CONSENSUS OR CONTROVERSY?

Clinical Investigators Provide Perspectives on the Treatment of Metastatic Non-Small Cell Lung Cancer in Patients Without Targetable Tumor Mutations

March 17, 2017
7:30 PM – 9:00 PM

Faculty

Julie R Brahmer, MD
Corey J Langer, MD
Naiyer Rizvi, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck

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Disclosures for Dr Rizvi

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Grants	Clovis Oncology, Exelixis Inc, Gilead Sciences Inc, Pharmacyclics LLC, an AbbVie Company, Xcovery

Disclosures for Moderator Neil Love, MD

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Module 1: Front-Line Treatment

In general, which first-line treatment regimen would you most likely recommend for a younger patient with metastatic nonsquamous cell lung cancer and no identified targetable mutations with a PD-L1 TPS of 60%? A patient with squamous lung cancer?

	NONSQUAMOUS	SQUAMOUS
 JULIE R BRAHMER, MD	Pembrolizumab	Pembrolizumab
 COREY J LANGER, MD	Pembrolizumab	Pembrolizumab
 HEATHER WAKELEE, MD	Pembrolizumab	Pembrolizumab
 RAMASWAMY GOVINDAN, MD	Pembrolizumab	Pembrolizumab
 JOEL W NEAL, MD, PHD	Pembrolizumab	Pembrolizumab
 GREGORY J RIELY, MD, PHD	Pembrolizumab	Pembrolizumab

Would you generally order a PD-L1 assay for an otherwise healthy patient who presents with metastatic NSCLC?

 JULIE R BRAHMER, MD	Yes, PD-L1 IHC 22C3 pharmDx
 COREY J LANGER, MD	Yes, PD-L1 IHC 22C3 pharmDx
 HEATHER WAKELEE, MD	Yes, PD-L1 IHC 22C3 pharmDx
 RAMASWAMY GOVINDAN, MD	Yes, PD-L1 IHC 22C3 pharmDx
 JOEL W NEAL, MD, PHD	Yes, PD-L1 IHC 22C3 pharmDx
 GREGORY J RIELY, MD, PHD	Yes, PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx

A 65-year-old patient presents with significant respiratory distress and highly symptomatic metastatic nonsquamous lung cancer and a PD-L1 TPS of 60%. What would be your most likely treatment recommendation?

 JULIE R BRAHMER, MD	Pembrolizumab
 COREY J LANGER, MD	Pembrolizumab
 HEATHER WAKELEE, MD	Pembrolizumab
 RAMASWAMY GOVINDAN, MD	Carbo/pem/pembrolizumab
 JOEL W NEAL, MD, PHD	Pembrolizumab +/- carbo/pemetrexed
 GREGORY J RIELY, MD, PHD	Pembrolizumab

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A 65-year-old patient presents with significant respiratory distress and highly symptomatic metastatic squamous cell cancer of the lung and a PD-L1 TPS of 60%. What would be your most likely treatment recommendation?

 JULIE R BRAHMER, MD	Pembrolizumab
 COREY J LANGER, MD	Pembrolizumab
 HEATHER WAKELEE, MD	Pembrolizumab
 RAMASWAMY GOVINDAN, MD	Carbo/*nab* paclitaxel/pembrolizumab
 JOEL W NEAL, MD, PHD	Pembrolizumab +/- carbo/*nab* paclitaxel
 GREGORY J RIELY, MD, PHD	Pembrolizumab

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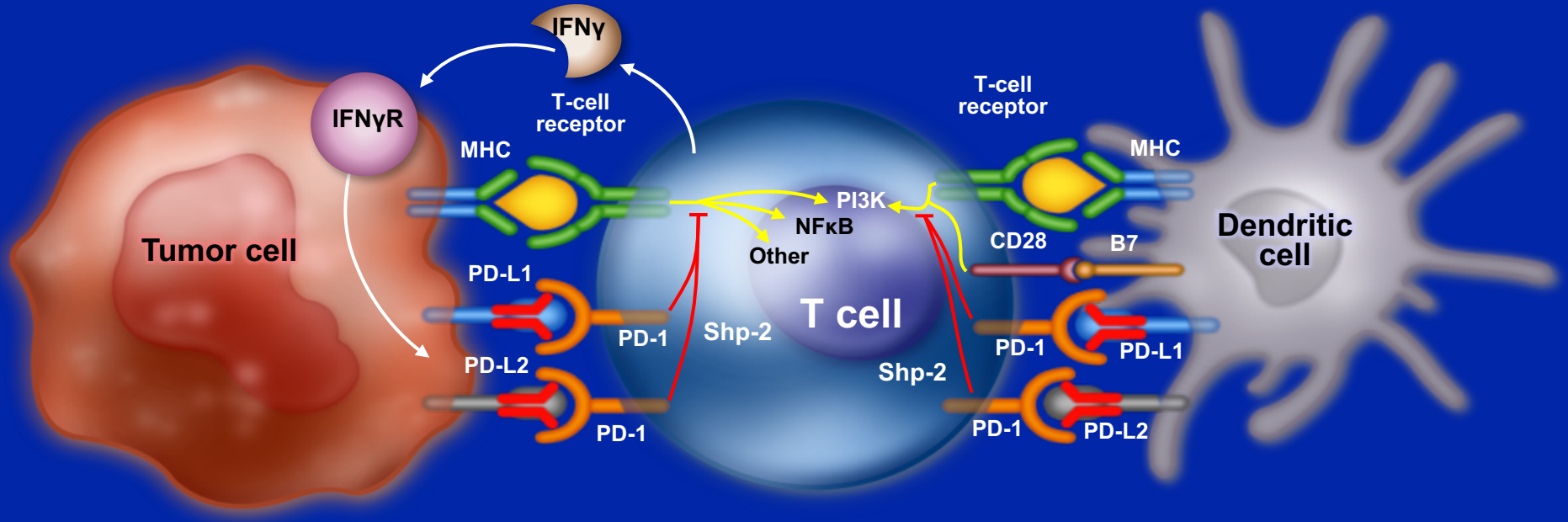
Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
- 3 Approved Drugs:
- Nivolumab/pembrolizumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
- Atezolizumab binds PD-L1 receptors



