First Line Therapy With PD-1/PD-L1 Inhibitors

Roy S. Herbst, MD, PhD
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

February 11, 2017

Immunotherapy: Case

- **72-year-old woman with 50 pack-year smoking history presents with cough and fatigue. Zubrod PS 1.**
- **Diagnosed with stage IV NSCLC-adenocarcinoma. RUL hilar mass with metastases to bone and lymph nodes.**
- **MRI of brain negative.**
- ***EGFR*-mut by PCR, *ALK* FISH, *ROS1* FISH testing is negative.**
- **PD-L1 testing by IHC 22C3 antibody. 80% PD-L1 expression is noted.**

First Line Therapy With PD-1/PD-L1 Inhibitors

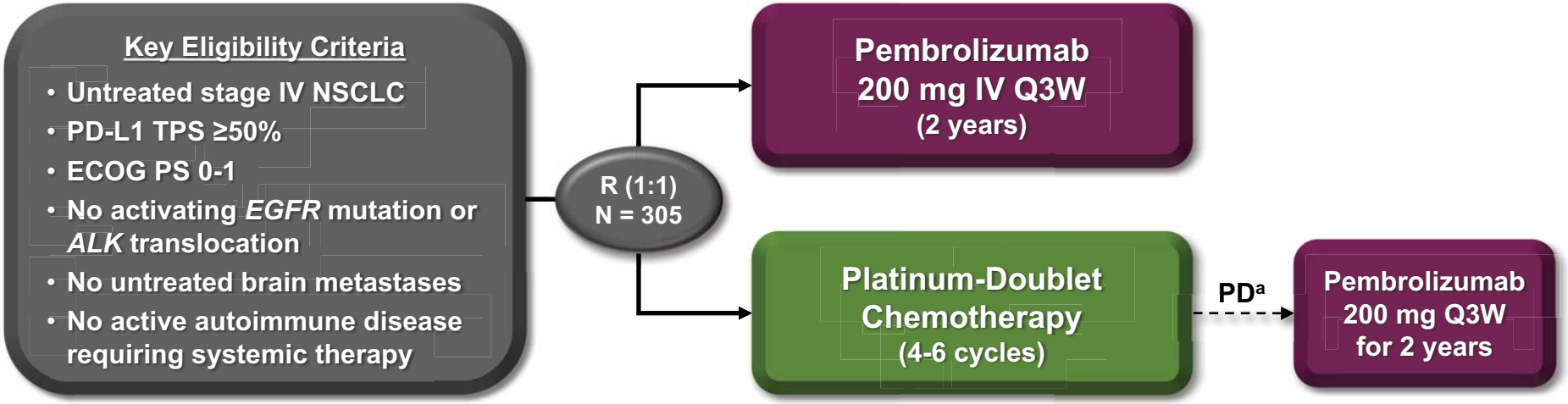
Roy S. Herbst, MD, PhD
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

February 11, 2017

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Kolltan Pharmaceuticals Inc, Lilly, Merck, Pfizer Inc
Contracted Research	Genentech BioOncology, Merck

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

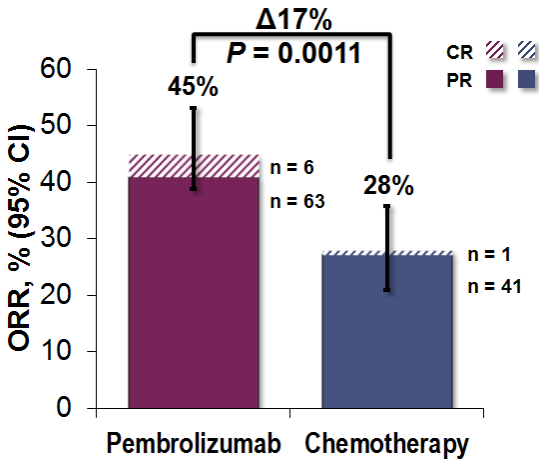
Primary: PFS (RECIST v1.1 per blinded, independent central review)

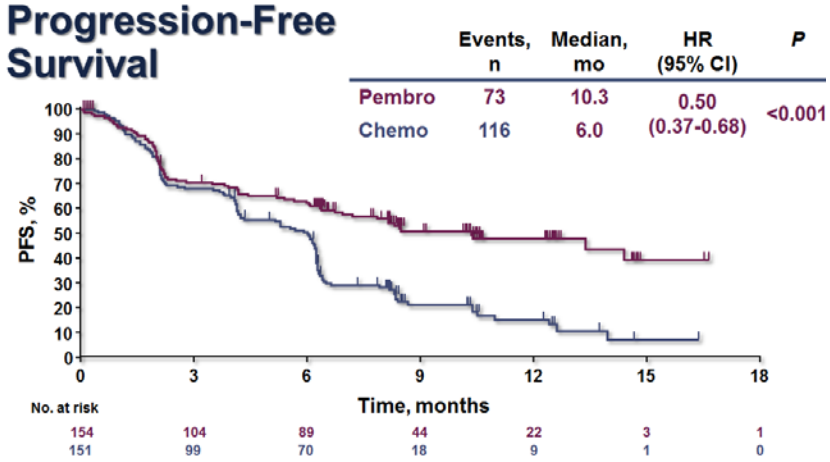
Secondary: OS, ORR, safety

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.

