ESMO Preceptorship on
Non-Small Cell Lung Cancer
Copenhagen July 7-8th 2015

Session 6: Future development

Immunotherapy of Lung Cancer

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NSCLC and Immunotherapy
A long lasting journey

- Evidence of possible immune reaction to tumors
  - Ehrlich (1909), Burnet & Thomas 1950
  - TAA
- Tumor immunology extensively studied since the 1970

- Disappointing results until recently
  - Non-specific immune stimulation
    - PolyA-PolyU, BCG, C Parvum, γIFN, αIFN, Interleukine 2,

  - Specific, Antigen mediated immune stimulation with vaccine:
    - Mage3, MUC 1, BEC 1, 1E10, Anti EGF…
    - Tumor cell vaccine + TGFß (Lucanix)
    - All failed in large randomized trials despite promising earlier results and documented immune response

NSCLC: Role of the Immune System and Potential for Immunotherapy

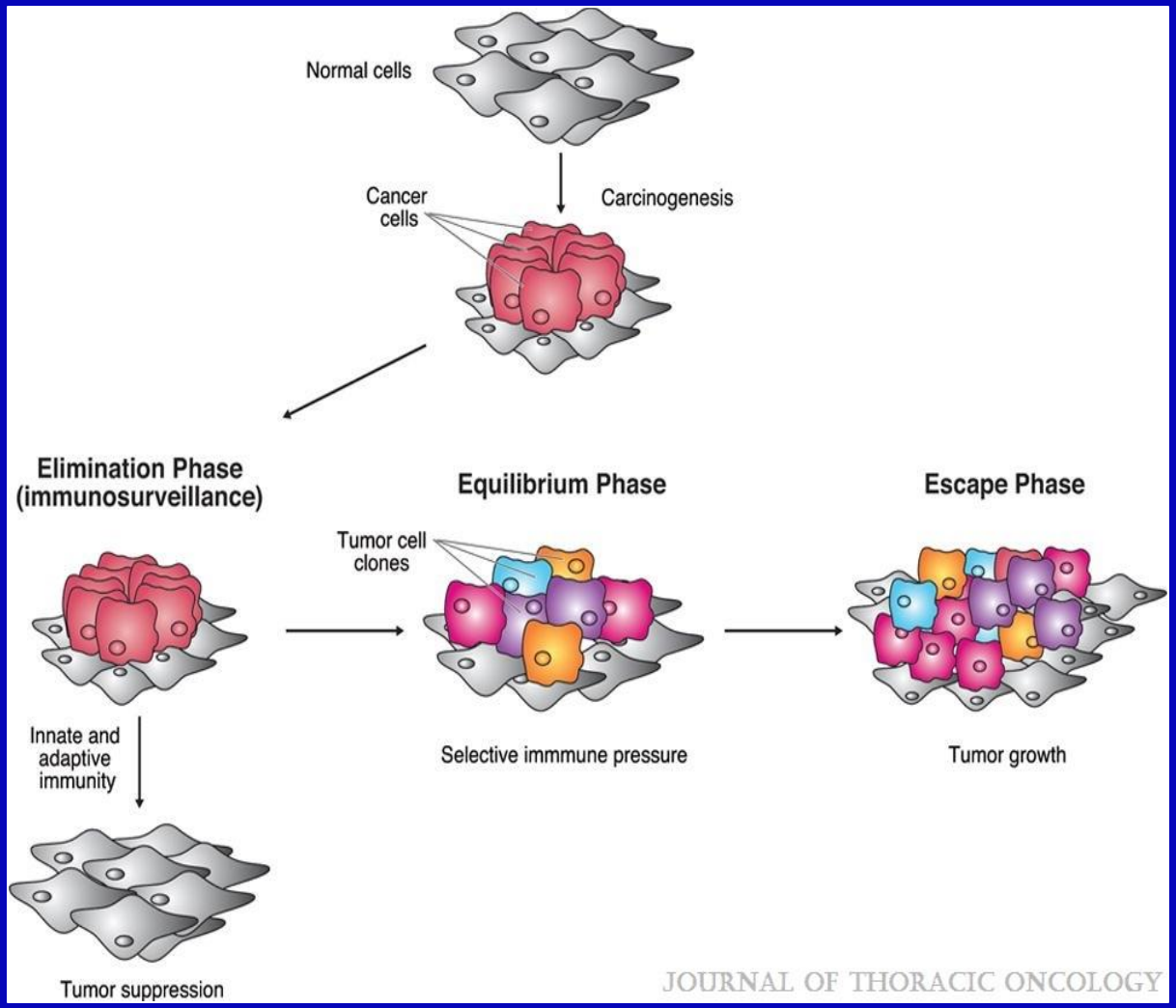


FIGURE 2. Cancer immunoediting. The proposed process of cancer immunoediting consists of three distinct phases: elimination, equilibrium, and escape. In the elimination phase, innate and adaptive immune responses recognize and destroy cancer cells (immunosurveillance), suppressing tumor development. In the equilibrium phase, tumor clones that escape the elimination phase remain dormant, during which tumor growth does not occur but the immunogenicity of the tumor cells continues to be shaped by selective immune pressure. In the escape phase, tumor cell clones that are resistant to the immune system proliferate unchecked. Adapted with permission from Annu Rev Immunol 2011;29:235–271.

Carbone, David P.; Gandara, David R.; Antonia, Scott J.; Zielinski, Christoph; Paz-Ares, Luis
Journal of Thoracic Oncology. 10(7):974-984, July 2015.

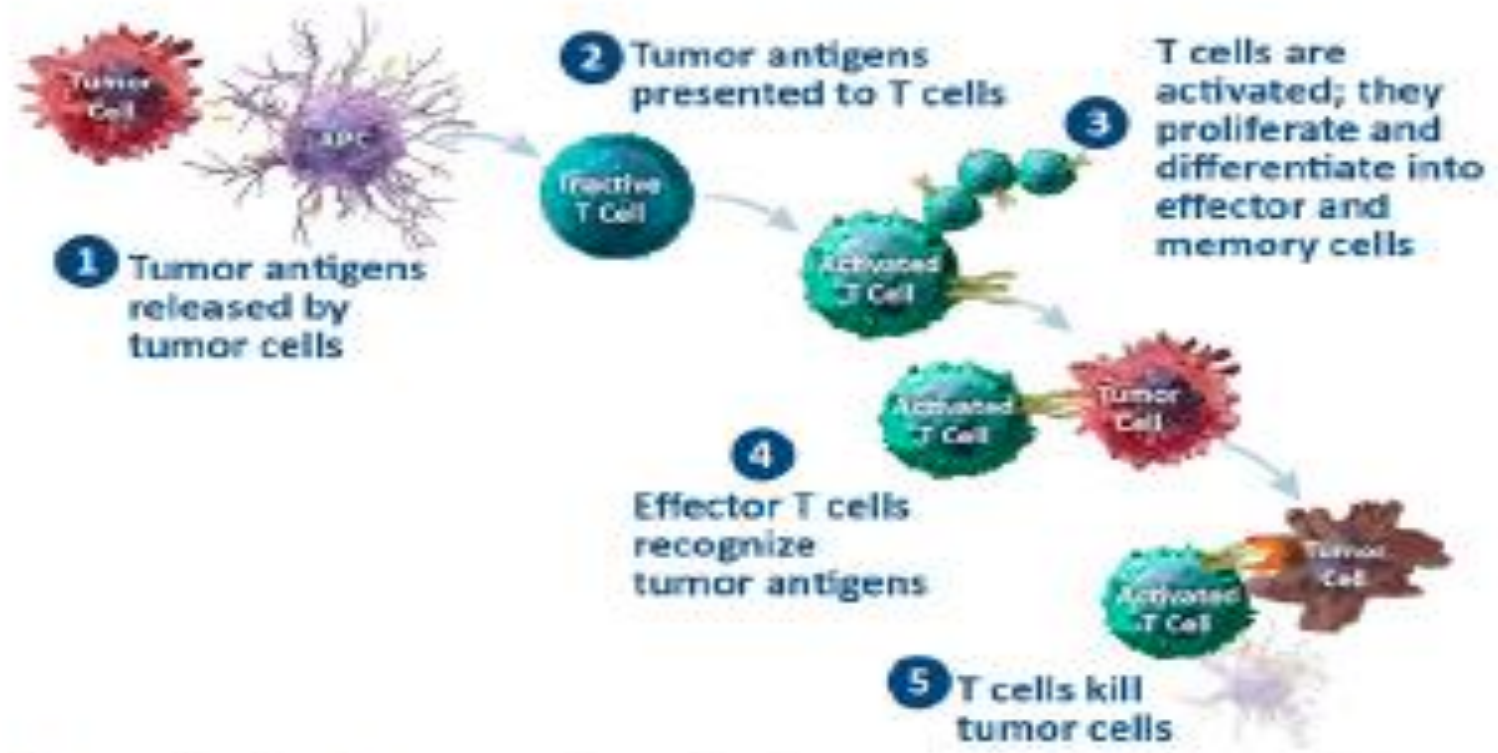
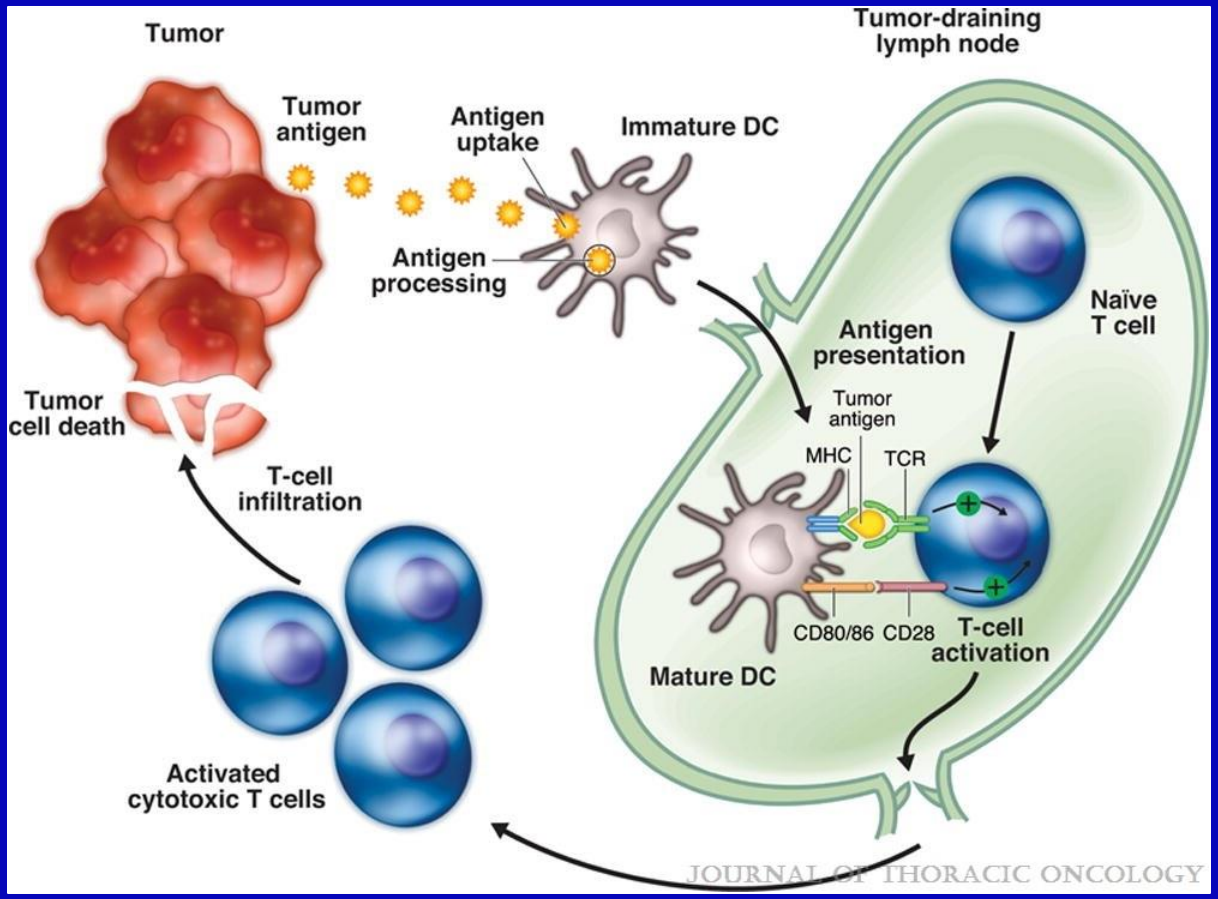


Figure 1. T cells are an important component of the antitumor immune response.

Abbreviation: APC, antigen-presenting cell.