Nivolumab/Pembrolizumab: PD-1 Receptor Blocking Ab
Atezolizumab: PD-L1 Receptor Blocking Ab

PD-1/PD-L1 Inhibitors in NSCLC

Checkpoint inhibitor	Antibody type	Stage	PD-L1 test
Anti-PD-1			
Nivolumab (BMS-936558)	IgG4	Approved 2nd line CheckMate 057/017	28-8 "complementary"
Pembrolizumab (MK-3475)	IgG4 (humanized)	1st line – PD-L1 ≥50% 2nd line – PD-L1 ≥1% Keynote 010/024	22C3 "companion"
Anti-PD-L1			
Atezolizumab (MPDL3280A)	IgG1 (engineered)	Approved 2nd line OAK, BIRCH, IMpower	SP142 "complementary"
Durvalumab (MEDI-4736)	IgG1	Phase III (ATLANTIC, PACIFIC, BR31, ARCTIC, MYSTIC, LUNG-MAP)	SP263
Avelumab (MSB0010718C)	IgG1	Phase III (JAVELIN)	

National Institutes of Health. Available at: http://clinicaltrials.gov

Biomarkers: PD-L1 (IHC) as a Biomarker in Lung Cancer for Anti-PD-(L)1 Therapy

Drug	Nivolumab[1,2]		Pembrolizumab[3]		Atezolizumab[4]	Durvalumab[5]
Assay	Rabbit mAb 28-8 automated IHC		Murine mAb 22C3 IHC		Rabbit mAb SP142 automated IHC	Rabbit mAb SP263 automated IHC
Cells scored	Tumor cell membrane		Tumor cell (and stroma)		Infiltrating immune cells	Tumor cell membrane
Tissue	FFPE		FFPE		FFPE	FFPE
Cut-point	1%-50%	1%-50%	1%-50%	1%-50%	TC1 or IC1	NR

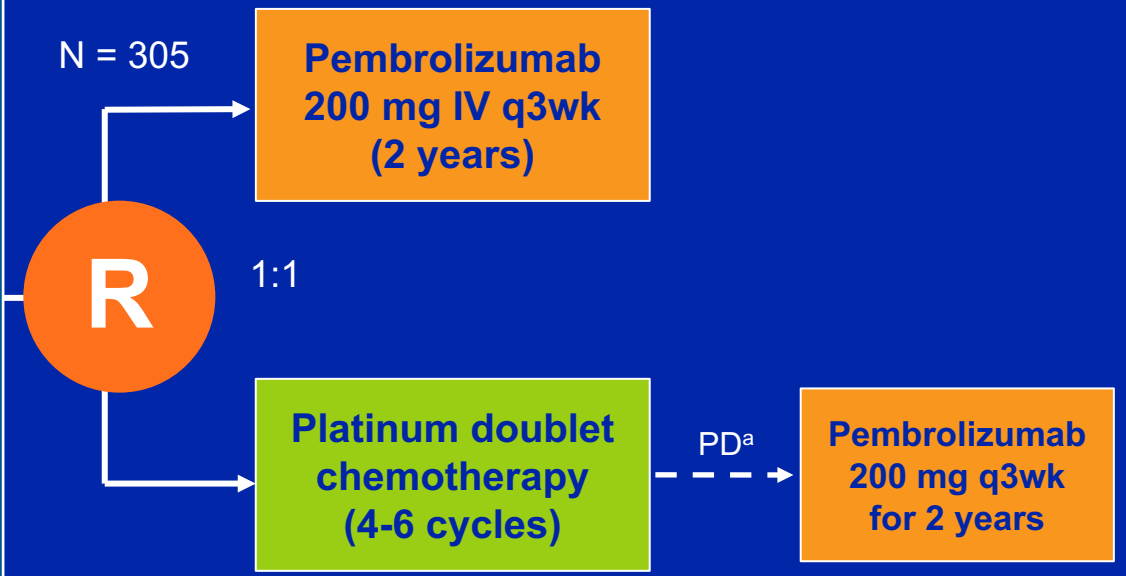
1. Gettinger SN et al. *J Clin Oncol* 2015;33(suppl);Abstract 8025. 2. Gettinger SN et al. *J Clin Oncol* 2015.
3. Garon EB et al. *N Engl J Med* 2015;372(21):2018-28. 4. Horn L et al. *J Clin Oncol* 2015;33(suppl);Abstract 8029.
5. Rebelatto MC et al. *J Clin Oncol* 2015;33(suppl);Abstract 8033.

