Immunotherapy in lung cancer

Saurabh maji

- Worldwide, lung cancer is the most common cause of cancer-related deaths
- Small cell lung cancer (SCLC) presents with widespread disease at the time of diagnosis, represents about 15% of all lung cancer cases
- NSCLC represents the remaining 85% of lung cancers, and the 5-year overall survival (OS) rate is about 15%

J Thorac Oncol. 2015;10: 974–984)

THE IMMUNE SYSTEM AND CANCER

- The antitumor immune response:

  -Destroy cancer cells and inhibit tumor growth

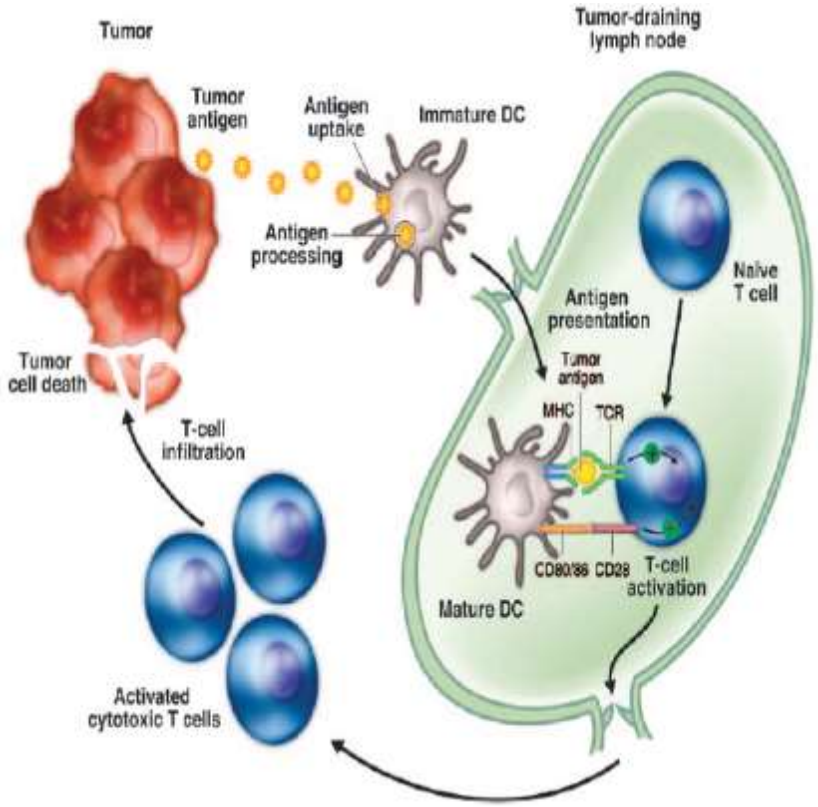
  -Elicited by its innate and adaptive arms

  -Innate immune responses are antigen nonspecific, develop quickly, and are mediated by various effector cells NK cell,PMNS,mast cell antigen presenting cell macrophages and dendritic cells [DCs]), which lead to the secretion of interferon gamma (IFN-γ) and perforin, as well as inflammatory cytokines that induce apoptosis of tumor cells

J Immunother2012;35:299–308

- Adaptive immune responses are antigen specific, develop more slowly, offer immune memory, and comprise both humoral and cellular immunity mediated by B and T cells, respectively
- Adaptive rather than innate immunity offers the greatest potential for durable, robust anticancer immune responses
- Some of the cells involved in innate immunity, such as DCs, macrophages, and NK cells, also play a role in adaptive immunity

J Immunother2012;35:299–308



Immature DCs, which capture and process tumor Antigens

DCs undergo maturation
and migrate to tumor-draining lymph nodes

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

J Thorac Oncol. 2015;10: 974–984

Promotion of tumour growth by immune system

- Immune escape phase are able to create an immunosuppressive state within the tumor microenvironment by subverting the same mechanisms that under normal conditions help regulate the immune response and prevent damage to healthy tissue

- Key immunosuppressive cells are regulatory T (Treg)

  cells, myeloid-derived suppressor cells (MDSCs), and tumor associated macrophages

Science 2011;331:1565–1570

- Treg cells, which are positive for CD4, CD25 suppress the function and proliferation of tumor-specific CD4+ and CD8+ T cells and NK cells
- MDSCs induce Treg cells and limit effector T-cell proliferation by means of the production of various immunosuppressive molecules

Nature 2011;480:480–489

- Tumor-associated macrophages and stromal cells may also secrete cytokines that inhibit an adaptive immune response, such as IL-10 and transforming growth factor-β (TGF-β)

Immunol Cell Biol 2011;89:332–339

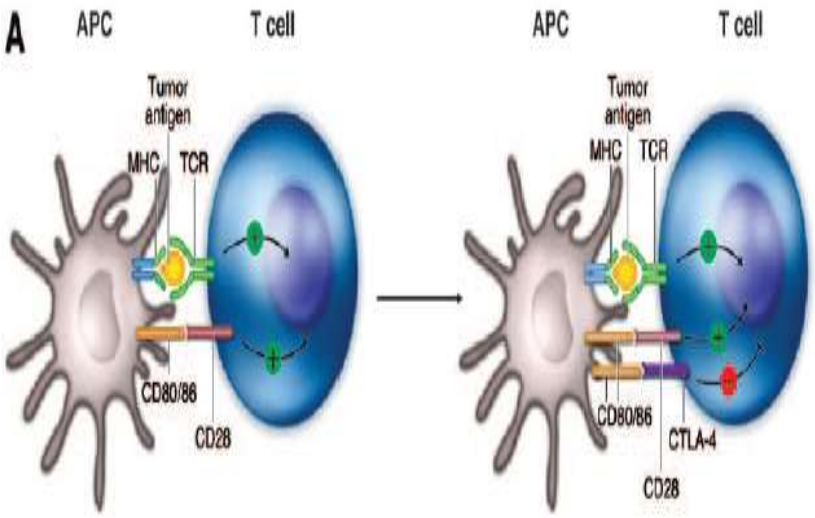
- Both tumor cells and other cells present in the tumor microenvironment express the immunosuppressive enzyme indoleamine- 2,3-dioxygenase, which depletes the amino acid tryptophan(essential for T-cell function), increases local Treg populations, and induces tumor- specific T-cell deactivation