G. Pennok, L . Chow TheOncologist 2015;20:1–11 www.TheOncologist.com ahead of print June 11 2015

Figure 1



[Non–Small-Cell Lung Cancer: Role of the Immune System and Potential for Immunotherapy]

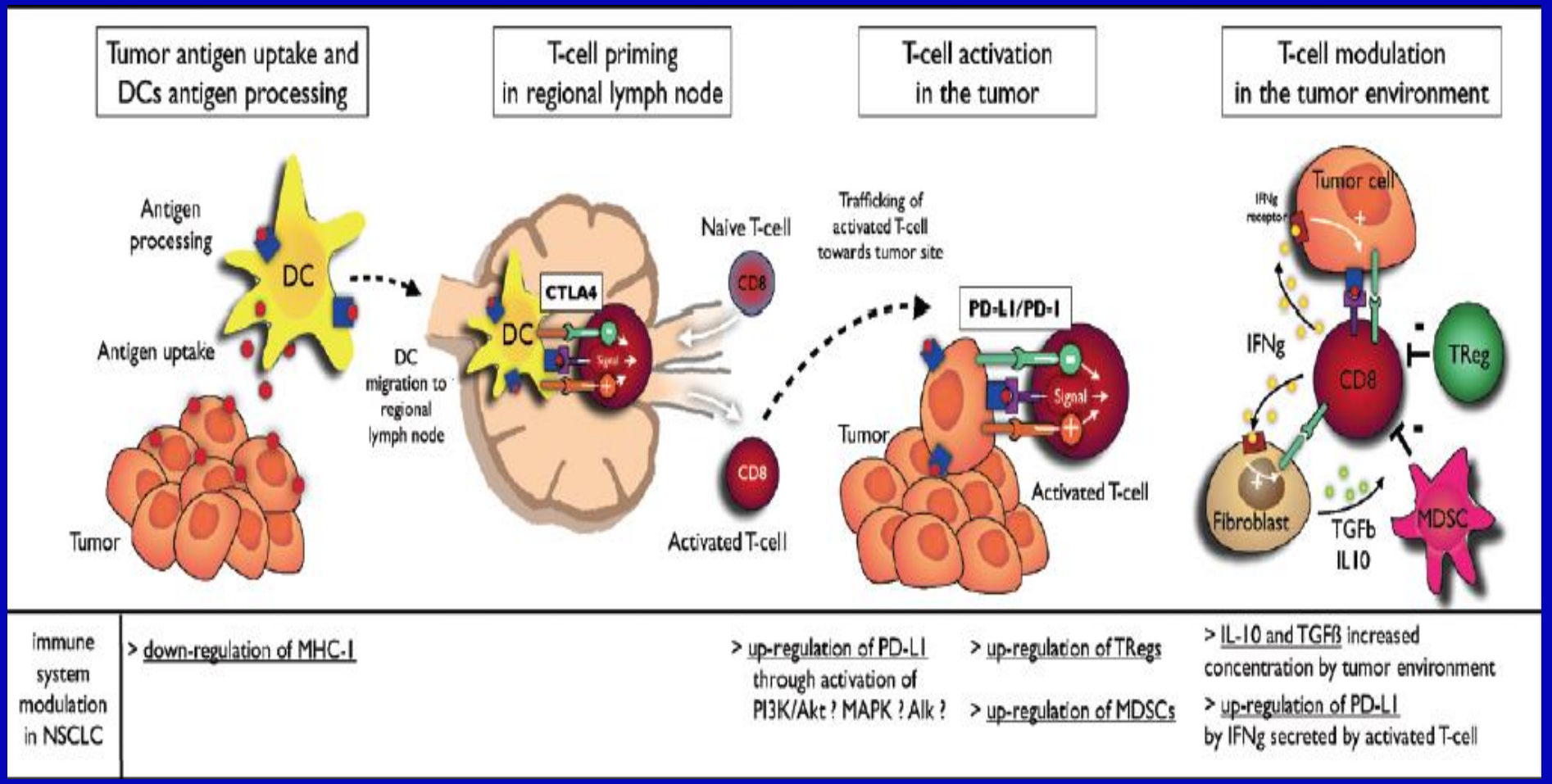
Carbone, David P.; Gandara, David R.; Antonia, Scott J.; Zielinski, Christoph; Paz-Ares, Luis

Journal of Thoracic Oncology. 10(7):974-984, July 2015.
doi: 10.1097/JTO.0000000000000551

FIGURE 1. Adaptive anticancer immunity. The adaptive anticancer immune response is initiated by immature DCs, which capture and process tumor antigens. DCs subsequently undergo maturation and migrate to tumor-draining lymph nodes, where they present tumor antigens within MHC molecules to naïve T cells, triggering a protective T-cell response. T-cell activation requires interaction not only between the antigen–MHC complex on DCs and TCRs but also among an array of co-stimulatory molecules, including CD80/86 on DCs and the CD28 receptor on T cells. The adaptive anticancer immune response culminates with the infiltration of activated cytotoxic T cells into the tumor, killing cancer cells. DC, dendritic cell; MHC, major histocompatibility; TCR, T-cell receptor.

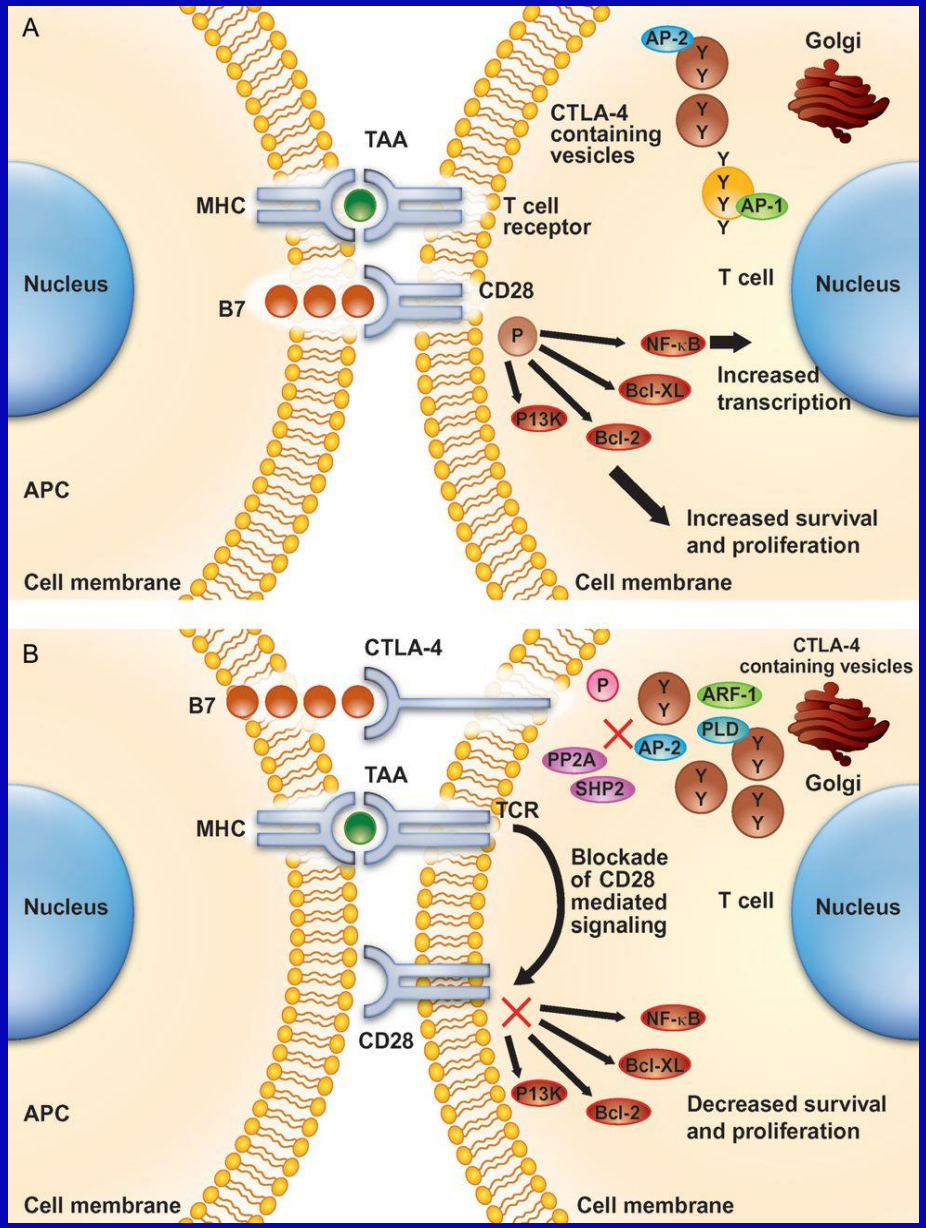
Incorporating Immune-Checkpoint Inhibitors into Systemic Therapy of NSCLC

Stéphane Champiat, MD, *Ecaterina Ileana, MD, Giuseppe Giaccone, MD, PhD, Benjamin Besse, MD, PhD, Giannis Mountzios, MD, PhD, Alexander Eggermont, MD, PhD, and Jean-Charles Soria, MD, PhD*



J Thorac Oncol. **2014;9: 144–153**

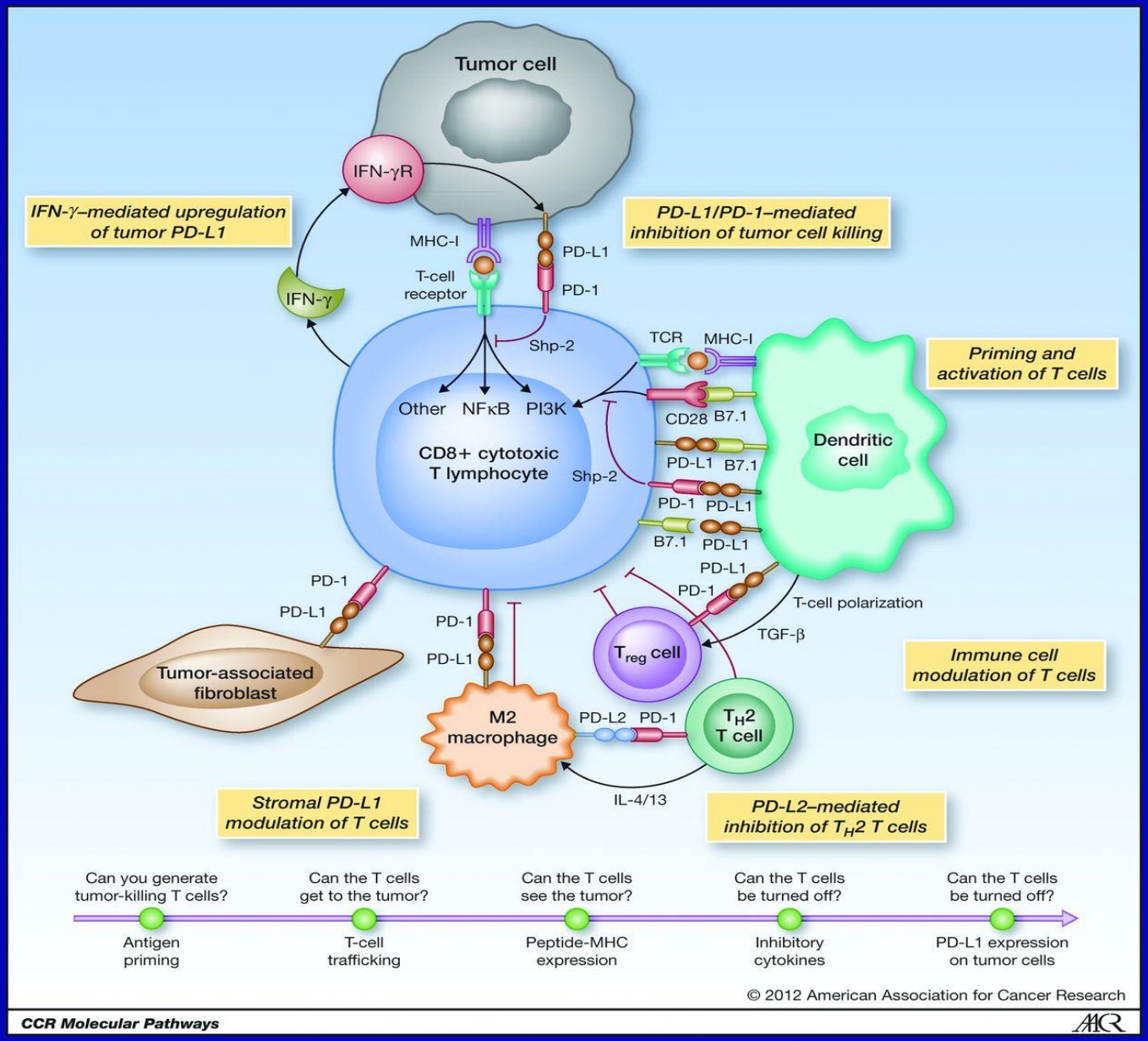
The action of CTLA-4 in the T cell.