KEYNOTE-024 Study Design

NCT02142738

Key Eligibility Criteria

- Untreated Stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



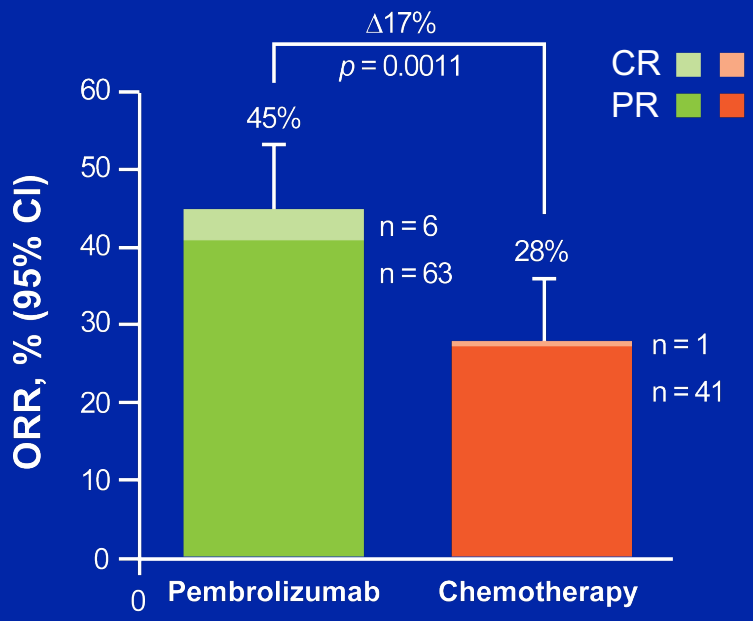
Key endpoints

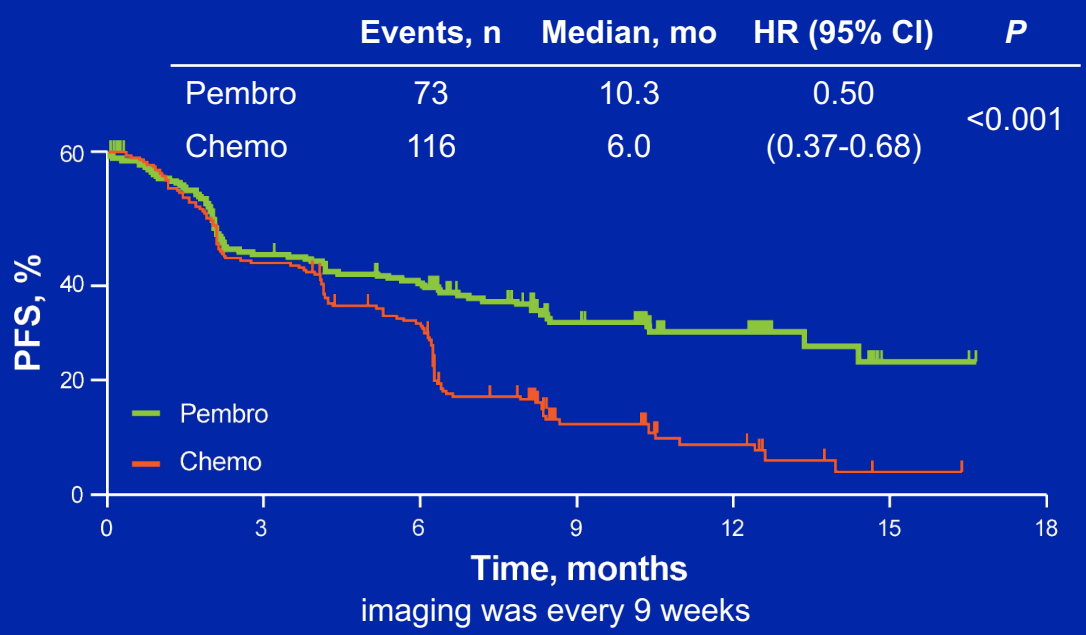
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Reck M et al. *N Engl J Med* 2016;375(19):1823-33.

KEYNOTE-024: Response and Progression-Free Survival



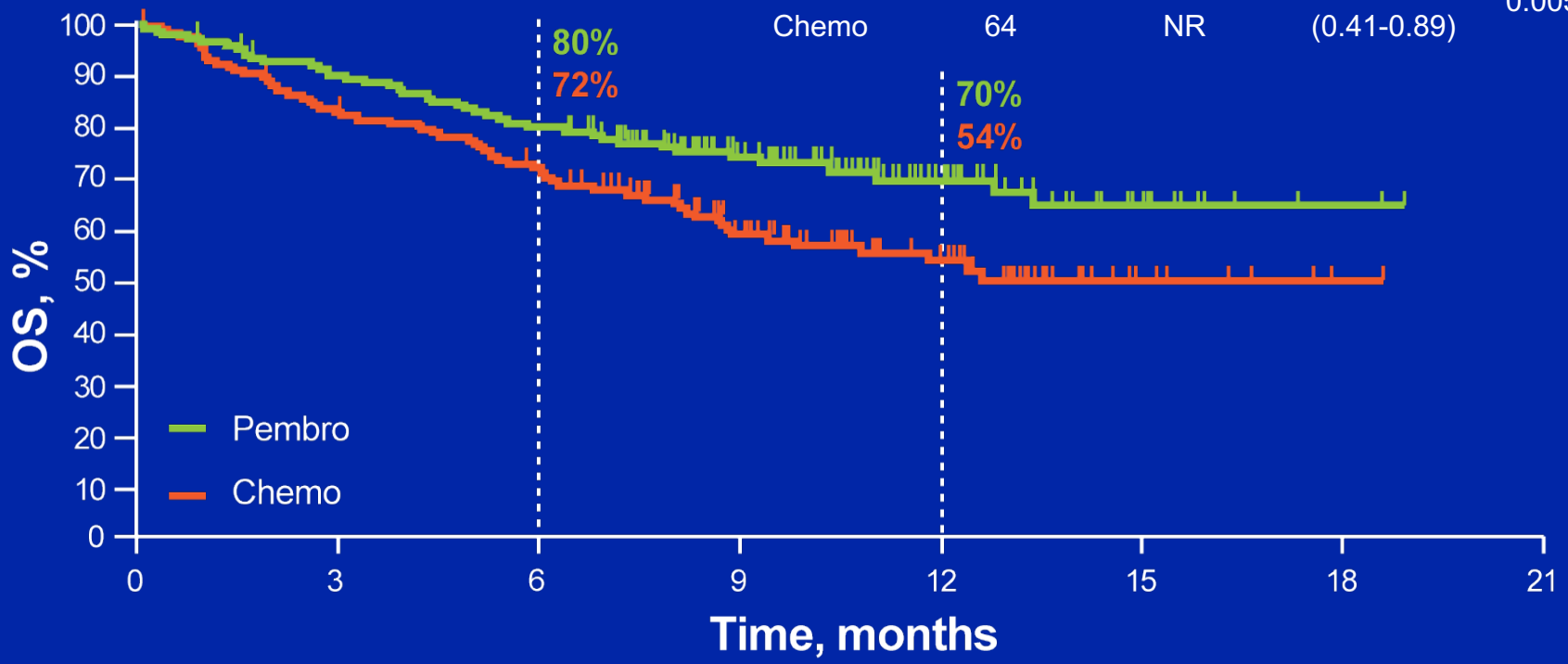


- ORR is improved, with a control arm that performs as expected (from other Phase III trials)
- **45% ORR is the best RR ever reported in 1st line setting (and with a monotherapy!)**
- Time to response is identical between pembrolizumab and chemotherapy
- **PFS is improved by 4.3 months** (**HR of 0.50**)
- Improvement of PFS in all subgroups (except female/never smokers)
- **Strongest signal of PFS benefit observed in SCC** (HR of 0.35)

Reck M et al. *N Engl J Med* 2016;375(19):1823-33, *Proc ESMO* 2016;Abstract LBA8_PR.

