Immune checkpoint inhibitors role in lung cancer other than metastatic/relapsed setting

G.Ratnakar

05-02-2021

Division

- Definitions
- Immune surveillance
- ICI
- Role in NSCLC
- Role in SCLC

Definition

- Advanced NSCLC refers to those patients with metastatic NSCLC and treatment objectives focus on prolonging survival and improving quality of life of these patients
- Early-stage NSCLC comprises those tumours between stages I and III of the TNM classification system and treatment aim is curative

    - T3 describes locally advanced, but potentially resectable tumour
    - T4 describes locally advanced, technically unresectable tumour

Definition

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

***Table 1* - Definition of small cell lung cancer consists of two stages:**
(1) Limited-stage: Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
(2) Extensive-stage: Stage IV (T any, N any, M 1a/b/c), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

Limited-stage disease — LS-SCLC is defined as disease that is limited to the ipsilateral hemithorax and regional lymph nodes and can be encompassed in a safe radiotherapy field

ES-SCLC is disease that has spread beyond this and may include distant metastases, malignant pericardial or pleural effusions, and/or contralateral supraclavicular and contralateral hilar lymph node involvement

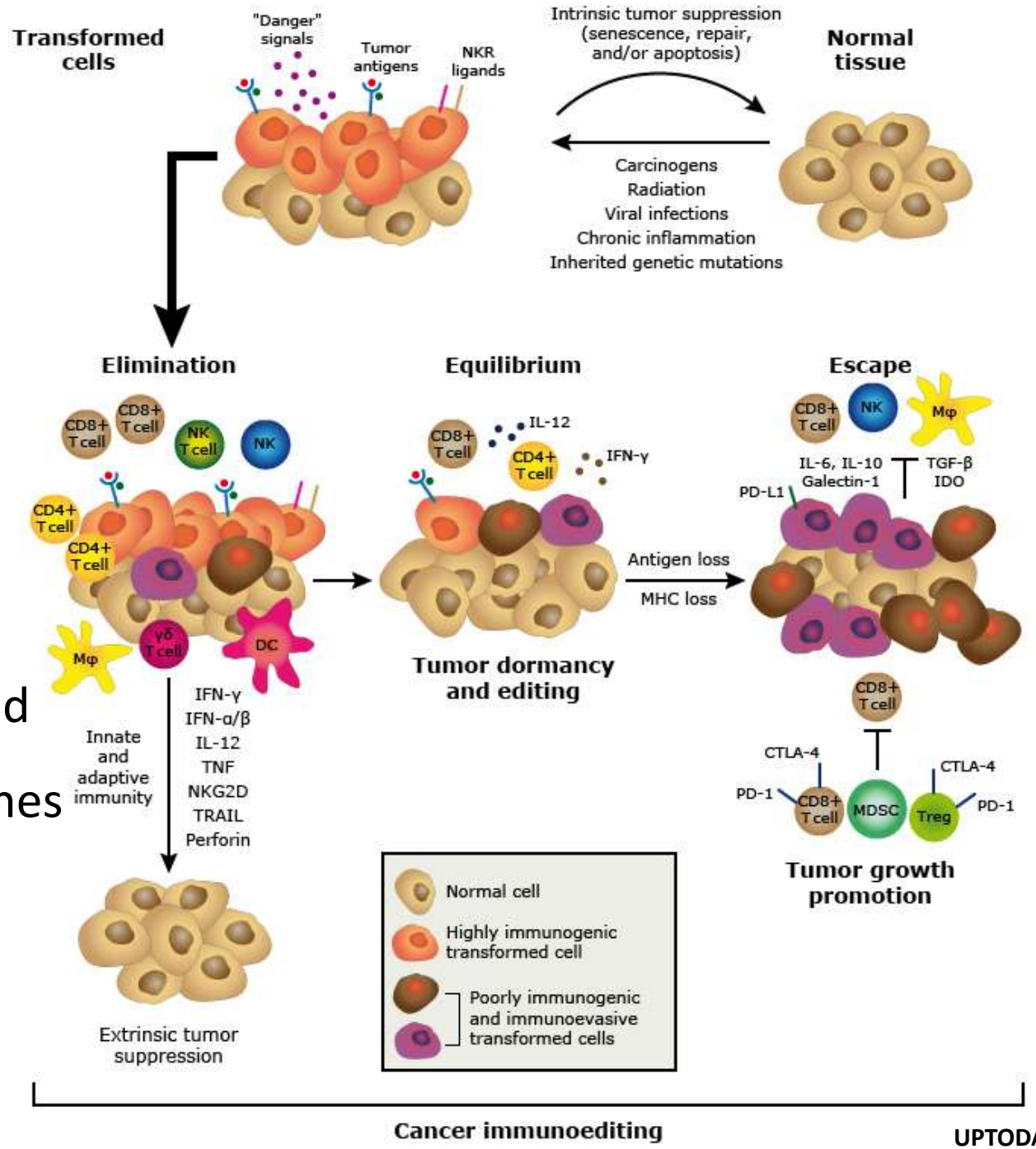
NCCN-2020

Cancer Immunoediting

Interaction b/w immune system and cancer

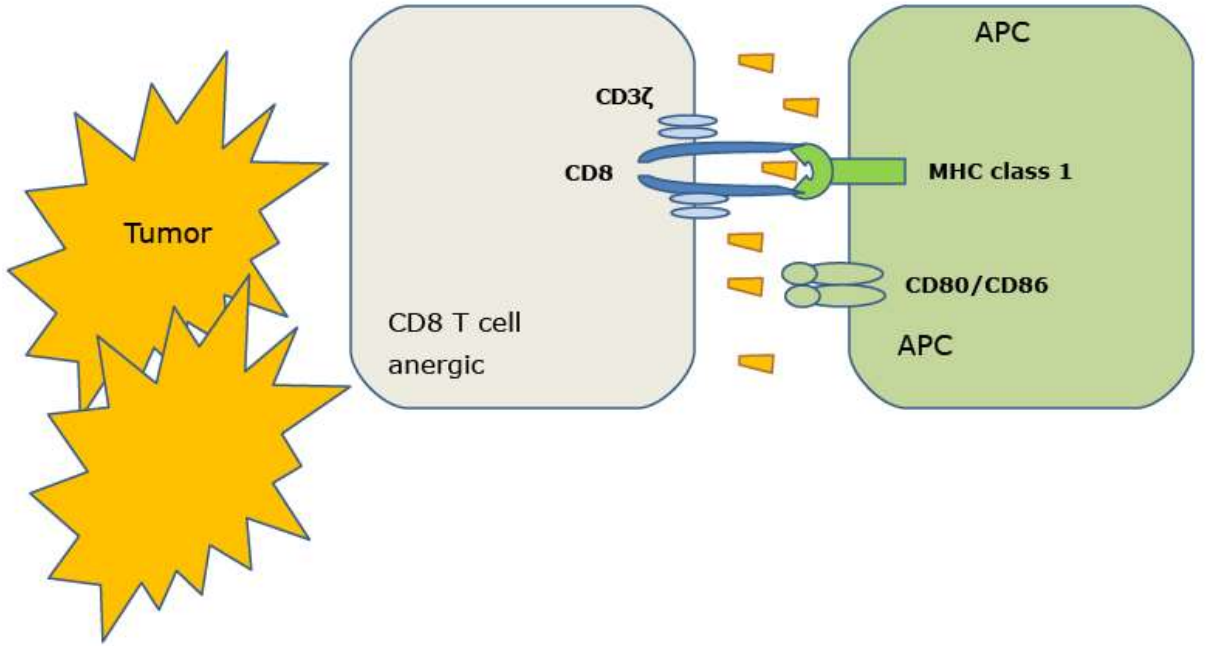
Three sequential phases of interaction

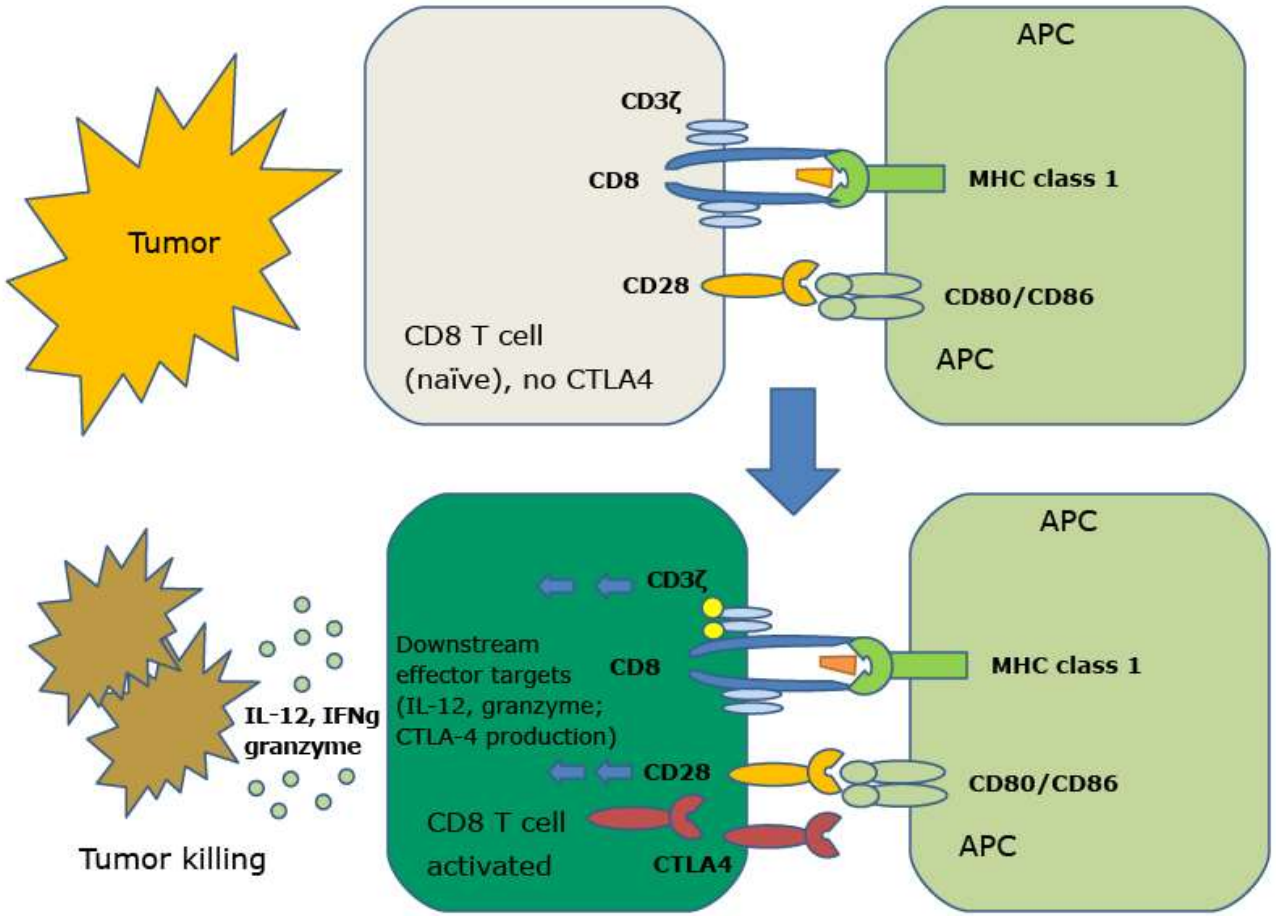
- Elimination : Body's immunity detects and responds to tumour antigens
- Equilibrium : balance b/w immune mediated destruction and persistence of malignant clones
- Escape : evasion of immune response by malignant clones



UPTODATE

Immune synapse





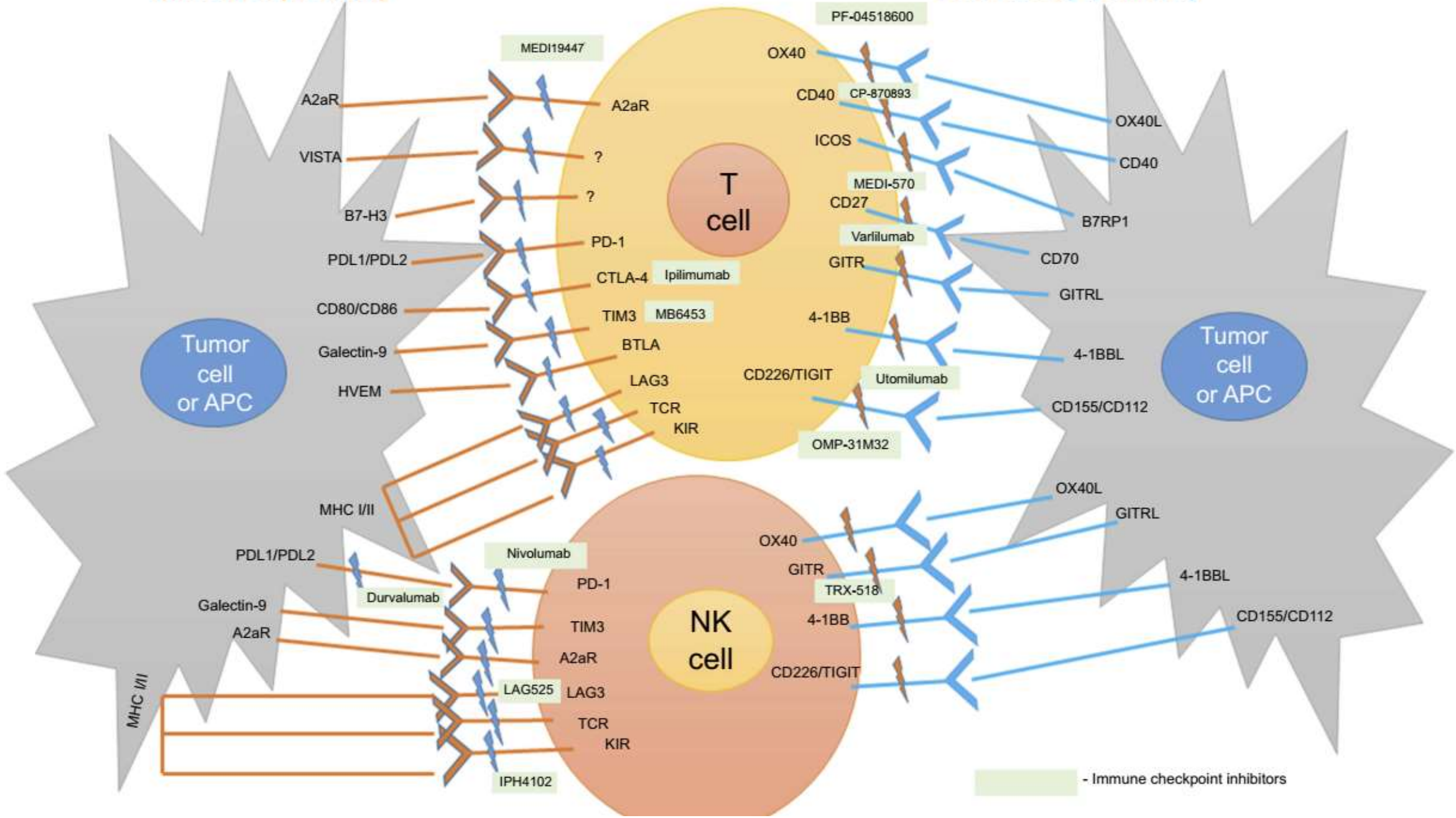
In the absence of the "second signal,T cells can become anergic and do not mount a response to antigen