C. Zielinski et al. Ann Oncol 2013;24:1170-1179

Annals of Oncology

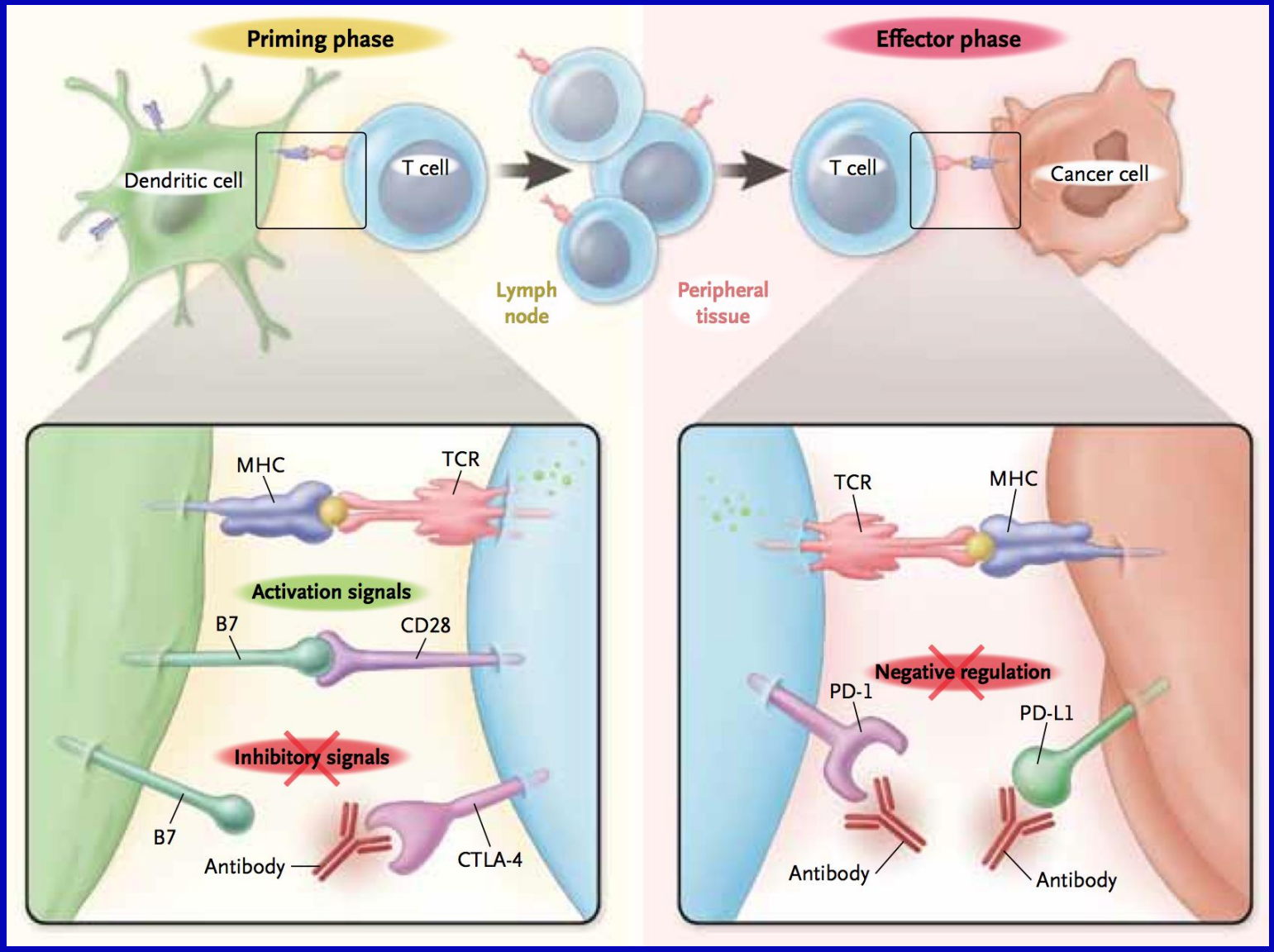
Tumor immunology and the PD-L1/PD-1 pathway.



Daniel S. Chen et al. Clin Cancer Res 2012;18:6580-6587

Clinical Cancer Research
AACR American Association for Cancer Research

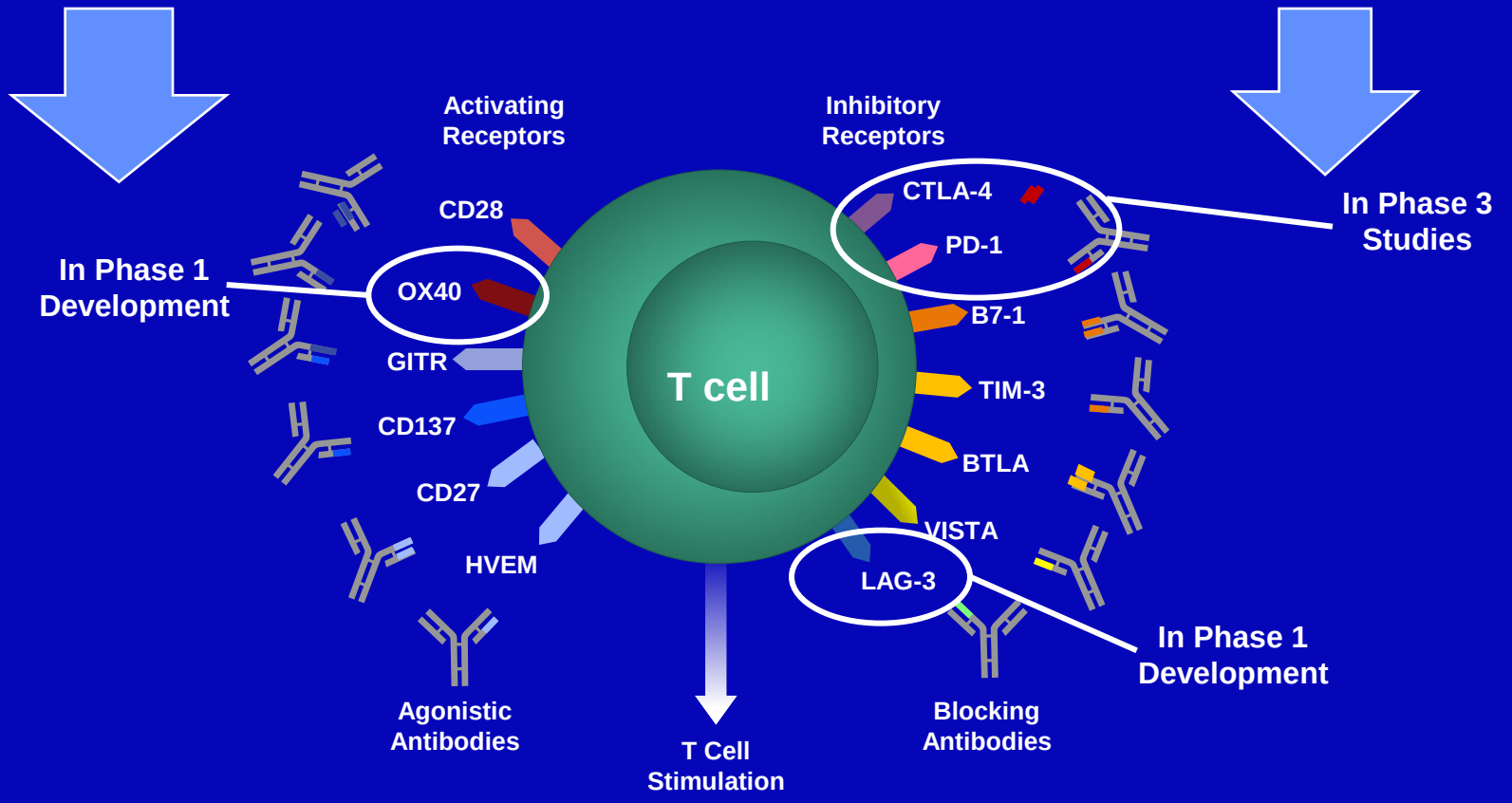
CTLA-4 versus PD-1



Ribas, NEJM 2012

T cell immune checkpoints as targets for immunotherapy

- Agonistic antibodies directed towards activating co-stimulatory molecules
- Blocking antibodies against co-inhibitory molecules to enhance T-cell stimulation to promote tumor destruction



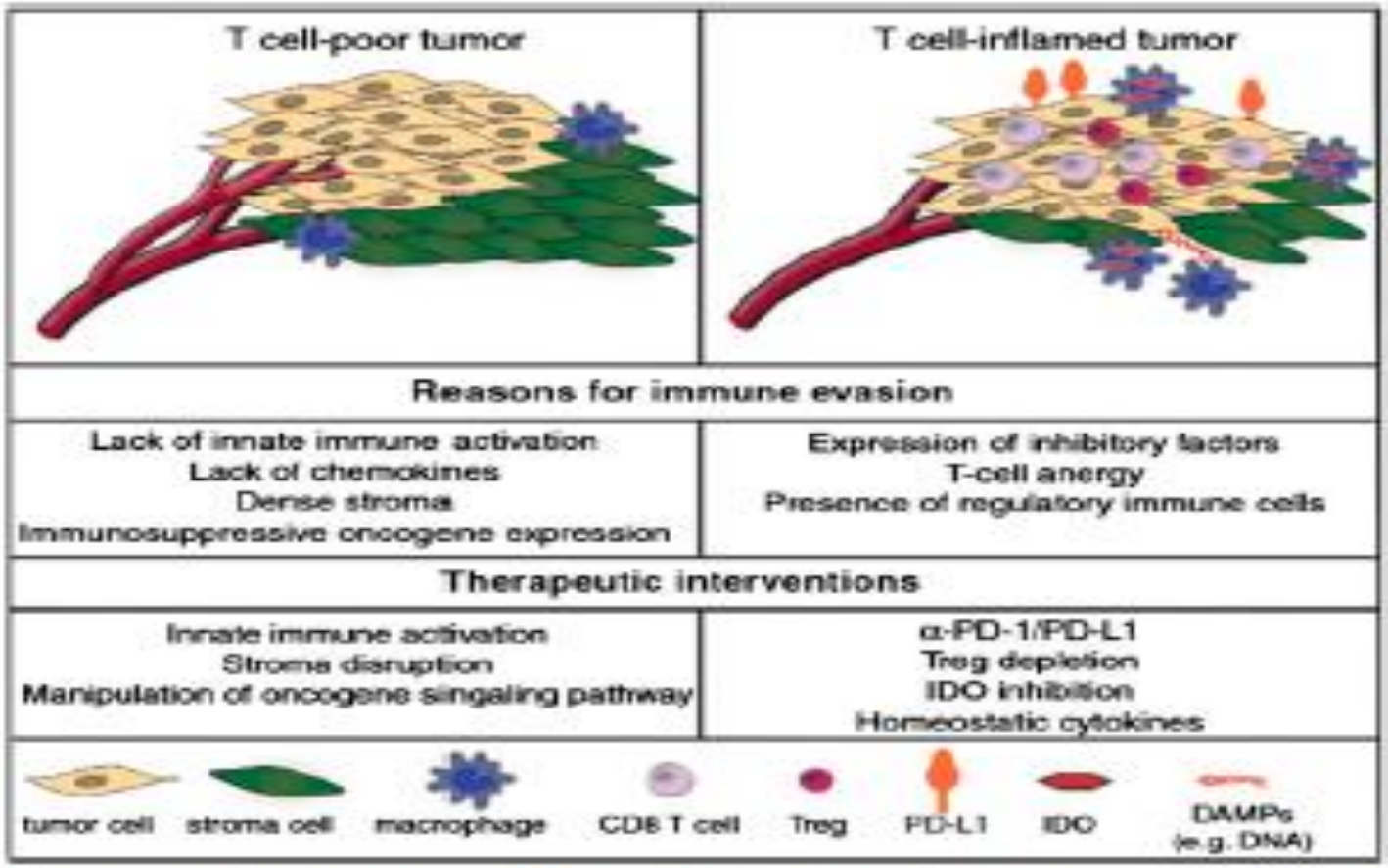
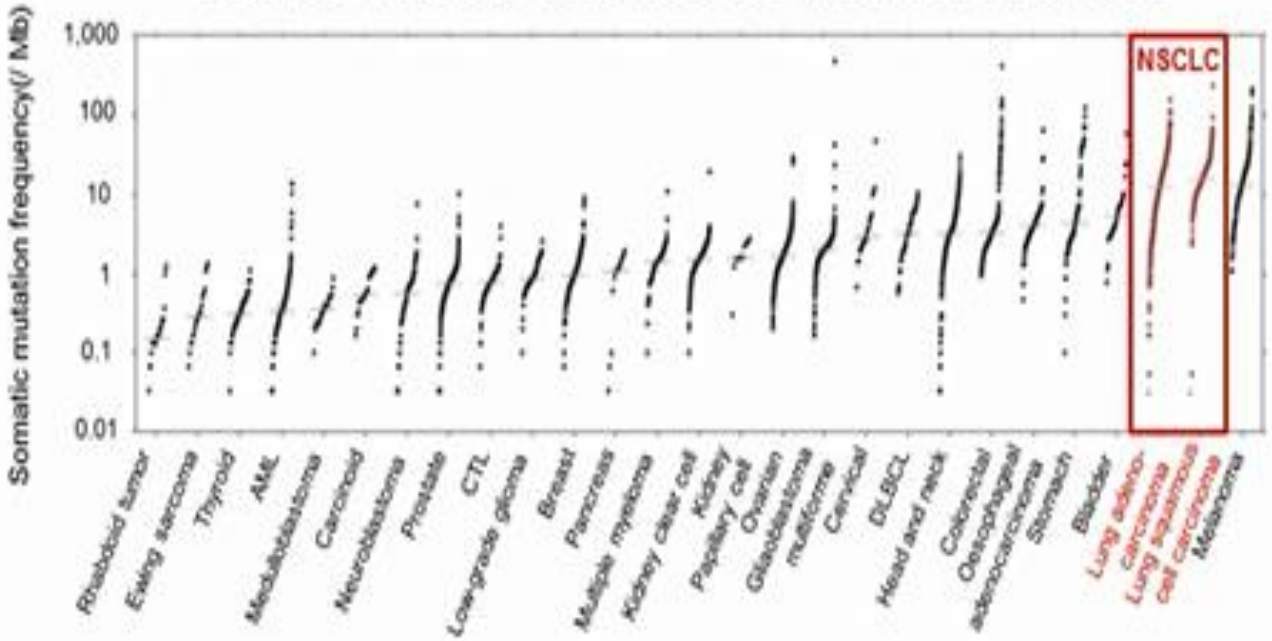


Figure 4. The immune status of the tumor microenvironment may have implications for the selection and success of immunotherapy. From [23] with permission from Elsevier.

G. Pennok, L . Chow TheOncologist 2015;20:1–11 www.TheOncologist.com ahead of print June 11 2015

Somatic mutation frequencies in different tumors[1]



- High rates of somatic mutations in lung cancer may contribute to increased immunogenicity[2]
- Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC

[1]Reprinted by permission from Macmillan Publishers Ltd: Lawrence MS, et al. Nature. 2013;499(7457):214-218, copyright 2013
[2]Chen DS, et al. CCR 2012

Programmed Death-Ligand1 IHC in Lung cancer: in what state is this art?