Nat Rev Cancer 2005;5:263–274

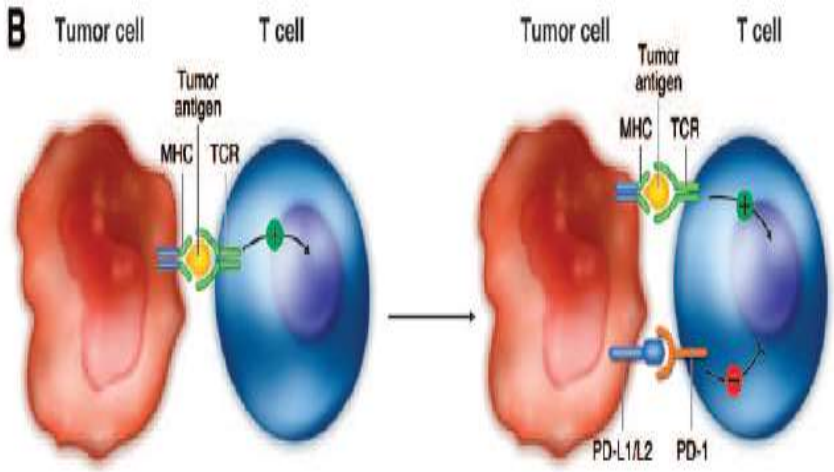
- specific physiologic regulatory mechanisms, or “checkpoints,” play a key role in maintaining normal self-tolerance

- Two of the most investigated checkpoint receptors in terms of immunotherapeutic targets for cancer are cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) receptor, which down regulate T-cell activation, proliferation, and function through different mechanisms

Nat Rev Cancer 2012;12:252–264



- Cytotoxic CTLA-4 is expressed on T cells after activation and competes with the co-stimulatory T-cell CD28 receptor for CD80/86 expressed by APCs, providing an inhibitory signal to the T cell



- PD-1 receptor is upregulated on activated T cells and subsequently binds to one of its ligands, PD-L1 or PD-L2, which are usually expressed on tumor cells, providing an inhibitory signal to the T cell

- Other mechanism:PD-1 is also expressed at high levels on Treg cells, enhancing their proliferation in the presence of a PD-1 ligand
- PD-1 may be induced on activated NK cells, thereby limiting their lytic activity
- Induction of tumor PD-L1 expression can also be upregulated by oncogenic signaling intrinsic to the tumor cells themselves

Cancer Discov 2013;3:1330–1332

Immune Checkpoint Inhibitors

- Most significant advances in NSCLC immunotherapy have been made by targeting immune checkpoint pathways to prevent or reduce tumor-mediated immune suppression
- Monoclonal antibodies that block immune checkpoint pathways, such as those involving PD-1 and CTLA-4, are being investigated in clinical trials with NSCLC
- Advantage of enhancing the host's own antitumor immune response without regard to the specific tumor antigen
- Conferring broader clinical application than antigen-specific immunotherapies, such as vaccines

Immunotherapeutic Agents for the Treatment of Advanced NSCLC

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
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

Immunotherapeutic Agents for the Treatment of Advanced NSCLC

Vaccines	
Tecemotide (liposomal BLP25)	Vaccine composed of the exposed core peptide of tumor
Racotumomab	Patient idiotype-specific vaccine against tumor antigen
TG4010	Vaccine that uses a recombinant vaccinia virus (modified virus of Ankara) that encodes for human Mucin-1 and IL-2
Nonspecific immune stimulator Talactoferrin alfa	Recombinant human lactoferrin

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Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

Scott N. Gettinger, Leora Horn, Leena Gandhi, David R. Spigel, Scott J. Antonia, Naiyer A. Rizvi, John D. Powderly, Rebecca S. Heist, Richard D. Carvajal, David M. Jackman, Lecia V. Sequist, David C. Smith, Philip Leming, David P. Carbone, Mary C. Pinder-Schenck, Suzanne L. Topalian, F. Stephen Hodi, Jeffrey A. Sosman, Mario Sznol, David F. McDermott, Drew M. Pardoll, Vindira Sankar, Christoph M. Ahlers, Mark Salvati, Jon M. Wigginton, Matthew D. Hellmann, Georgia D. Kollia, Ashok K. Gupta, and Julie R. Brahmer

See accompanying editorial on page 1993 and article on page 2013

Baseline characterestics

Table 1. Baseline Characteristics and Prior Therapy of All Treated Patients With NSCLC

Characteristic	All Treated Patients (N = 129) No.	%
Age, years		
Median	65	
Range	38-85	
Sex		
Male	79	61.2
Female	50	38.8
Tumor cell histology		
Squamous	54	41.9
Nonsquamous	74	57.4
Unknown	1	0.8
ECOG performance status[17]		
0 or 1	127	98.4
2*	2	1.6
No. of prior systemic treatment regimens		
1-2	59	45.7
≥ 3	70	54.3
Nature of prior therapy		
Platinum-based chemotherapy	128	99.2
Tyrosine kinase inhibitor	36	27.9
Surgery†	85	65.9
Radiotherapy†	75	58.1
Hormonal, immunologic, or biologic therapy	16	12.4
Other	9	7.0
EGFR tumor mutation status		
Mutant	12	9.3
Wild type	56	43.4
Unknown‡	61	47.3
KRAS tumor mutation status		
Mutant	21	16.3
Wild type	36	27.9
Unknown‡	72	55.8

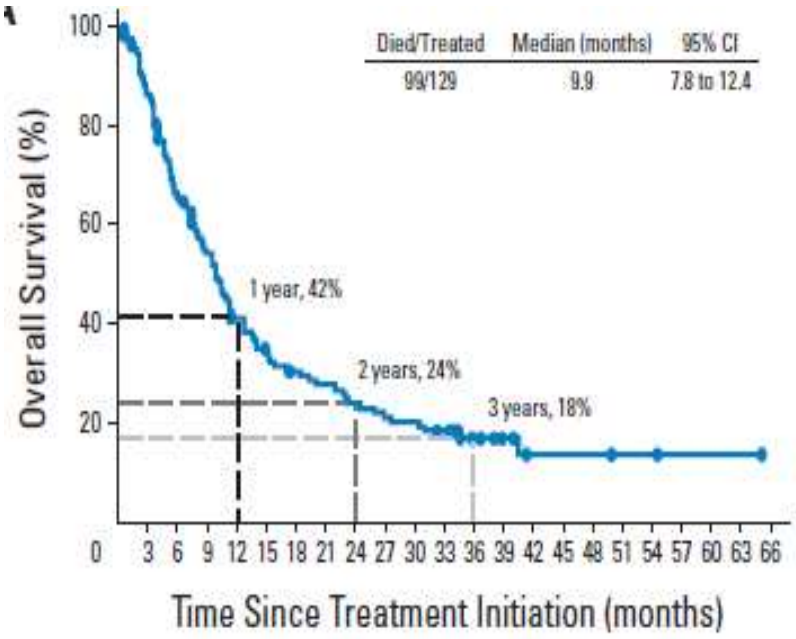
- Nivolumab was administered intravenously as a 1-hour infusion every 2 weeks in 8-week treatment cycles in an outpatient setting
- During dose escalation, patients with all cancer types received 1-, 3-, or 10-mg/kg doses of Nivolumab
- Patients continued treatment for up to 96 weeks (12 cycles) or until unacceptable toxicity, confirmed complete response, confirmed disease progression, or withdrawal of consent