UPTODATE

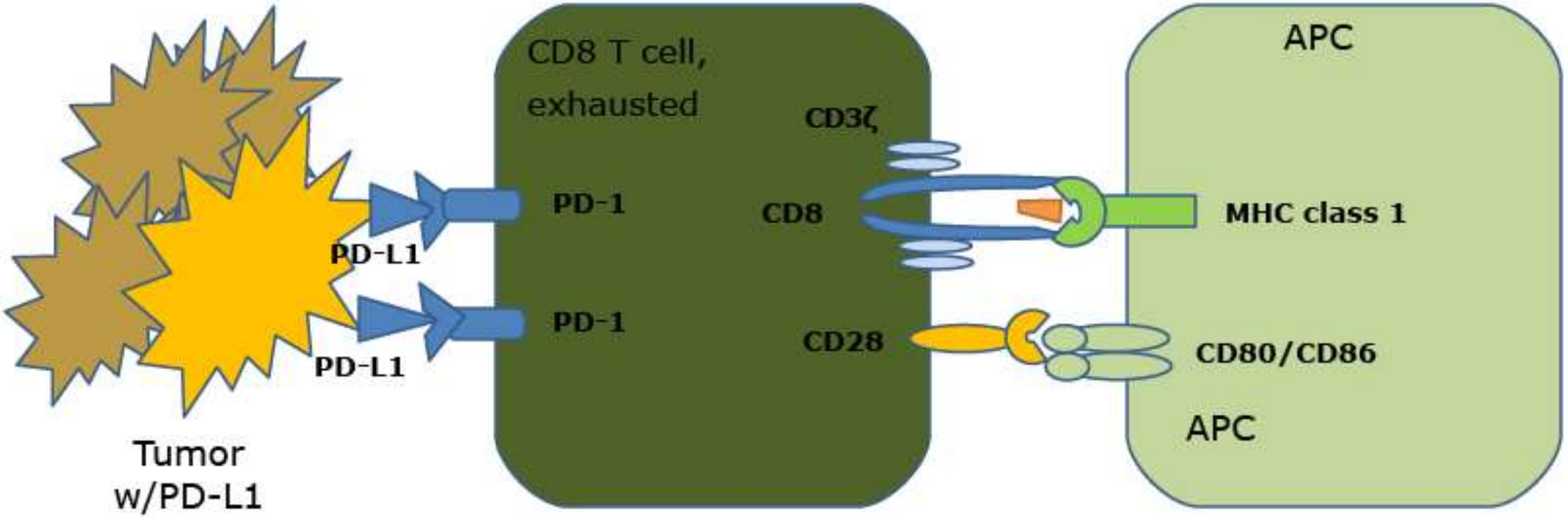
Immune synapse

- Most important costimulatory signal in naïve T cells is CD28, which binds to B7-1 and B7-2 (CD80/86) on the APC
- Costimulatory process is tightly regulated by both "agonist" molecules (eg, GITR, OX40, ICOS) and inhibitory signals on both the APC and T cells, often collectively referred to as "immune checkpoint" molecules

UpToDate


Inhibition pathway
Stimulatory pathway
MEDI19447
A2aR
A2aR
VISTA
?
?
B7-H3
PD-1
PDL1/PDL2
CTLA-4
Ipilimumab
CD80/CD86
TIM3
MB6453
Galectin-9
BTLA
HVEM
LAG3
TCR
KIR
T cell
Tumor cell or APC
PF-04518600
OX40
CD40
CP-870893
ICOS
MEDI-570
CD27
Varlilumab
GITR
4-1BB
CD226/TIGIT
Utomilumab
OMP-31M32
OX40L
CD40
B7RP1
CD70
GITRL
4-1BBL
CD155/CD112
Tumor cell or APC
MHC I/II
PDL1/PDL2
Nivolumab
PD-1
Durvalumab
Galectin-9
TIM3
A2aR
A2aR
LAG525
LAG3
TCR
KIR
IPH4102
NK cell
OX40
GITR
TRX-518
4-1BB
CD226/TIGIT
OX40L
GITRL
4-1BBL
CD155/CD112
MHC I/II
- Immune checkpoint inhibitors

In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFNgamma, etc) can upregulate PD-1 expression on the T cell; tumor clones can also select for PD-L1 expression. With PD-1-PD-L1 binding, even in the presence of the costimulatory molecule, "peripheral exhaustion" can occur



UpToDate

Mechanisms for escape from immune surveillance

- Loss or alteration of specific antigens or antigenic machinery
- Tumors can promote an immune-tolerant microenvironment by manipulation of cytokines that encourage infiltration of Treg cells, myeloid derived suppressor cells (MDSCs), and other cell types that inhibit cytotoxic T cell function
- Upregulate the expression of immune checkpoint molecules
- Oncogenic cell signaling pathways that are viewed as accelerators of cell division and growth are now understood to be mediators of immunologic escape

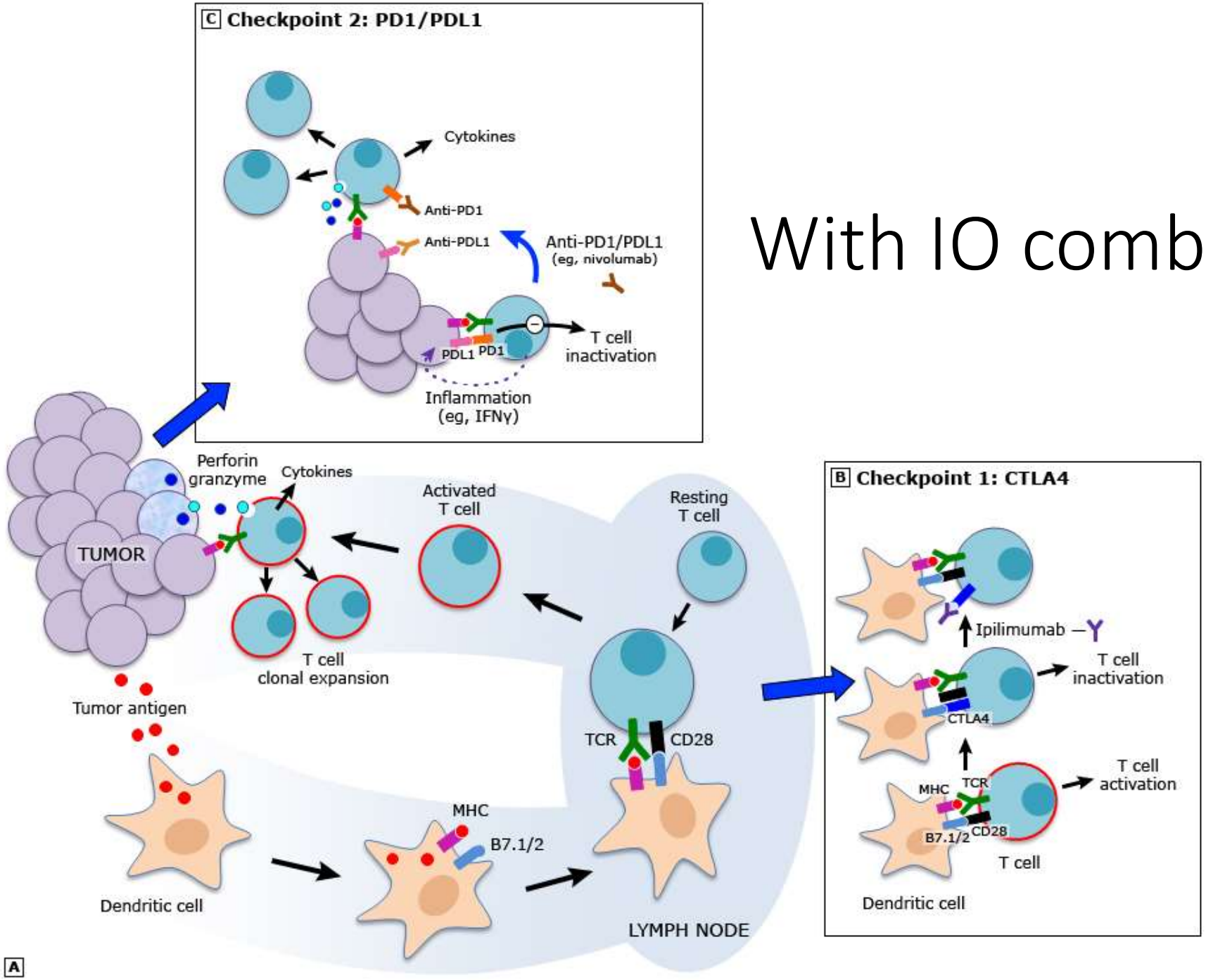
UpToDate

Immune Checkpoints Inhibitors

Name	Antibody Type	Mechanism of Action	Company
Nivolumab	Human IgG4	PD-1 inhibitor	Bristol-Myers Squibb
Pembrolizumab	Humanized IgG4	PD-1 inhibitor	MSD
Atezolizumab	Humanized IgG1k	PD-L1 inhibitor	Roche/Genentech
Durvalumab	Human IgG1k	PD-L1 inhibitor	Medimmune/Astra Zeneca
Ipilimumab	Human IgG1	CTLA-4 inhibitor	Bristol-Myers Squibb

Cancers 2020, 12, 3459; doi:10.3390/cancers12113459

With IO combinations



Uptodate

Role of ICS in lung cancer

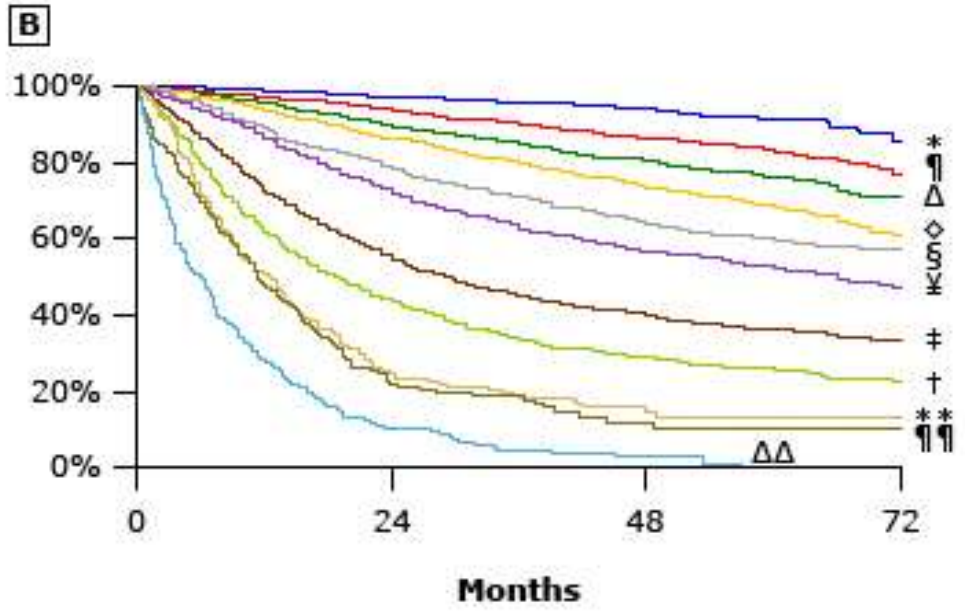
- NSCLC
  - Early
    - Neo-adjuvent
    - Adjuvent
    - Consolidation treatment after chemoradiation
  - Advanced
- SCLC
  - Limited
  - Extented

NSCL

Patients present with

- 20% with localized disease (stages I and II)
- 30% with locally advanced disease (stage III)
- 50% with metastatic disease (stage IV)

In recent years increase in patients diagnosed with localized NSCLC, from 16.6% in 1988 to 23.6% in 2015 (SEER database)



8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
¶¶ IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

IASCLC Atlas, 2nd edition

Problem

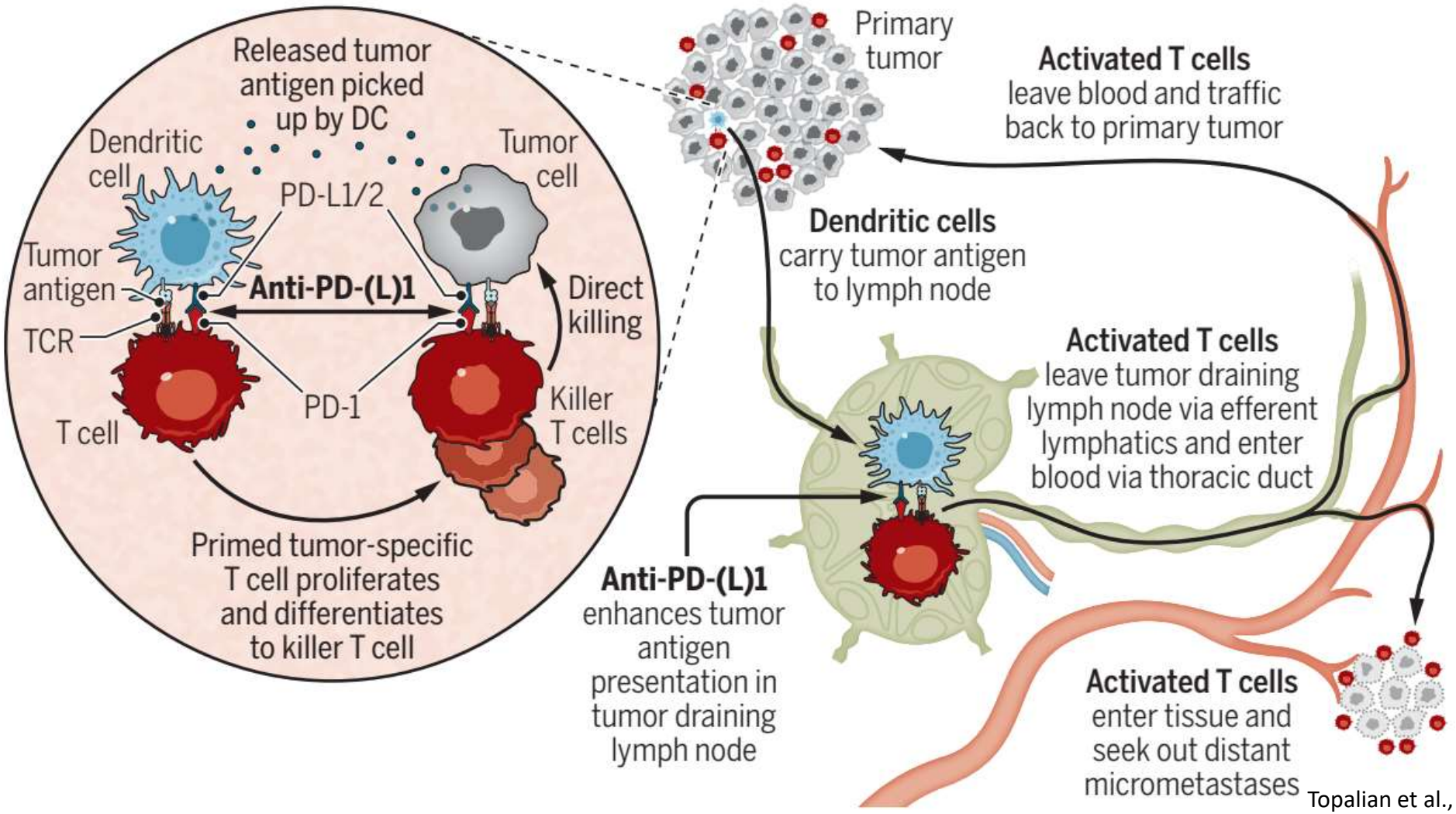
- Patients with resectable NSCLC are treated with surgical resection followed by systemic adjuvant therapy
- Addition of cisplatin based adjuvant CT offers a 4% to 8% survival benefit at 5 yrs
- Despite surgery and adjuvant therapy, about 20% to 30% of patients with stage I, 50% of patients with stage II, and 60% of patients with stage IIIA disease die within 5 years
- Urgent need to explore novel treatment approaches to reduce the risk of recurrence and improve survival of resectable NSCLC