Efficacy data

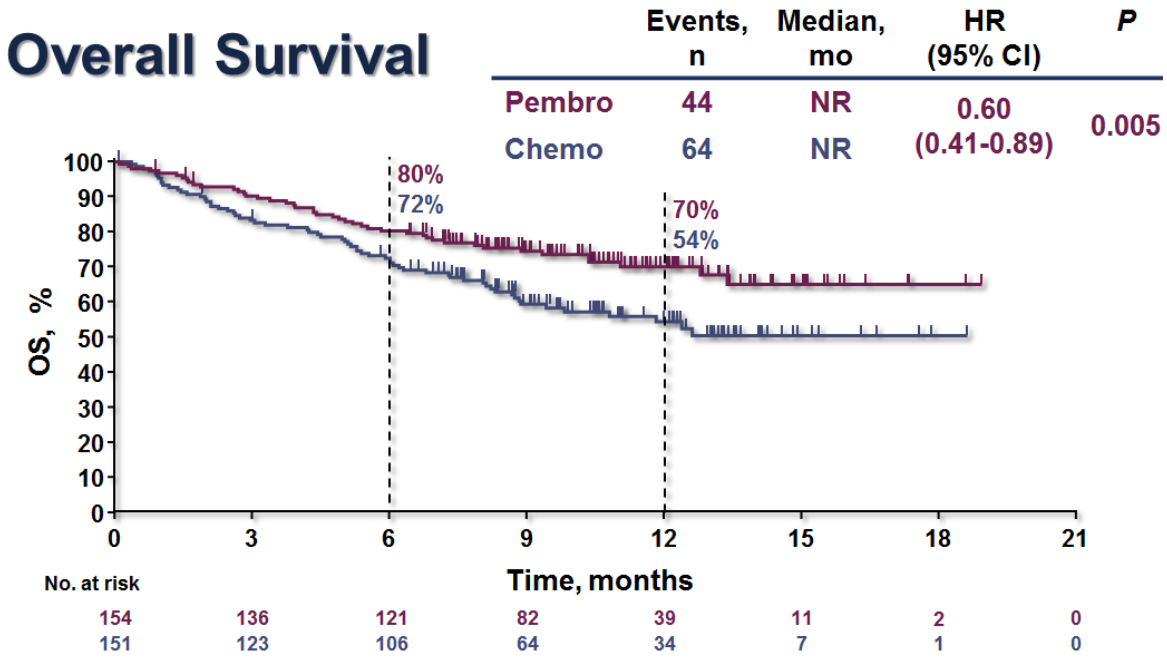




imaging was every 9 weeks

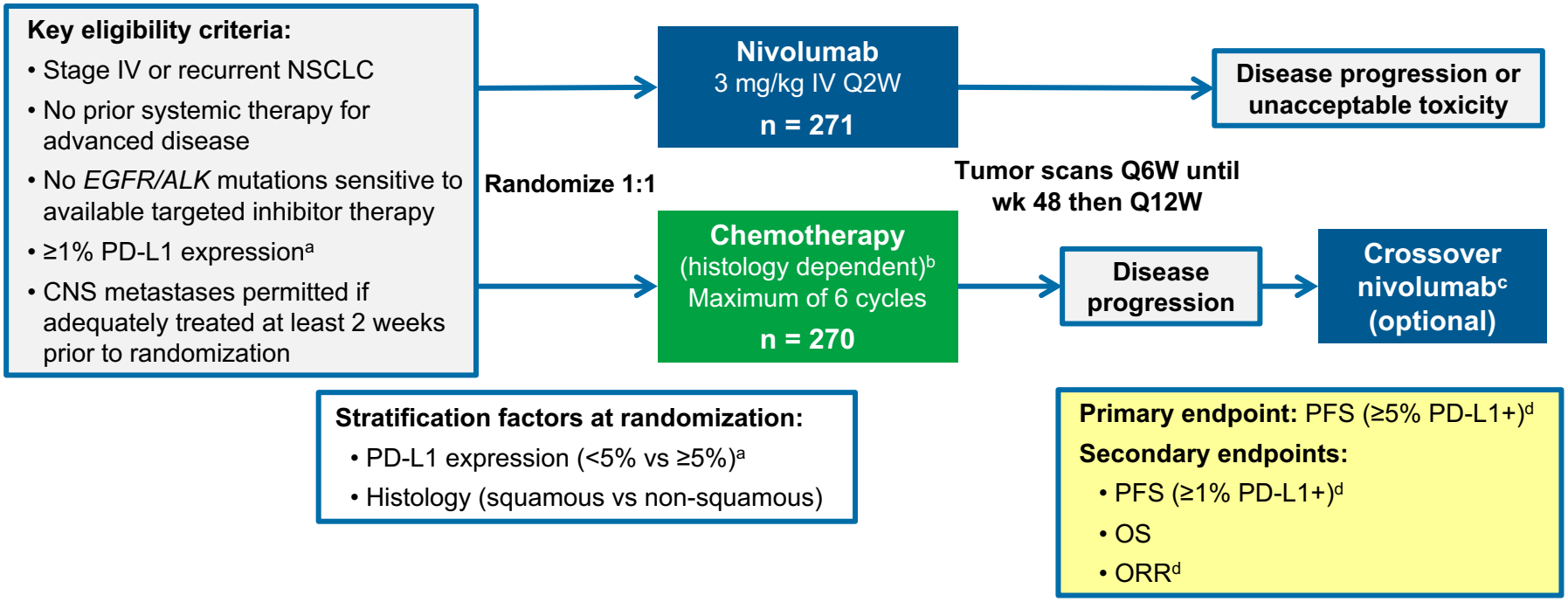
- **Clear and strong signal of activity**
  - → ORR is improved, with a control arm that performs as expected (from other phase III trials)
  - → 45% ORR is the best RR ever reported in 1st line setting (and with a monotherapy !)
  - → Time to Response is identical between Pembro & Ct
  - → PFS is improved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