Outcome

Table 2. Clinical Activity of Nivolumab in Patients With NSCLC*

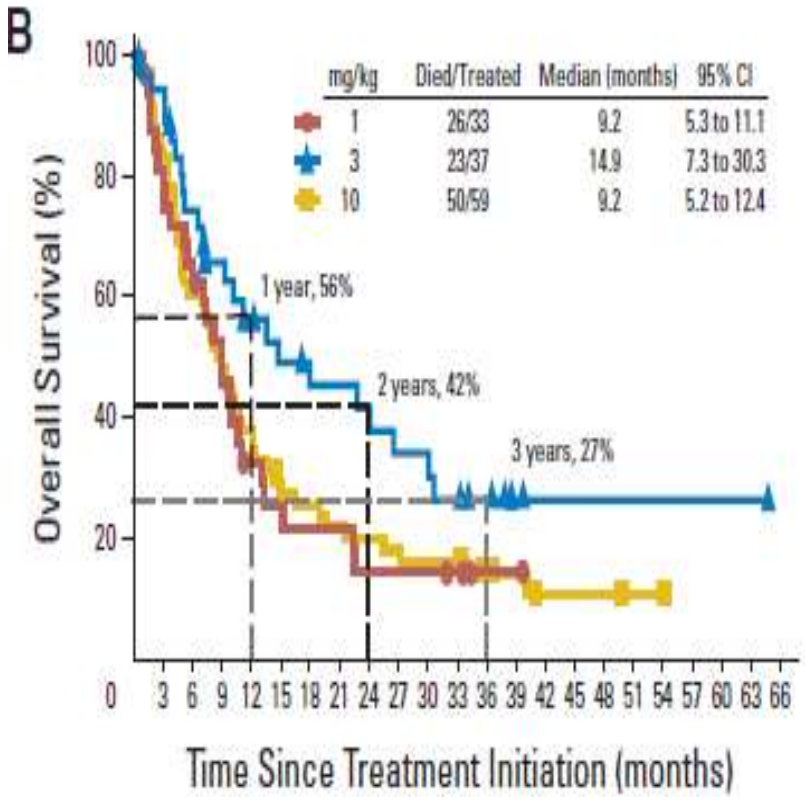
		ORR†		Duration of Response (months)‡§		OS (months)§‖		OS Rate§								
								1 Year			2 Years			3 Years		
Dose (mg/kg)	No. of Patients	%	95% CI	Median	Range	Median	95% CI	%	95% CI	No. at Risk	%	95% CI	No. at Risk	%	95% CI	No. at Risk
NSCLC¶																
All doses	22 of 129	17.1	11.0 to 24.7	17.0	1.4+ to 36.8+	9.9	7.8 to 12.4	42	33 to 50	48	24	17 to 33	26	18	11 to 25	12
1	1 of 33	3.0	0.1 to 15.8	14.7	14.7 to 14.7	9.2	5.3 to 11.1	33	17 to 49	9	15	5 to 30	4	15	5 to 30	1
3	9 of 37	24.3	11.8 to 41.2	17.0	3.7+ to 32.6+	14.9	7.3 to 30.3	56	38 to 71	17	42	24 to 58	11	27	12 to 43	5
10	12 of 59	20.3	11.0 to 32.8	19.1	1.4+ to 36.8+	9.2	5.2 to 12.4	38	26 to 50	22	20	11 to 31	11	14	7 to 25	6
Squamous NSCLC																
All doses	9 of 54	16.7	7.9 to 29.3	NR#	3.7 to 36.8+	9.2	7.3 to 12.5	41	27 to 54	20	24	14 to 37	12	19	9 to 32	6
1	0 of 15	0	0	0	0	8.0	2.4 to 13.3	29	9 to 52	4	14	2 to 37	2	0	0	0
3	4 of 18	22.2	6.4 to 47.6	NR#	3.7+ to 32.6+	9.5	5.3 to NE	49	23 to 71	7	35	13 to 58	5	28	9 to 51	3
10	5 of 21	23.8	8.2 to 47.2	19.1	3.7 to 36.8+	10.5	4.9 to 16.7	43	22 to 62	9	24	9 to 43	5	18	5 to 37	3
Nonsquamous NSCLC																
All doses	13 of 74	17.6	9.7 to 28.2	14.2	1.4+ to 29.9	10.1	5.7 to 13.7	42	30 to 53	27	23	14 to 34	13	16	8 to 26	6
1	1 of 18	5.6	0.1 to 27.3	14.7	14.7 to 14.7	9.9	5.3 to 22.5	36	15 to 58	5	15	3 to 36	2	15	3 to 36	1
3	5 of 19	26.3	9.1 to 51.2	13.6	5.6 to 17.0	18.2	5.2 to 30.8	62	37 to 80	10	48	22 to 69	6	24	6 to 48	2
10	7 of 37	18.9	8.0 to 35.2	18.3	1.4+ to 29.9	7.4	4.5 to 11.0	34	19 to 49	12	16	6 to 30	5	12	4 to 26	3

Overall survival



- Total population of patients with NSCLC, across all dose levels 1, 2,and 3year survival rates were 42%, 24% and 18%, respectively