LACE Collaborative Group
IASLC TNM staging

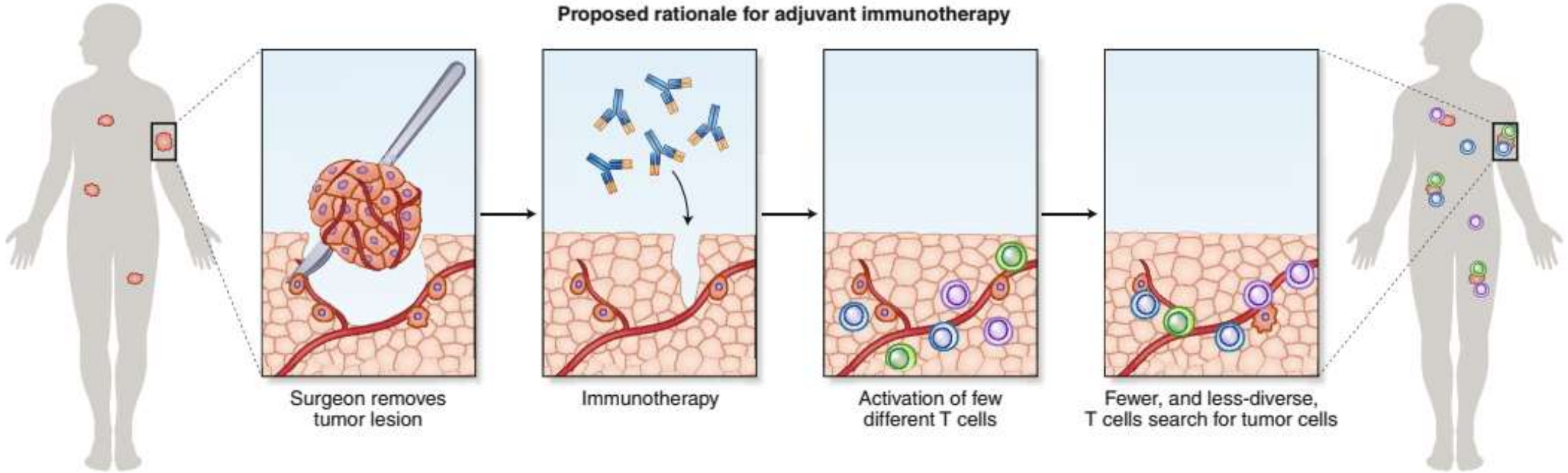
Mechanism of ICS in the

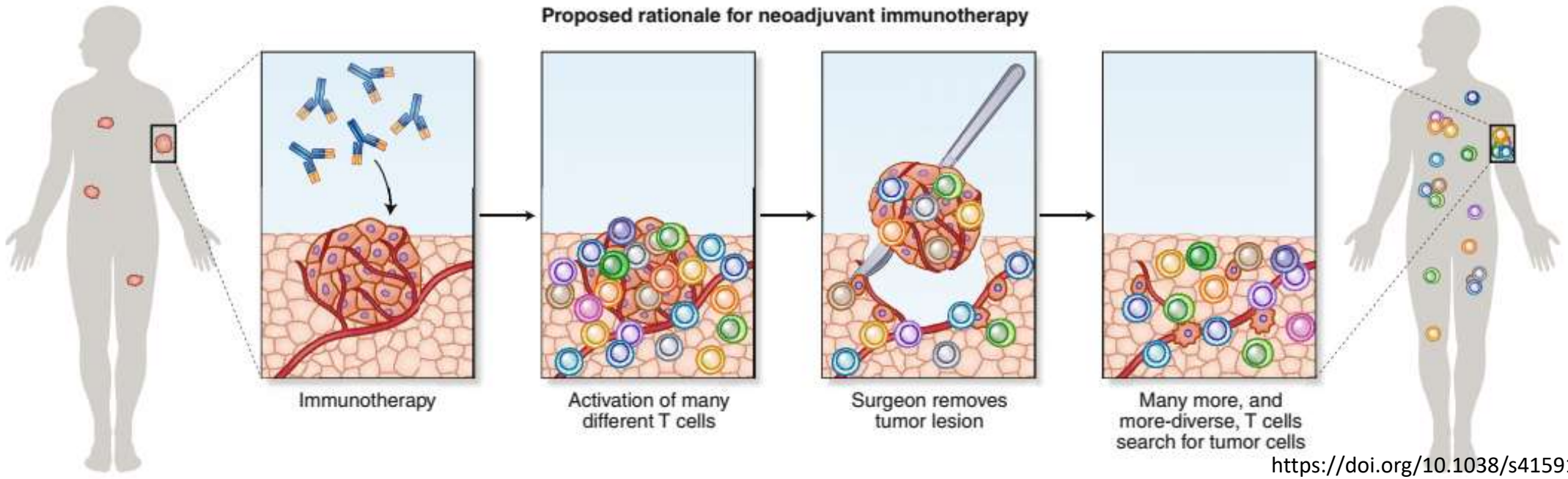
Neo-adjuvant & Adjuvant settings

Enhancement of systemic antitumor T cell immunity after neoadjuvant PD-1 blockade



Topalian et al., Science 367, 525 (2020)

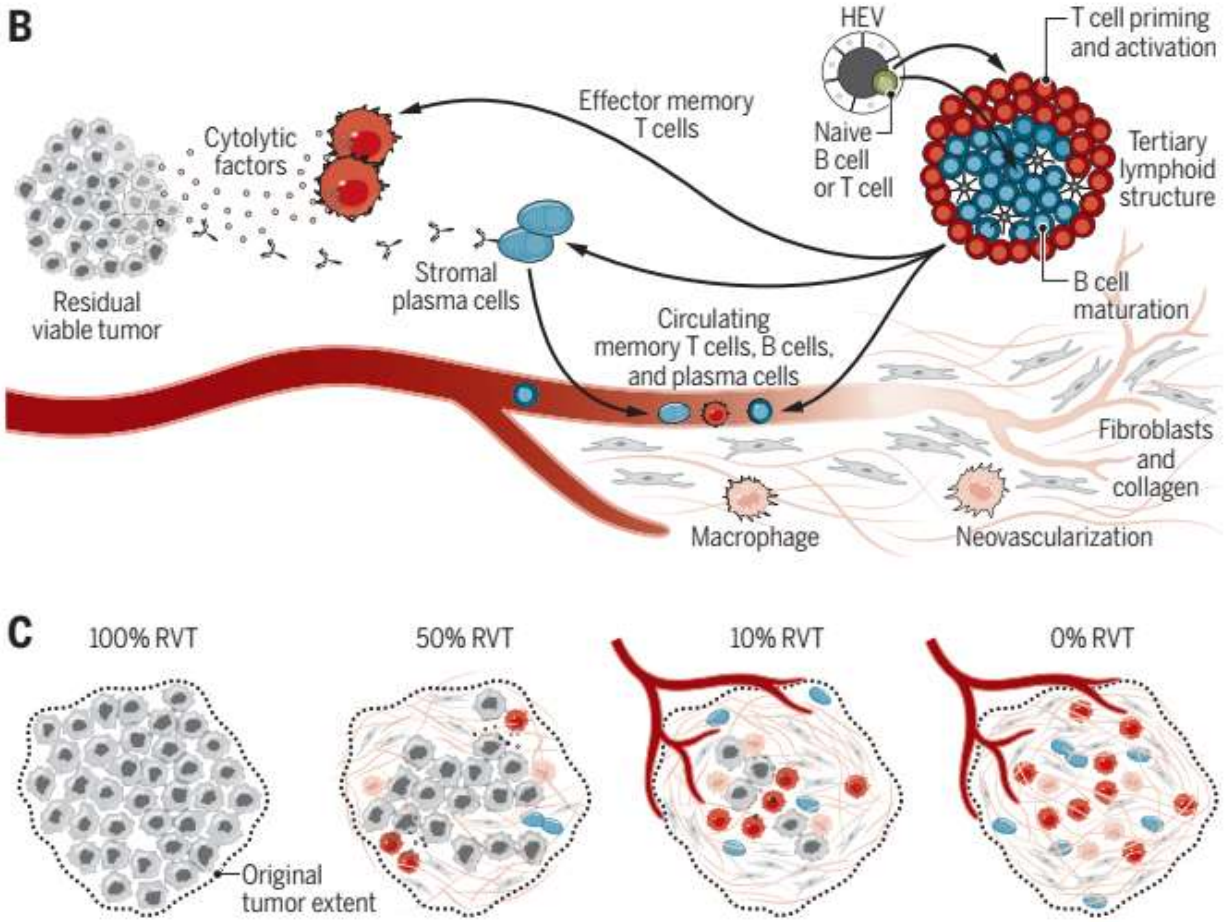


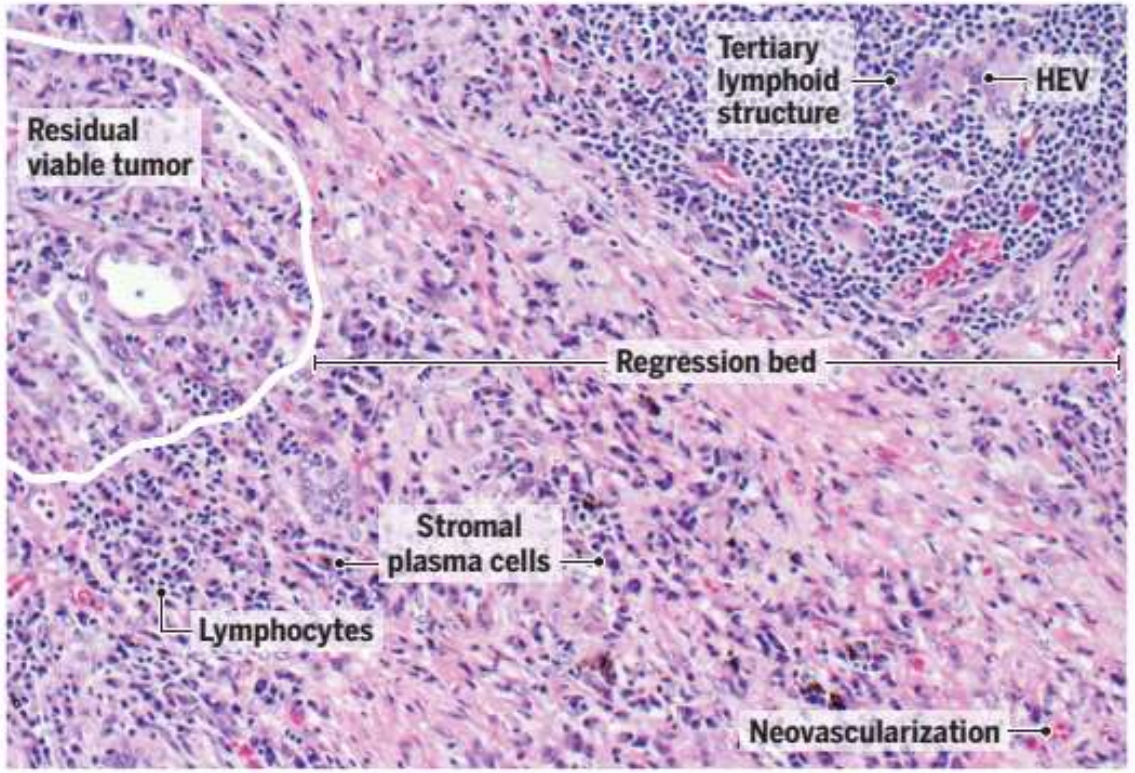


https://doi.org/10.1038/s41591-020-0829-0

Pathologic response assessment

Major pathologic response(MPR), describing a treatment effect resulting in ≤10% residual viable tumor (RVT)





Topalian et al., Science 367, 525 (2020)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann,

Pilot study

Inclusion Criteria

- 8 years of age or older
- Stage I, II, or IIIA NSCLC (surgically resectable)
- ECOG-0 or 1
- Normal organ function, & adequate pulmonary function

Key exclusion criteria

- Immunodeficiency
- Ongoing systemic immunosuppressive therapy,
- Active autoimmune or infectious disease

Intervention

2 preoperative doses of nivolumab(at a dose of 3 mg per kilogram of body weight) was administered I.V every 2 weeks, with surgery planned approximately 4 weeks after the first dose

Primary end points

- Safety and feasibility

Also evaluated the tumor pathological response, expression of PD-L1, mutational burden, and mutation-associated, neoantigen-specific T-cell responses

Results

- 20 patients [2 partialresponse (PR) and 18 stable disease (SD)] undergoing curative surgery after neoadjuvant nivolumab and 45% achieving major pathologic response (MPR).
- At follow-up, the recurrence rate within 18 months was 73%, the OS rate was 95%, and the 24-month relapse-free survival (RFS) estimated by the Kaplan–Meier curve was 69%.
- Although the sample size was small, this trial confirmed the safety of neoadjuvant immunotherapy for NSCLC, laying the foundation for subsequent studies

LCMC3 Trial: Neoadjuvant Atezolizumab for Patients With Stage IB to IIIB Resectable Lung Cancer

181 patients with stage IB–IIIB NSCLC and no targetable mutations

- 2 cycles of atezo 1200 mg (days 1, 22) and underwent surgical resection between 30 and 50 days from the first cycle
- Patients who benefitted from the therapy could continue adjuvant atezolizumab for 12 months

Primary endpoint

Major pathological response (MPR), defined as ≤ 10% viable tumor cells in the resection specimen

Secondary endpoints

- Safety and correlation of response with PD-L1 expression
- Tumor mutation burden (TMB)
- Gene expression signatures

Results

- Surgery was performed on 159 patients, and 144 were included in the efficacy analysis
- MPR was 21%, with 7% of patients achieving a cPR
- At 1.5 years, disease-free survival was 79% for stage I/II patients and 77% for stage III patients (*P* = .88); overall survival was 91% and 87%, respectively (*P* = .45)
- R0 (clear surgical margins) status was achieved in 92%

ORIGINAL ARTICLE

Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC

Check for updates

Shugeng Gao, MD,[a] Ning Li, MD,[b] Shunyu Gao, MD,[a] Qi Xue, MD,[a] Jianming Ying, MD,[c]

40 patients
- Resectable NSCLC
- (stage IA–IIIB)
- ECOG-0
- Adequate organ function

- Two cycles of sintilimab (200 mg intravenously, day 1 out of 22) Operation was performed
- between day 29 and 43

Primary end point
- Safety

Efficacy end points
- Rate of major pathologic response (MPR)
- Objective response rate
- Expression of PD-L1

Results

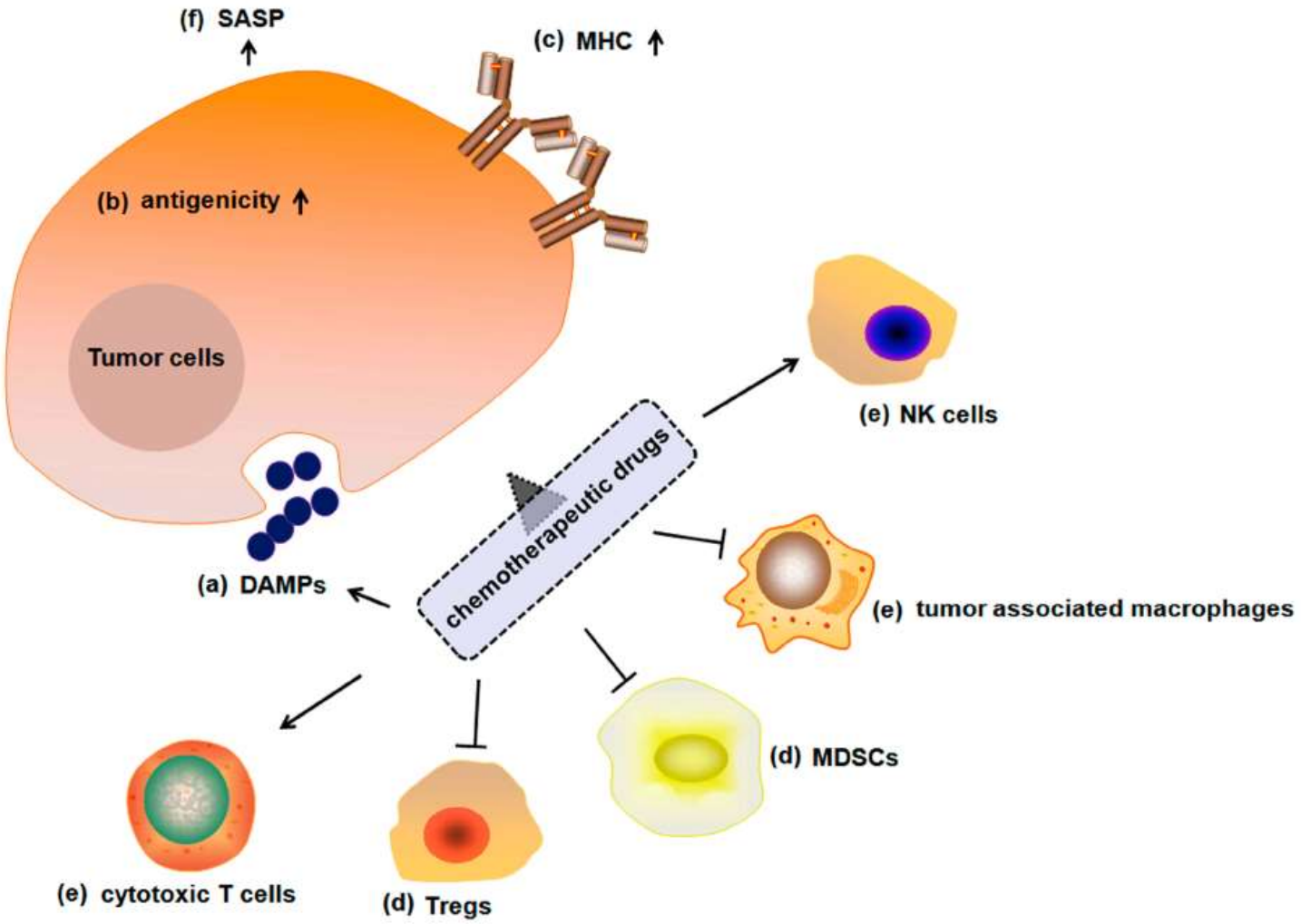
- 37 underwent radical resection
- 15 (40.5%) achieved MPR
- 6 (16.2%) with a pCR in primary tumor and 3 (8.1%) in lymph nodes
- Squamous cell NSCLC exhibited superior response compared with adenocarcinoma (MPR: 48.4% versus 0%)
- 21 patients (52.5%) experienced (TRAEs).
- Four patients (10.0%) experienced grade 3 or higher TRAEs
- One patient had grade 5 TRAE.