Survival data



- Clear survival benefit
  - Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)
  - HR for death: **0.60**
  - but cross-over **was limited to 50% of the patients**

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



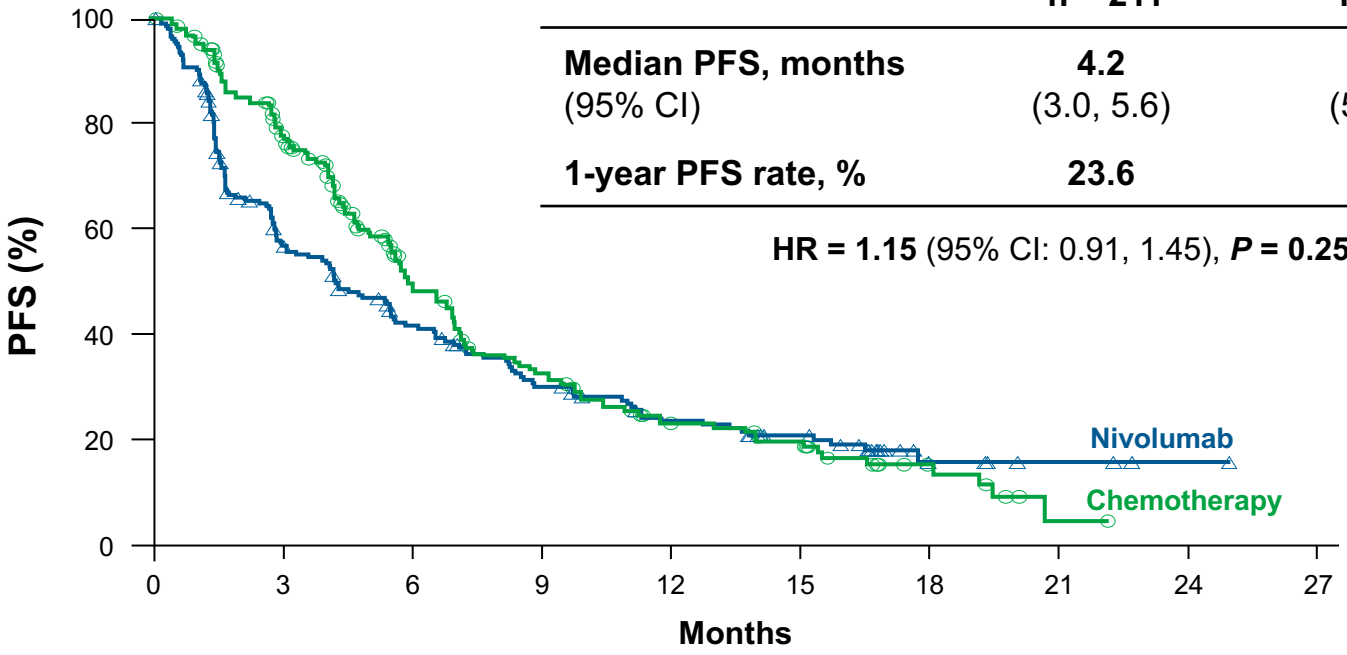
[a]PD-L1 IHC 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review
[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review