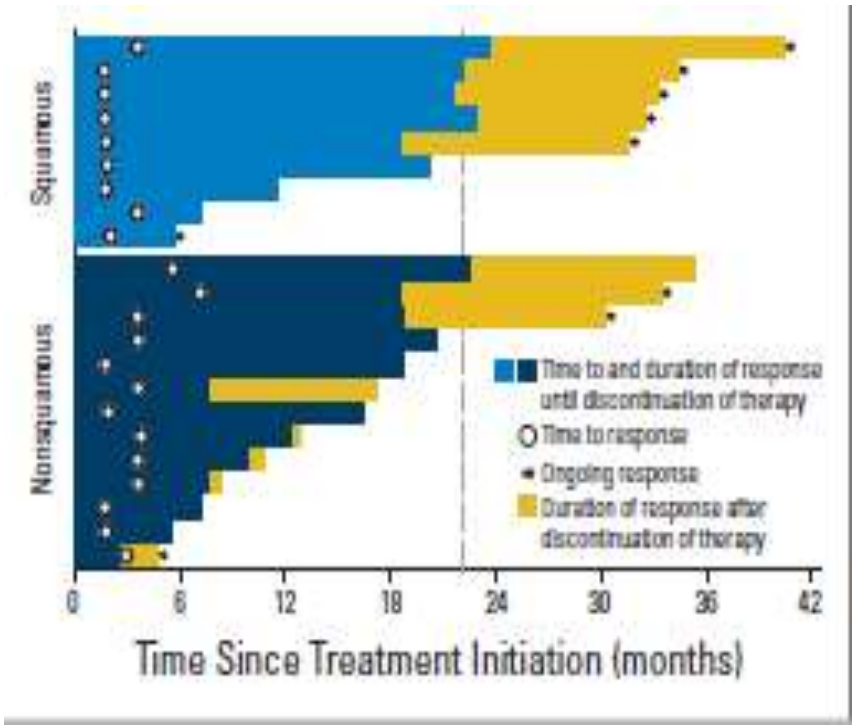
Overall survival



- At 3-mg/kg dose 1, 2 and 3 year OS rates were 56%, 42% and 27% respectively

- Median OS was 9.9 months (95% CI, 7.8 to 12.4) for all 129 patients with NSCLC
- patients receiving Nivolumab 3 mg/kg, median OS was 14.9 months (95% CI, 7.3 to 30.3). MedianOS was 9.2months in both the 1- and 10-mg/kg cohorts
- Median OS and survival rate was similar in both squamous and non squamous histology
- Median progression-free survival (PFS) across doses was 2.3 months (95% CI,1.8 to 3.7), with PFS rates at 6 months, 1 year, and 2 years of 33%, 22%, and 9%, respectively
- Patients with squamous and no squamous histology had similar ORRs(17% and 18%, respectively)
- ORRs by dose were 3% (1 mg/kg), 24% (3mg/kg), and 20% (10 mg/kg)

- Among the 22 patients with objective responses median duration of response was 17.0 months
- Median PFS of the 22 responders was 20.6 months (95% CI, 11.4 to not reached; range, 4.7 to 40.3months



- Among 18 responders who discontinued Nivolumab therapy for reasons other than disease progression had responses for more than 9 months after the end of therapy (range, 9.2 to 16.4 months)

- Analysis of tumor PD-L1 expression, using an automated immunohistochemistry assay (Dako North America, Carpinteria, CA), on archived tumor samples from 68 patients found no clear association between PD-L1 expression and response or survival
- Retrospectively by select sites of response by smoking exposure in 80 evaluable patients found ORR was higher in patients with a smoking history of more than 5 pack-years (30%; n 66) than in those with a history of 5 pack-years or less (no responses; n 14).

Table 4. Treatment-Related Select AEs Occurring in All Treated Patients in NSCLC Population*

	All Patients (N = 129)			
	Any Grade†		Grades 3 to 4	
Select AE	No.	%	No.	%
Any AE	53	41.1	6	4.7
Skin	20	15.5	0	0
GI	15	11.6	1	0.8
Pulmonary	9‡§	7.0§	3‡	2.3
Endocrinopathies	8	6.2	0	0
Hepatic	6	4.7	1	0.8
Infusion reaction	5	3.9	1	0.8
Renal	4	3.1	0	0

- Among the treated patients with NSCLC, 71% had experienced treatment-related adverse events of any grade
- The most common were fatigue (24%), decreased appetite (12%), and diarrhea (10%).
- Eighteen patients (14%) experienced grade 3 to 4 treatment-related adverse events, and the most common was fatigue

- Four patients (3%) had treatment-related grade- 3 pneumonitis, including one with grade 5 pneumonitis
- Three treatment-related deaths occurred among patients with NSCLC, each associated with pneumonitis (two with unresolved grade 4 pneumonitis, and one with grade 5 pneumonitis
- No clear relationships between the occurrence of pneumonitis and dose level or treatment duration

Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial

Phase 2

Single-arm trial

stage IIIB or IV squamous non-small-cell lung cancer

Age more than 18 years

Ecog0- 1

Baseline characterstics

	Patients (n=117)
Age (years)	
Median (IQR)	65 (57–71)
<75	101 (86%)
≥75	16 (14%)
Sex	
Male	85 (73%)
Female	32 (27%)
Ethnic origin	
White	99 (85%)
Black or African American	11 (9%)
Asian	2 (2%)
Other	5 (4%)
ECOG PS	
0	26 (22%)
1	91 (78%)
Disease stage	
IIIB	20 (17%)
IV	97 (83%)
History of smoking	108 (92%)
CNS metastasis	2 (2%)*
Previous systemic therapy	
Platinum-based therapy	117 (100%)
Other	117 (100%)
EGFR TKI	39 (33%)
Experimental treatment	13 (11%)
Number of previous systemic treatments	
2	41 (35%)
3	52 (44%)
≥4	24 (21%)
Previous radiotherapy	87 (74%)
Best response to most recent previous treatment	
CR or PR	5 (4%)
SD	32 (27%)
Progressive disease	71 (61%)
Unknown	9 (8%)
Months from completion of most recent previous regimen to treatment in this study	
<3	89 (76%)
3–6	16 (14%)
>6	12 (10%)

procedure

- Received Nivolumab 3 mg/kg as every 2 weeks (1 cycle) until disease progression or unacceptable toxic effects
- Radiographic tumour assessments were done at screening, at 8 weeks then every 6 weeks thereafter until disease progression or until discontinuation of Nivolumab for patients treated beyond progression
- PD-L1 protein expression was done in pre-treatment, formalin-fixed, paraffin-embedded tumour specimens with a validated, automated immune histochemical assay
- categorized as positive when tumour cell membranes were stained to any intensity in 1%, 5%, and 10% of cells in a section with a minimum of 100 assessable tumour cells

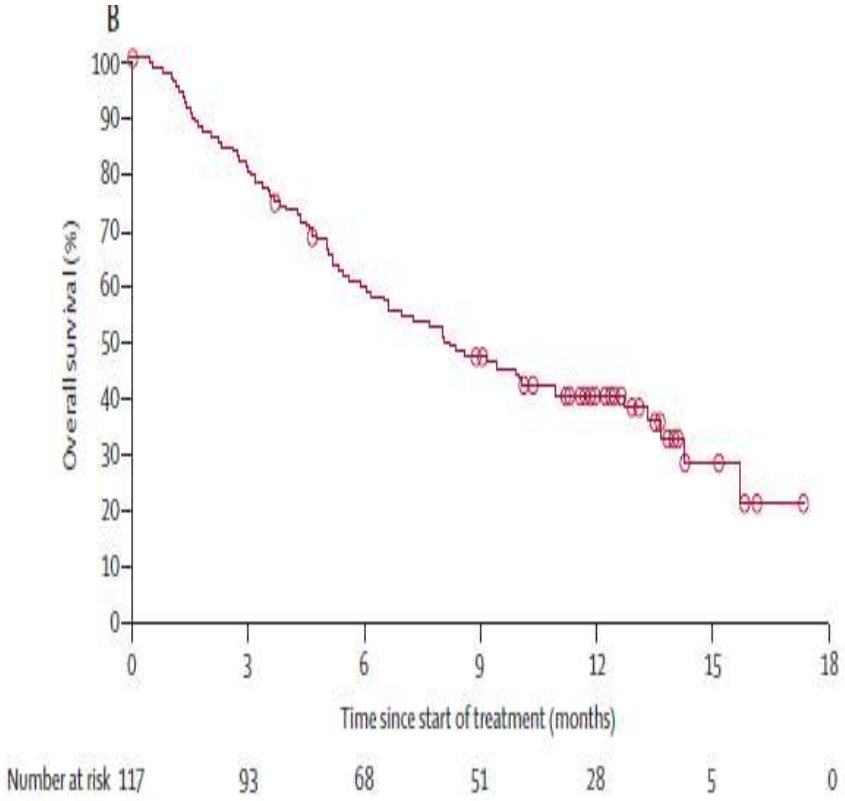
- Primary endpoint: confirmed objective response as assessed by an independent radiology review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1)
- Secondary endpoint: confirmed objective response by investigator using RECIST 1.1
- Exploratory endpoints: safety and tolerability of Nivolumab, progression-free survival and overall survival