Completed clinical trials of neoadjuvant therapy with ICIs for resectable NSCLC

Clinical trial	Phase	Stage	Intervention used	Sample size	Primary endpoint	Primary outcomes
Check Mate 159	I	I–IIIA	Nivolumab	22	Safety and feasibility	MPR: 45%, pCR: 10%
LCMC3 A	II	IB–IIIA	Atezolizumab	101	MPR	MPR: 18%, pCR: 5%
Li et al.	II	IA–IIIB	Sintilimab	40	Safety	MPR: 40.5%, pCR: 16.2%
Li et al. ChiCTR-OIC-17013726	IB	IA–IIIA	Sintilimab	22	Drug-related adverse event; surgery complications; no-delay surgery rate	MPR:45.5%, pCR: 18.2%

Immune Checkpoint Inhibitor-Based Neoadjuvant Combination Therapy

Immunomodulation effects of chemotherapeutic drugs-



Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial

Catherine A Shu, Justin F Gainor, Mark M Awad, Codruta Chiuzan, Claud M Grigg, Aliyah Pabani, Robert F Garofano, Mark B Stoopler, Simon K Cheng, Abby White, Michael Lanuti, Frank D'Ovidio, Matthew Bacchetta, Joshua R Sonett, Anjali Saqi, Naiyer A Rizvi

- open-label
- phase 2 trial
- 18 years of age or older
- Stage I, II, or IIIA NSCLC (surgically resectable)
- ECOG-0 or 1
- smoking exposure

Atezolizumab (1200 mg) on day 1, nabpaclitaxel (100 mg/m^2) on days 1, 8, and 15, and Carboplatin (AUC 5; 5 mg/mL per min) on day 1, of each 21-day cycle

Primary endpoint MPR-presence of 10% or less residual viable tumour

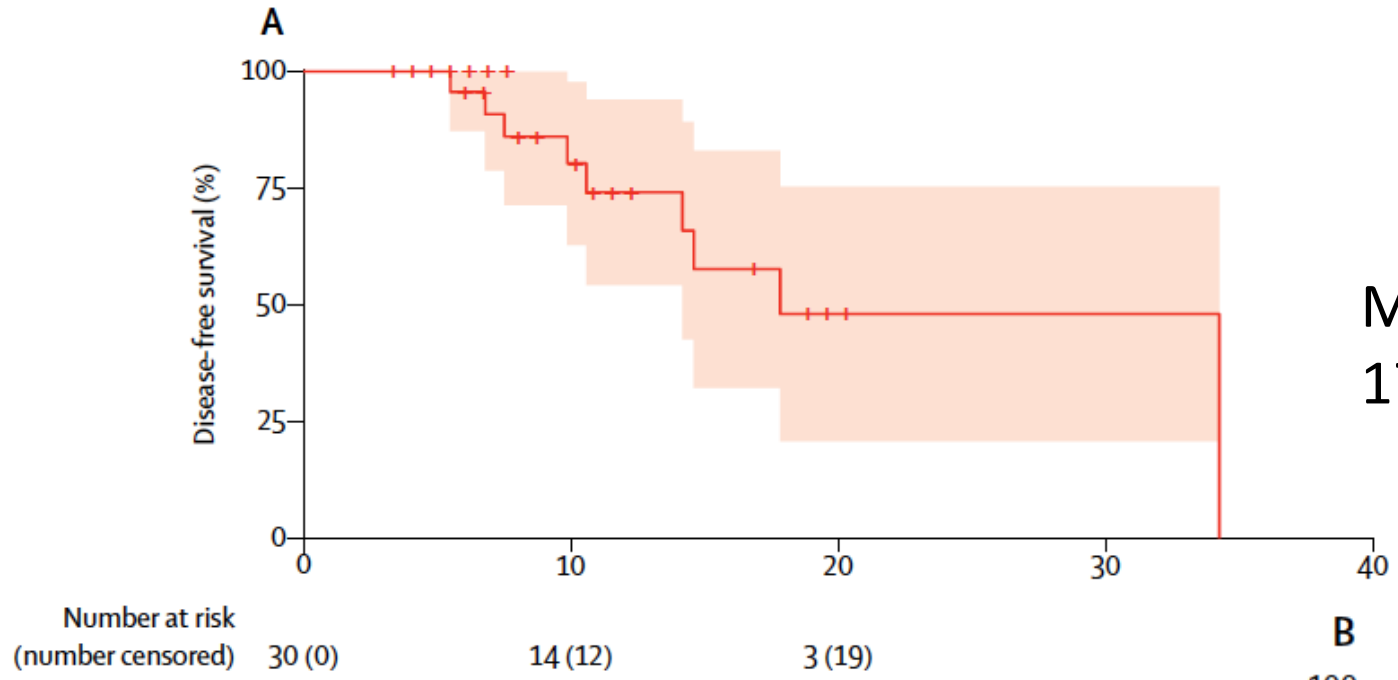
Median follow-up period was 12.9 months

	Patients (n=30)
Age	67 (62–74)
Sex	
Male	15 (50%)
Female	15 (50%)
Histology	
Adenocarcinoma	17 (57%)
Squamous cell carcinoma	12 (40%)
Large cell neuroendocrine	1 (3%)
Stage at presentation*	
IIA	4 (13%)
IIB	3 (10%)
IIIA	23 (77%)
PD-L1 expression†	
≥50%	8 (27%)
≥1%	16 (55%)
<1%	12 (40%)
Unknown	2 (7%)

	Patients (n=29)*
Had successful surgical resection with curative intent	26/29 (87%)†
Type of surgery	
Video-assisted thoracoscopic surgery	12/26 (46%)
Thoracotomy	14/26 (54%)
Surgical resection	
Lobectomy	19/26 (73%)
Bilobectomy	4/26 (15%)
Pneumonectomy	3/26 (12%)
Margins	
Negative	26/26 (100%)
Positive	0
Downstaging of nodal status in patients with N2 at baseline*	
N2 to N0	11/19 (58%)
N2 to N1	2/19 (11%)
N2 to N2	5/19 (26%)
Surgical complications	
Intraoperative platelet or blood transfusion	2/29 (7%)
30-day mortality	1/29 (3%)‡
30–90-day mortality	0
Length of hospital stay, days	4 (3–6)
Readmission within 30 days	1/29 (3%)§
Postoperative arrhythmia	3/29 (10%)
Urinary tract infection or urinary retention	2/29 (7%)

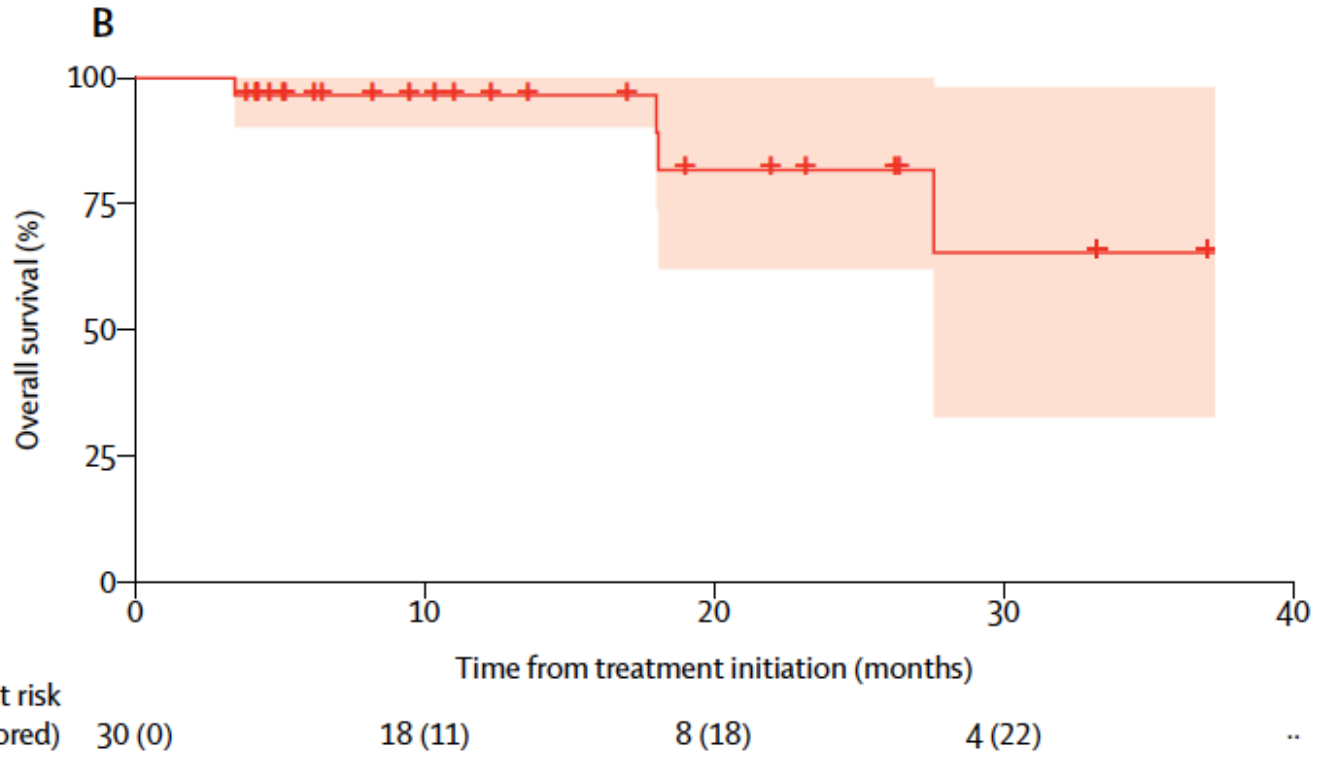
Data are n/N (%) or median (IQR). *One patient progressed on neoadjuvant therapy and did not undergo surgical resection. †Three patients were taken to surgery but were considered not to have resectable disease. ‡Patient had pneumonia and

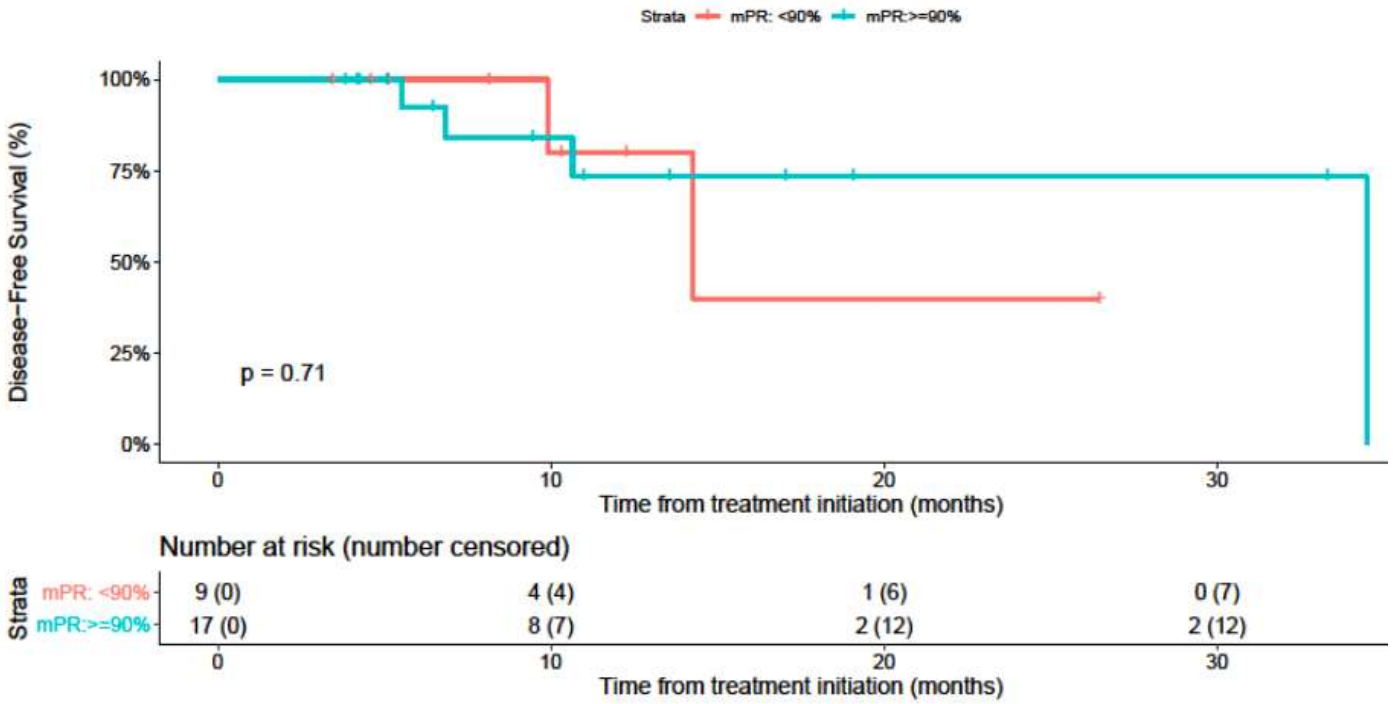
	Major pathological response	Pathological complete response
Intention-to-treat population	17/30 (57%; 95% CI 37–75)	10/30 (33%; 95% CI 17–53)
Cancer type*		
Adenocarcinoma	8/15 (53%)	5/15 (33%)
Squamous cell carcinoma	8/10 (80%)	5/10 (50%)
p value	0·17	0·41



Median disease-free survival
17.9 months (95% CI 14.3 to not reached)

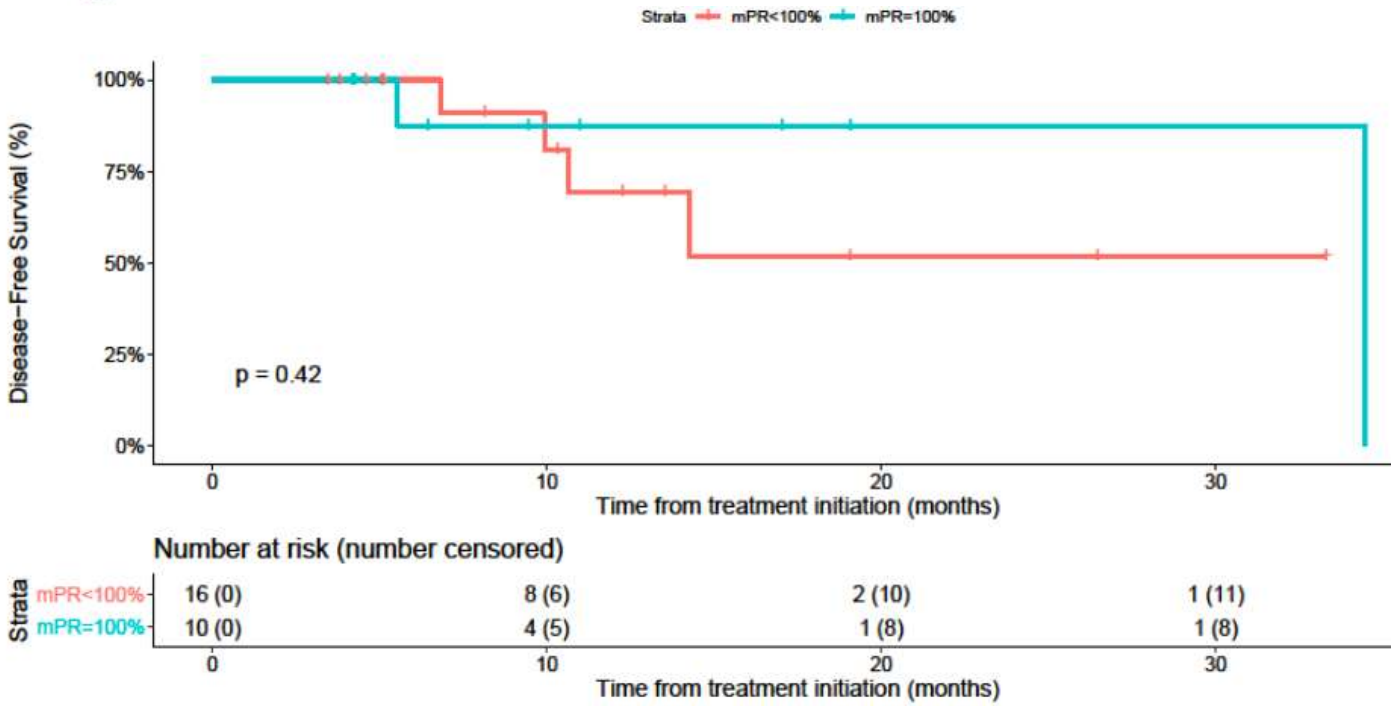
Median overall survival
Not reached (95% CI 27.6 to not reached





major pathological
response had a median disease-free survival of 14.3 months (95% CI 9.9 to not reached), compared with
34.5 months (95% CI 10.7 to not reached) in those
patients who had a major pathological response (hazard
ratio 0.7 [95% CI 0.1–4.3], p=0.71