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

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**



No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

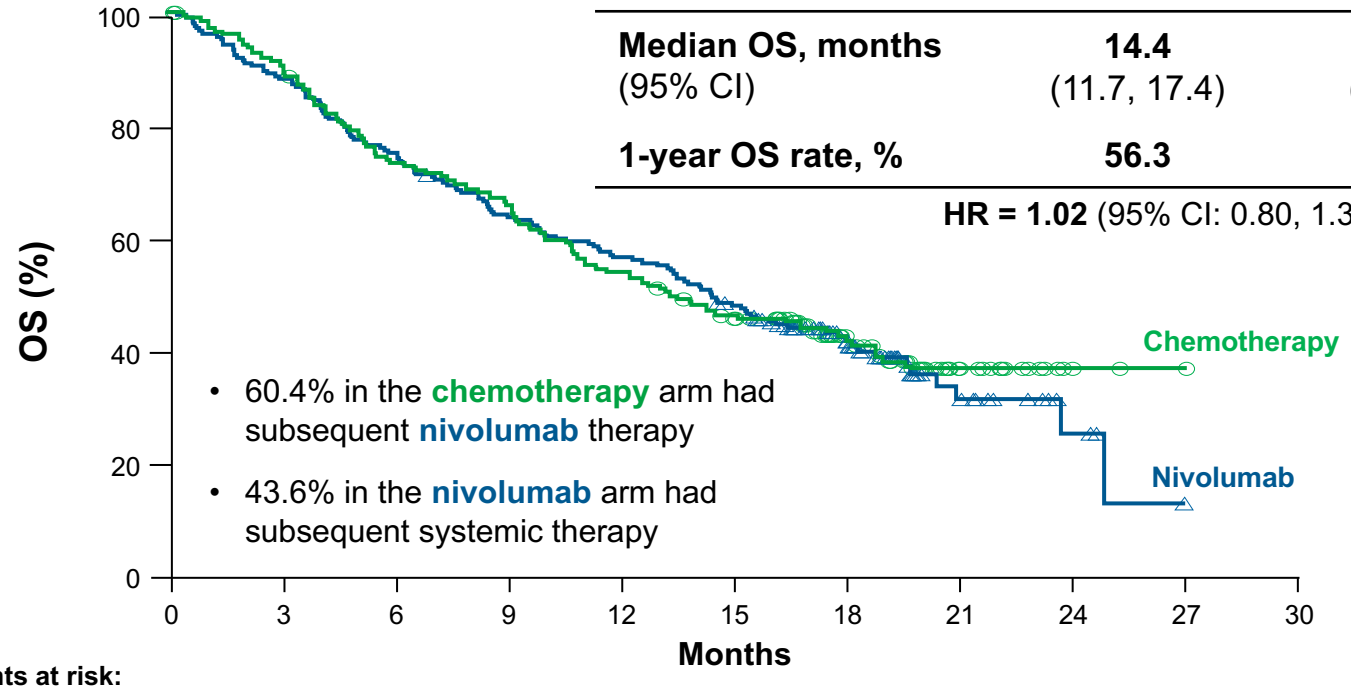
All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**

HR = 1.02 (95% CI: 0.80, 1.30)



No. of patients at risk:

Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

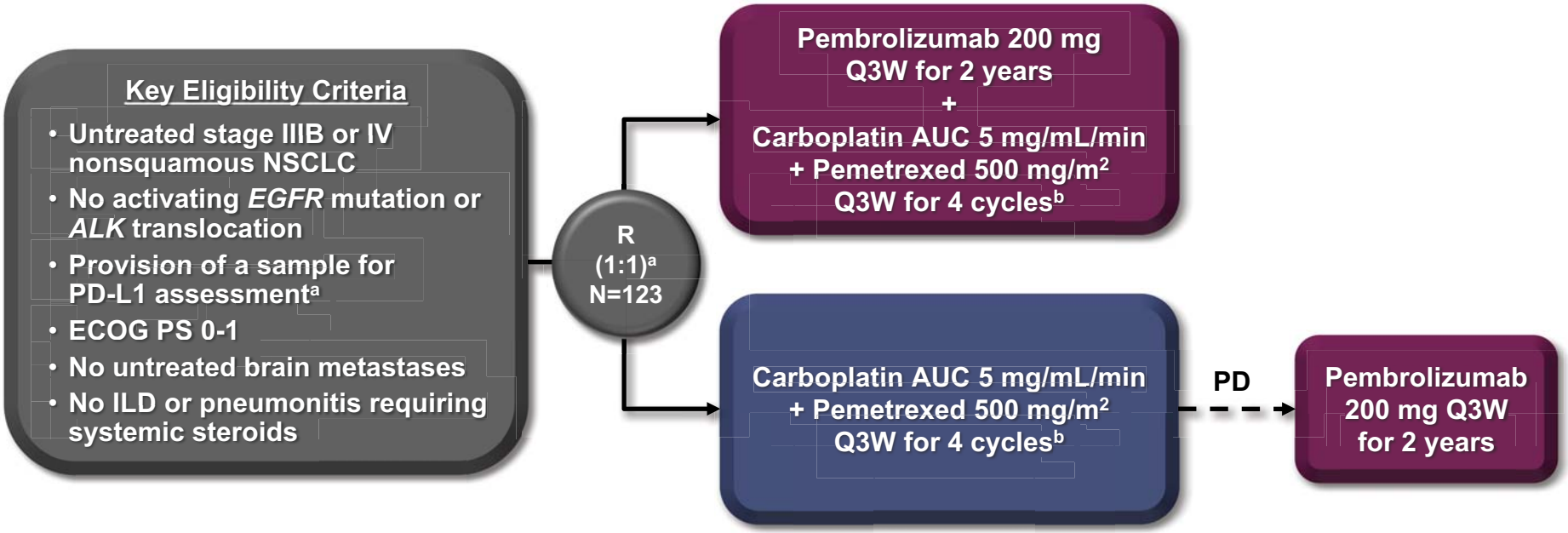
CheckMate 026 (CM 026) vs. KEYNOTE-024 (KN 024)

