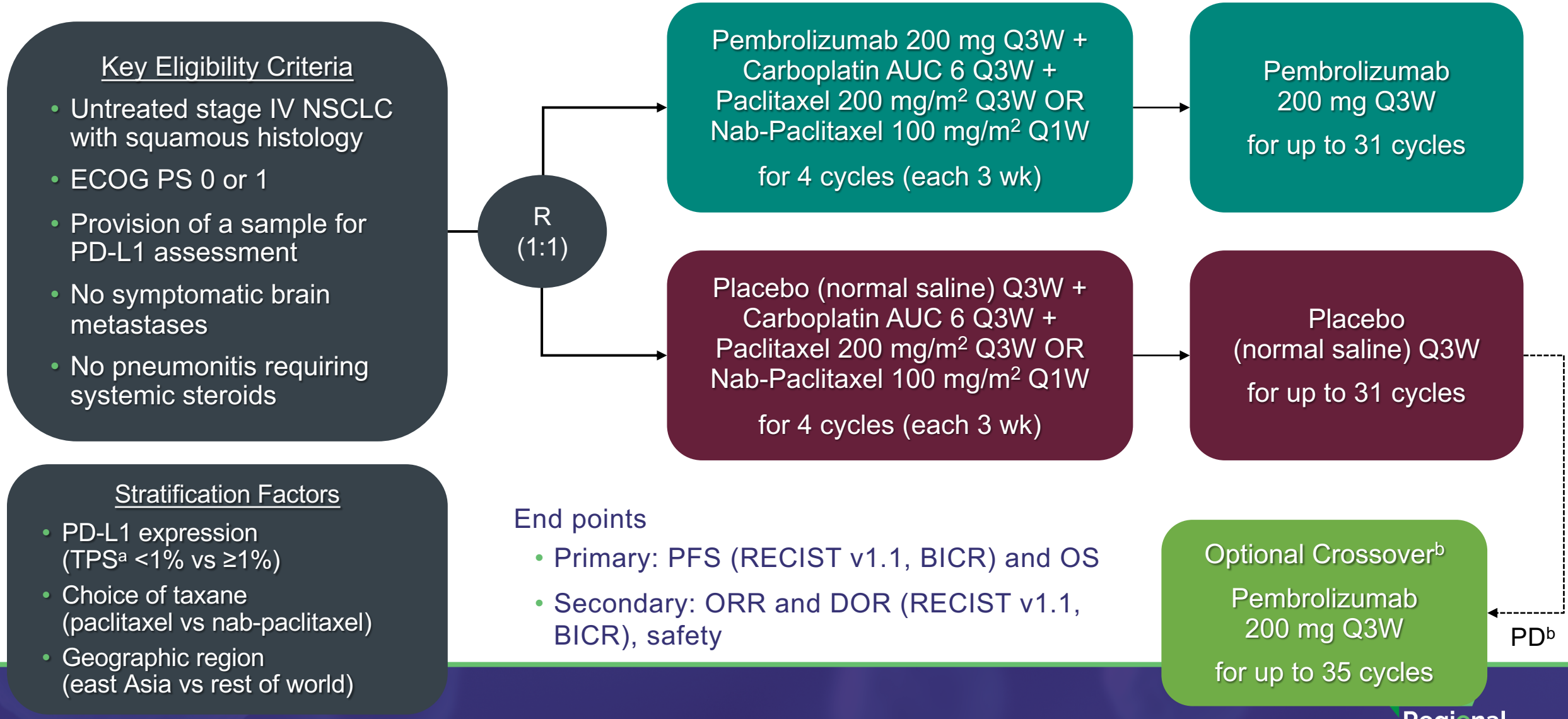
- Same concept as nonsquamous, platinum-based chemotherapy
- Other than
  - No pemetrexed
  - No bevacizumab

NCCN Guidelines: Chemotherapy First-Line Treatment of Squamous NSCLC

- Albumin-bound paclitaxel
- Carboplatin/albumin-bound paclitaxel
- Carboplatin/docetaxel
- Carboplatin/etoposide
- Carboplatin/gemcitabine
- Carboplatin/paclitaxel
- Cisplatin/docetaxel
- Cisplatin/etoposide
- Cisplatin/gemcitabine
- Cisplatin/paclitaxel
- Gemcitabine
- Gemcitabine/docetaxel
- Gemcitabine/vinorelbine
- Paclitaxel
- Pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel

NCCN Guidelines. Non-Small Cell Lung Cancer. Version 7.2019.