Median
disease-free survival in patients who had a pathological
complete response was 34.5 months, and median disease-free survival in patients who did not have a pathological complete response was not reached (hazard
ratio 0.4 [95% CI 0.04–3.70], p=0.42



	Grade 1–2	Grade 3	Grade 4
Alanine aminotransferase increased*	4 (13%)	2 (7%)	0
Alopecia	14 (47%)	0	0
Anaemia	20 (67%)	1 (3%)	0
Anorexia	3 (10%)	0	0
Arthralgia or myalgia*	5 (17%)	0	0
Aspartate aminotransferase increased*	3 (10%)	2 (7%)	0
Constipation	7 (27%)	0	0
Diarrhoea*	8 (30%)	1 (3%)	0
Dysgeusia	7 (27%)	0	0
Dyspnoea	3 (10%)	0	0
Epistaxis	3 (10%)	0	0
Fatigue	16 (53%)	1 (3%)	0
Febrile neutropenia	0	1 (3%)	0
Fever	3 (10%)	0	0
Hyperglycaemia*	0	0	1 (3%)
Hyponatraemia	1 (3%)	1 (3%)	0
Hypomagnesaemia	3 (10%)	0	0
Hypophosphataemia	3 (10%)	0	0
Hypothyroidism*	3 (10%)	0	0
Mucositis oral	4 (13%)	0	0
Nausea	13 (43%)	0	0
Peripheral sensory neuropathy	5 (17%)	0	0
Neutropenia	11 (37%)	12 (40%)	3 (10%)
Paresthesia	3 (10%)	0	0
Rash	5 (17%)	0	0
Thrombocytopenia	17 (57%)	1 (3%)	1 (3%)
Vomiting	5 (17%)	0	0
Weight loss	1 (3%)	1 (3%)	0

Serious treatment-related adverse events
included one (3%) patient with grade 3 febrile neutropenia,
one (3%) patient with grade 4 hyperglycaemia,
and one (3%) patient with grade 2 bronchopulmonary Haemorrhage
No treatment-related deaths

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

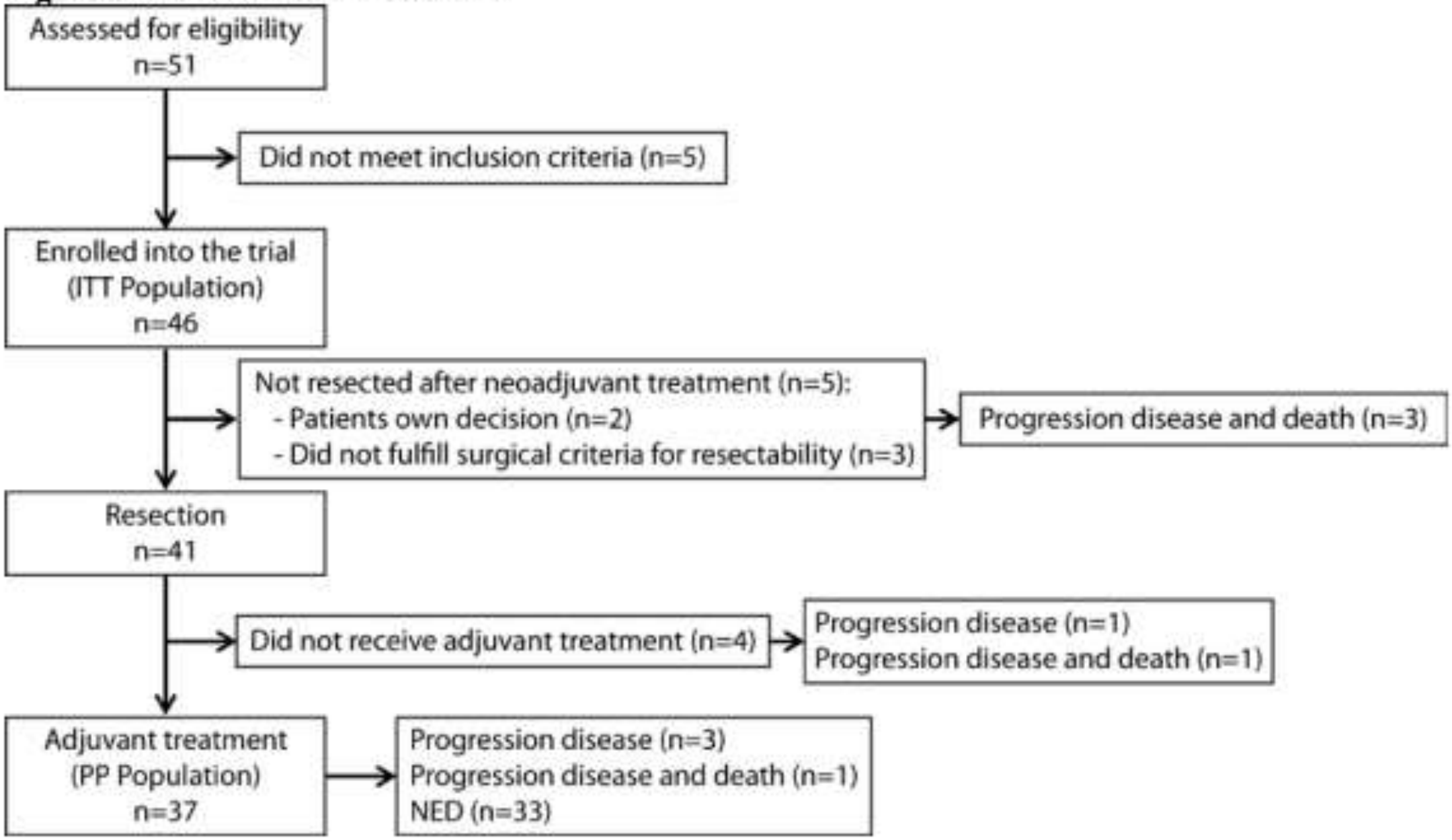
Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem,

Age 18 years or older
treatment-naive
stage IIIA NSCLC
ECOG-0 or 1

Neoadjuvant treatment
with I.V paclitaxel (200 mg/mÇ) and carboplatin (AUC 6; 6 mg/mL per min) plus nivolumab
(360 mg) on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant intravenous
nivolumab monotherapy for 1 year (240 mg every 2 weeks for 4 months,
followed by 480 mg every 4 weeks for 8 months)

Primary endpoint
progression-free survival at 24 months, assessed in the modified ITT, which included all patients who received neoadjuvant treatment, and in the per-protocol population, which included all patients who had tumour resection and received at least one cycle of adjuvant treatment.
Safety was assessed in the modified intention-to-treat population

Figure S1. NADIM trial flowchart



	Patients (n=46)
Age, years	63 (58–70)
Sex	
Male	34 (74%)
Female	12 (26%)
ECOG performance status	
0	25 (54%)
1	21 (46%)
Smoking status	
Former smoker (≥1 year)	25 (54%)
Current smoker	21 (46%)
Pack-years	49 (39–61)
Histology	
Adenocarcinoma	26 (57%)
Squamous cell carcinoma	16 (35%)
Not specified or undifferentiated	4 (9%)
Comorbidities	
Yes	43 (93%)
No	3 (7%)
Dyslipidaemia	16 (35%)
Hypertension	15 (33%)
Diabetes	9 (20%)
Chronic obstructive pulmonary disease	9 (20%)
Heart disease	7 (15%)
Hypercholesterolaemia	4 (9%)
Depressive disorder or anxiety	4 (9%)
Nephropathy	2 (4%)
Asthma	1 (2%)
Vasculopathy	1 (2%)
Tumour lesion size, mm	35 (23–60)
Nodal stage	
N0	9 (20%)
N1	3 (7%)
N2	34 (74%)
Single	9 (20%)
Multiple	25 (54%)
Tumour, Node, Metastasis staging classification	
T1N2M0	15 (33%)
T2N1M0	1 (2%)
T2N2M0	6 (13%)
T3N1M0	1 (2%)
T3N2M0	13 (28%)
T4N0M0	9 (20%)
T4N1M0	1 (2%)

Results

- After neoadjuvant combination therapy, 93% patients had downstaging, and R0 resection was performed in 41/46 patients; MPR was 83% and pCR reached 71% after operation; PR was 72% and CR was 6.5%

Results

		modified ITT population	per protocol population
Progression-free survival	12 months	95.7% (95% CI 83.7–98.9)	100% (95% CI not estimable)
	18 months,	87.0% (73.3–93.9)	91.9% (76.9–97.3
	24 months	77.1% (59.9–87.7)	87.9% (69.8–95.3)
overall survival	12 months	97.8% (95% CI 85.5–99.7)	100% (95% CI not estimable)
	18 months,	93.5% (81.1–97.8)	97.3% (82.3–99.6)
	24 months	89.9% (74.5–96.2)	97.3% (82.3–99.6)

	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	43 (93%)	14 (30%)	2 (4%)
Asthenia or fatigue	23 (50%)	1 (2%)	0
Alopecia	16 (35%)	1 (2%)	0
Nausea	15 (33%)	0	0
Neurotoxicity	13 (28%)	2 (4%)	0
Arthralgia	12 (26%)	0	0
Diarrhoea	11 (24%)	0	0
Skin disorders (rash)	10 (22%)	1 (2%)	0
Myalgia	9 (20%)	0	0
Vomiting	8 (17%)	0	0
Decreased appetite or anorexia	8 (17%)	1 (2%)	0
Constipation	8 (17%)	0	0
Paraesthesia	8 (17%)	0	0
Pruritus	7 (15%)	0	0
Anaemia	7 (15%)	0	0
Increased aminotransferases	4 (9%)	1 (2%)	0
Neutropenia	2 (4%)	1 (2%)	1 (2%)
Increased serum amylase	1 (2%)	2 (4%)	0
Increased creatinine	1 (2%)	2 (4%)	0
Increased lipase	0	2 (4%)	1 (2%)
Febrile neutropenia	0	3 (7%)	0
Pemphigoid of the hand	0	1 (2%)	0

Data are n (%). Toxicity was monitored continuously for 100 days after the last dose of neoadjuvant nivolumab. No grade 5 treatment-related adverse events were observed.

Table 2: **Treatment-related adverse events during neoadjuvant treatment in the modified intention-to-treat population (n=46)**

	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	32 (86%)	7 (19%)	1 (3%)
Skin disorders (rash)	19 (51%)	1 (3%)	0
Asthenia or fatigue	18 (49%)	0	0
Pruritus	13 (35%)	0	0
Decreased appetite or anorexia	7 (19%)	0	0
Diarrhoea	7 (19%)	0	0
Arthralgia	7 (19%)	0	0
Myalgia	5 (14%)	0	0
Nausea	5 (14%)	0	0
Vomiting	4 (11%)	0	0
Constipation	4 (11%)	0	0
Paraesthesia	4 (11%)	0	0
Increased lipase	1 (3%)	3 (8%)	1 (3%)
Increased serum amylase	1 (3%)	3 (8%)	0
Adrenal insufficiency	0	1 (3%)	0
Pemphigoid of the hand	0	1 (3%)	0

Data are n (%). No grade 5 treatment-related adverse events were observed.

Table 3: **Treatment-related adverse events during adjuvant treatment in the per-protocol population (n=37)**

Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study.

- N=44
- Stage I-IIIA (single N2) resectable NSCLC (AJCC 7th)
- PS 0-1

- N-23 (3 mg/kg IV, D1, 15, 29)

Vs

- N plus I-21(1 mg/kg IV, D1) followed by surgery

Primary endpoint

- MPR (≤10% viable tumor), hypothesized to be higher than MPR to induction chemotherapy historical controls
- Tumor immune infiltrates and pre- & post-ICI tumor PD-L1 % were assessed by flow cytometry & IHC

Results

- Mean age 66, 64% males,
- 18% never smokers
- 59% adenocarcinomas
- Stages: IA 8 (18%), IB 15 (34%), IIA 7 (16%) IIB 5 (11%); IIIA 9 (20%)
- 34 pts had surgery post ICIs (7 not resected [7/41], 17%, [2 N, 5 NI], 3 pending)

Results

- 34 pts had surgery post ICIs (7 not resected [7/41], 17%, [2 N, 5 NI], 3 pending)
- in 41 pts overall 10 MPRs (24%, 4 N, 6 NI), of which 6 were path CRs (15%, 2 N [9%], 4 NI [21%])
- 34 resected pts, MPR rate was 29% (N 20%, NI 43%)
- Median % of viable tumor was lower post NI vs N (20% vs 65%, p = .097).
- ORR was 22% (8 PRs [5 N, 3 NI], 1 CR [NI]); 15% of pts had PD (3 N, 3 NI).