	KN 024	CM 026
Tumor biopsy	After metastatic diagnosis	Within 6 months
PD-L1 cut off	50% (22C3 clone)	5% (28-8 clone)
Prevalence	30%	50%
Imaging interval	Q 9 weeks	Q 6 weeks for first 48 weeks
Primary endpoint	PFS (RECIST)	PFS (IRRC)
Never smokers (PD-1)	3%	11%
Squamous histology	19%	24%
Time from diagnosis to treatment	?	2 months
Prior radiation	? [1]	37.6 %

[1] Prior radiation therapy of > 30 Gy disallowed within 6 months of first dose of trial treatment

Socinski et al, ESMO 2016
Reck et al, ESMO 2016, NEJM 2016

KEYNOTE-021 Cohort G



End Points

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

Key secondary: PFS

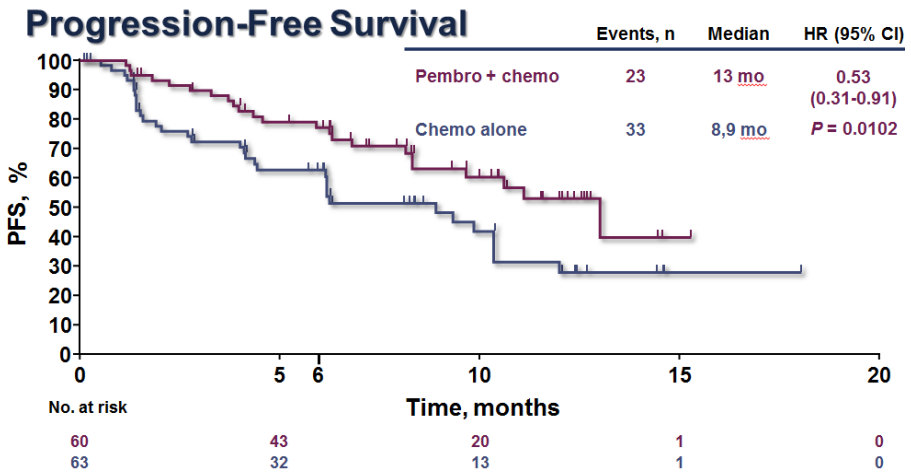
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

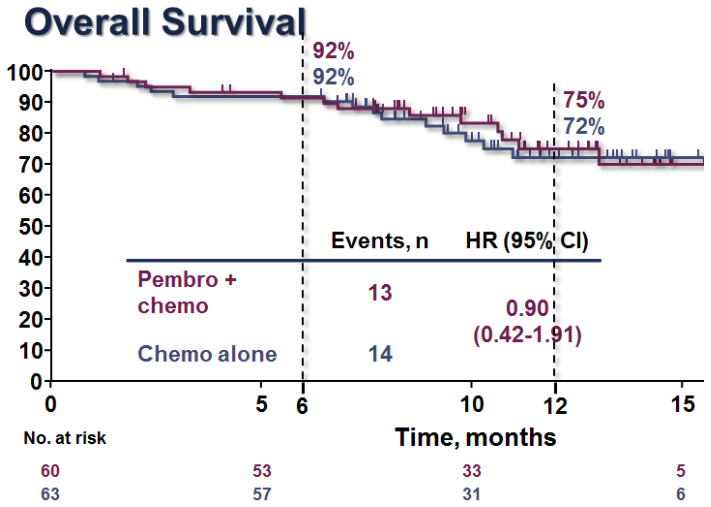
PD=progressive disease.

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

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

Survival data

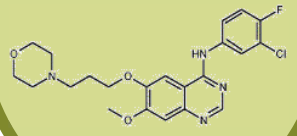




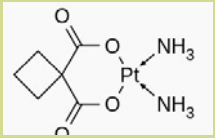
- Clear PFS benefit and no OS advantage
  - **Median PFS improved by 4.1 months**
  - PFS HR is 0.53
  - No difference for OS
  - Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
  - In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