KEYNOTE-024: Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Clear survival benefit

- Estimated rate of OS at 12 months: 70% (pembro) vs 54% (chemo)
- HR for death: **0.60**
- Crossover **was limited to 50% of the patients**

Reck M et al. *N Engl J Med* 2016;375(19):1823-33.

KEYNOTE-024: Select Adverse Events

Adverse event, n (%)	Pembrolizumab (N = 154)		Chemotherapy (N = 150)	
	All grades	Grade ≥3	All grades	Grade ≥3
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Immune-mediated adverse event				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Colitis	3 (1.9)	2 (1.3)	0	0

Reck M et al. *N Engl J Med* 2016;375(19):1823-33.

FDA Approval of Pembrolizumab as First-Line Therapy for Patients with PD-L1-Positive NSCLC

"On October 24, 2016, the US Food and Drug Administration approved pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 [Tumor Proportion Score ≥50%] as determined by an FDA-approved test.

This is the first FDA approval of a checkpoint inhibitor for first-line treatment of lung cancer. This approval also expands the indication in second-line treatment of lung cancer to include all patients with PD-L1-expressing NSCLC."

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526430.htm

CheckMate 026: A Phase III Trial of Nivolumab vs Chemotherapy in First-Line NSCLC

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

R

1:1

Nivolumab
3 mg/kg IV q2wk
n = 271

Disease progression or unacceptable toxicity

Tumor scans q6wk until wk 48 then q12wk

Chemotherapy
(histology dependent)
Maximum of 6 cycles
n = 270

Disease progression

Crossover nivolumab (optional)

Stratification factors at randomization:

- PD-L1 expression (<5% vs ≥5%)
- Histology (squamous vs nonsquamous)

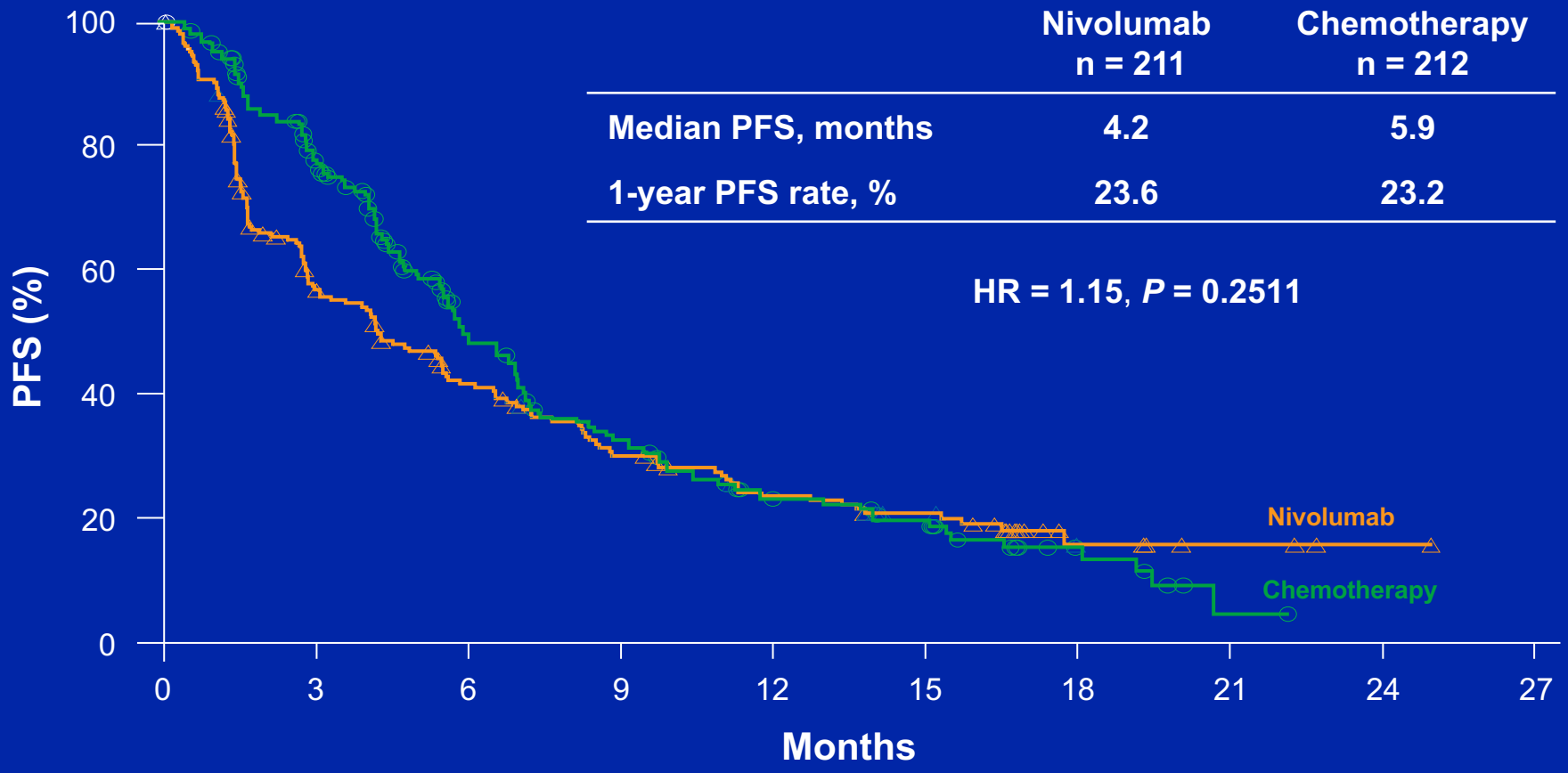
Primary Endpoint: PFS (≥5% PD-L1+)

Secondary Endpoints:

- PFS (≥1% PD-L1+)
- OS
- ORR

Socinski M et al. *Proc ESMO* 2016;Abstract LBA7_PR.