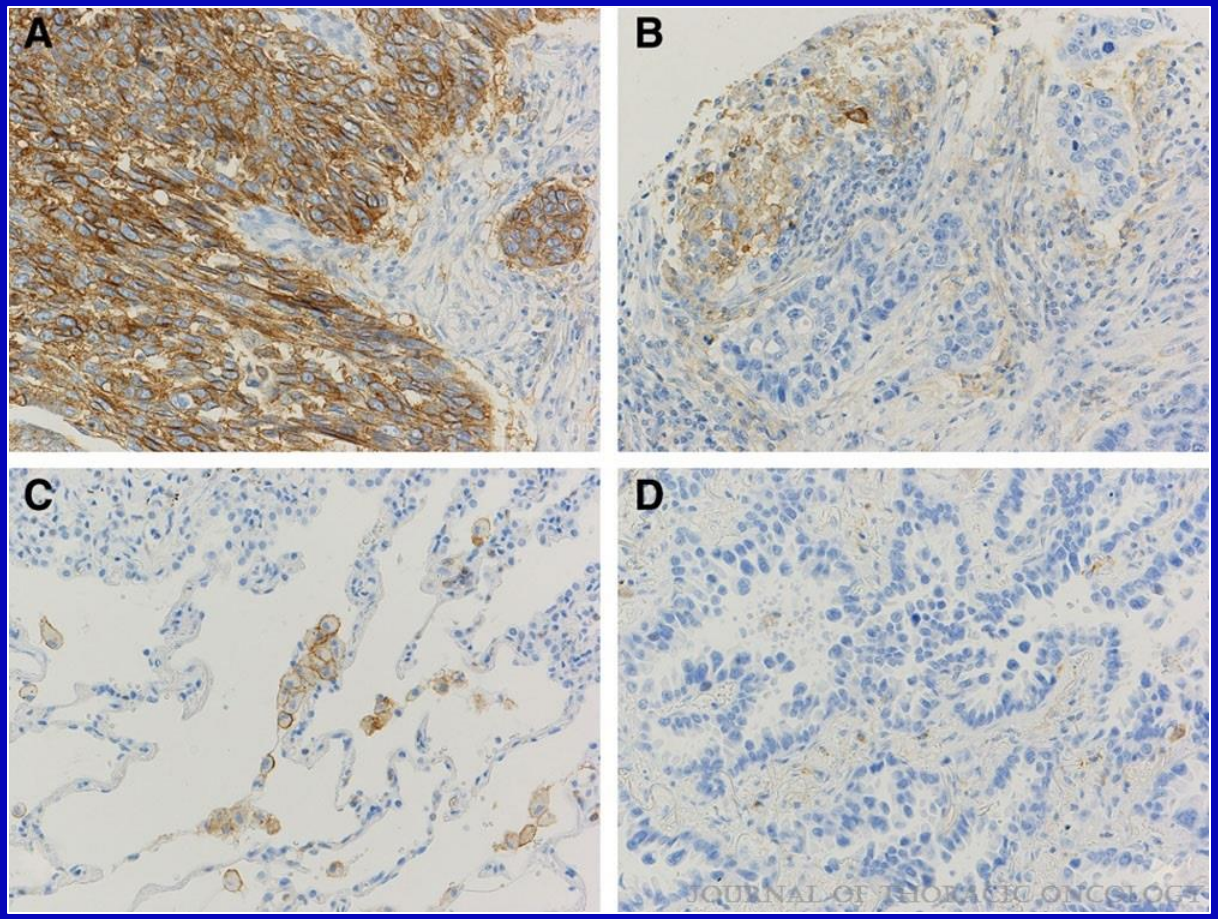


FIGURE 1. Programmed death receptor-1 with its ligand (PDL-1) immunostaining performed using the E1LN3N clone anti-PD-L1 from Cell Signaling Technology (Boston) with standard detection techniques. A, Squamous cell carcinoma showing a strong, uniform positive reaction in tumor cells. B, Despite being negative in tumor cells in the center of the image, there is a positive reaction in macrophages and other immune cells in the tumor stroma. C, Most alveolar macrophages are positive for PD-L1. D, This adenocarcinoma is negative for PD-L1

Kerr, Keith M.; Tsao, Ming-Sound; Nicholson, Andrew G.; Yatabe, Yasushi; Wistuba, Ignacio I.; Hirsch, Fred R.; On behalf of the IASLC Pathology Committee

Journal of Thoracic Oncology. 10(7):985-989, July 2015.

NSCLC: Role of the Immune System and Potential for Immunotherapy

Agent	Description
Checkpoint inhibitors	
Nivolumab	Fully human IgG4 monoclonal antibody directed against PD-1 on T cells
Pembrolizumab (MK-3475)	Humanized IgG4 monoclonal antibody directed against PD-1 on T cells
BMS-936559	Fully human IgG4 monoclonal antibody directed against PD-L1 on tumor cells
MPDL3280A	Human IgG1 monoclonal antibody directed against PD-L1 on tumor cells
MEDI4736	Fully human IgG1 monoclonal antibody directed against PD-L1 on tumor cells
Ipilimumab	Fully human IgG1 monoclonal antibody directed against CTLA-4 on T cells
Lirilumab (IPH2102)	Fully human monoclonal antibody directed against the killer-cell immunoglobulin-like receptor on NK cells
BMS-986016	Monoclonal antibody directed against the lymphocyte-activation gene 3 on tumor infiltrating lymphocytes
Vaccines	
Tecemotide (liposomal BLP25)	Vaccine composed of the exposed core peptide of MUC-1
Racotumomab	Patient idiotype-specific vaccine against NGg GM3
TG4010	Vaccine that uses a recombinant vaccinia virus (modified virus of Ankara) that encodes for human MUC-1 and IL-2
Nonspecific immune stimulator	
Talactoferrin alfa	Recombinant human lactoferrin

CTLA-4, cytotoxic T lymphocyte antigen-4; IgG, immunoglobulin G; IL-2, interleukin-2; MUC-1, mucin 1; NGg, N-glycolil; NK, natural killer; NSCLC, non–small-cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

JOURNAL OF THORACIC ONCOLOGY

TABLE 1. Immunotherapeutic Agents in Clinical Development for the Treatment of Advanced Non–Small-Cell Lung Cancer

Carbone, David P.; Gandara, David R.; Antonia, Scott J.; Zielinski, Christoph; Paz-Ares, Luis
Journal of Thoracic Oncology. 10(7):974-984, July 2015.1

NSCLC: Role of the Immune System and Potential for Immunotherapy

Agent (Reference)	Study Design (Study Name)	Number of Patients	Median Follow-Up	Objective Response Rate, % (n/N)	Median (Range) Response Duration, Weeks	Median Progression-Free Survival	Median Overall Survival (Months)	1-Year Survival Rate (%)	2-Year Survival Rate (%)	Incidence of Adverse Events (%)
Nivolumab (Brahmer et al.[47])	Phase I dose-ranging study of nivolumab (1, 3, and 10 mg/kg IV Q2W) in previously treated patients with advanced solid tumors, including advanced NSCLC	129 (NSCLC cohort)	27 months	Across all doses: 17 (22 of 129)[a] 3 mg/kg Q2W dose[b]: 24 (9 of 37)[a]	Across all doses: 74.0 (6.1+ to 133.9+) 3 mg/kg Q2W dose: 74.0 (16.1+ to 133.9+)	Across all doses: 2.3 months (95% CI, 1.8–3.7)[a] 3 mg/kg Q2W dose: 1.9 months (95% CI, 1.7–7.3)[a]	Across all doses: 9.9 (95% CI, 7.8–12.4) 3 mg/kg Q2W dose: 14.9 (95% CI, 7.3–NE)	Across all doses: 42 (95% CI, 34–51) 3 mg/kg Q2W dose: 56 (95% CI, 38–71)	Across all doses: 24 (95% CI, 16–32) 3 mg/kg Q2W dose: 45 (95% CI, 27–61)	Treatment-related any grade: fatigue, 24; decreased appetite, 12; diarrhea, 10 Treatment-related grade 3–4: 14
Nivolumab (Gettinger et al.[48])	Phase I multi-cohort study of nivolumab as monotherapy or combined with chemotherapy, targeted therapy, or ipilimumab in chemotherapy-naïve patients with advanced NSCLC (CheckMate 012)	20 (cohort treated with nivolumab 3 mg/kg IV Q2W)	66.1 weeks	30 (6 of 20)[a]	NR	36.1 weeks[a]	NR	75 (95% CI, 50–89)	NA	Treatment-related any grade: fatigue, 40; nausea, 20; rash, 20; diarrhea, 15 Treatment-related grade 3–4: 20
Nivolumab (Rizvi et al.[49])		21 (nonsquamous EGFR MT cohort treated with nivolumab 3 mg/kg IV Q2W plus erlotinib 150 mg/day PO)	71.9 weeks	19 (4 of 21)[a]	NR	29.4 weeks[a]	NR	73 (95% CI, 46–88)	NA	Treatment-related any grade: rash, 48; fatigue, 29; paronychia, 29; diarrhea, 24; skin fissures, 24 Treatment-related grade 3–4: 24
Nivolumab (Rizvi et al.[50])	Phase II single-arm study of nivolumab 3 mg/kg IV Q2W in patients with advanced, refractory squamous NSCLC (CheckMate 063)	117	8.0 months	15 (17 of 117)[a]	NR	1.9 months (95% CI, 1.8–3.2)[a]	8.2 (95% CI, 6.1–10.9)	40.8 (95% CI, 31.6–49.7)	NA	Treatment-related any grade: fatigue, 33; nausea, 15; asthenia, 12; diarrhea, 10 Treatment-related grade 3–4: 17
Pembrolizumab (Garon et al.[52])	Phase I study of pembrolizumab (2 mg/kg IV Q3W, 10 mg/kg IV Q3W, and 10 mg/kg IV Q2W) with treatment-naïve and previously treated patients with advanced NSCLC (KEYNOTE-001)	262	NA	21 (treatment-naïve patients: 26; previously treated patients: 20)[a]	NA	Treatment-naive patients: 27 weeks (95% CI, 14–45)[a] Previously treated patients: 10 weeks (95% CI, 9.1–15.3)[a]	Treatment-naive patients: NR (95% CI, NE–NE) Previously treated patients: 8.2 (95% CI, 7.3–NR)	NA	NA	Treatment-related any grade: fatigue, 20; pruritus, 9; arthralgia, 8; decreased appetite, 8; diarrhea, 7 Treatment-related grade 3–4: 9
MPDL3280A (Soria et al.[53])	Phase I study of MPDL3280A IV Q3W in patients with squamous or nonsquamous NSCLC	53	NA	24 (9 of 37)[a]	Median was not reported (range: 1+ to 214+ days)	NA	NA	NA	NA	All-cause grade 3–4: 34 (pericardial effusion, 6; dehydration, 4; dyspnea, 4; fatigue, 4)
MEDI4736 (Brahmer et al.[54])	Phase I dose-escalation dose-expansion study of MEDI4736 (0.1–10 mg/kg IV Q2W; 15 mg/kg IV Q3W) in patients with advanced solid tumors, including advanced NSCLC	155 (NSCLC cohort)	6 weeks	Across all doses: 16 (9 of 58)[a]	NA	NA	NA	NA	NA	Treatment-related any grade: 29 Treatment-related grade 3–4: 3
Ipilimumab (Lynch et al.[55])	Phase II study of ipilimumab (10 mg/kg IV Q3W) plus paclitaxel/carboplatin (concurrent or phased administration) versus paclitaxel/carboplatin (control) in chemotherapy-naïve patients with advanced NSCLC	204	NA	Control: 18 (12 of 66)[c] Concurrent: 21 (15 of 70)[c] Phased: 32 (22 of 68)[c]	NA	Control: 4.6[c] Concurrent: 5.5[c] (HR, 0.81; $p = 0.13$ versus control) Phased: 5.7[c] (HR, 0.72; $p = 0.05$ versus control)	Control: 8.3 Concurrent: 9.7 (HR, 0.99; $p = 0.48$ versus control) Phased: 12.2 (HR, 0.87; $p = 0.23$ versus control)	Control: 39 Concurrent: 50 Phased: 42	Control: 18 Concurrent: 18 Phased: 16	Treatment-related grade 3–4: Control: 37 Concurrent: 41 Phased: 39

[a]Based on Response Evaluation Criteria In Solid Tumors (RECIST).
[b]The nivolumab dose selected for phase 3 studies.
[c]Based on irRC.
CI, confidence interval; EGFR MT, epidermal growth factor receptor mutant; HR, hazard ratio; irPFS, immune-related progression-free survival; NA, not available; NE, not estimable; NR, not reached; NSCLC, non–small-cell lung cancer; PO, oral administration; Q2W, every 2 weeks; Q3W, every 3 weeks; irRC, immune-related response criteria.

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TABLE 2. Results of Trials of Immune Checkpoint Inhibitors in Clinical Development for the Treatment of Patients with Advanced Non–Small-Cell Lung Cancer

Wolters Kluwer

Carbone, David P.; Gandara, David R.; Antonia, Scott J.; Zielinski, Christoph; Paz-Ares, Luis
Journal of Thoracic Oncology. 10(7):974-984, July 2015.