KEYNOTE-407 Study (NCT02775435)

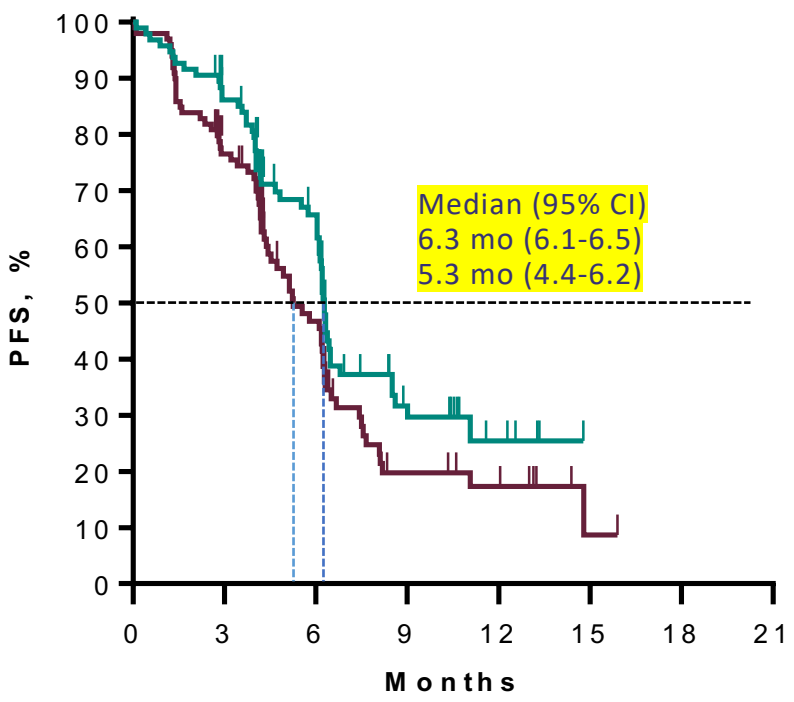


BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and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