CheckMate 026: Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)



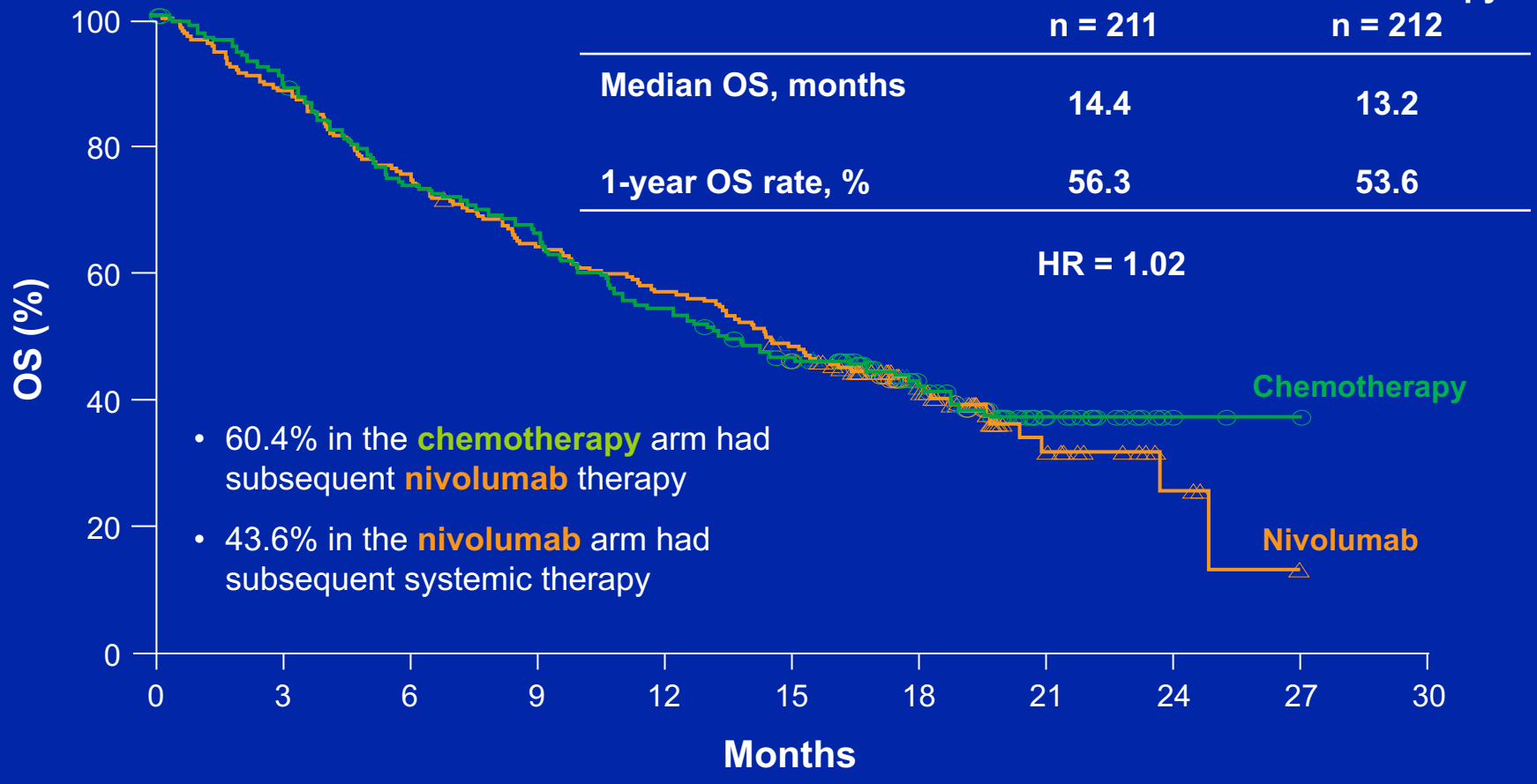
	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months	4.2	5.9
1-year PFS rate, %	23.6	23.2

HR = 1.15, *P* = 0.2511

All randomized patients (≥1% PD-L1+): HR = 1.17

Socinski M et al. *Proc ESMO* 2016;Abstract LBA7_PR.

CheckMate 026: Overall Survival (≥5% PD-L1+)



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months	14.4	13.2
1-year OS rate, %	56.3	53.6

HR = 1.02

All randomized patients (≥1% PD-L1+): HR = 1.07

Socinski M et al. *Proc ESMO* 2016;Abstract LBA7_PR.

Have you or would you use an anti-PD-1/PD-L1 antibody in combination with chemotherapy for a patient with metastatic NSCLC?

 JULIE R BRAHMER, MD	I have
 COREY J LANGER, MD	I have
 HEATHER WAKELEE, MD	I haven’t and would not
 RAMASWAMY GOVINDAN, MD	I haven't but would for the right patient
 JOEL W NEAL, MD, PHD	I haven’t but would for the right patient
 GREGORY J RIELY, MD, PHD	I haven’t and would not

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KEYNOTE-021 Cohort G

Key Eligibility Criteria

- Untreated Stage IIIB or IV nonsquamous NSCLC
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0-1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

N = 123

R

1:1

Pembrolizumab 200 mg q3wk for 2 years + carboplatin AUC 5 mg/mL/min + pemetrexed 500 mg/m^2 q3wk for 4 cycles