Results

- Median pre-treatment tumor PD-L1 was higher in responders (MPR+, CR+PR) vs non-responders (80% vs 1%, p = .024), and the % of viable tumor was lower in tumors with PD-L1 > 1% vs PD-L1 ≤1% (median 20% vs 80%, p = .046)
- Surgical complications included 2 bronchopleural fistulas (BPFs) in N & 8 air leaks (5 N, 3 NI)
- G3 pneumonia, hypoxia, hypermagnesemia (1 each, all N), G3 diarrhea (1 NI)

Conclusions

- Overall a 24% MPR rate to neoadjuvant ICIs was observed
- NI induced a higher % of non-viable tumor when compared to N
- Antitumor activity was associated with higher pre-treatment PD-L1 levels

Clinical trials ongoing with neo/adjuvant ICI with or without chemotherapy

Trial Name	Registration Number	Phase	Stage	N	Study Arm	Control Arm	Primary Objective	Estimated Completion Date
KEYNOTE-671 [32]	NCT03425643	3	IIB-IIIA	786	CT (CG or CP) + pembrolizumab 200 mg IV every 3 weeks, 4 cycles—pembrolizumab 200 mg IV every 3 weeks postoperatively	CT + placebo - and postoperative placebo	DFS, OS	2024
CheckMate 816 [33]	NCT02998528	3	IB-IIIA	350	CT + nivolumab 360 mg IV every 3 weeks, 3 cycles	CT, 3 cycles	DFS, pCR	2020
IMpower 030 [34]	NCT03456063	3	II-IIIA-IIIB (T3N2)	374	CT + atezolizumab 1200mg IV every 3 weeks, 4 cycles - Atezolizumab 1200 mg IV every 3 weeks postoperatively	CT + placebo - and postoperative placebo	MPR	2024
Checkmate 77T	NCT04025879	3	II-IIIB	452	CT + nivolumab 360 mg IV every 3 weeks, 4 cycles - nivolumab 480 mg IV every 4 weeks for one year postoperatively	CT + placebo - and postoperative placebo	DFS	2023
AEGEAN	NCT03800134	3	IIA-IIIA-IIIB (N2)	300	CT + Durvalumab 1500 mg IV every 3 weeks, 4 cycles -Durvalumab 1500 mg IV every 4 weeks, 12 cycles	CT + placebo - and postoperative placebo	MPR	2024
SAKK 16/14	NCT02572843	2	IIIA (N2)	68	CT, 2 cycles—Durvalumab 750 mg, 2 cycles—durvalumab 750 mg for 1 year		DFS	2021
NADIM 2	NCT03838159	2	IIIA-IIIB	90	CT + nivolumab 360 mg IV every 3 weeks, 3 cycles—nivolumab 480 mg IV every 4 weeks for 6 months postoperatively	CT	pCR	2022

Role in adjuvant settings

Ongoing clinical trials with adjuvant ICIs

Name	Trial Registration Number	Phase	Stage	N	Study Arm	Control Arm	Primary Objective	Trial Completion Date
PEARLS/ KEYNOTE-091	NCT02504372	3	IB (≥4 cm)-IIIA	1080	Pembrolizumab 200 mg IV every 3 weeks for one year	Placebo, one year	DFS	2024
BR31/LINC	NCT02273375	3	IB (≥4 cm)-IIIA	1360	Durvalumab 10 mg/kg IV every 2 weeks for 6 months 20 mg/kg IV every 4 weeks for 6 months	Placebo, one year	DFS PD-L1+ DFS global	2024
ANVIL	NCT02595944	3	IB (≥4 cm)-IIIA	903	Nivolumab 240 mg IV every 2 weeks for 1 year	Observation	DFS OS	2024
IMpower 010	NCT02486718	3	IB (≥4 cm)-IIIA	1280	Atezolizumab 1200 mg IV every 3 weeks for one year	Observation	DFS II-IIIA DFS II-IIIA PD-L1+ DFS ITT	2027
CANOPY-A	NCT03447769		II-IIIA, IIIB (T > 5 cm and N2)	1500	Canakinumab 200 mg sc every 3 weeks for year	Placebo, one year	DFS	2027

ICI: immune checkpoint inhibitor; IV: intravenous; SC, subcutaneous; DFS: disease-free survival; OS: overall

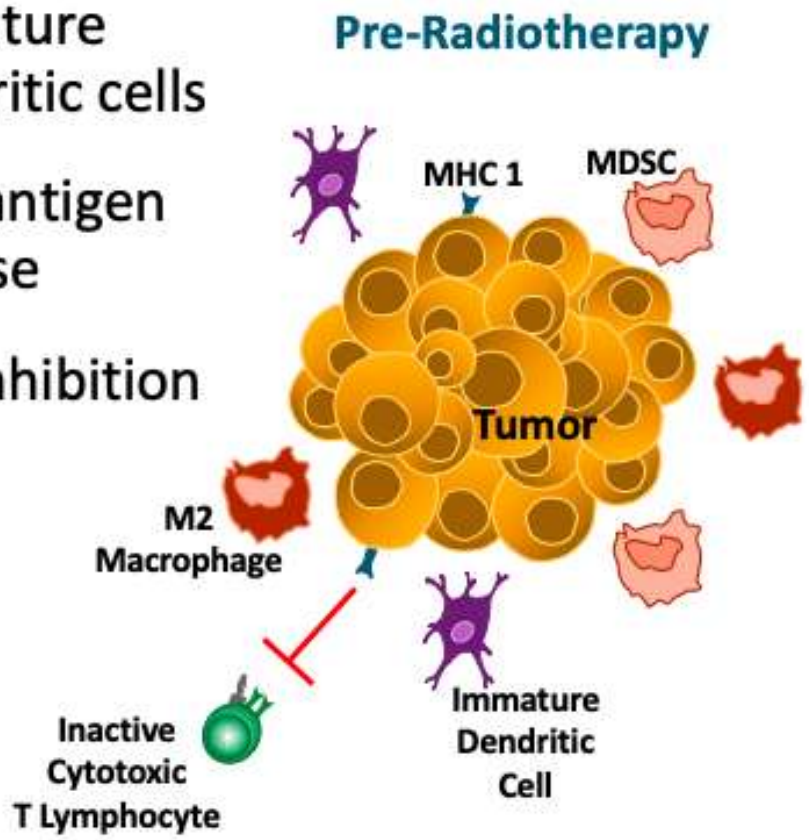
Role of SBRT and ICIs

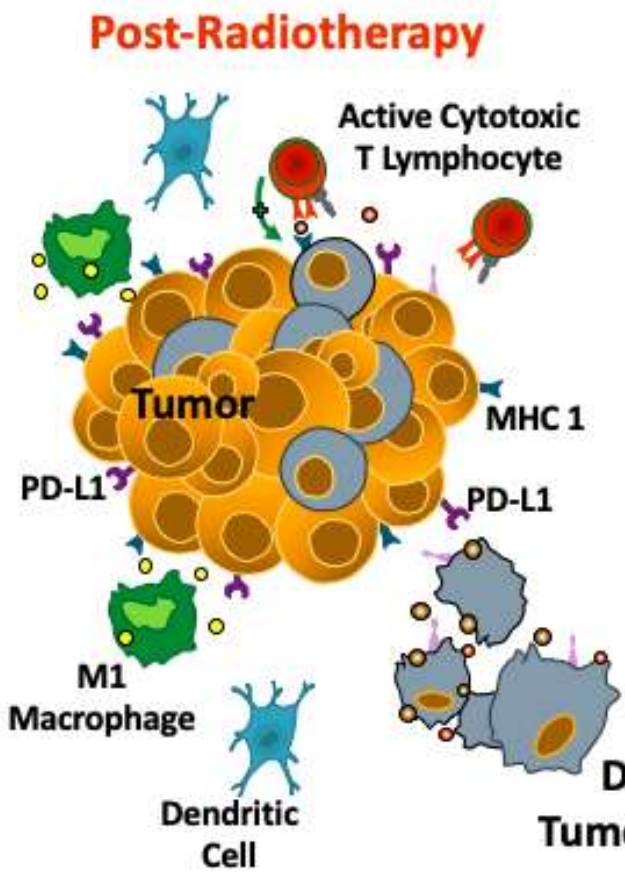
Role of SBRT and ICIs

- Most patients with ES-NSCLC who are candidates for SBRT (but not surgery) cannot safely receive CT
- combination of adjuvant CT plus SBRT has not shown positive results in frail patients with ES-NSCLC who have multiple underlying pathologies
- Combination of immunotherapy—which is generally better tolerated than CT
- SBRT+ICI evaluated primarily in patients with metastatic disease, with promising clinical result
- SBRT + immunotherapy offers synergistic benefits

RT immune modulatory effects

- Immature dendritic cells
- Less antigen release
- CTL inhibition





- Primed dendritic cells
- Increased antigen release
- Upregulation of PD-L1
- Upregulation of immunogenic cell surface markers

Study Name	Study Type	Type of Patients	Treatment	Primary Objective	Secondary Objectives	Current Status
SWOG S1914 NCT04214262	Phase 3 clinical trial (Sponsor: National Cancer Institute (NCI)	Stages I-IIA NSCLC	-ARM 1: Atezolizumab 8 cycles every 21 days. SBRT (3–5 fr) with cycle 3 of atezolizumab -ARM 2: SBRT (3–5 fr) at 21 days post- randomisation without atezolizumab	- OS	-SLP -Adverse effects	Recruiting
PACIFIC-4/ RTOG-3515 NCT03833154	Phase 3 multicentre, double-blind clinical trial (Sponsor: Astra Zeneca)	NSCLC stages I-II with negative nodes	-ARM 1: Durvalumab 1500 mg every 4 weeks up to 24 months of treatment or progression. SBRT (from 3–8 fr) ARM 2: Placebo an SBRT (from 3–8 fr)	-DFS	-OS -Lung cancer-specific mortality -Others	Recruiting
ASTEROID NCT03446547	Phase 2 multicentre, randomised clinical trial (Sponsor: Vastra Gotaland Region)	NSCLCT1-2N0M0	-Arm 1: SBRT (3–4 fr) -Arm 2: SBRT (3–4 fr) followed by durvalumab 1500 mg every 4 weeks 12 months	-TTP	-OS -Control local	Recruiting

Study Name	Study Type	Type of Patients	Treatment	Primary Objective	Secondary Objectives	Current Status
STILE NCT03383302	Phase 2, single arm, multicentric trial (Sponsor: Royal Marsden NHS Foundation Trust)	Stages I-II NSCLC	- SBRT (54 Gy in 3 fr of 18 Gy or 55 Gy in 5 fr of 11Gy) - Sequential nivolumab, 1 year	-Evaluation of lung toxicity	- Other toxicities -Local relapse rates, OS, DFS	Recruiting
NCT03110978	Phase 2, single arm trial (Sponsor: M.D. Anderson Cancer Center)	Stage I-IIA NSCLC	-SBRT (50 Gy in 4 fr or 70 Gy in 10 fr) -Nivolumab 12 weeks, started with 1st fraction of SBRT	-DFS	-OS -Adverse events -Analysis of immunological markers	Recruiting
NCT03446911	Randomised clinical trial (Sponsor: VU University Medical Center)	Stage I NSCLC	-ARM 1: SBRT with 2 cycles of pembrolizumab started on the 1st day of RT followed by lobectomy -ARM 2: SBRT without pembrolizumab followed by lobectomy	-Incidence and severity of adverse effects	-Expression of PD-1, PDL-1, CD4, among others	Unknown
NCT02444741	Randomised phase 1/2 clinical trial (Sponsor: M.D. Anderson Cancer Center)	NSCLC: early and advanced stages	Distinct groups included with varying combinations between pembrolizumab, SBRT or hypofractionated RT Pembrolizumab is started before SBRT (4 fr) or hypofractionated RT (15 fr). It is administered every 21 days until reach a maximum of 16 cycles	-Response rate and determination of radiological response -Toxicity Maximum tolerate dose of pembrolizumab	-DFS -OS	Recruiting

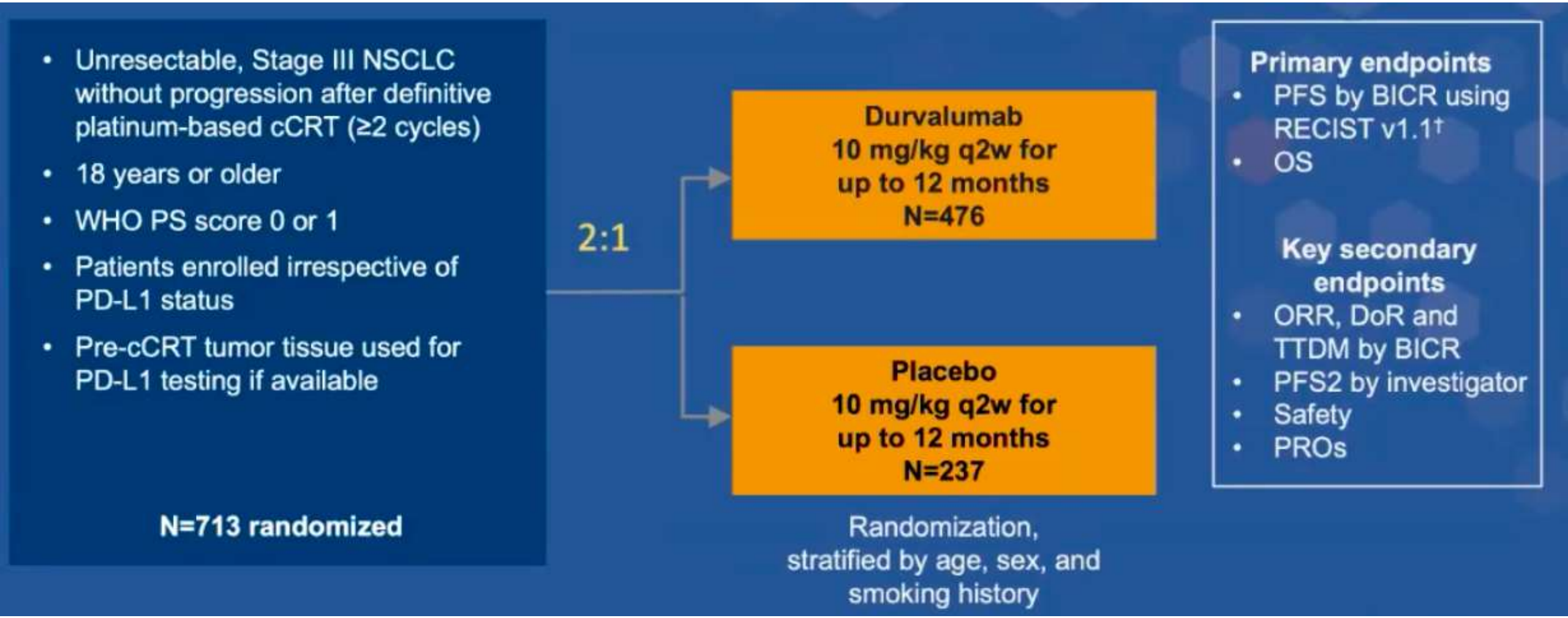
Unresectable Stage III NSCLC

Unresectable Stage III NSCLC

- One-third of NSCLC patients have stage III disease at diagnosis
- Standard of care (SoC) is concurrent platinum-based CT+RT
- OS remains poor, with a median OS ranging from 20 to 26 months and 3- and 5-year OS of 30% and 15%, respectively
- Novel strategies employed to date—such as adding induction or consolidation CT, the incorporation of EGFR inhibitors, or higher dose RT—have been shown to improve the OS versus SoC

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit,



Characteristic	Durvalumab (N = 476)	Placebo (N = 237)	Total (N = 713)
Age — yr			
Median	64	64	64
Range	31–84	23–90	23–90
Sex — no. (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race — no. (%)†			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Disease stage — no. (%)			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)
WHO performance-status score — no. (%)§			
0	234 (49.2)	114 (48.1)	348 (48.8)
1	240 (50.4)	122 (51.5)	362 (50.8)
Tumor histologic type — no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Nonsquamous	252 (52.9)	135 (57.0)	387 (54.3)

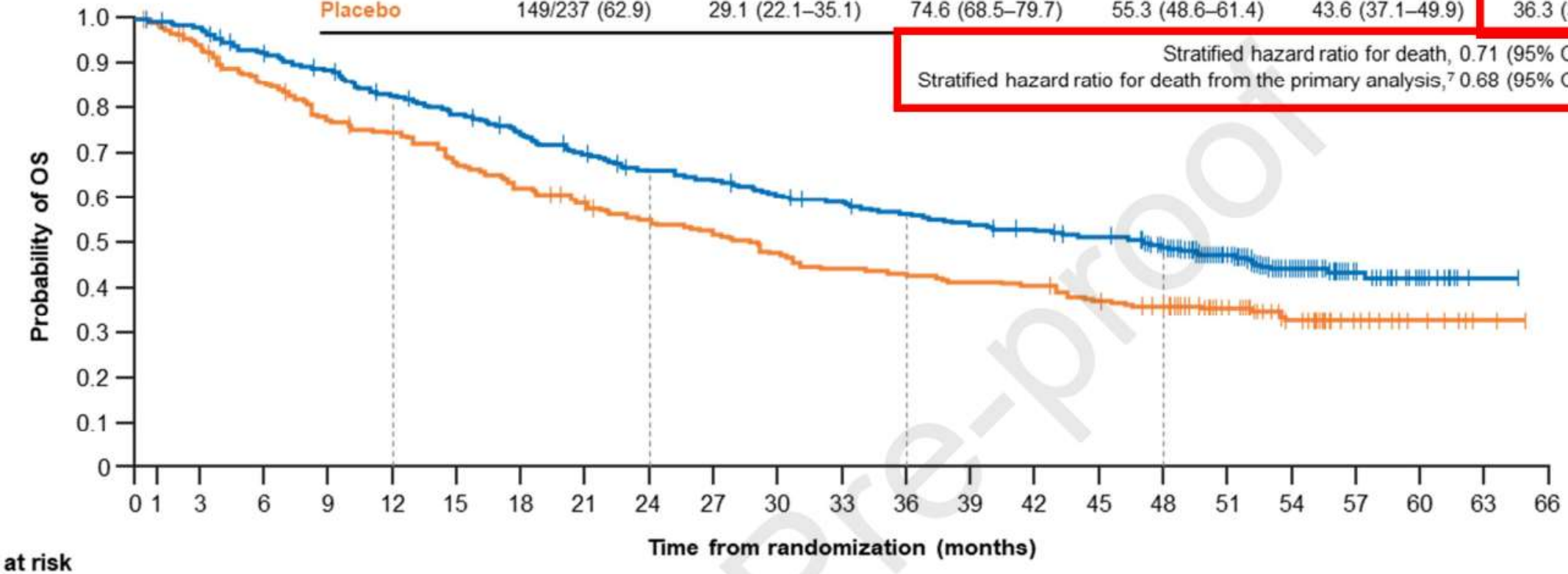
Characteristic	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Tumor histologic type — no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Nonsquamous	252 (52.9)	135 (57.0)	387 (54.3)
Smoking status — no. (%)			
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
Previous radiotherapy — no. (%)¶			
<54 Gy	3 (0.6)	0	3 (0.4)
≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
Previous chemotherapy — no. (%)‖			
Induction	123 (25.8)	68 (28.7)	191 (26.8)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)
Best response to previous chemoradiotherapy — no. (%)			
Complete response	9 (1.9)	7 (3.0)	16 (2.2)
Partial response	232 (48.7)	111 (46.8)	343 (48.1)
Stable disease	222 (46.6)	114 (48.1)	336 (47.1)