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

TPS < 1%

	Events	HR (95% CI)
Pembro + Chemo	57.9%	0.68 (0.47-0.98)
Placebo + Chemo	67.7%	

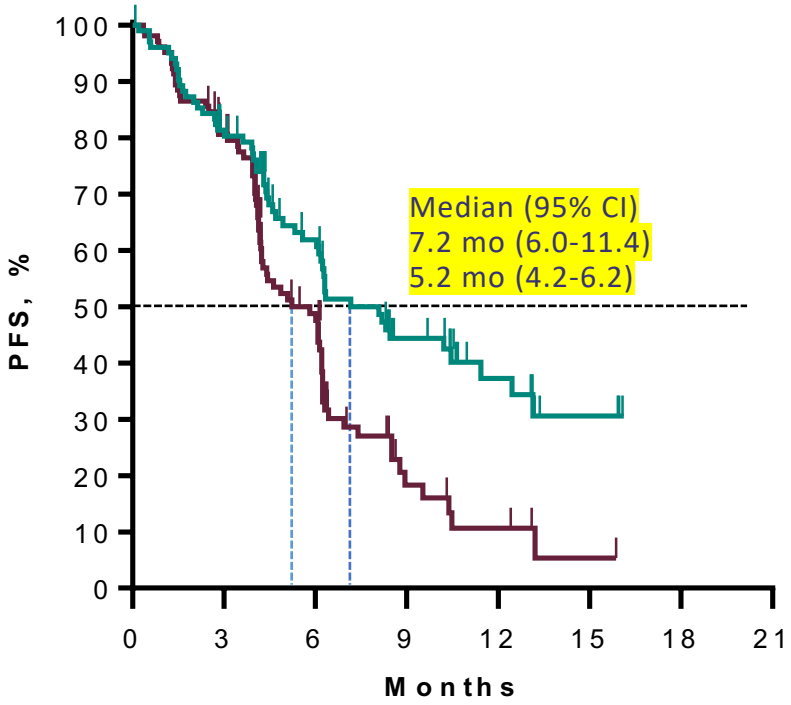


No. at Risk

95	78	48	16	5	0	0	0
99	71	35	11	6	1	0	0

TPS 1%–49%

	Events	HR (95% CI)
Pembro + Chemo	52.4%	0.56 (0.39-0.80)
Placebo + Chemo	70.2%	

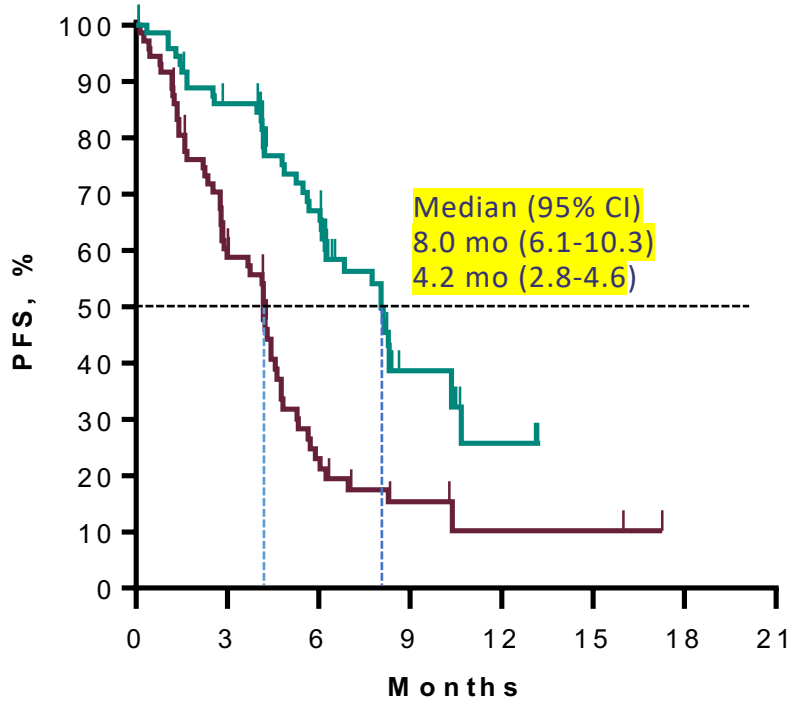


No. at Risk

103	79	49	26	13	5	0	0
104	79	40	8	4	1	0	0

TPS ≥ 50%

	Events	HR (95% CI)
Pembro + Chemo	53.4%	0.37 (0.24-0.58)
Placebo + Chemo	75.3%	



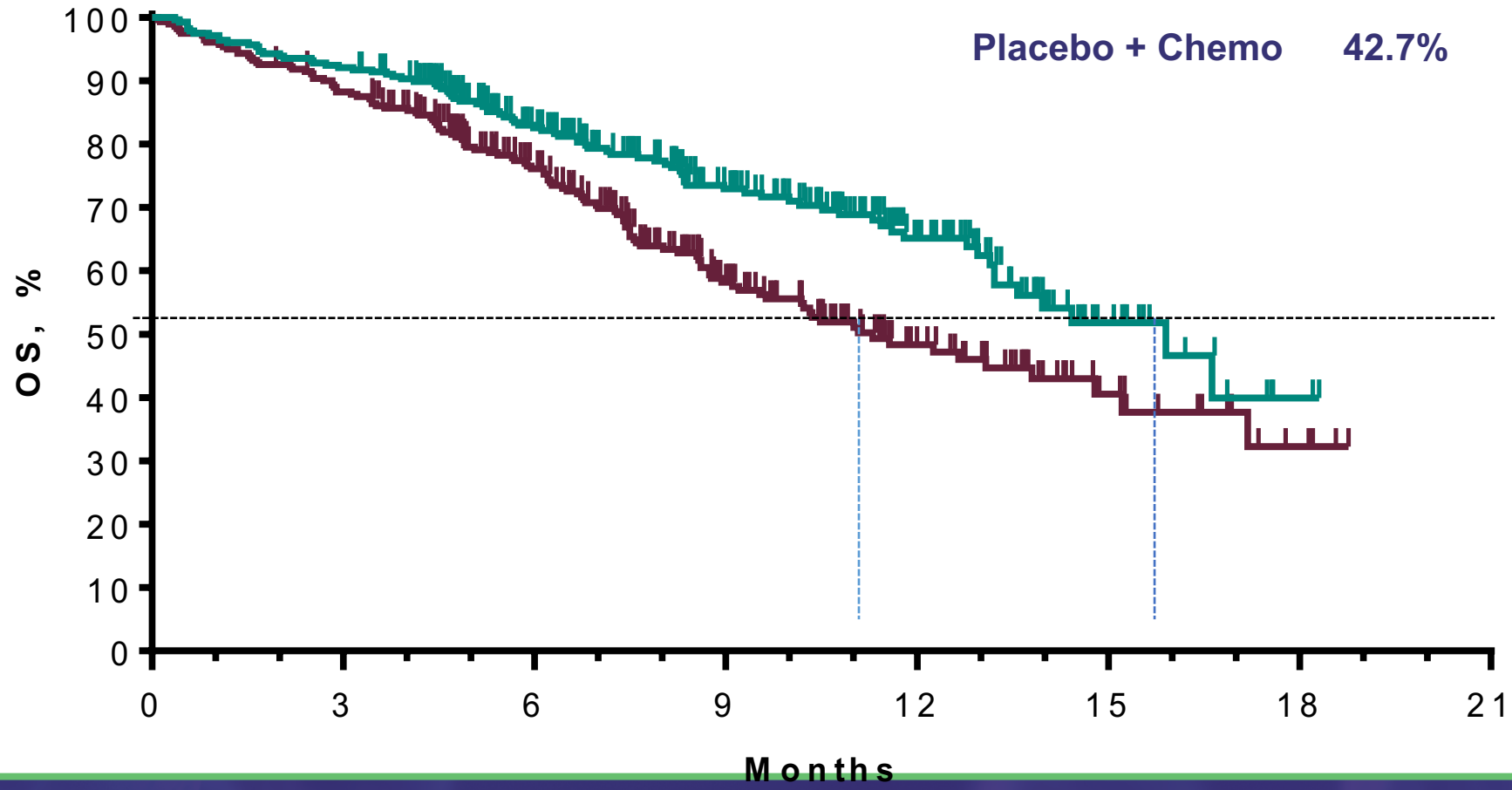
No. at Risk

73	60	41	12	4	0	0	0
73	38	13	5	2	2	0	0

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

Overall Survival at IA2, ITT

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



Median (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

Data cutoff date: Apr 3, 2018.

Case study: Mr. Squam

- 72-year-old, diabetic, metastatic squamous cell NSCLC, PD-L1 negative 0%
- What treatment would you recommend and why?
- Would you perform molecular testing?
- What if he has h/o heart transplant?

Summary of First-Line Therapy in NSCLC

- Pembrolizumab plus chemotherapy for both squamous and nonsquamous NSCLC is standard of care
- Atezolizumab plus bevacizumab plus chemotherapy is reasonable as well in nonsquamous NSCLC
- No role for nivolumab currently in first-line setting
- Platinum-based chemotherapy standard of care with immunotherapy
- In PD-L1 ≥ 50% should consider single-agent pembrolizumab.