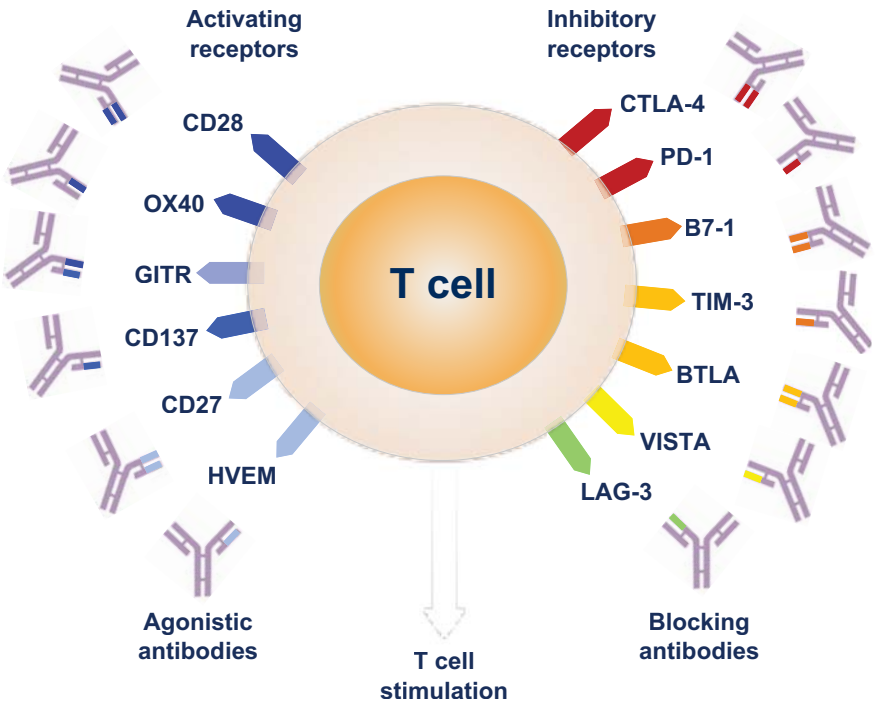
T-Cell Immune Checkpoints as Targets for Immunotherapy

Targeted Therapy

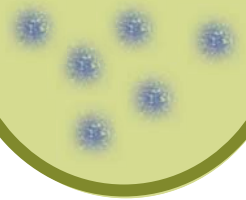


Chemotherapy





Cell Therapies



Vaccines

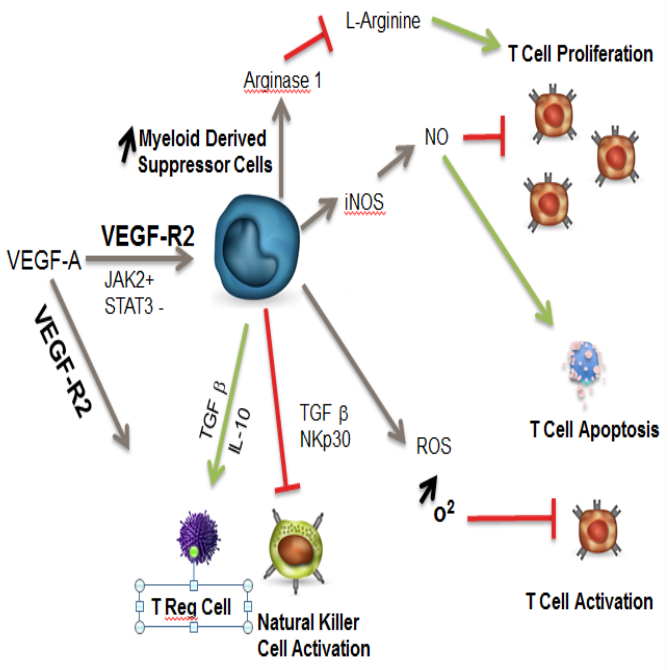
Adapted from Mellman I et al. *Nature*. 2011;480:481–489.

Anti-PD/PD-L1 as Backbone to Combination Tx?