Result

- A median of six doses (IQR 3·0–14·0) of Nivolumab were administered, with a median treatment duration of 2·3 months (95% CI 1·4–2·8).
- The minimum follow-up for IRC-assessed response was 11·0 months, and the median follow-up for overall survival was 8·0 months
- Median overall survival was 8·2 months (95% CI 6·1–10·9) and overall survival at1 year was 40·8% (31·6–49·7

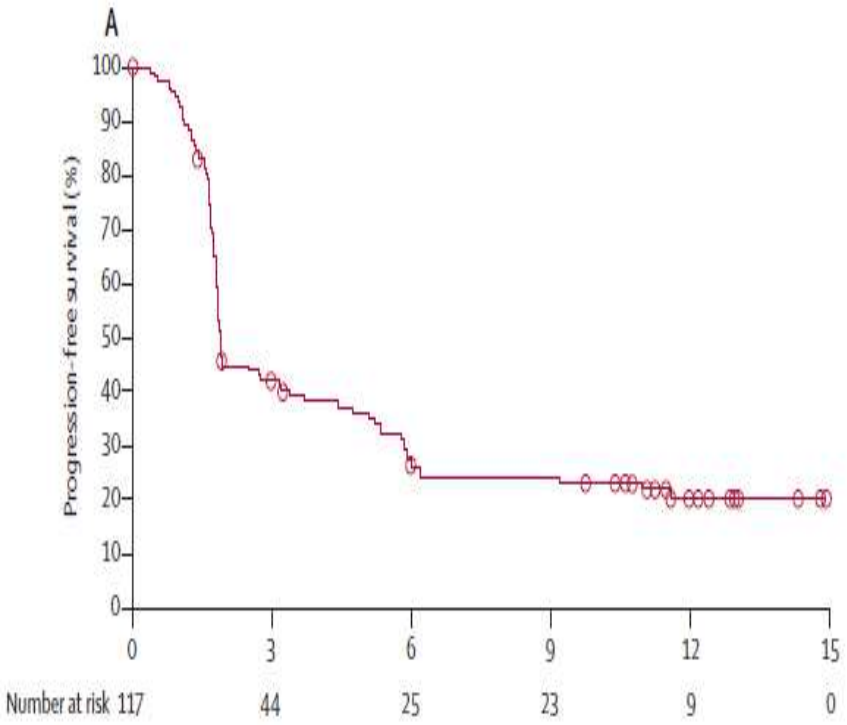
- 51 patient (44%, 34–53) had progressive disease
- 7 patient (6%, 2–12) had indeterminate best overall response
- 12 (10%, 5–17) were not reported
- Median time to response was 3·3 months (IQR 2·2–4·8).
- 13 (77%) of 17 responding patients had ongoing responses at the time of analysis
- Median progression-free survival was 1·9 months(95% CI 1·8–3·2), with progression-free survival of25·9% (18·0–34·6) at 6 months and 20·0% (12·7–28·5) at 1 year
- Median overall survival was 8·2 months (95% CI 6·1–10·9) and overall survival at1 year was 40·8% (31·6–49·7

Overall survival



- Median OS was 8·2 months (95% CI 6·1–10·9) and overall survival at 1 year was 40·8%.

Progression free survival



- Median progression-free survival was 1·9 months (95% CI 1·8–3·2), with progression-free survival of 25·9% (18·0–34·6) at 6 months and 20·0% (12·7–28·5) at 1 year

Overall response by PD-L1 expression status

	Partial response	Stable disease	Progressive disease
<5% (n=51)	7 (14%)	10 (20%)	25 (49%)
≥5% (n=25)	6 (24%)	6 (24%)	11 (44%)
Unevaluable (n=10)	3 (30%)	4 (40%)	2 (20%)

Data are n (%). Patients with indeterminate best overall response (n=7), and best overall response not reported by the IRC (n=5) are not included. PD-L1 expression was evaluable in all these patients, except one with best overall response not reported.

- Reductions in target tumour lesion burden were more common in patients with PD-L1-positive tumours - 52% than in those with PD-L1- negative tumours 38%

Adverse effect

	Any grade	Grade 3–4
Any	87 (74%)	20 (17%)
General disorders		
Fatigue	38 (33%)	5 (4%)*
Asthenia	14 (12%)	0
Gastrointestinal disorders		
Nausea	18 (15%)	0
Diarrhoea	12 (10%)	3 (3%)*
Dry mouth	7 (6%)	0
Vomiting	7 (6%)	0
Constipation	6 (5%)	0
Metabolism and nutrition disorders		
Decreased appetite	22 (19%)	0
Skin and subcutaneous tissue disorders		
Rash	13 (11%)	1 (1%)*
Pruritus	7 (6%)	1 (1%)*
Musculoskeletal disorders		
Myalgia	6 (5%)	1 (1%)*
Respiratory disorders		
Dyspnoea	6 (5%)	0
Pneumonitis	6 (5%)	4 (3%)*
Blood and lymphatic system disorders		
Anaemia	7 (6%)	1 (1%)*

- Grade 3–4 treatment-related adverse events occurred in about a sixth of patients, most commonly fatigue, pneumonitis, and diarrhea
- Pneumonitis and grade 3-4 diarrhea were treated with corticosteroids, with a median time to resolution of 3·4 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

- This randomized, open-label, international, phase 3 study
- Evaluate the efficacy and safety of Nivolumab, as compared with docetaxel