Second-Line Treatment: Chemotherapy and Immunotherapy

NSCLC

Second-Line (Subsequent) Therapy

- NCCN-recommended second-line treatment for NSCLC:
  - Docetaxel +/– ramucirumab
  - Pemetrexed (nonsquamous histology only, if not used first line)
  - Nivolumab, pembrolizumab, atezolizumab, if not used first line
  - Gemcitabine

CheckMate, KEYNOTE, and POPLAR Studies: Efficacy Summary – Overall Survival

	CheckMate[1]		KEYNOTE[2]			POPLAR[3]	
Endpoint	Nivolumab (n = 135)	Docetaxel (n = 137)	Pembro 2 (n = 344)	Pembro 10 (n = 346)	Docetaxel (n = 343)	Atezolizumab (n = 144)	Docetaxel (n = 143)
Median OS in intent-to-treat population (mo)	9.2	6.0	10.4	12.7	8.5	12.6	9.7
Median OS in pts with TPS score ≥ 50% (mo)	Rates of OS in PD-L1 subgroups favored nivolumab and were similar to those in primary population		14.9[a]	17.3[b]	8.2	• TC3 or IC3: 15.5 • TC2/3 or IC2/3: 15.1 • TC1/2/3 or IC1/2/3: 15.5 • TC0 and IC0: 9.7	• TC3 or IC3: 11.1 • TC2/3 or IC2/3: 7.4 • TC1/2/3 or IC1/2/3: 9.2 • TC0 and IC0: 9.7
1-yr OS (% of pts)	42	24					

OS = overall survival

[a]*P* = .0002 vs docetaxel; [b]*P* < .0001 vs docetaxel

Brahmer J, et al. *N Engl J Med.* 2015;373:123-135; 2. Herbst RS, et al. *Lancet.* 2016;387:1540-1550; 3. Fehrenbacher L, et al. *Lancet.* Published Online March 9, 2016.

CheckMate, KEYNOTE, and POPLAR Studies: Efficacy Summary – Progression-Free Survival

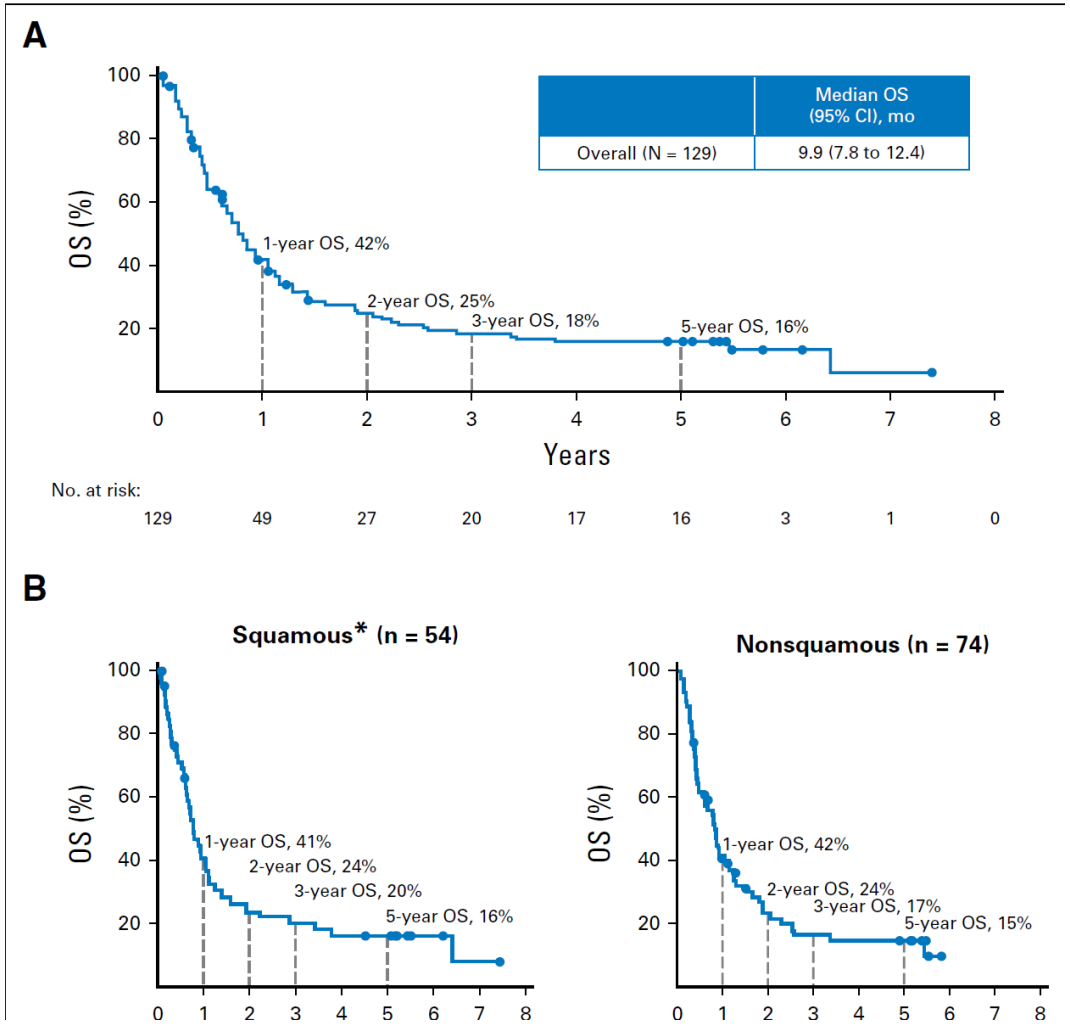
	CheckMate[1]		KEYNOTE[2]			POPLAR[3]	
Endpoint	Nivolumab (n = 135)	Docetaxel (n = 137)	Pembro 2 (n = 344)	Pembro 10 (n = 346)	Docetaxel (n = 343)	Atezolizumab (n = 144)	Docetaxel (n = 143)
Median PFS (mo) in intent-to-treat population (mo)	3.5	2.8	3.9	4.0	4.0	2.7	3.0
Median PFS in pts with TPS score ≥ 50% (mo)	Rates of OS in PD-L1 subgroups favored nivolumab and were similar to those in primary population		5.0[a]	5.2[b]	4.1	• TC3 or IC3: 7.8 • TC2/3 or ICT2/3: 3.4 • TC1/2/3 or IC1/2/3: 2.8 • TC0 and IC0: 1.7	• TC3 or IC3: 3.9 • TC2/3 or IC2/3: 2.8 • TC1/2/3 or IC1/2/3: 3.0 • TC0 and IC0: 4.1
1-yr PFS (% of pts)	21	6	NR			NR	