Carboplatin AUC 5 mg/mL/min + pemetrexed 500 mg/m^2 q3wk for 4 cycles

PD

Pembrolizumab 200 mg q3wk for 2 years

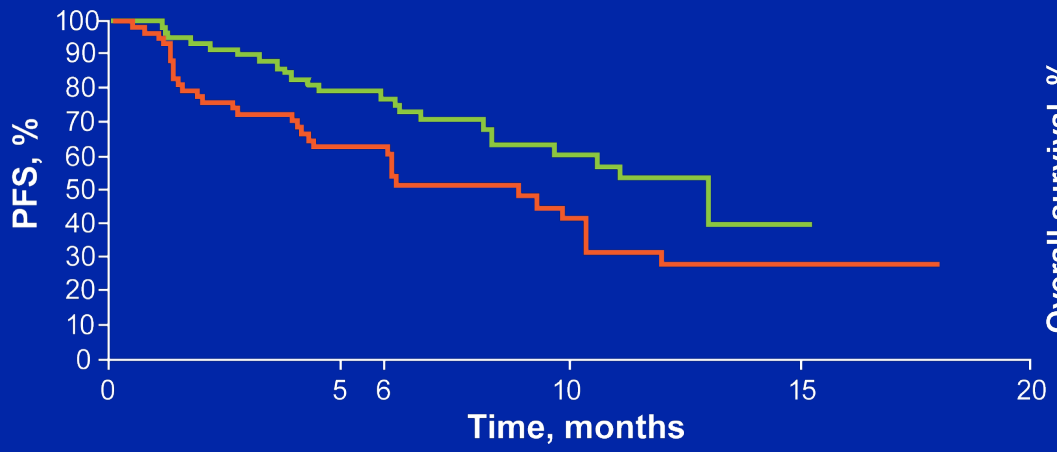
Endpoints

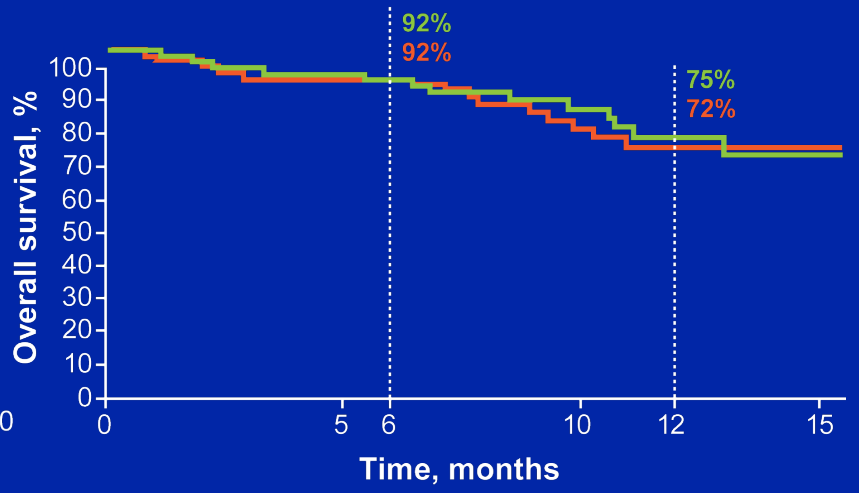
Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

Langer C et al. *Lancet Oncol* 2016;17(11):1497-1508, *Proc ESMO* 2016;Abstract LBA46_PR.

KEYNOTE-021: Survival data





	Events, n	Median	HR (95% CI)
Pembro + chemo (n = 60)	23	13.0 mo	0.53 (0.31-0.91)
Chemo alone (n = 63)	33	8.9 mo	*p* = 0.0102

	Events, n	HR (95% CI)
Pembro + chemo	13	0.90 (0.42-0.91)
Chemo alone	14	

- **Median PFS improved by 4.1 months**
- No difference in OS
  - Estimated rate of OS @ 12 months: 75% (combo) vs 72% (CT)
- In chemotherapy arm, crossover is 51% to anti-PD-1/PD-L1 therapies (pembrolizumab and others)

Langer C et al. *Lancet Oncol* 2016;17(11):1497-1508, *Proc ESMO* 2016;Abstract LBA46_PR.

KEYNOTE-021: Select Adverse Events

	Pembrolizumab + Carbo/Pemetrexed (n = 59)		Carbo/Pemetrexed (n = 62)	
AEs	**Grade 1-2**	**Grade ≥3**	**Grade 1-2**	**Grade ≥3**
Fatigue	61%	3%	40%	0
Anemia	20%	12%	39%	15%
Decreased neutrophil count	12%	5%	10%	3%
Decreased lymphocyte count	5%	3%	3%	2%
Thrombocytopenia	2%	4%	3%	3%
Hypothyroidism	15%	0	5%	0
Hyperthyroidism	8%	0	2%	0
Pneumonitis	3%	2%	0	0

Langer CJ et al. Lancet Oncol 2016;17(11):1497-1508.

Issues in First-Line Treatment of Patients with TPS < 50%

- **Nonsquamous NSCLC**
  - Choice of platinum doublet
  - Use of bevacizumab
  - Use of maintenance therapy
- **Squamous NSCLC**
  - Choice of platinum doublet
  - Role, if any, of necitumumab

In general, which first-line treatment regimen would you most likely recommend for a younger patient with metastatic nonsquamous lung cancer and no identified targetable mutations with a PD-L1 TPS of 10%?

 JULIE R BRAHMER, MD	Carbo/pem/bev
 COREY J LANGER, MD	Carbo/pem/bev
 HEATHER WAKELEE, MD	Carbo/pem/bev
 RAMASWAMY GOVINDAN, MD	Carbo/pem
 JOEL W NEAL, MD, PHD	Carbo/pem
 GREGORY J RIELY, MD, PHD	Carbo/pem/bev

In general, which first-line treatment regimen would you most likely recommend for a younger patient with metastatic squamous lung cancer and no identified targetable mutations with a PD-L1 TPS of 10%?

 JULIE R BRAHMER, MD	Carbo/gem or carbo/*nab* paclitaxel
 COREY J LANGER, MD	Carbo/paclitaxel or carbo/*nab* paclitaxel
 HEATHER WAKELEE, MD	Cis/gem
 RAMASWAMY GOVINDAN, MD	Carbo/*nab* paclitaxel
 JOEL W NEAL, MD, PHD	Carbo/paclitaxel
 GREGORY J RIELY, MD, PHD	Cis/gem

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A 55-year-old patient in otherwise excellent health is about to be treated up front for metastatic squamous cell lung cancer with a TPS of 10% and is interested in any option that will help extend his survival. Would you offer this patient necitumumab as part of up-front treatment?