Immunotherapy of Lung Cancer

TARGETING
IMMUNE CHECK-POINT INHIBITORS

CTLA 4
PD1
PD-L1

CTLA 4 as Immune check-point inhibitor

- CTLA 4: Cytotoxic T-Lymphocyte-Associated Anitigen 4
- Is acting the early phase of immune response
- Mostly in tumor draining lymph nodes
- At the Priming phase of Cytotoxic T cells
- Ipilumumab and Tremelimumab are 2 anti CTLA4 MoAbs

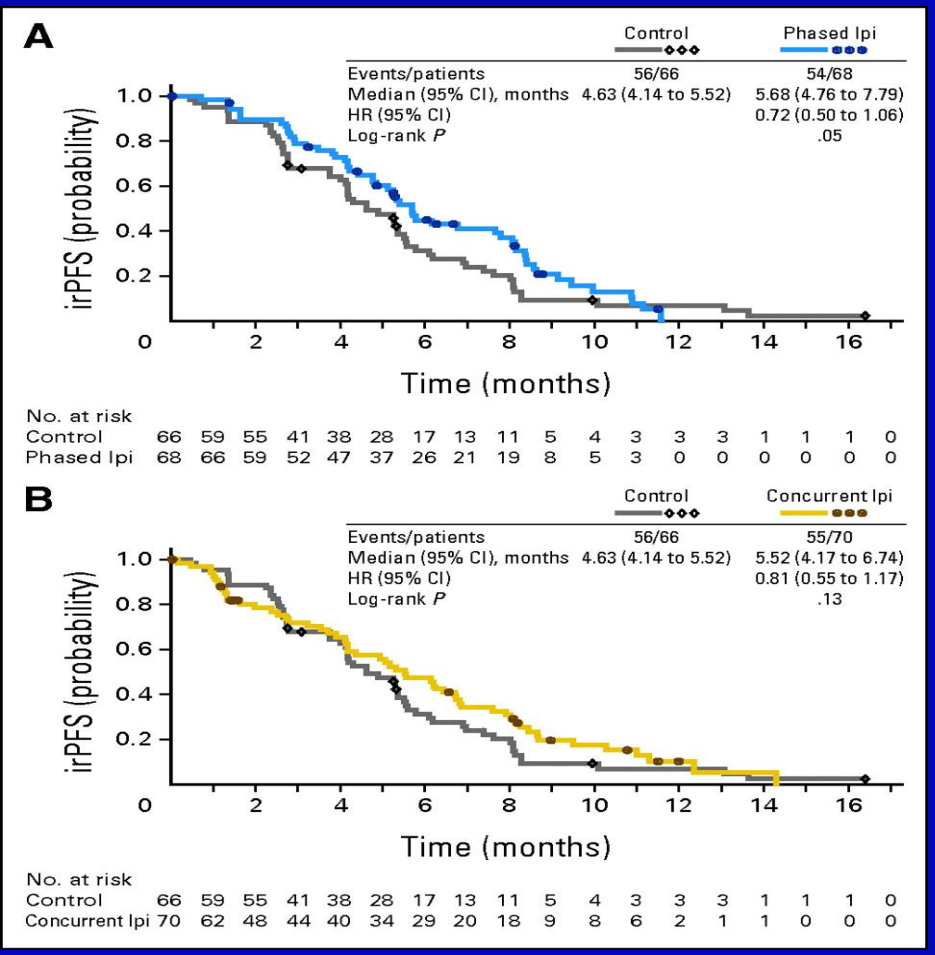
JOURNAL OF CLINICAL ONCOLOGY

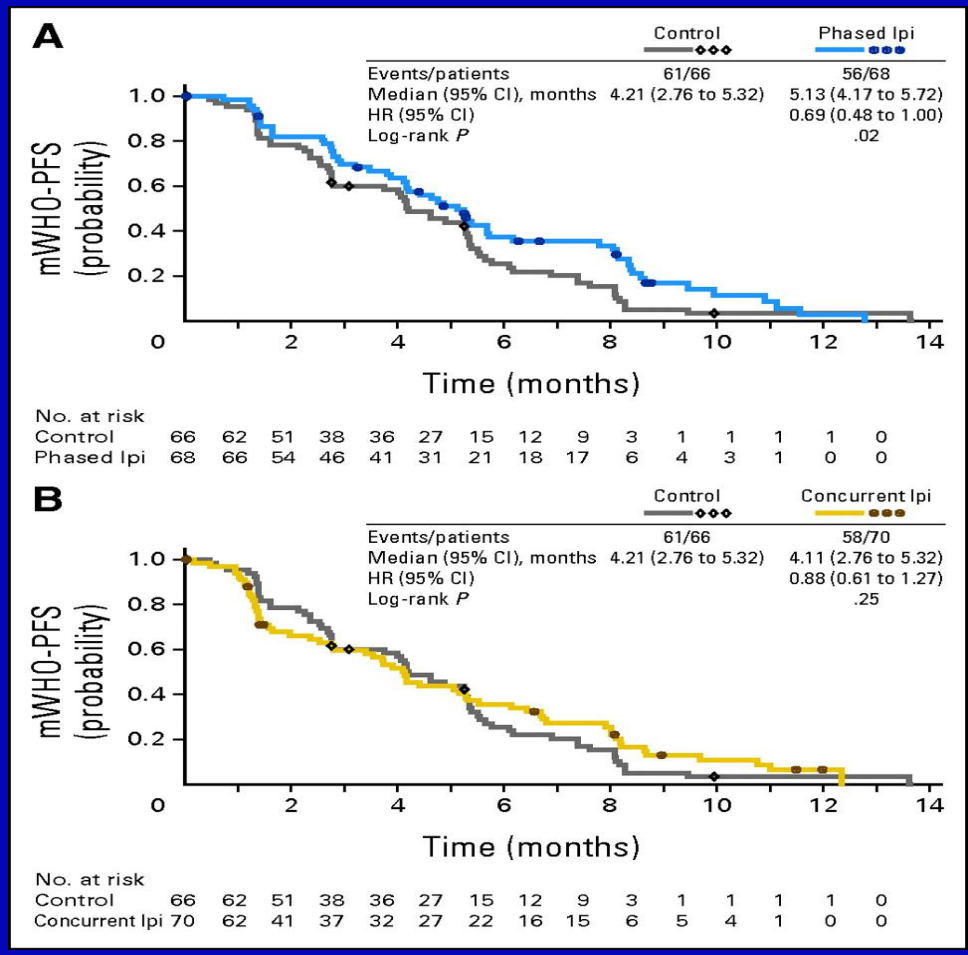
ORIGINAL REPORT

Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study

Thomas J. Lynch, Igor Bondarenko, Alexander Luft, Piotr Serwatowski, Fabrice Barlesi, Raju Chacko, Martin Sebastian, Joel Neal, Haolan Lu, Jean-Marie Cuillerot, and Martin Reck

Progression-free survival per immune-related response criteria (irPFS) and WHO criteria.

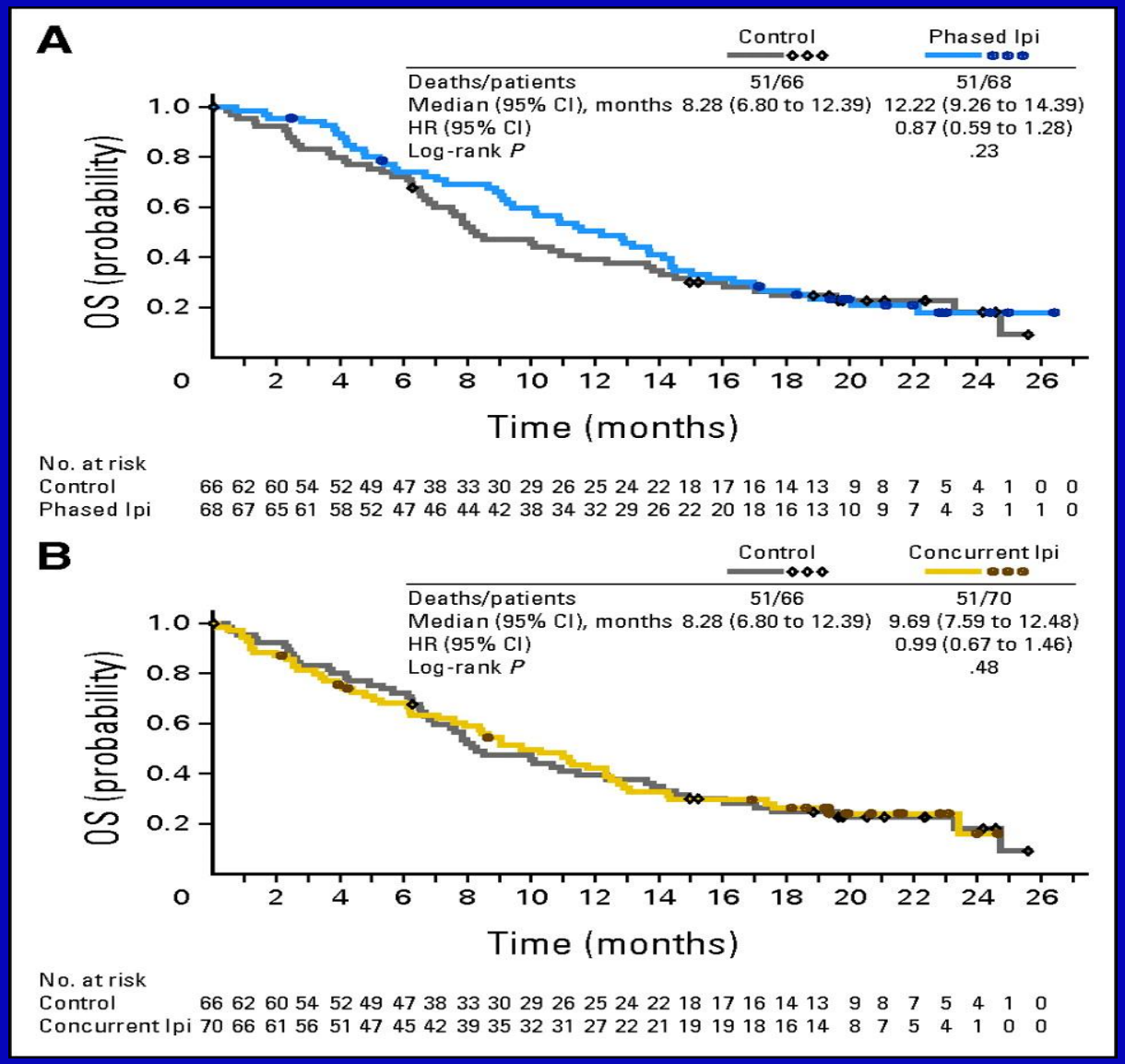




Thomas J. Lynch et al. JCO 2012;30:2046-2054

JOURNAL OF CLINICAL ONCOLOGY ASCO

Kaplan-Meier plots for overall survival (OS).



Thomas J. Lynch et al. JCO 2012;30:2046-2054

JOURNAL OF CLINICAL ONCOLOGY ASCO

Ipilimumab in Lung Cancer

- Ipilimumab (YERVOY®) is not approved in NSCLC
- Presently being evaluated also in SCLC

Targeting
immune check-point inhibitors

PD1-PD-L1

PD1:

Nivolumab (Opdivo®) EMA approved

Pembrolizumab (Keytruda®)

PD-L1:

MPDL3280A (Atezolizumab)

MEDI4736

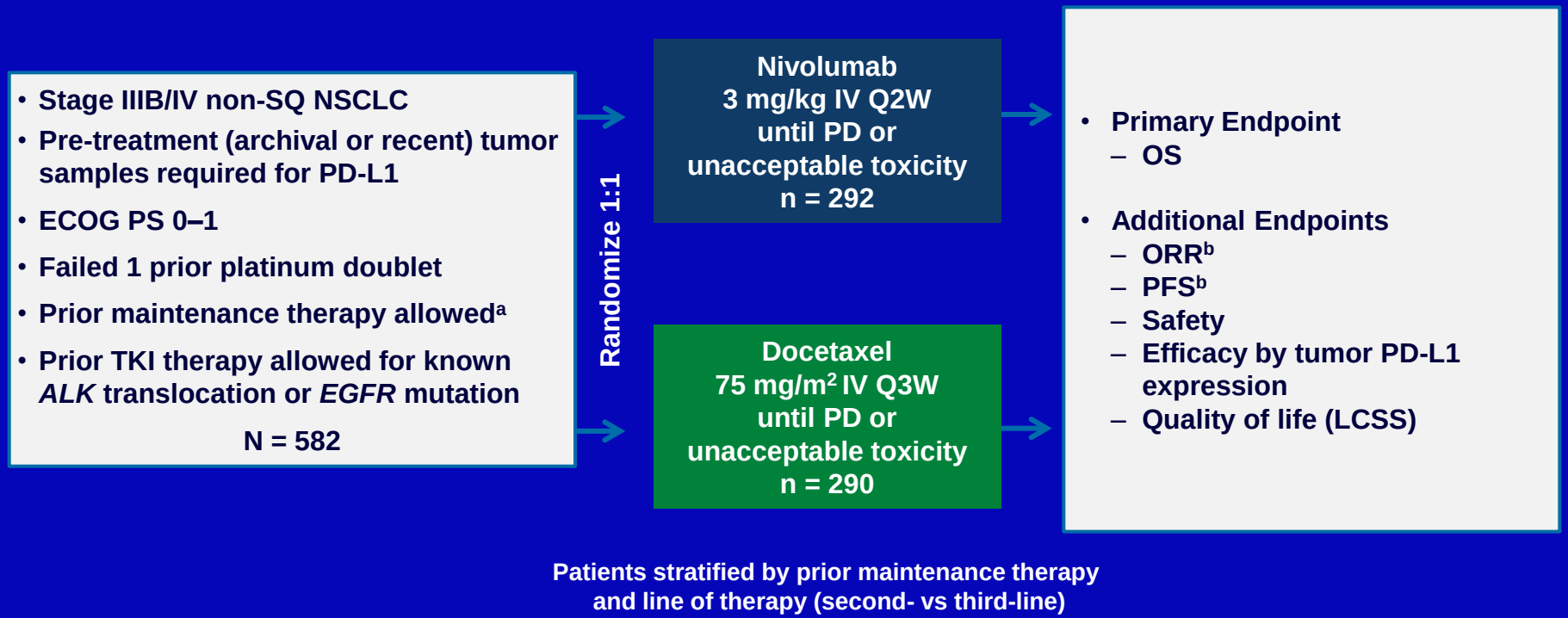
Phase III, Randomized Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC)