Patient profile

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy.*

Characteristic	Nivolumab (N = 135)	Docetaxel (N = 137)	Total (N = 272)
Age — yr			
Median	62	64	63
Range	39–85	42–84	39–85
Age category — no. (%)			
<65 yr	79 (59)	73 (53)	152 (56)
≥65 to <75 yr	45 (33)	46 (34)	91 (33)
≥75 yr	11 (8)	18 (13)	29 (11)
Sex — no. (%)			
Male	111 (82)	97 (71)	208 (76)
Female	24 (18)	40 (29)	64 (24)
Race — no. (%)†			
White	122 (90)	130 (95)	252 (93)
Black	6 (4)	2 (1)	8 (3)
Asian	4 (3)	2 (1)	6 (2)
Other	1 (1)	2 (1)	3 (1)
Not reported	2 (1)	1 (1)	3 (1)
Disease stage — no. (%)			
IIIB	29 (21)	24 (18)	53 (19)
IV	105 (78)	112 (82)	217 (80)
Not reported	1 (1)	1 (1)	2 (1)
ECOG performance-status score — no. (%)‡			
0	27 (20)	37 (27)	64 (24)
1	106 (79)	100 (73)	206 (76)
Not reported	2 (1)	0	2 (1)
Central nervous system metastasis — no. (%)			
Yes	9 (7)	8 (6)	17 (6)
No	126 (93)	129 (94)	255 (94)
Smoking status — no. (%)			
Current or former smoker	121 (90)	129 (94)	250 (92)
Never smoked	10 (7)	7 (5)	17 (6)
Unknown	4 (3)	1 (1)	5 (2)
Geographic region — no. (%)			
United States or Canada	43 (32)	43 (31)	86 (32)
Europe	77 (57)	78 (57)	155 (57)
Rest of world§	15 (11)	16 (12)	31 (11)
Other systemic cancer therapy — no. (%)¶			
Bevacizumab	1 (1)	1 (1)	2 (1)
Cetuximab	0	2 (1)	2 (1)
Etoposide	17 (13)	11 (8)	28 (10)
Fluorouracil	1 (1)	0	1 (<1)
Gemcitabine	60 (44)	71 (52)	131 (48)
Paclitaxel	46 (34)	46 (34)	92 (34)
Pemetrexed	3 (2)	3 (2)	6 (2)
Vinorelbine	20 (15)	24 (18)	44 (16)

Table 1. (Continued.)

Characteristic	Nivolumab (N = 135)	Docetaxel (N = 137)	Total (N = 272)
Best response to most recent prior systemic regimen, according to the investigator — no. (%)			
Complete or partial response	48 (36)	43 (31)	91 (33)
Stable disease	33 (24)	47 (34)	80 (29)
Progressive disease	44 (33)	41 (30)	85 (31)
Unknown or not reported	10 (7)	6 (4)	16 (6)
Time from completion of most recent prior systemic regimen — no. (%)			
<3 mo	64 (47)	59 (43)	123 (45)
3–6 mo	35 (26)	40 (29)	75 (28)
>6 mo	35 (26)	37 (27)	72 (27)
Unknown	1 (1)	1 (1)	2 (1)

The primary end point: Overall survival

Additional end points :

Progression free survival

patient-reported outcome efficacy according to tumor PD-L1 expression

Safety

PD-L1 Analysis: done retrospectively in pretreatment (archival or recent) tumor-biopsy specimens with the use of a validated automated immunohistochemical assay

Overall survival

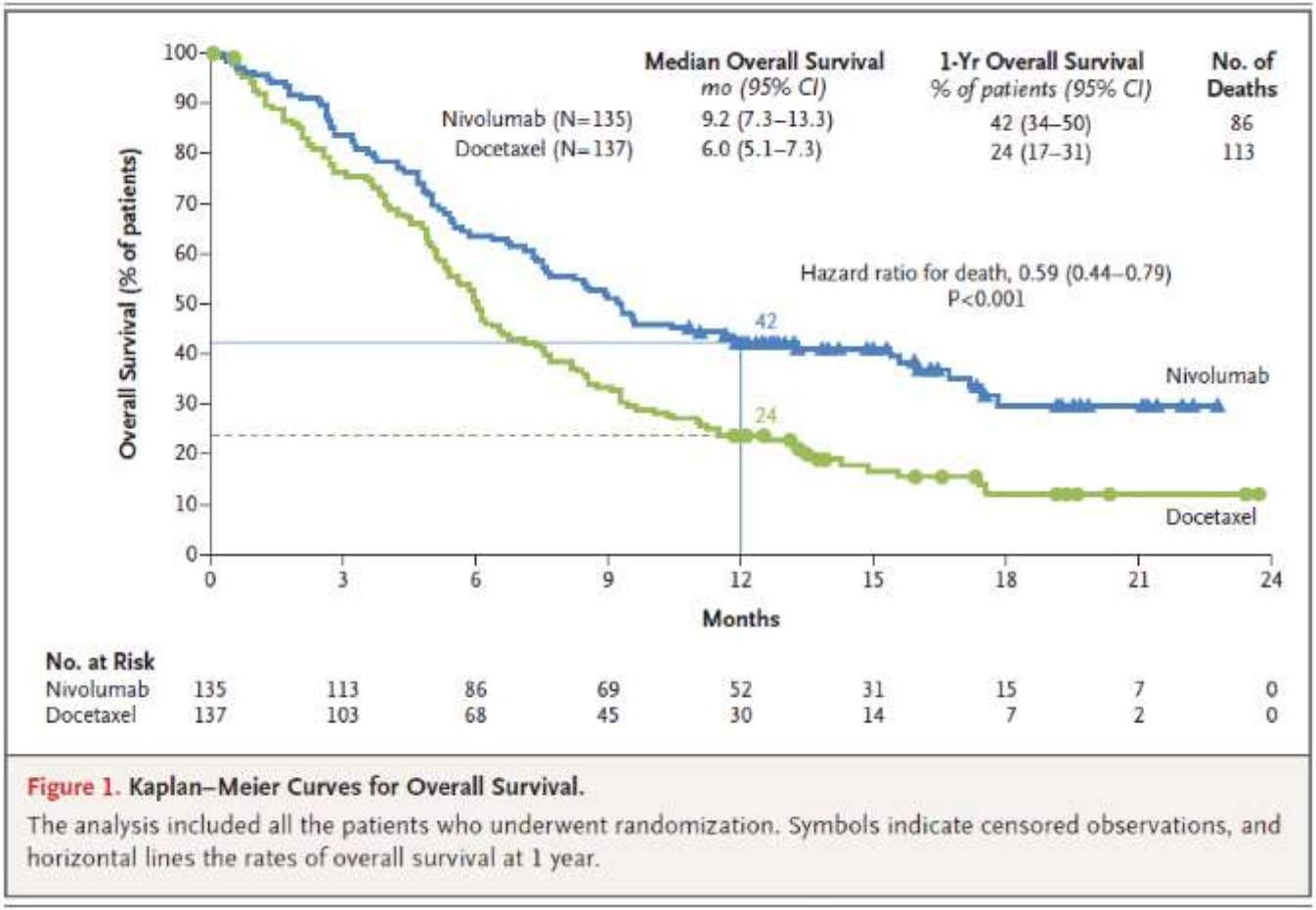
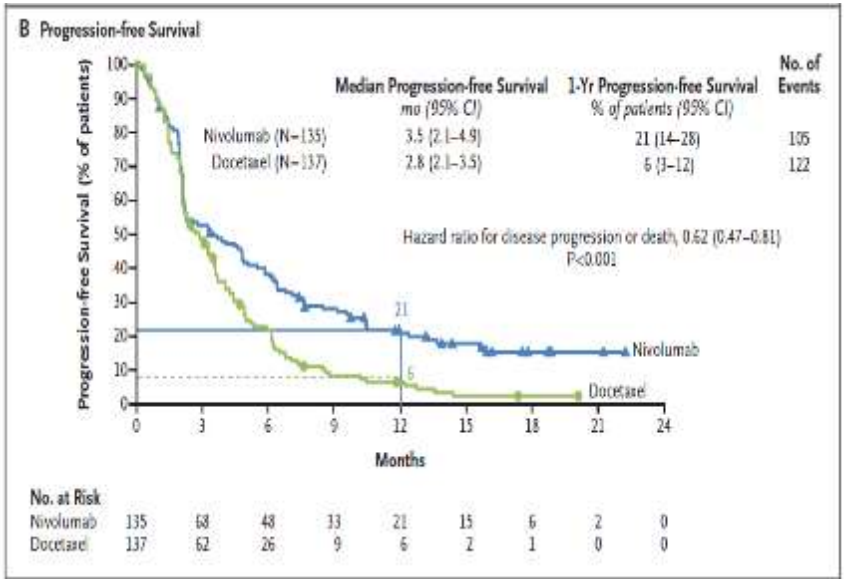