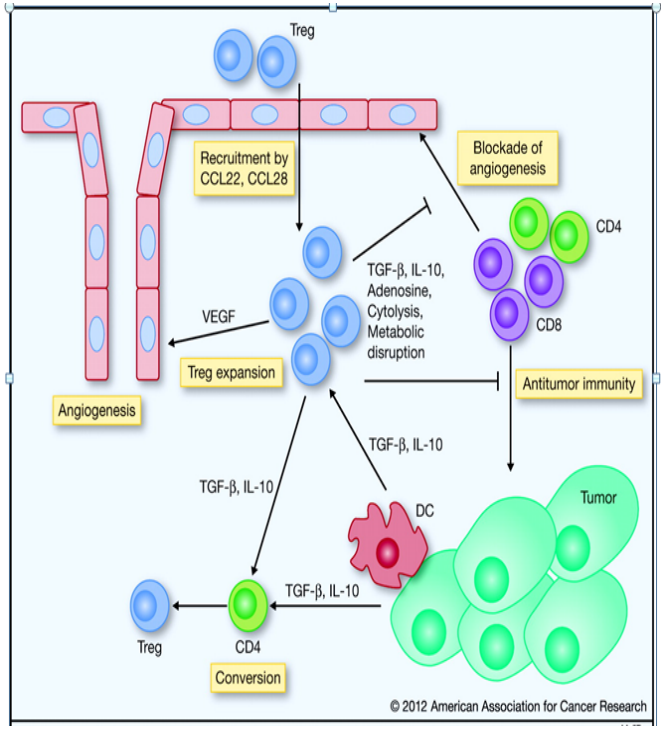
Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
- Chemotherapy - Radiation/ Ablation - EGFR/ ALK TKI - Anti-VEGF/ VEGFR inhibitor - Vasc Disrupt Agent - Hypomethylating Agent - HDAC inhibitor - SPK Inhibitor - C-Met inhibitor - Glutaminase inhibitor - Dasatinib - Vaccine - Gene therapy - IL15 agonist - PEG IL10 - $TGF_{\beta}R1$ inhibitor - Anti-CD27 - Ant-CXCR4 - Anti-CSF-1R - IDO-1 inhibitor - Anti-CTLA4 - Anti-LAG - Anti-TIM-3 - Anti-KIR	- Chemotherapy - Radiation - EGFR/ ALK TKI - Anti-VEGF/VEGFR inhibitor - Hypomethylating Agent - HDAC inhibitor - CDK Inhibitor - BTK inhibitor - PI3K Inhibitor - KIT/CSF1R/FLT3 Inh - FGFR inhibitor - JAK1 Inhibitor - CRM1 Inhibitor - FAK Inhibitor - Anti-EGFR - Anti-CEACAM1 - PEG hyaluronidase - Vaccine - Oncolytic - PEG IL10 - Anti-CSF-1 - IDO1 Inhibitor - Anti-CTLA4 - Anti-B7-H3	- Chemotherapy - Radiation - EGFR/ ALK TKI - Anti-VEGF/Ang-2 - MEK Inhibitor - Vaccine - Adoptive Cell Therapy - Anti-CEA/CD3 - Anti-CEA/ IL-2 - Anti-OX40 - Anti-CD40 - Anti-CD27 - Anti-CSF-1 - Adenosine A2A Inhibitor - IDO-1 Inhibitor - Anti-CTLA4 - Anti-TIGIT	- Chemotherapy - Radiation - EGFR/ALK TKI - VEGFR Inhibitor - BTK Inhibitor - MEK Inhibitor - HAD Inhibitor - PARP Inhibitor - WEE1 Inhibitor - ATR Inhibitor - Anti-OX40 - CXCR4 Inhibitor - CSF - Anti-CD73 - Anti-CCR4 - Anti-CSF1R - Anti-NKG2A - Adenosine A2a Inhibitor - IDO1 Inhibitor - Anti-CTLA4 - Anti-PD-1
		Avelumab: ALK inhibitor (crizotinib and lorlatinib), Anti-41BB, Anti-OX40	

Ramucirumab: Immune Supportive Agent
--- Immunological Pathways (MDSC and Treg): VEGF-A/VEGF-R2 pathway Induces Immunosuppression (2 of 2)

VEGF-A through binding to VEGF-R2 induces immunosuppression:



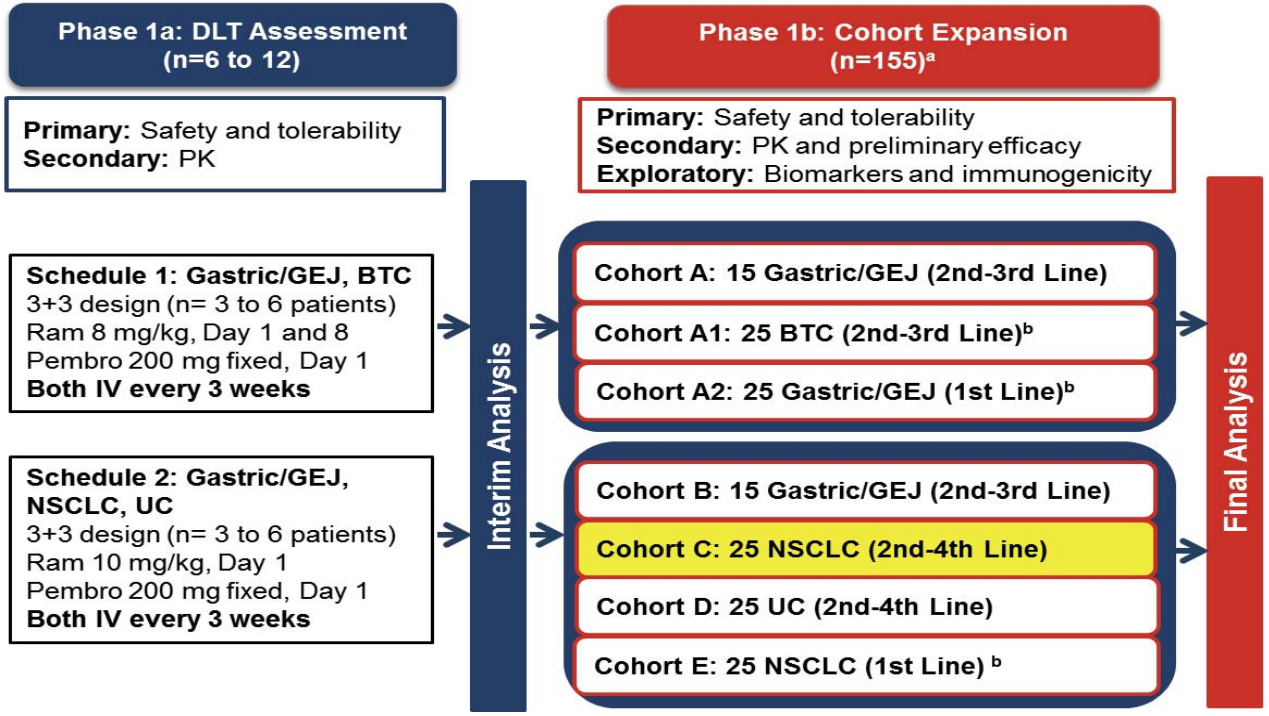
Treg: limit antitumor immunity and promote angiogenesis