 JULIE R BRAHMER, MD	No
 COREY J LANGER, MD	Yes
 HEATHER WAKELEE, MD	Yes
 RAMASWAMY GOVINDAN, MD	No
 JOEL W NEAL, MD, PHD	Yes
 GREGORY J RIELY, MD, PHD	Yes

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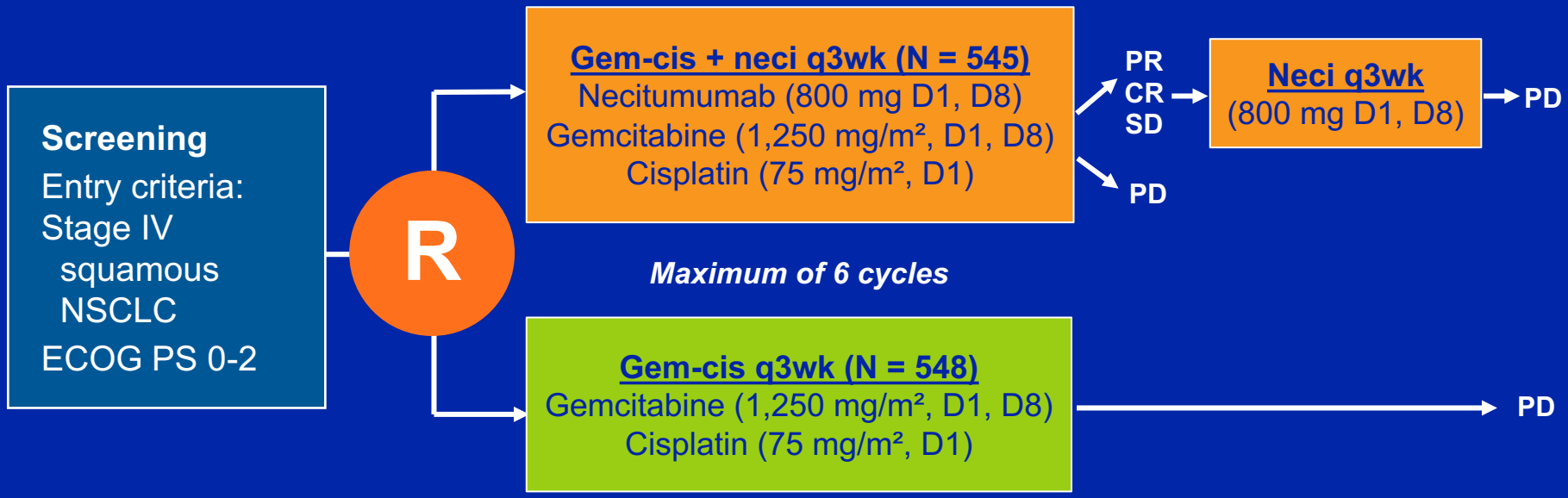
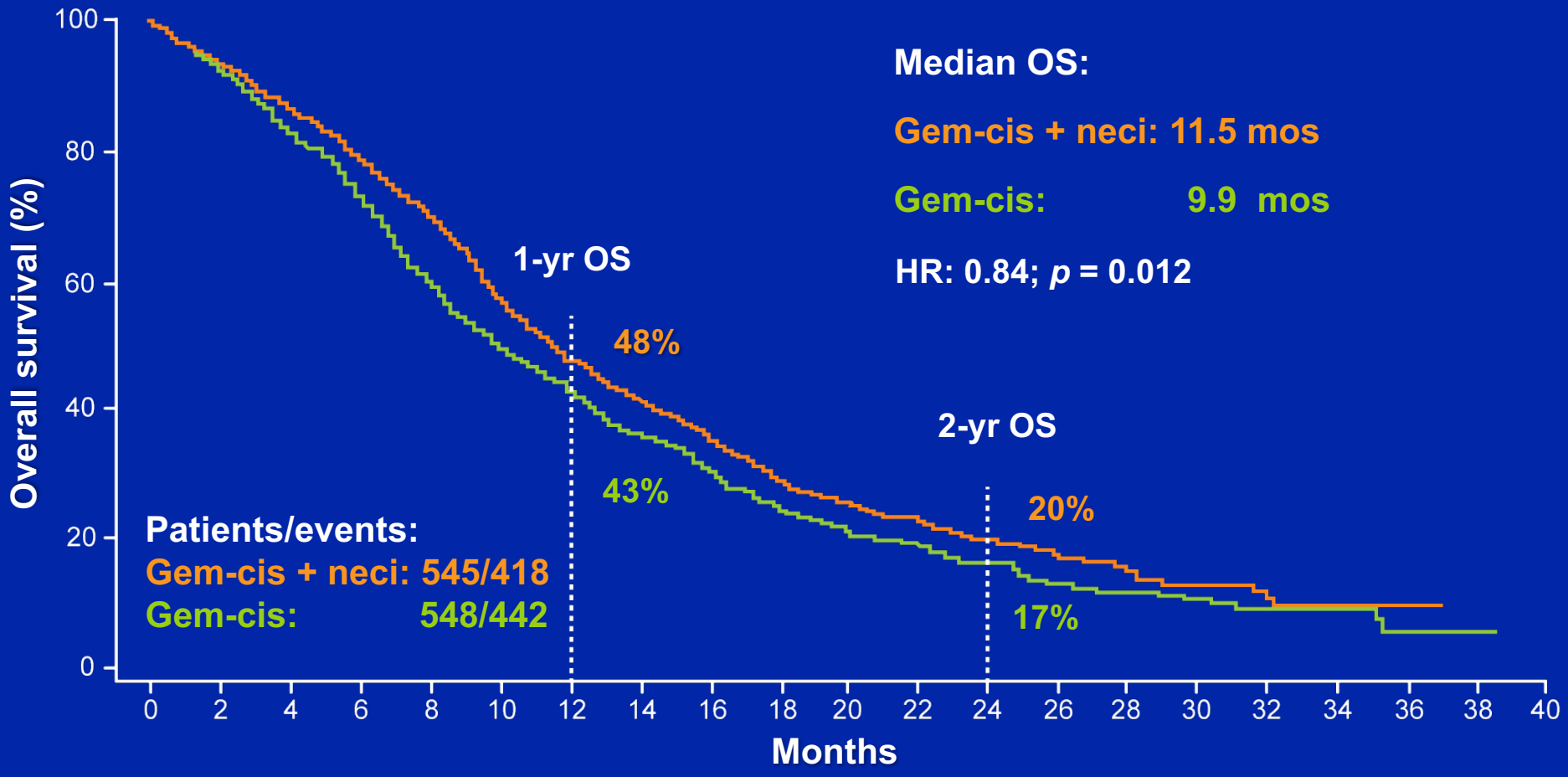
SQUIRE: Necitumumab with Cisplatin/Gemcitabine in Stage IV Squamous Carcinoma of the Lung