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N=135)	Docetaxel (N=137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.5
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+



- The median progression-free survival was 3.5 months (95% CI, 2.1 to 4.9) in the Nivolumab group and 2.8 months (95% CI, 2.1 to 3.5) in the docetaxel group

Significance of Programmed Cell Death-Ligand 1 Expression and its Association with Survival in Patients with Small Cell Lung Cancer

- Retrospective study was to investigate the prevalence and prognostic roles of programmed cell death -ligand 1 (PD-L1) expression in small cell lung cancer and role of PD-L1 antibody

Patient characteristics and PD-L1 expression

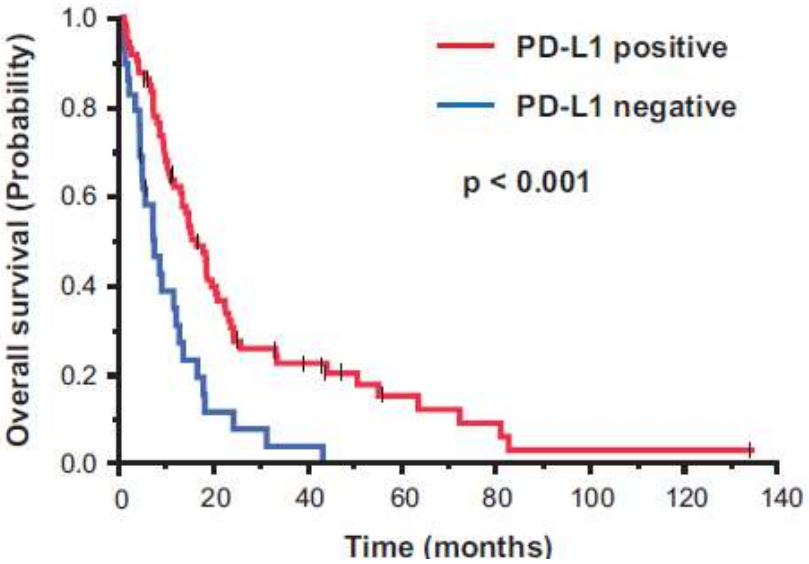
Variables	No. of Patients	PD-L1 Expression		*p* Value
		Positive	Negative	
Age				
<70	51	39	12	0.272
≥70	51	34	17	
Sex				
Men	89	66	23	0.186
Woman	13	7	6	
Performance status				
0–1	87	63	24	0.758
2–3	15	10	5	
Stage				
LD	41	35	6	0.011
ED	61	38	23	
Serum LDH level				
Normal	37	30	7	0.108
Abnormal	65	43	22	
Serum pro-GRP level				
Median	294	304	265	0.609
Range	12.6–33,300	13.8–31,400	12.6–33,300	
Serum NSE level				
Median	22.4	19.6	26.7	0.666
Range	5.2–581	5.2–581	5.6–309	

PD-L1, programmed cell death-ligand 1; LDH, lactate dehydrogenase; LD, limited disease; ED, extensive disease; Pro-GRP, pro-gastrin-releasing peptide; NSE, neuron-specific enolase.

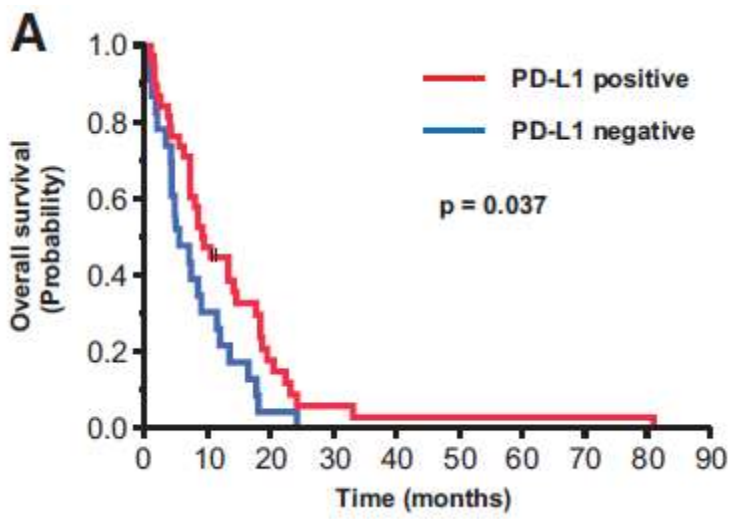
Correlation between PD-L1 Expression and Patient Characteristics

- Expression of PD-L1 was significantly higher in SCLC patients with LD than in those with ED ($p = 0.011$)
- No significant correlation was observed between PD-L1 expression and age ($p = 0.272$), sex ($p = 0.186$), PS ($p = 0.758$), serum LDH level ($p = 0.108$), serum pro-gastrin-releasing peptide level ($p = 0.609$), and serum NSE level ($p = 0.666$).