Updated OS-PACIFIC 4-year survival update

- 29% reduction in the risk of death
- Median OS-47.5 Vs 29.1 months

	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified hazard ratio for death, 0.71 (95% CI, 0.57–0.88)
Stratified hazard ratio for death from the primary analysis,[7] 0.68 (95% CI, 0.53–0.87)



No. at risk

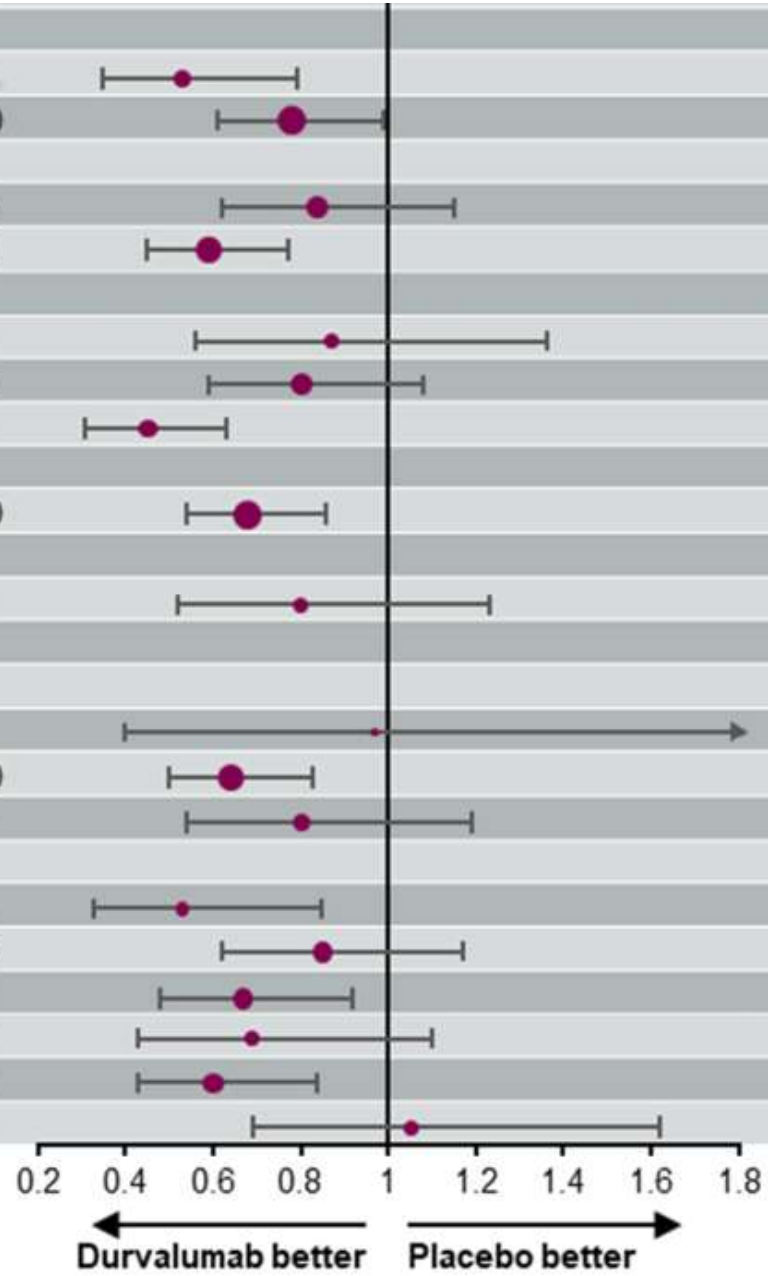
Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

Pre-proof

	No. of events / No. of patients (%)		Unstratified hazard ratio (95% CI)
	Durvalumab	Placebo	
All patients	247/476 (51.9%)	149/237 (62.9%)	0.70 (0.57–0.86)
Sex			
Male	183/334 (54.8%)	107/166 (64.5%)	0.75 (0.59–0.96)
Female	64/142 (45.1%)	42/71 (59.2%)	0.59 (0.40–0.87)
Age at randomization			
<65 years	120/261 (46.0%)	75/130 (57.7%)	0.64 (0.48–0.86)
≥65 years	127/215 (59.1%)	74/107 (69.2%)	0.77 (0.58–1.03)
Smoking status			
Smoker	227/433 (52.4%)	134/216 (62.0%)	0.73 (0.59–0.91)
Non-smoker	20/43 (46.5%)	15/21 (71.4%)	0.42 (0.21–0.82)
NSCLC disease stage			
Stage IIIA	129/252 (51.2%)	87/125 (69.6%)	0.61 (0.47–0.81)
Stage IIIB	111/212 (52.4%)	59/107 (55.1%)	0.81 (0.59–1.12)
Tumor histologic type			
Squamous histology	128/224 (57.1%)	64/102 (62.7%)	0.79 (0.59–1.07)
All other histology	119/252 (47.2%)	85/135 (63.0%)	0.61 (0.46–0.81)
Best response to prior treatment			
Complete response	5/9 (55.6%)	3/7 (42.9%)	Not calculated*
Partial response	112/237 (47.3%)	65/112 (58.0%)	0.70 (0.52–0.96)
Stable disease	125/223 (56.1%)	78/115 (67.8%)	0.68 (0.51–0.90)
Type of prior chemotherapy			
Gemcitabine-based	5/9 (55.6%)	2/5 (40.0%)	Not calculated*
Non-gemcitabine-based	242/467 (51.8%)	147/232 (63.4%)	0.69 (0.56–0.84)
Cisplatin	125/266 (47.0%)	78/129 (60.5%)	0.64 (0.48–0.84)
Carboplatin	113/199 (56.8%)	66/102 (64.7%)	0.80 (0.59–1.08)
Cisplatin and carboplatin	6/8 (75.0%)	4/5 (80.0%)	Not calculated*

Preproof

	No. of events / No. of patients (%)		Unstratified hazard ratio (95% CI)
	Durvalumab	Placebo	
Last radiation to randomization			
<14 days	59/120 (49.2%)	41/62 (66.1%)	0.53 (0.35–0.79)
≥14 days	188/356 (52.8%)	108/175 (61.7%)	0.78 (0.61–0.99)
WHO performance status			
Normal	114/234 (48.7%)	61/114 (53.5%)	0.84 (0.62–1.15)
Restricted	133/242 (55.0%)	88/123 (71.5%)	0.59 (0.45–0.77)
Region			
Asia	52/109 (47.7%)	32/68 (47.1%)	0.87 (0.56–1.36)
Europe	116/217 (53.5%)	63/102 (61.8%)	0.80 (0.59–1.08)
North and South America	79/150 (52.7%)	54/67 (80.6%)	0.45 (0.31–0.63)
Race			
White	185/337 (54.9%)	109/157 (69.4%)	0.68 (0.54–0.86)
Black/African-American	5/12 (41.7%)	2/2 (100.0%)	Not calculated*
Asian	54/120 (45.0%)	34/72 (47.2%)	0.80 (0.52–1.23)
Other	3/6 (50.0%)	4/6 (66.7%)	Not calculated*
***EGFR* mutation**			
Positive	17/29 (58.6%)	7/14 (50.0%)	0.97 (0.40–2.33)
Negative	156/317 (49.2%)	105/165 (63.6%)	0.64 (0.50–0.83)
Unknown	74/130 (56.9%)	37/58 (63.8%)	0.80 (0.54–1.19)
PD-L1 status			
≥25%	50/115 (43.5%)	26/44 (59.1%)	0.53 (0.33–0.85)
<25%	102/187 (54.5%)	62/105 (59.0%)	0.85 (0.62–1.17)
Unknown	95/174 (54.6%)	61/88 (69.3%)	0.67 (0.48–0.92)
1–24% (posthoc analysis)	47/97 (48.5%)	28/47 (59.6%)	0.69 (0.43–1.10)
≥1% (posthoc analysis)	97/212 (45.8%)	54/91 (59.3%)	0.60 (0.43–0.84)
<1% (posthoc analysis)	55/90 (61.1%)	34/58 (58.6%)	1.05 (0.69–1.62)

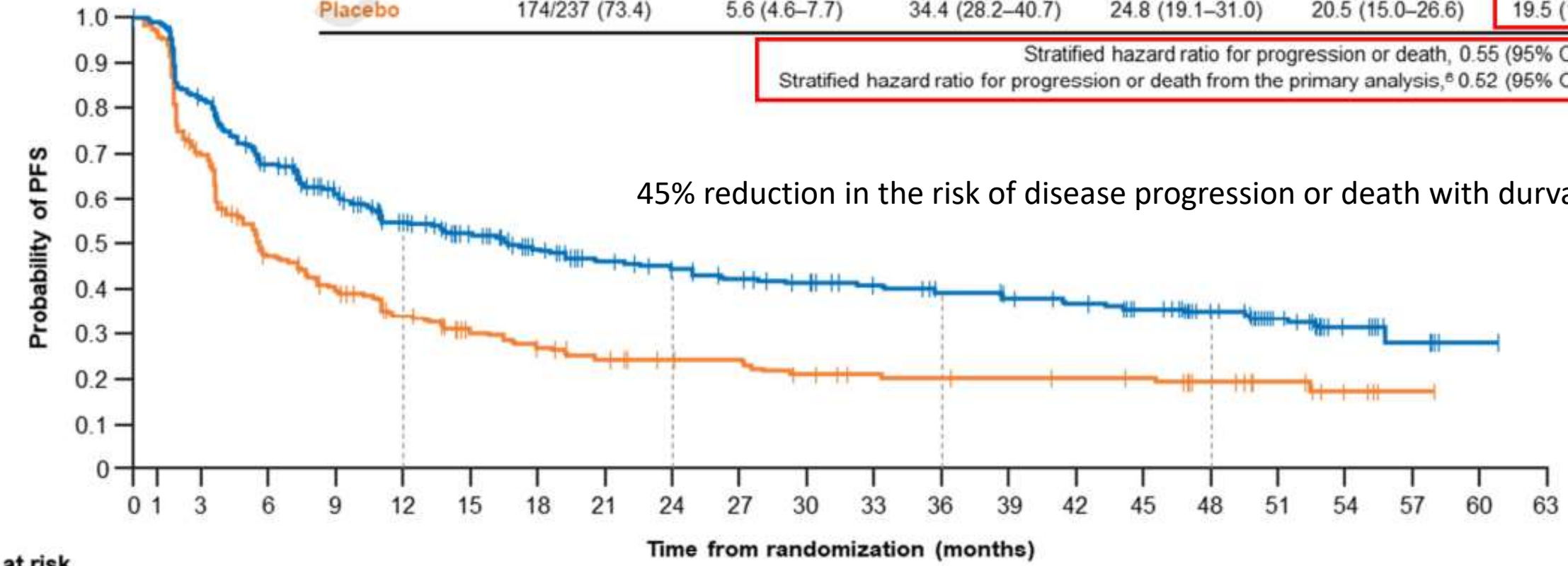


Journal Pre

Updated PFS-PACIFIC 4-year survival update

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-month PFS rate (95% CI) %	24-month PFS rate (95% CI) %	36-month PFS rate (95% CI) %	48-month PFS rate (95% CI) %
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)	44.8 (39.8–49.6)	39.8 (34.8–44.8)	35.3 (30.3–40.4)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)	24.8 (19.1–31.0)	20.5 (15.0–26.6)	19.5 (14.1–25.7)

Stratified hazard ratio for progression or death, 0.55 (95% CI, 0.44–0.67)
Stratified hazard ratio for progression or death from the primary analysis,[6] 0.52 (95% CI, 0.42–0.65)



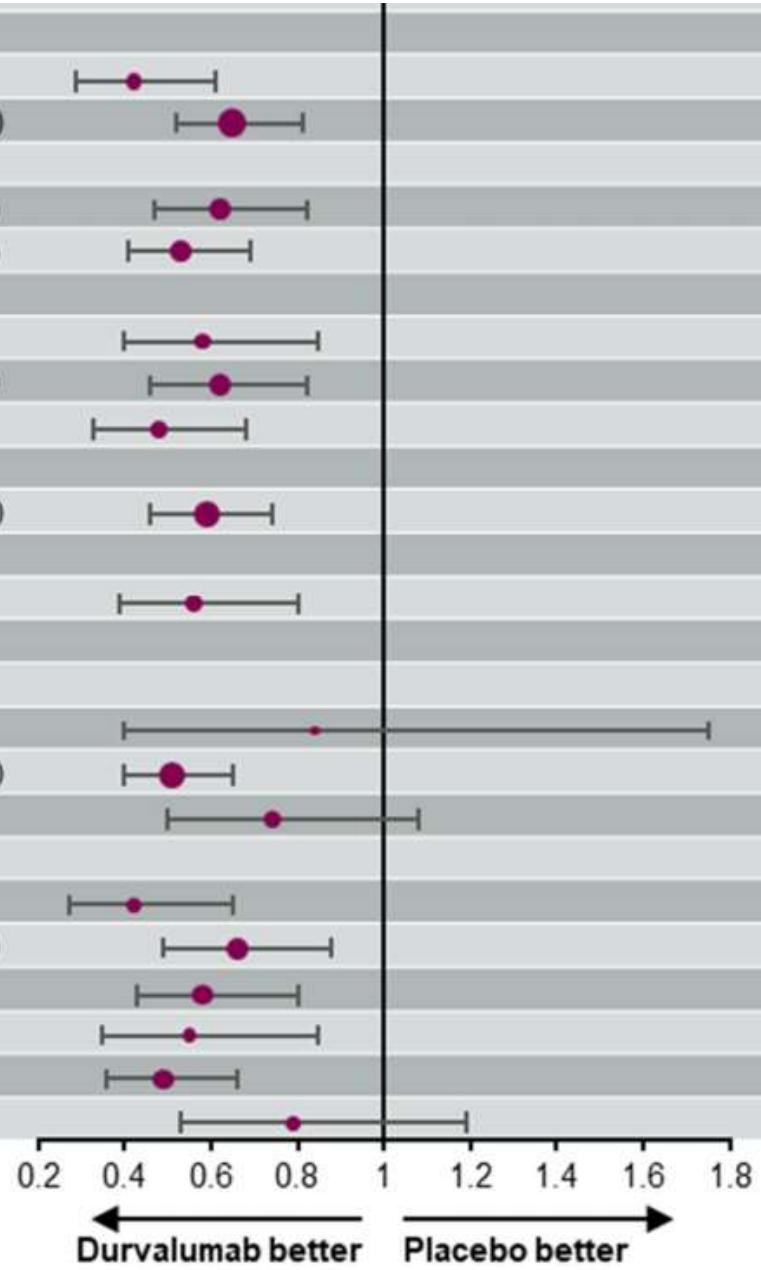
45% reduction in the risk of disease progression or death with durvalumab

No. at risk																					
Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