T. Voron, et al., Frontiers in Oncology, April 2014 Volume 4 Article 70
Andrea Facciabene et al. Cancer Res 2012;72:2162-2171

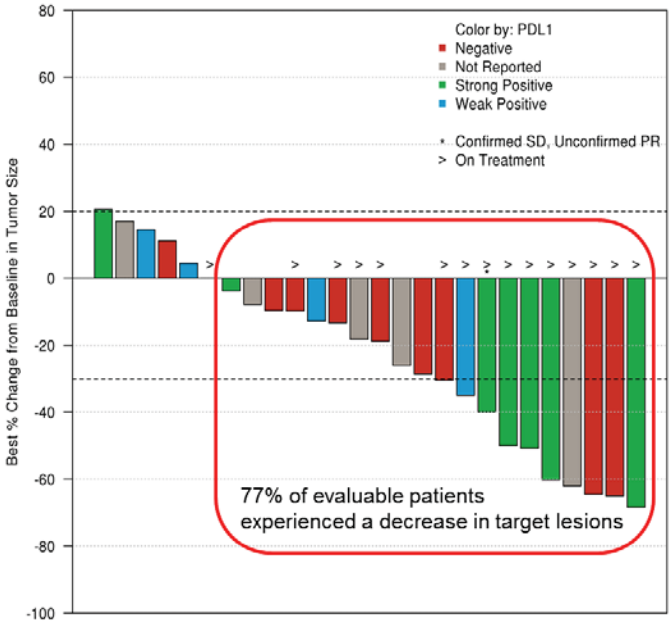
Lilly ONCOLOGY

STUDY JVDF (NCT02443324) PHASE 1A/B STUDY DESIGN

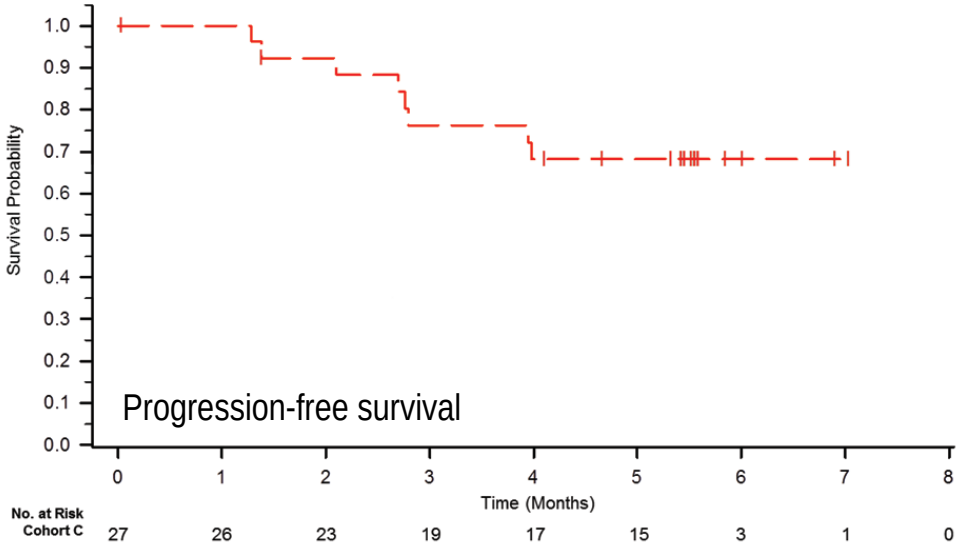


[a]Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. [b]Protocol was recently amended to add cohorts A1, A2 and E; cohorts are currently enrolling. DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab

COHORT C: INTERIM CLINICAL ACTIVITY



ITT Population	Cohort C NSCLC (n=27)
Objective response rate, n (%)	8 (30%)
Disease control rate, n (%)	23 (85%)



PD-L1 Status	Patients	Events	Median PFS, Mo (95% CI)
All Patients	27	8	NR (3.98, --)
Negative	10	2	NR
Weak positive	4	2	3.98 (2.76, --)
Strong positive	7	2	NR
Not reported	6	2	NR

First Line Therapy With PD-1/PD-L1 Inhibitors

Roy S. Herbst, MD, PhD
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

February 11, 2017