- Of note, avelumab was studied in this same schema and recent results showed that it failed to meet endpoints and will not be approved in this second-line setting for NSCLC

PFS = progression-free survival; NR = not reported.
[a]*P* = .0001 vs docetaxel; [b]*P* < .0001 vs docetaxel.
1. Brahmer J, et al. *N Engl J Med.* 2015;373:123-135; 2. Herbst RS, et al. *Lancet.* 2016;387:1540-1550; 3. Fehrenbacher L, et al. *Lancet.* Published online March 9, 2016.

CheckMate-017 and -057 5-Year Updates

- Pooled analysis of 2 trials of patients tx with nivolumab vs docetaxel in second-line setting
- 16% patients alive at 5 years (16% squam, 15% adeno)
- 88% were current or former smokers
- Conclusion: durable responses in those responders



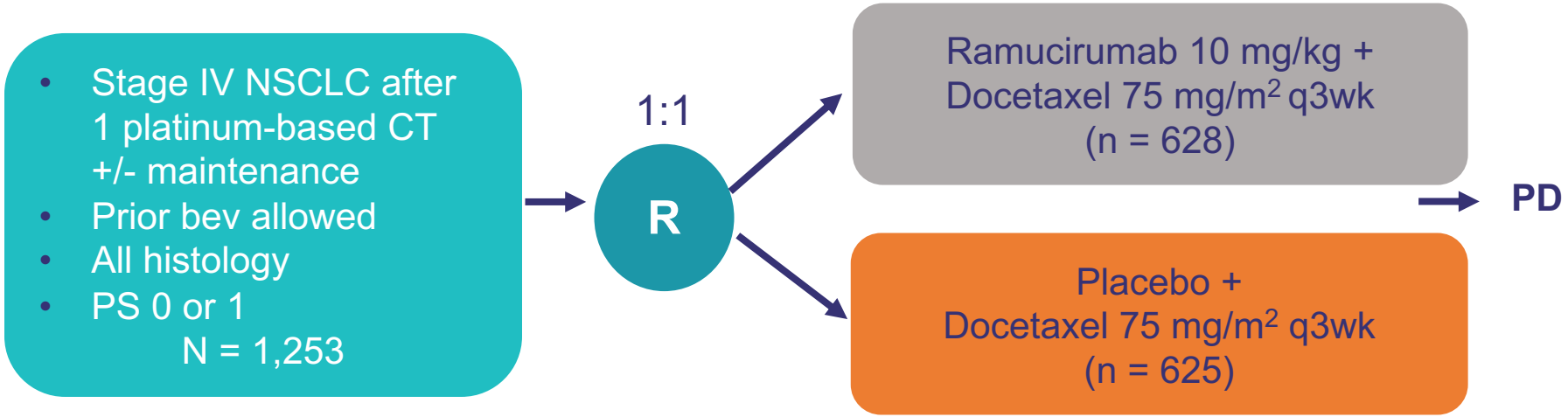
Gettinger S et al. 2018. *J Clin Oncol* 36:1675-1684.