Primary endpoint: Overall survival

Thatcher N et al. *Lancet Oncol* 2015;16(7):763-74.

SQUIRE: Primary Outcome Overall Survival (ITT)

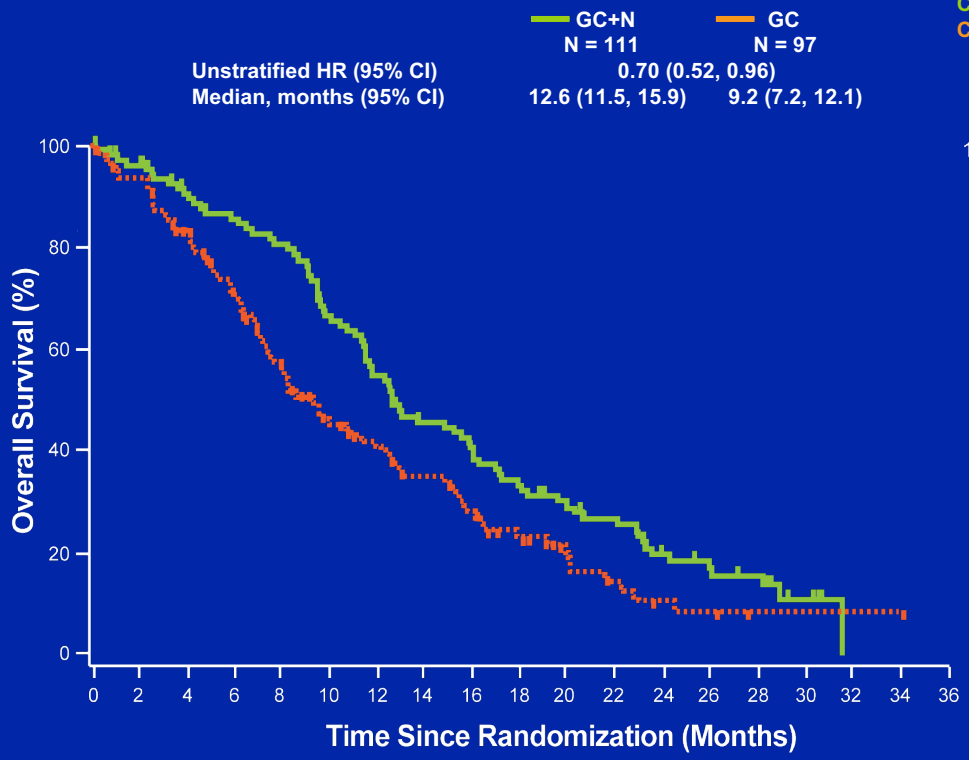


Toxicities (Gr ≥ 3) – Skin rash 7.0% vs <1%, hypomagnesemia 9.0% vs <1%, HSR 0.4% vs 0.0

Thatcher N et al. *Lancet Oncol* 2015;16(7):763-74.

Overall Survival in Patients With EGFR-Positive NSCLC

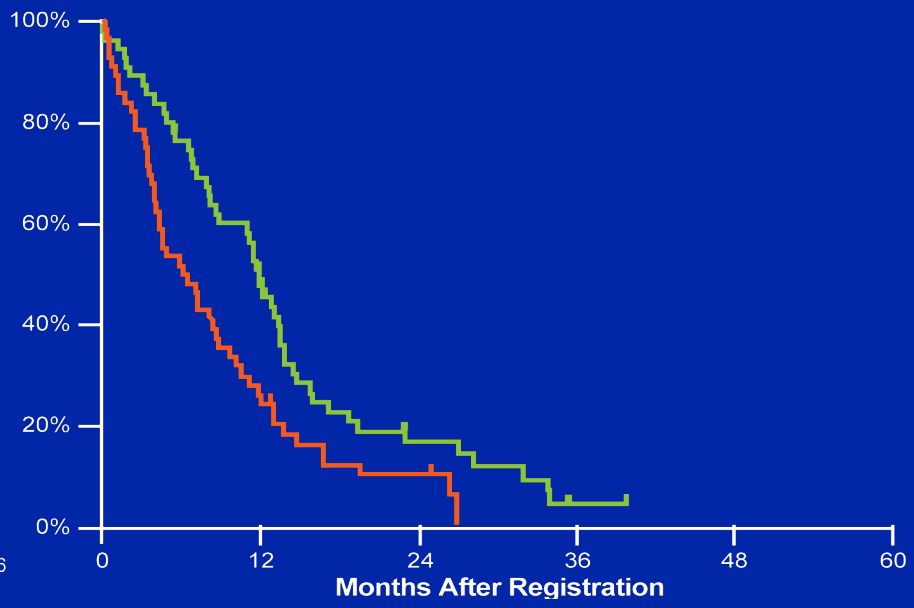
SQUIRE (EGFR FISH+)[1]



S0819 (SqCLC-EGFR FISH+)[2]

	N	Events	Median in Months	95% Conf. Int
Cetuximab Arm	55	50	11.8	(8.6 – 13.5)
Control Arm	56	52	6.4	(4.2 – 8.7)

P = 0.006
HR=0.56 (0.37-0.84)



1. Hirsch FR et al. WCLC 2015;Abstract ORAL32.05;
2. Herbst R et al. WCLC 2015;Abstract PLEN04.01