Luis Paz-Ares,[1] Leora Horn,[2] Hossein Borghaei,[3] David R. Spigel,[4] Martin Steins,[5] Neal E. Ready,[6] Laura Q. Chow,[7] Everett E. Vokes,[8] Enriqueta Felip,[9] Esther Holgado,[10] Fabrice Barlesi,[11] Martin Kohlhäufl,[12] Oscar Arrieta,[13] Marco Angelo Burgio,[14] Jérôme Fayette,[15] Scott N. Gettinger,[16] Christopher T. Harbison,[17] Cécile Dorange,[17] Friedrich Graf Finckenstein,[17] Julie R. Brahmer[18]

[1]Hospital Universitario Virgen Del Rocio, Sevilla, Spain; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]Fox Chase Cancer Center, Philadelphia, PA, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [5]Thoraxklinik, Heidelberg University Hospital, Heidelberg, Germany; [6]Duke University Medical Center, Durham, NC, USA; [7]University of Washington, Seattle, WA, USA; [8]University of Chicago Medicine & Biological Sciences, Chicago, IL, USA; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Hospital De Madrid, Norte Sanchinarro, Spain; [11]Aix Marseille University; Assistance Publique Hôpitaux de Marseille, Marseille, France; [12]Robert-Bosch-Krankenhaus, Gerlingen, Germany; [13]Instituto Nacional De Cancerologia, Mexico City, Mexico; [14]IRST IRCCS Meldola (Forlì - Cesena) Italy; [15]Centre Léon Bérard, Lyon, France; [16]Yale Comprehensive Cancer Center, New Haven, CT, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Courtesy of L Paz-Ares ASCO 2015 Abstract

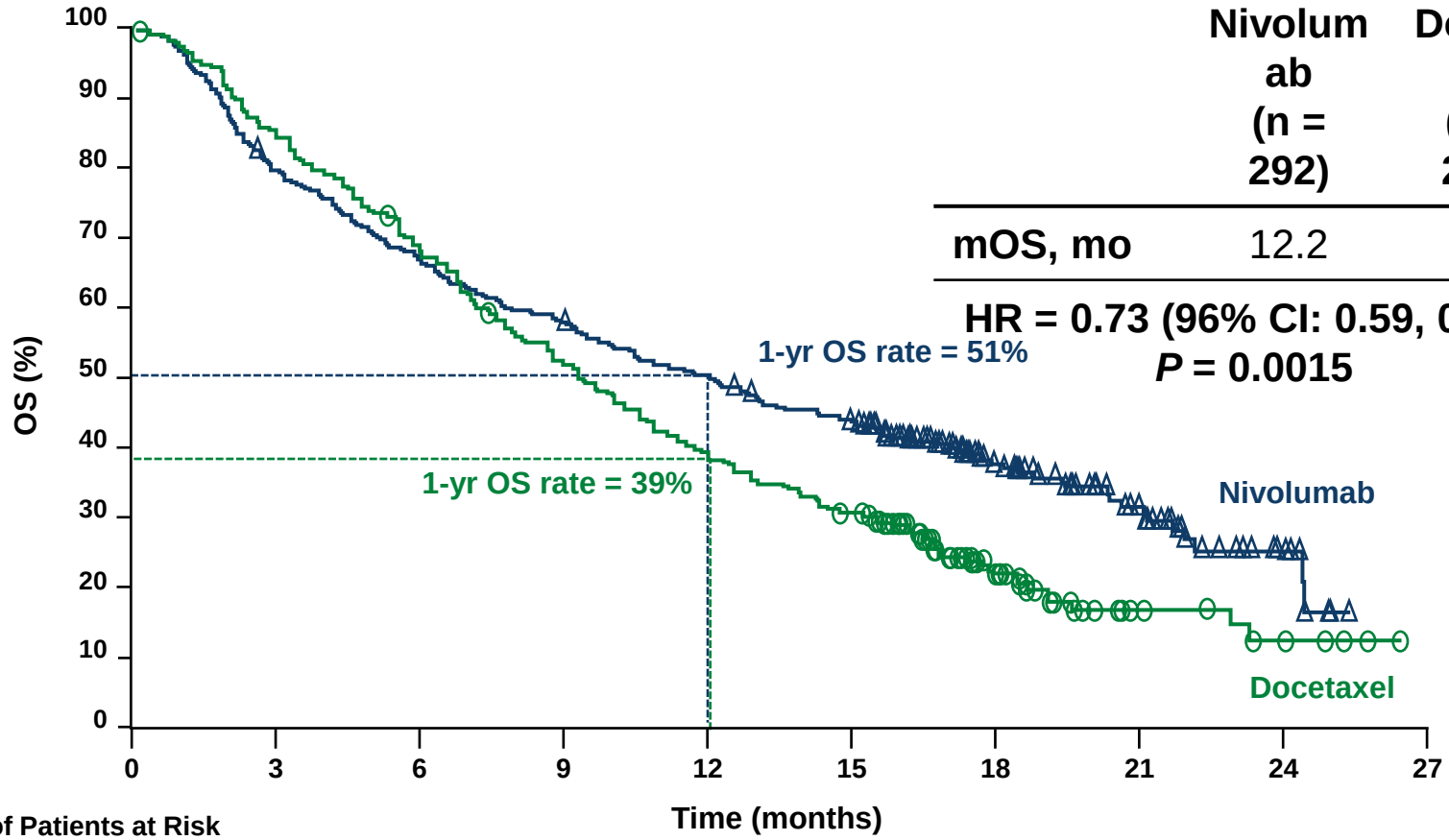
CheckMate 057 (NCT01673867) Study Design



- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

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

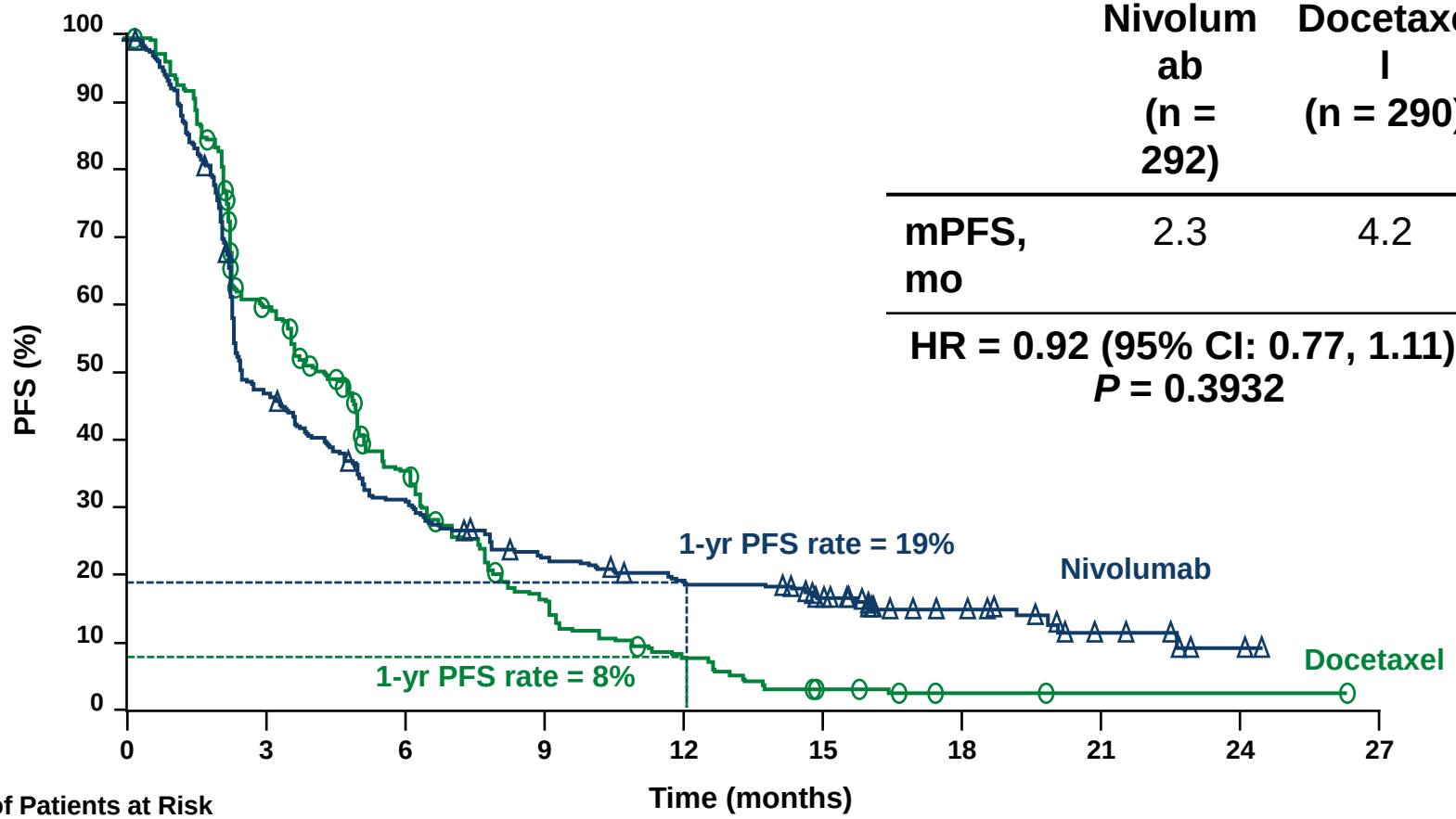
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Progression-free Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

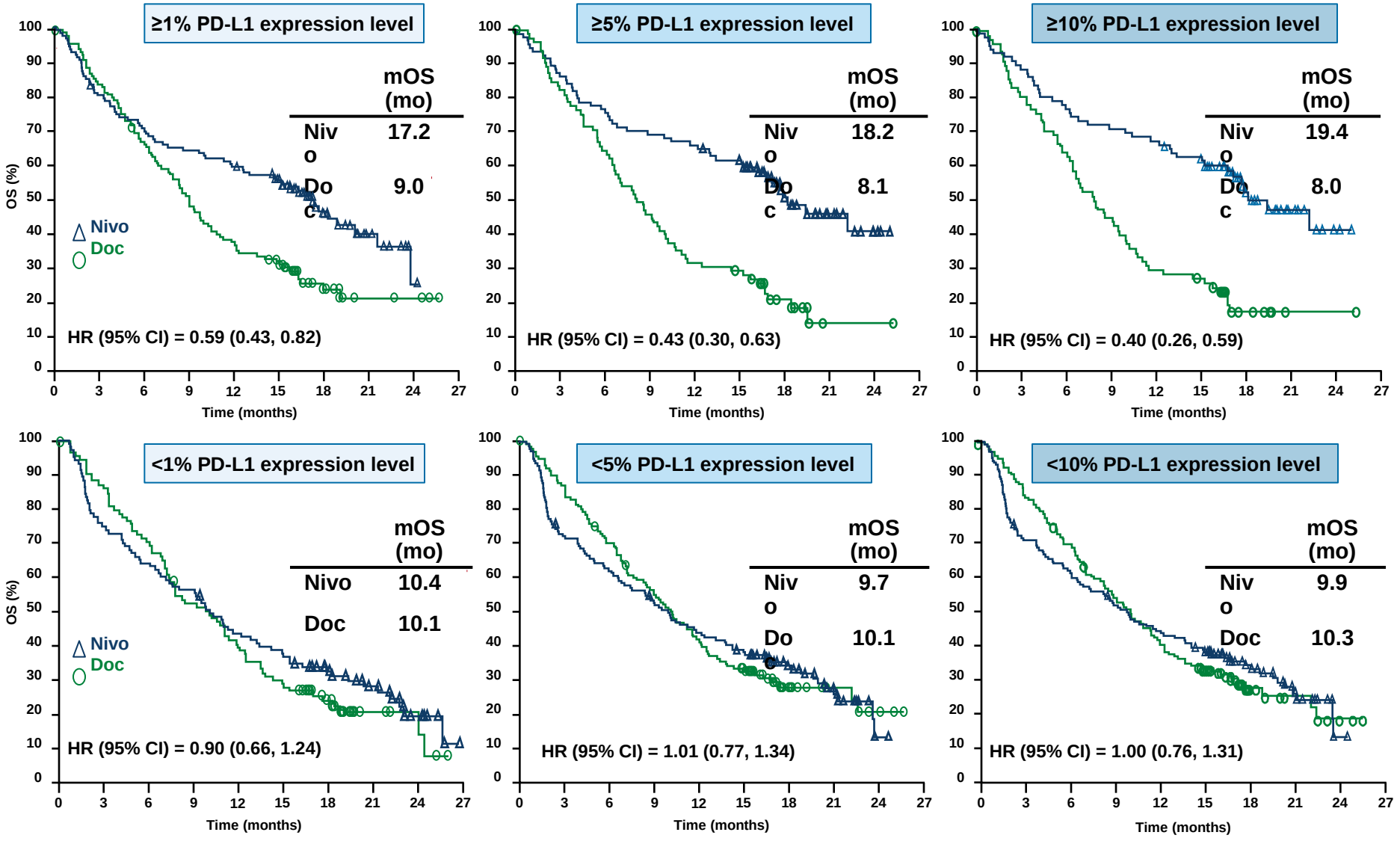


Number of Patients at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

OS by PD-L1 Expression



Symbols represent censored observations.