Since Most Immunotherapy Used in First Line now: What About Chemotherapy Options in Second-Line Setting After Failure of Chemo/IO?

Case Study of Mr. Squam

- 72-year-old with metastatic squamous cell NSCLC, PD-L1 negative
- Received nab-paclitaxel/carboplatin/pembrolizumab first line and after 11 months, currently on the pembrolizumab maintenance, has developed disease progression.
- He has good PS of 1, has some symptoms; however, would like to pursue further treatment.
- What second-line treatments are available for him?

REVEL Trial: Ramucirumab



Stratification factors

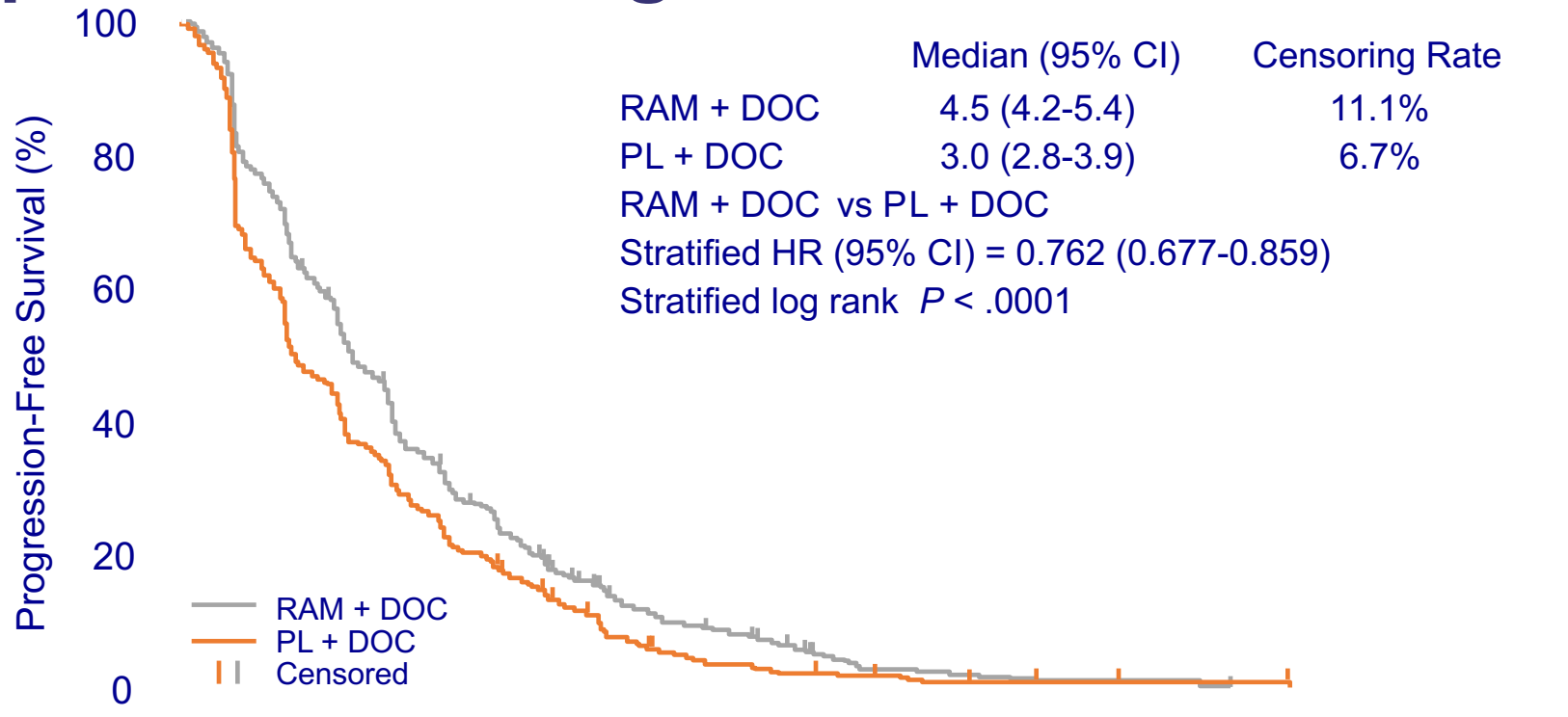
- ECOG PS 0 vs 1
- Gender
- Prior maintenance
- East Asia vs rest of the world