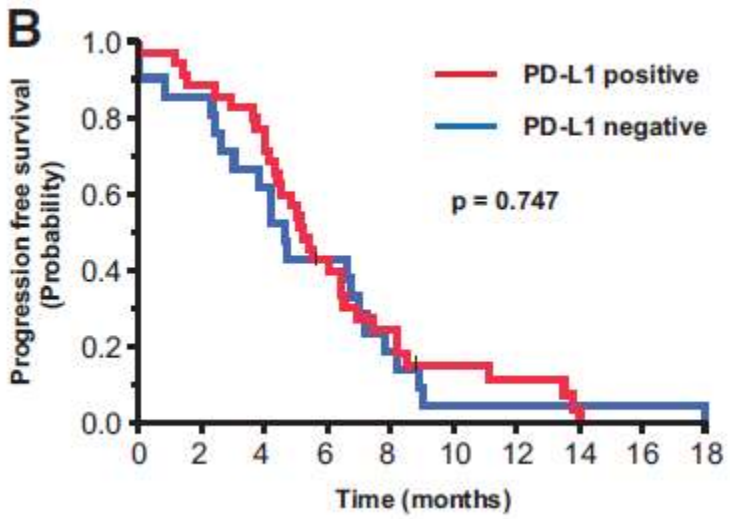
Survival analysis



- PD-L1-positive group showed significantly longer OS than the PD-L1-negative group (median 16.3 months versus 7.3 months, $p < 0.001$;



- Sub-analysis of ED-SCLC patients showed that the PD-L1-positive group had a longer OS than PD-L1-negative group (median 9.2 months versus 5.4 months, p = 0.037



No significant difference in PFS between the positive and negative groups (median 5.2 months in the positive group versus 4.6 months in the negative group(p = 0.747)

KEYNOTE-001:subanalysis of phase1 Prembluzumab trial in NSCLC

- Phase 1 study
- To determine efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced non–small-cell lung cancer
- To validate the expression level of the PD-1 ligand 1 (PD-L1) that is associated with the likelihood of clinical benefit
- 495 patients receiving pembrolizumab (at a dose of either 2 mg or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks) to either a training group (182 patients) or a validation group (313 patients)

- PD-L1 expression in tumor samples using immunohistochemical analysis, with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score) was performed
- Response was assessed every 9 weeks by central review

Overall response rete

ORR by RACIST,%,95%CI	N	ALL COHORT
TOTAL	495	19.4(16.0-23.2)
TREARMENT NAIVE	101	24.8(16.7-34.4)
PREVIOUSLY TREATED	394	18.0(14.4-22.2)
NON SQUAMOUS	401	18.7(15.0-22.9)
SQUAMOUS	85	23.5(15.0-34.0)

Progression free survival

MEDIAN PFS	N	DURATION(MONTH)
ALL	495	3.7 (95% CI, 2.9 to 4.1)
TREATMENT NAVIE	101	3 (95% CI, 2.2 to 4.0)
PREVIOUSLY TREATED	394	6 (95%CI, 4.1 to 8.6)

OVERALL SURVIVAL RATE

MEDIAN OS	N	DURATION(MONTH)
ALL PATIENT	495	12.0 (95% CI, 9.3-14.7)
TREATMENT NAIVE	101	9.3 (95% CI,8.4 - 12.4)
PREVIOUSLY TREATED	394	16.2 (95% CI, 16.2 to not reached)

ORR BY RACIST,%(95% CI)	N	ALL COHORT
% PDL1 STAINING		
> 50%	73	45.2(33.5-57.3)
1%-49%	103	16.5(9.9-25.1)
< 1%	28	10.7(2.3-28.2)

SIDE EFFECT

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.

PHASE 2 POPLAR TRIAL

- ATEZOLIZUMAB(MPDL3280A)(anti-PDL1) has demonstrated promising response rates in NSCLC that correlated with PD-L1 expression on tumor-infiltrating immune cells (IC) and/or tumor cells (TC)
- Previously treated 287NSCLC patients were stratified by PD-L1 IC status, histology and prior lines of therapy and randomized to 1200 mg IV q3w Atezolizumab or 75 mg/m2 IV q3w docetaxel
- PD-L1 expression was centrally evaluated by IHC. Patients were scored as TC0, 1, 2 or 3 and IC0, 1, 2 or 3
- The primary endpoint was OS

OUTCOME-INTERIM

Interim median OS (Month)outcome	Atezolizumab (n-144)	Docetexel (n-143)	HR(95%)CL	P value
Total population (N-287)	11.4	9.5	0.77(.55-1.06)	.11
Subgroup based on PDL-1 expression				
TC0/ICO(N-92)	9.7	9.7	1.12(0.64-1.93)	.7O
TC1/2/3orIC1/2/3(N-195)	NR	9.1	0.63(0.42-0.94)	.024
TC2/3 or IC2/3 (N-105)	13.0	7.4	0.56(0.33-0.94)	0.26
TC3 or IC3 (N-47)	NR	11.1	0.46(0.19-1.09)	.070

Agent	Population	Efficacy	Tolerability
Durvalumab (AntiPDL-1)	Squamous(N88) Nonsquamous(112)	ORR-16% 27%PDLA-1 +VE 5%PDLA-1 –VE Squamous-21% Nonsquamous-13%	Tx related AEs Any toxicity-50% Grade3/4-8%
Durvalumab+ Tremelimumab (Anti CTLA-4)	AdvanceNSCLC (N-102)	ORR-27% 33%PDLA-1 +VE 27%PDLA-1 –VE	Tx related AEs Any toxicity-80% Grade3/4-50% Immune related AE-Colitis-9%,pneumonitis-4%
Prembrolizumab+ Ipilimumab	Recurrent NSCLC (N-18)	ORR-39%	Tx related AEs Any toxicity-83% Grade3/4-57% Immune related AE-Colitis-12%,pneumonitis-8%

TOXICITY OF PD1 OR PDL-1 BLOCKER

- Occasional(3%-20%)

1. Fatigue
2. Rash:maculopaapular and pruritic-tropical treatment
3. Diarrhea or colitis-need steroid treatment
4. Hepatitis
5. Infusion reaction
6. Endocrinopathy:thyroid,adrenal ,hypophysitis

- Infrequent(less than5%)

1. Pneumonitis

Immune adverse event

- Onset

  -average 6-12 weeks after onset of treatment

  -can occur within hrs. of first dose,after several months of treatment, even after stoppage of treatment

- Patient complains are autoimmune or drug related until proven otherwise

  -rule out metabolic abnormality,infection,tumer effect

- Early recognition and treatment is essential

Treatment

- Any grade1 side effect-treat symptomatically and continue PDL-1 treatment and monitor
- Grade2 or more-hold PD-1 Tx, and administer steroid-after improvement to grade 1 or less taper steroid over at least 1 month
- Permanently stoppage of drug
  - If no improvement to grade 1 or less within 12 week
  - Can’t taper steroid to less than 10 mg /day within 12 week

Conclusion

- Immunotherapy for lung cancer can induce durable response and can result in prolong OS
- Immune related adverse effect are unique spectrum of adverse event with checkpoint inhibition that require learning new ways to manage toxicity
- Improve understanding of the immume system and ongoing clinical trial with immunotherapy likely result in an ongoing evolution in treatment for pt with NSCLC