Summary

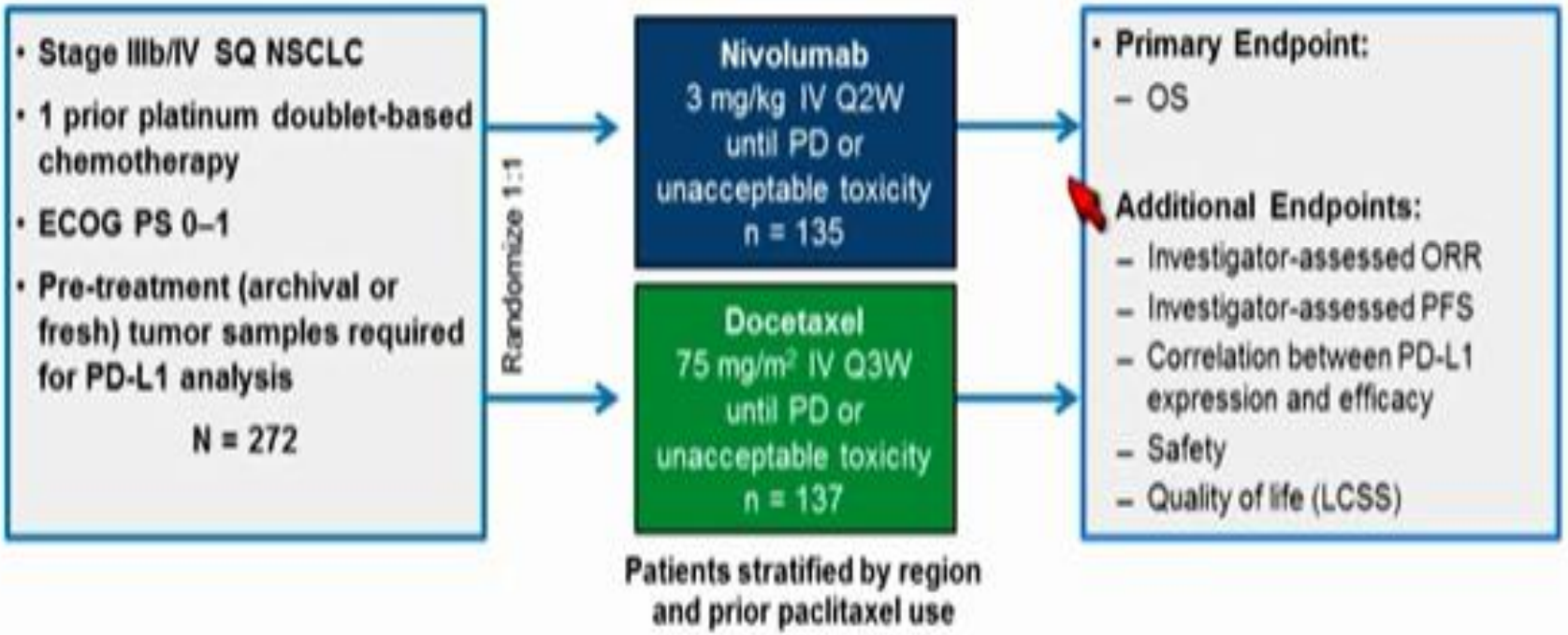
- Nivolumab is the first PD-1 inhibitor to significantly improve OS vs docetaxel in previously treated patients with advanced non-SQ NSCLC
  - 27% reduction in risk of death (HR = 0.73; *P* = 0.0015)
- Nivolumab significantly improved ORR vs docetaxel (*P* = 0.0246)
- PD-L1 expression is predictive of benefit with nivolumab, starting at the lowest expression level (1%)
  - Median OS nearly doubled with nivolumab vs docetaxel across PD-L1 expression continuum
  - No difference in OS seen when PD-L1 was not expressed in the tumor
  - ORR nearly tripled in PD-L1 expressors
- Safety profile of nivolumab was favorable vs docetaxel and consistent with prior studies
- CheckMate 057 is the second phase III trial to demonstrate superior survival of nivolumab over docetaxel in advanced NSCLC

A Phase III Study (CheckMate 017) of Nivolumab (Anti-Programmed Death-1) vs Docetaxel in Previously Treated Advanced or Metastatic Squamous (SQ) Cell Non-Small-Cell Lung Cancer (NSCLC)

David R. Spigel,[1] Karen Reckamp,[2] Nalyer Rizvi,[3] Elena Poddubskaya,[4] Howard West,[5] Wilfried Ernst Erich Eberhardt,[6] Paul Baas,[7] Scott J. Antonia,[8] Adam Pluzanski,[9] Everett E. Vokes,[10] Esther Holgado,[11] David Waterhouse,[12] Neal Ready,[13] Justin Gainor,[14] Osvaldo Arén Frontera,[15] Leora Horn,[16] Luis Paz-Ares,[17] Christine Bausselet,[18] Brian Lestini,[18] Julie Brahmer[19]

ASCO 2015 Abstract 8009

CheckMate 017 (NCT01642004) - Study Design



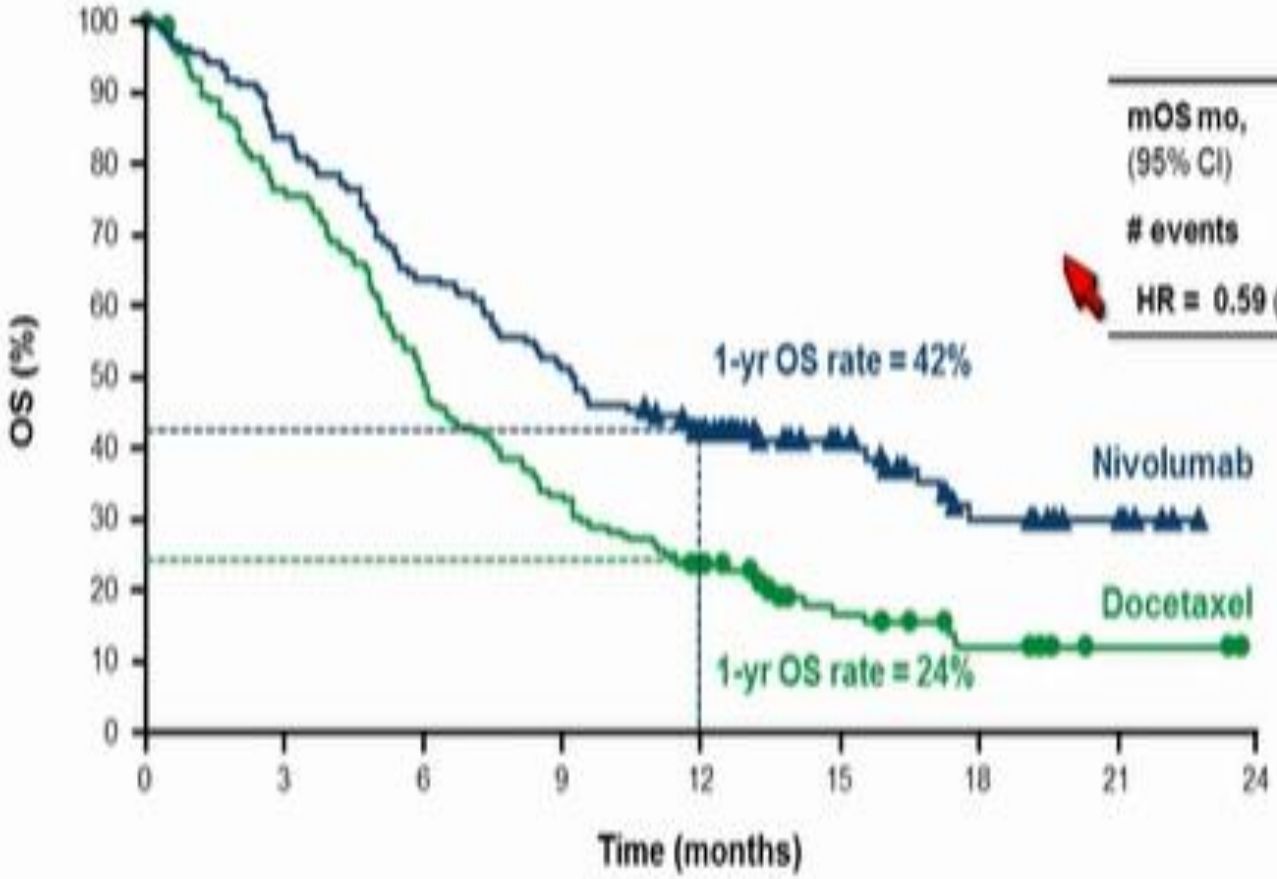
- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

Baseline Characteristics

	Nivolumab n = 135	Docetaxel n = 137
Median age, years (range)	62 (39–85)	64 (42–84)
≥75, %	8	13
Male, %	82	71
Disease stage,[a] %		
Stage IIIb	21	18
Stage IV	78	82
Performance status, %		
0	20	27
1	79	73
CNS metastasis, %	7	6
Prior paclitaxel, %	34	34
Current/former smoker, %	90	94
PD-L1 expression,[b] %		
≥1%	47	41
≥5%	31	29
≥10%	27	24
Not quantifiable	13	21

- 83% (225/272) of patients had quantifiable PD-L1 expression

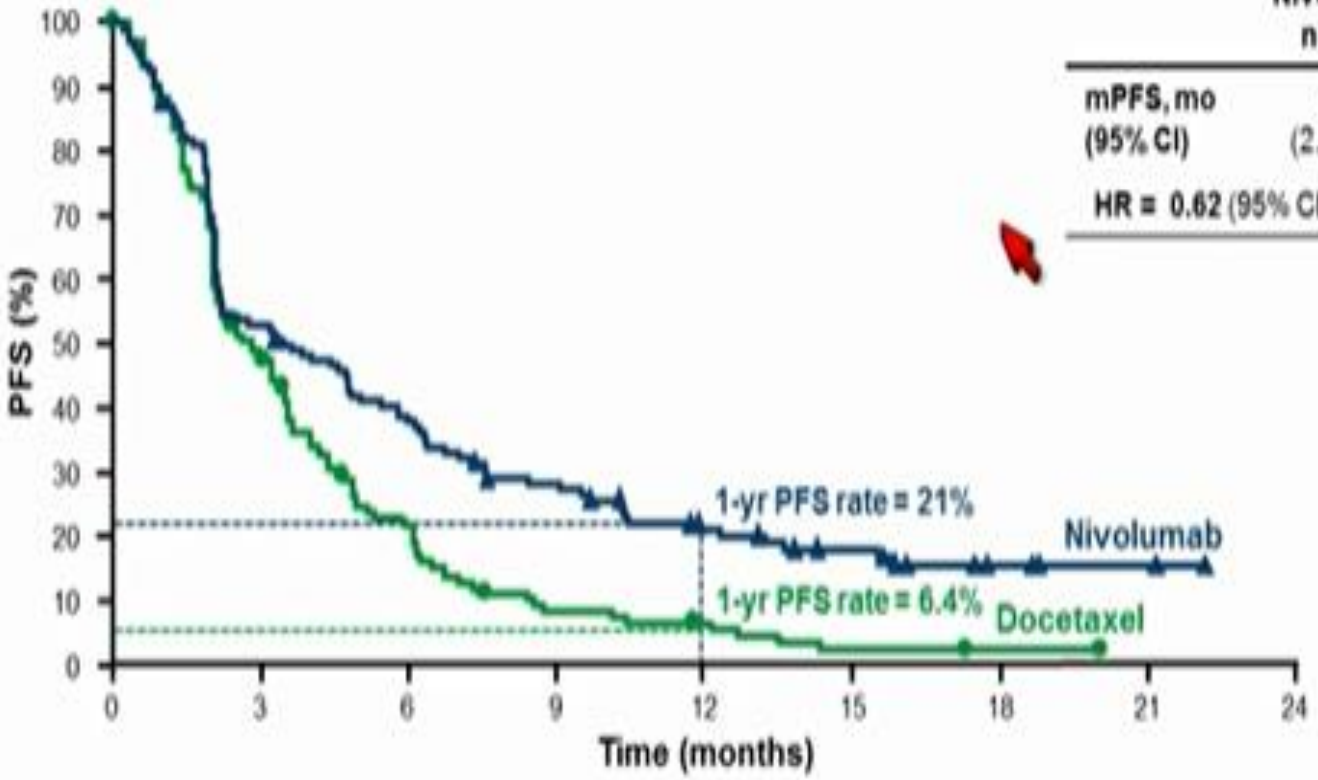
Overall Survival



	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

Progression-Free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

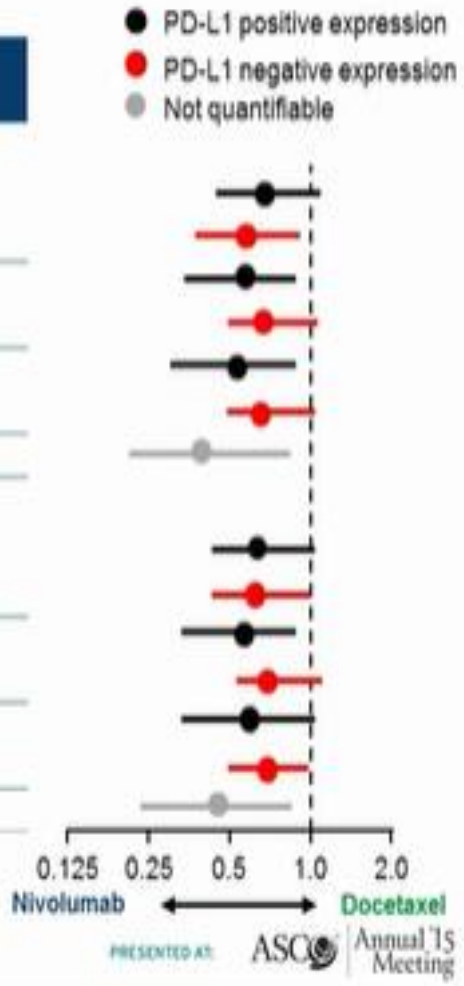
HR = 0.62 (95% CI: 0.47, 0.81); *P* = 0.0004