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety, patient-reported outcomes

CT, chemotherapy; Bev, bevacizumab, OS, overall survival; PFS, progression-free survival, Ram, ramucirumab.

Perol M, et al. *J Clin Oncol.* 2014;32(18 suppl). Abstract LBA8006;
Garon EB, et al. *Lancet.* 2014;384(9944):665-673.

REVEL: Progression-Free Survival, ITT Population, Investigator Assessment



	Median (95% CI)	Censoring Rate
RAM + DOC	4.5 (4.2-5.4)	11.1%
PL + DOC	3.0 (2.8-3.9)	6.7%

RAM + DOC vs PL + DOC

Stratified HR (95% CI) = 0.762 (0.677-0.859)

Stratified log rank $P < .0001$

Number at Risk

RAM + DOC	628	383	204	120	59	38	11	7	3	3	0	0	0
PL + DOC	625	301	172	95	37	17	9	4	3	2	0	0	0

Perol M, et al. *J Clin Oncol.* 2014;32(18 suppl). Abstract LBA8006; Garon EB, et al. *Lancet.* 2014;384(9944):665-673.

REVEL: Adverse Effects of Ramucirumab

Adverse event	Ramucirumab	Placebo
Hypertension	11%	5%
Stomatitis/mucosal inflammation	37%	19%
Neutropenia (grade 3/4)	49%	40%
Hemoptysis	⬇	⬇
Nonsquamous	7% (1% grade 3)	6% (1% grade 3)
Squamous	10% (2% grade 3)	12% (2% grade 3)

Perol M, et al. *J Clin Oncol*. 2014;32(18 suppl). Abstract LBA8006; Ramucirumab package insert 2/19/2015, available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

Third-Line and Beyond?

Use whatever you didn’t use yet, clinical trial, or best supportive care

Going back to platinum?

Clinical Pearls

- Chemotherapy + immunotherapy is standard of care first-line, can use single-agent pembrolizumab in select population
- 5-year OS for high PD-L1 in first-line 29.6%—incredible
- Second line is mostly chemotherapy now given IO used mostly in front line
- Consider toxicities for all regimens and discuss with patient

Audience Response Question

A 68-year-old male presents with metastatic NSCLC with adenocarcinoma histology. He is fit, has a good performance status, and is ready to start first-line treatment. He would like to learn more about which treatment offers the longest survival. Based on this goal, which treatment would you offer as best positioned to meet his goal?

A. Pemetrexed/carboplatin/nivolumab
B. Pemetrexed/carboplatin/pembrolizumab
C. Taxane/carboplatin/bevacizumab/atezolizumab
D. Taxane/carboplatin/pembrolizumab
E. Unsure

Audience Response Question

The 5-year survival rate for patients with metastatic NSCLC who had a PD-L1 score of 50% or greater and were treated with single-agent first-line pembrolizumab was approximately:

A. 5%
B. 10%
C. 20%
D. 30%
E. Unsure

Questions?