OS and PFS by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	0.56
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	0.47
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	0.41
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	0.70
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	0.16
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	0.35
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

- PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]



PRESENTED AT: ASCO Annual '15 Meeting

Treatment-related AEs (≥10% of patients)

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Total patients with an event, %	**58**	**7**	**86**	**55**
Fatigue	16	1	33	8
Decreased appetite	11	1	19	1
Asthenia	10	0	14	4
Nausea	9	0	23	2
Diarrhea	8	0	20	2
Vomiting	3	0	11	1
Myalgia	2	0	10	0
Anemia	2	0	22	3
Peripheral neuropathy	1	0	12	2
Neutropenia	1	0	33	30
Febrile neutropenia	0	0	11	10
Alopecia	0	0	22	1

Summary

- Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with advanced SQ NSCLC
  - 41% reduction in risk of death (HR 0.59; $P = 0.00025$)
  - 1-yr OS: 42% vs 24%
  - mOS: 9.2 vs 6.0 mo
- Nivolumab demonstrated superiority over docetaxel across all secondary efficacy endpoints
  - ORR: 20% vs 9% ($P = 0.0083$)
  - 1-yr PFS: 21% vs 6.4%; mPFS: 3.5 vs 2.8 mo (HR 0.62; $P = 0.0004$)
- Nivolumab benefit was independent of PD-L1 expression
- The safety profile of nivolumab was favorable versus docetaxel and consistent with prior studies
- Nivolumab received FDA approval in the US on March 4, 2015 for metastatic SQ-NSCLC with progression on or after platinum-based chemotherapy

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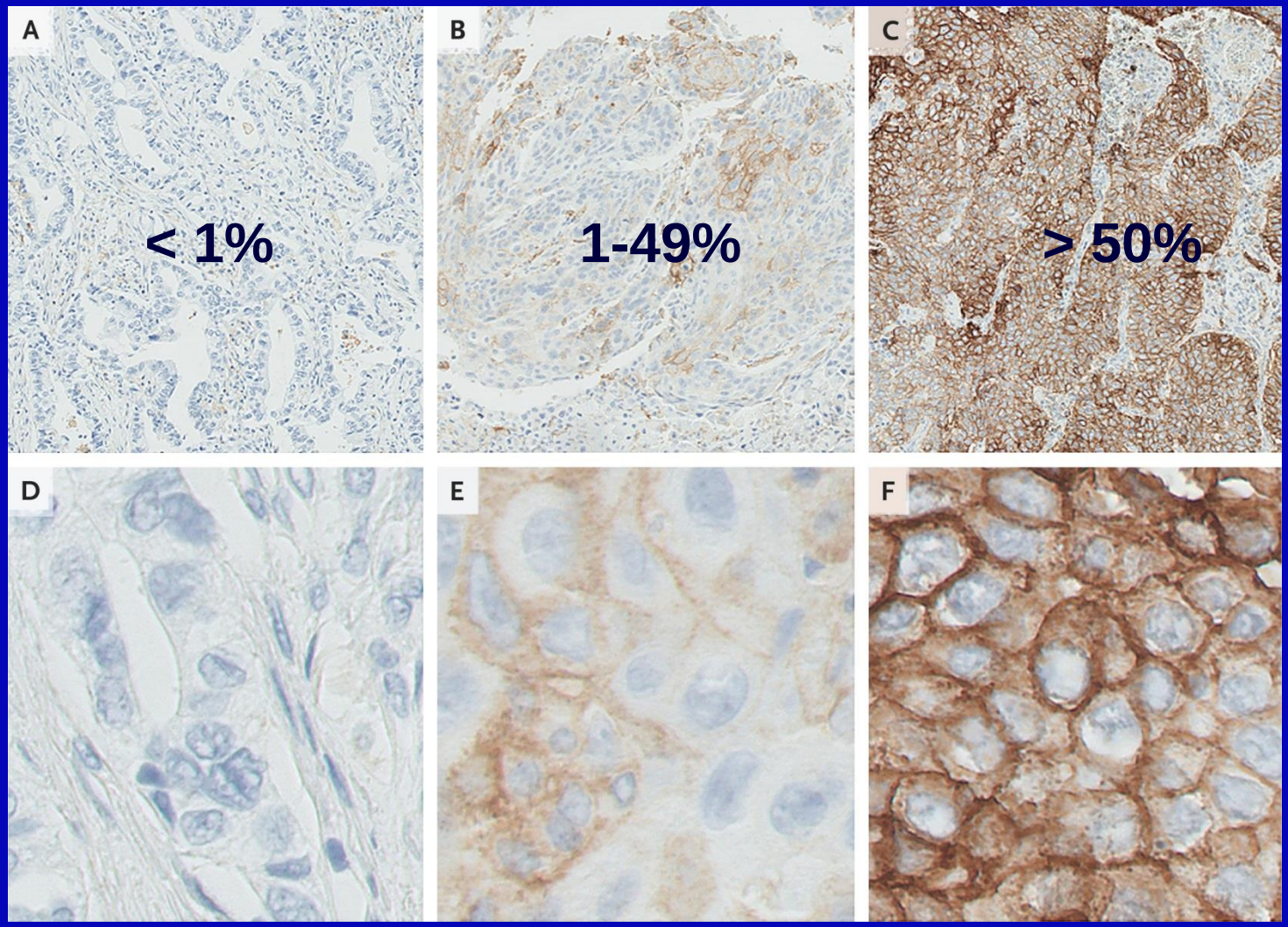
ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S.,

Garon E.B., et al.N Engl J Med 2015; 372:2018-2028

PD-L1 Expression in Non–Small-Cell Lung Cancers.



Garon EB et al. N Engl J Med 2015;372:2018-2028

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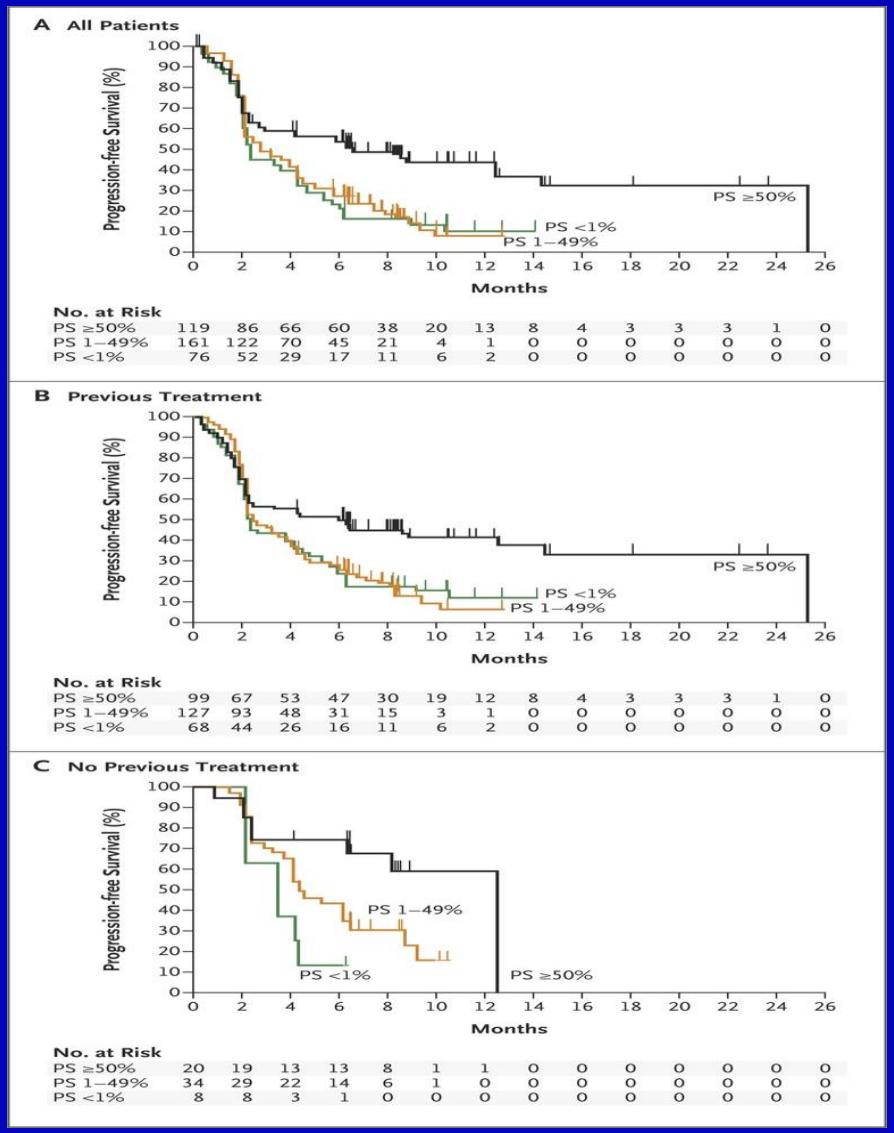
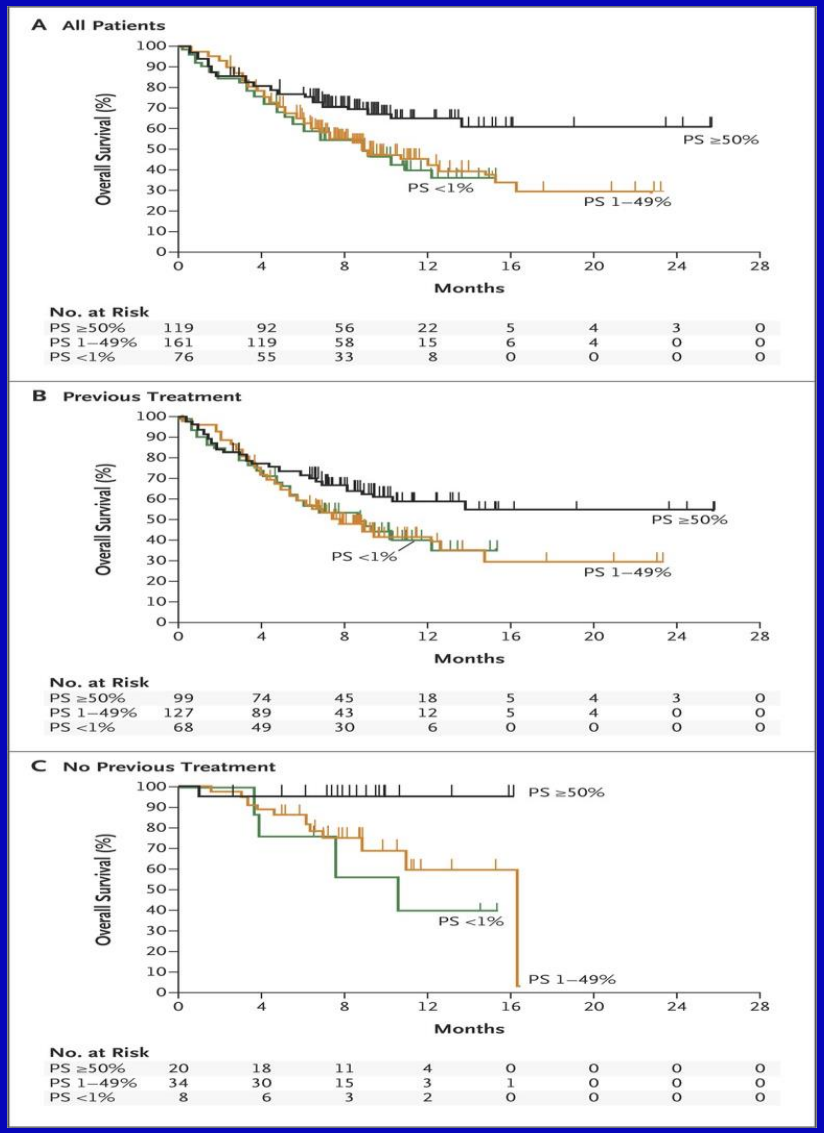
Progression-free Survival.



Overall Survival.



Garon EB et al. N Engl J Med 2015;372:2018-2028

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Adverse Events in 495 Patients in the Treated Population.

Table 1. Adverse Events in 495 Patients in the Treated Population.*

Adverse Event	Any Grade	Grade 3–5
	no. of patients (%)	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

* Listed are events that were considered to be related to treatment by the investigator and were reported in at least 2% of patients.
† Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.

Garon EB et al. N Engl J Med 2015;372:2018-2028

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Conclusions

- **Pembrolizumab had an acceptable side-effect profile and showed antitumor activity in patients with advanced non–small-cell lung cancer.**

- **PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab.**

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Anti PD-L1 Antibodies
Atezolizumab and MEDI4736

- Less advanced in their development

- **POPLART Trial** (ASCO 2015)
  - 2nd-3rd line vs. Docetaxel n=287 patients
  - Predictive score on PD-L1 expression on IC or TC
  - ⟶ Good corelation between score OS, PFS and RR

- **MEDI4736**
  - Ongoing trial vs. Placebo late line
  - Preliminary results only in early phase troals
    - No coeelation with PD-L1 expression.

Immunotherapy of Lung Cancer

- After years of failure, immunotherapy resuscitated in lung cancer
- Immune check-point inhibition with confirmed data
- More to come in early metastatic lines or stage and combination

- Just the beginning of it…
- May as well explain why vaccines have failed