	No. of events / No. of patients (%)		Unstratified hazard ratio (95% CI)
	Durvalumab	Placebo	
All patients	266/476 (55.9%)	174/237 (73.4%)	0.58 (0.48–0.70)
Sex			
Male	192/334 (57.5%)	121/166 (72.9%)	0.60 (0.48–0.76)
Female	74/142 (52.1%)	53/71 (74.6%)	0.52 (0.36–0.74)
Age at randomization			
<65 years	137/261 (52.5%)	98/130 (75.4%)	0.47 (0.36–0.61)
≥65 years	129/215 (60.0%)	76/107 (71.0%)	0.75 (0.56–0.99)
Smoking status			
Smoker	244/433 (56.4%)	157/216 (72.7%)	0.61 (0.50–0.74)
Non-smoker	22/43 (51.2%)	17/21 (81.0%)	0.33 (0.17–0.63)
NSCLC disease stage			
Stage IIIA	130/252 (51.6%)	93/125 (74.4%)	0.53 (0.41–0.69)
Stage IIIB	130/212 (61.3%)	78/107 (72.9%)	0.62 (0.47–0.83)
Tumor histologic type			
Squamous histology	138/224 (61.6%)	74/102 (72.5%)	0.69 (0.52–0.92)
All other histology	128/252 (50.8%)	100/135 (74.1%)	0.49 (0.37–0.63)
Best response to prior treatment			
Complete response	5/9 (55.6%)	4/7 (57.1%)	Not calculated*
Partial response	126/237 (53.2%)	85/112 (75.9%)	0.56 (0.42–0.74)
Stable disease	131/223 (58.7%)	83/115 (72.2%)	0.57 (0.43–0.76)
Type of prior chemotherapy			
Gemcitabine-based	4/9 (44.4%)	3/5 (60.0%)	Not calculated*
Non-gemcitabine-based	262/467 (56.1%)	171/232 (73.7%)	0.58 (0.48–0.70)
Cisplatin	144/266 (54.1%)	94/129 (72.9%)	0.53 (0.41–0.69)
Carboplatin	114/199 (57.3%)	75/102 (73.5%)	0.63 (0.47–0.85)
Cisplatin and carboplatin	5/8 (62.5%)	4/5 (80.0%)	Not calculated*

Preproof

	No. of events / No. of patients (%)		Unstratified hazard ratio (95% CI)
	Durvalumab	Placebo	
Last radiation to randomization			
<14 days	60/120 (50.0%)	49/62 (79.0%)	0.42 (0.29–0.61)
≥14 days	206/356 (57.9%)	125/175 (71.4%)	0.65 (0.52–0.81)
WHO performance status			
Normal	128/234 (54.7%)	81/114 (71.1%)	0.62 (0.47–0.82)
Restricted	138/242 (57.0%)	93/123 (75.6%)	0.53 (0.41–0.69)
Region			
Asia	60/109 (55.0%)	49/68 (72.1)	0.58 (0.40–0.85)
Europe	129/217 (59.4%)	75/102 (73.5%)	0.62 (0.46–0.82)
North and South America	77/150 (51.3%)	50/67 (74.6%)	0.48 (0.33–0.68)
Race			
White	192/337 (57.0%)	115/157 (73.2%)	0.59 (0.46–0.74)
Black/African-American	6/12 (50.0%)	2/2 (100.0%)	Not calculated*
Asian	64/120 (53.3%)	52/72 (72.2%)	0.56 (0.39–0.80)
Other	3/6 (50.0%)	5/6 (83.3%)	Not calculated*
***EGFR* mutation**			
Positive	21/29 (72.4%)	11/14 (78.6%)	0.84 (0.40–1.75)
Negative	167/317 (52.7%)	123/165 (74.5%)	0.51 (0.40–0.65)
Unknown	78/130 (60.0%)	40/58 (69.0%)	0.74 (0.50–1.08)
PD-L1 status			
≥25%	59/115 (51.3%)	33/44 (75.0%)	0.42 (0.27–0.65)
<25%	106/187 (56.7%)	75/105 (71.4%)	0.66 (0.49–0.88)
Unknown	101/174 (58.0%)	66/88 (75.0%)	0.58 (0.43–0.80)
1–24% (post-hoc analysis)	51/97 (52.6)	34/47 (72.3%)	0.55 (0.35–0.85)
≥1% (post-hoc analysis)	110/212 (51.9%)	67/91 (73.6%)	0.49 (0.36–0.66)
<1% (post-hoc analysis)	55/90 (61.1%)	41/58 (70.7%)	0.79 (0.53–1.19)



Journal

Incidence of New Lesions

New Lesion Site	Durvalumab Group (N=476)	Placebo Group (N=237)
	no. of patients (%)	
Any site	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal gland	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Results

- Most common adverse event of grade 3 or 4 was pneumonia (4.4% and 3.8%, respectively).
- 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued because of adverse events

Conclusion

- Progression-free survival was significantly longer with durvalumab than with placebo
- Secondary end points also favored durvalumab, and safety was similar between the groups

CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- **Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]**
- **Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m^2[†,§]**
- **Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]**
- **Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]**

Preferred (squamous)

- **Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]**
- **Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]**

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After 2 or More Cycles of Definitive Concurrent Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8]
(category 1 for stage III; category 2A for stage II)

A Phase 2 Trial of Consolidation Pembrolizumab Following Concurrent Chemoradiation for Patients With Unresectable Stage III Non–Small Cell Lung Cancer: Hoosier Cancer Research Network LUN 14-179

Greg A. Durm, MD [1]; Salma K. Jabbour, MD[2]; Sandra K. Althouse, MS[3]; Ziyue Liu, PhD[3]; Ahad A. Sadiq, MD[4];

tion in patients with unresectable stage III disease. **METHODS:** Patients with unresectable stage III NSCLC received concurrent chemo-radiation with cisplatin and etoposide, cisplatin and pemetrexed, or carboplatin and paclitaxel and 59.4 to 66.6 Gy of radiation. Patients with nonprogression of disease were enrolled and received pembrolizumab (200 mg intravenously every 3 weeks for up to 12 months). The primary endpoint was the time to metastatic disease or death (TMDD). Secondary endpoints included progression-free survival (PFS) and OS. **RESULTS:** The median follow-up for 93 patients (92 for efficacy) was 32.2 months (range, 1.2-46.6 months). The median

Base line charecters

Characteristic	Value
Age, y	
Mean (SD)	64.4 (8.6)
Median (range)	66.0 (45.0-84.0)
Sex, No. (%)	
Female	33 (36)
Male	59 (64)
Race, No. (%)	
White	84 (91.3)
Black or African American	3 (3.3)
Asian	4 (4.3)
Unknown	1 (1.1)
Disease stage, No. (%)	
IIIA	55 (60)
IIIB	37 (40)
Tumor histology type, No. (%)	
Squamous	41 (45)
Nonsquamous	51 (55)
Smoking status, No. (%)	
Current smoker	16 (17.4)
Former smoker	71 (77.2)
Never smoker	5 (5.4)
Prior radiation dose	
Mean (SD)	61.0 (6.2)
Median (range)	60.0 (6.6-66.6)
Prior chemotherapy received, No. (%)	
Cisplatin with etoposide	24 (26)
Carboplatin with paclitaxel	65 (71)
Cisplatin with pemetrexed	2 (2)
Carboplatin with paclitaxel and carboplatin with pemetrexed	1 (1)
PD-L1 status (n = 53), No. (%)[a]	
Negative	11 (20.8)
1%-49%	11 (20.8)
≥50%	31 (58.5)

Efficacy Endpoints

Endpoint	Value
Follow-up, median (range), mo	32.2 (1.2-46.6)
Time to metastatic disease or death	
Median (95% CI), mo	30.7 (18.7 to NR)
12 mo, %	77.6
18 mo, %	61.8
24 mo, %	55.3
36 mo, %	49.9
Progression-free survival	
Median (95% CI), mo	18.7 (12.4 to 33.8)
12 mo, %	61.2
18 mo, %	50.3
24 mo, %	46.3
36 mo, %	37.4
Overall survival	
Median (95% CI), mo	35.8 (24.2 to NR)
12 mo, %	81.1
18 mo, %	65.8
24 mo, %	62.0
36 mo, %	48.5

Outcomes by Variable

Variable	Comparison[a]	TMDD Hazard Ratio (95% CI)	TMDD *P*	PFS Hazard Ratio (95% CI)	PFS *P*	OS Hazard Ratio (95% CI)	OS *P*
Smoking status	Current vs former	1.11 (0.51-2.41)	.86	1.11 (0.55-2.23)	.90	1.17 (0.54-2.54)	.79
	Current vs never	1.53 (0.32-7.26)		1.35 (0.37-4.92)		1.70 (0.36-8.06)	
	Former vs never	1.38 (0.33-5.80)		1.21 (0.37-3.94)		1.46 (0.35-6.11)	
PD-L1 status (n = 53)[b]	Negative vs positive	0.96 (0.33-2.82)	.94	0.84 (0.34-2.04)	.70	0.79 (0.27-2.31)	.66
Type of chemotherapy	Carboplatin with paclitaxel vs cisplatin with etoposide	1.23 (0.60-2.51)	.57	1.53 (0.78-2.99)	.21	1.21 (0.59-2.46)	.61
ECOG	0 vs 1	0.79 (0.42-1.47)	.46	0.79 (0.45-1.38)	.40	0.69 (0.37-1.31)	.26
Time between radiation and pembrolizumab	4-6 vs 6-8 wk	1.01 (0.45-2.27)	.99	0.96 (0.45-2.05)	.92	1.11 (0.49-2.50)	.81

TABLE 4. Adverse Events Occurring in ≥10% of Patients (n = 93)[a]

Adverse Event	Any Grade, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Fatigue	44 (47.3)	16 (17.2)	4 (4.3)	0 (0.0)
Cough	24 (25.8)	16 (17.2)	1 (1.1)	0 (0.0)
Dyspnea	20 (21.5)	10 (10.8)	5 (5.4)	0 (0.0)
Anorexia	16 (17.2)	3 (3.2)	1 (1.1)	0 (0.0)
Arthralgia	15 (16.1)	8 (8.6)	1 (1.1)	0 (0.0)
Diarrhea	15 (16.1)	3 (3.2)	4 (4.3)	0 (0.0)
Rash	14 (15.1)	3 (3.2)	1 (1.1)	0 (0.0)
Nausea	13 (14.0)	3 (3.2)	1 (1.1)	0 (0.0)
Hypothyroidism	12 (12.9)	10 (10.8)	0 (0.0)	0 (0.0)
Pruritus	11 (11.8)	3 (3.2)	0 (0.0)	0 (0.0)

[a]Excluding pneumonitis (reported in Table 5).

TABLE 5. Potential Immune-Related Toxicities (n = 93)

Adverse Event	Any Grade, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Pneumonitis[a]	NR	10 (10.8)	4 (4.3)	1 (1.1)
Colitis	3 (3.2)	2 (2.2)	0 (0.0)	1 (1.1)
Increased creatinine	5 (5.4)	1 (1.1)	0 (0.0)	0 (0.0)
Elevated AST	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated ALT	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthyroidism	7 (7.5)	2 (2.2)	0 (0.0)	0 (0.0)
Hypothyroidism	12 (12.9)	10 (10.8)	0 (0.0)	0 (0.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported.
[a]Grade 1 pneumonitis was not recorded. One patient had grade 5 pneumonitis.

Phase II study of pembrolizumab (pembro) plus platinum doublet chemotherapy and radiotherapy as first-line therapy for unresectable, locally advanced stage III NSCLC: KEYNOTE-799

Phase 2, nonrandomized, open-label trial

Previously untreated, unresectable, pathologically confirmed stage IIIA–C NSCLC with measurable disease

Cohort A
17 cycles of pembro 200 mg Q3W starting with cycle 1 plus standard thoracic radiotherapy (60 Gy in 30 daily 2-Gy fractions) in cycles 2–3 and investigator's choice of paclitaxel 200 mg/m^2 + carboplatin AUC 6 Q3W for cycle 1, then paclitaxel 45 mg/m^2 + carboplatin AUC 2 QW for cycles 2–3

Cohort B
cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W (nonsquamous only) in cycles 1–3

- Primary endpoints were ORR by blinded independent central review
- Rate of grade ≥3 pneumonitis

Results

- 112 and 73 pts have been enrolled in cohorts A and B
- 63 in cohort A and 52 in cohort B continue on treatment
- Median (range) follow up was 8.3 (0.7–14.0) mo in cohort A and 5.8 (0.2–13.7) mo in cohort B

	Cohort A* N=112	Cohort B* N=53
ORR, % (90% CI)	67.0 (58.9–74.3)	56.6 (44.4–68.2)
Median (range) duration of response, mo	NR (1.6+ to 10.5+)	NR (1.7+ to 10.5+)
DOR ≥ 6 mo,† %	91.1	100
6-mo PFS rate,† %	81.4	85.2
6-mo OS rate,† %	87.2	94.8

Results and conclusion

- Grade ≥3 pneumonitis occurred in 9 pts (8.0%; 90% CI, 4.3%–13.6%) in cohort A and 4 pts (5.5%; 90% CI, 1.9%–12.1%) in cohort B
- Treatment-related grade ≥3 AEs occurred in 72 pts (64.3%) in cohort A and 30 pts (41.1%) in cohort B
- 4 pts had treatment-related grade 5 pneumonitis (all in cohort A)
- Need RCT

Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial

single-arm phase II trial in stage III NSCLC

Patients (pts) received 3 cycles of platinum-based chemotherapy and concurrent RT (66Gy/33fractions)

Nivolumab started concurrently with CRT (360mg, Q3W) and subsequently continued as monotherapy consolidation (480mg, Q4W)

Primary efficacy endpoint is the 1-year (1y) progression-free survival (PFS) rate

Results

- PFS is evaluated in 79 pts assigned to concurrent treatment
- Median follow-up is 16.4 months
- Majority of pts are male (67%), former smokers (68%), of median age 62 years
- 64% present with stage IIIb
- 1y PFS rate is 54% (95% CI: 41-65%), with median PFS 12.4 m (95% CI: 9, Not estimable)

Results

- 1y overall survival (OS) rate is 79% (95% CI: 68-87%) while median OS is not reached yet.
- Most frequent adverse events (AEs) were anaemia, fatigue and pneumonitis
- Need RCT

Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced NSCLC

trial called DETERRED combining atezolizumab (atezo) with cCRT followed by consolidation full dose carboplatin/paclitaxel (CP) with atezo (CP-atezo) for 2 cycles and then maintenance atezo for 1 year. The primary endpoint was safety/toxicity and feasibility. **Methods:** This study enrolled patients (pts) between February 2016 - April 2018 and was done in two parts: In part 1 (N=10), conventionally fractionated CRT (60-66 Gy in 30-33 fractions combined with weekly low dose CP) was followed by CP-atezo then maintenance atezo. Part 2 was cCRT (N=30) with atezo followed by CP-atezo then maintenance atezo. Atezo was given at 1200 mg IV Q3 weeks. Severe adverse events (SAEs) ≥ grade 3 were defined by CTCAE v5.0. Evaluable pts received at least one dose of atezo. PD-L1 staining utilizes the DAKO 22C3 platform. Kaplan Meier were analyzed for progression free survival (PFS) and overall survival (OS), and chi-square test

Results

Part 1, atezo related SAEs were seen in 4 pts (40%) (2 grade 3 arthralgia, 1 grade 3 dyspnea and 1 grade 5 TE fistula). Grade 2 radiation pneumonitis (RP) was seen in 1 pt. In Part 2, seven (23%) pts had atezo related SAEs (diarrhea, nephritis, dyspnea, fatigue and heart failure). RP was seen in 3 pts, 2 grade 2 and 1 grade 3, which led to atezo discontinuation. In Part 1, with an overall median follow up (f/u) time of 22.5 months and 27.4 months for survivors, the 1-year PFS is 50%, and OS is 79%. In part 2, with a median f/u time of 11.8 months and 13.7 months for survivors, the 1-year PFS was 57%, and OS is 79%. Baseline tumor biopsy PD-L1 status was evaluable for 34 pts. There were no significant differences in cancer recurrence for PD-L1 <1% (7/16=44%) vs ≥1% (6/18=33%), or for the PD-L1 cutoff of <50% (11/26=42%) vs ≥50% (2/8=25%). **Conclusions:** Concurrent atezo with CRT followed by CP-atezo and maintenance atezo is safe without increased toxicities compared to CRT alone followed by CP-atezo and maintenance atezo. Updated efficacy results from DETERRED will be presented.

Summary of the efficacy of immune checkpoint inhibitors in stage III NSCLC

Trial	Schedule	N	PFS	OS
PACIFIC [63,65],	CRT Durvalumab	713	17.2 m	3-y OS: 55% 4-y OS: 49.6% mOS: 47.5 m
LUN 14-179 [72]	CRT + P P	92	18.7 m.	3-y OS: 49% mOS: 36 m
KEYNOTE 799 [73]	CT CRT + P P	165	6-m PFS: 80%	
NICOLAS [75,76]	CRT+N N	79	12.4 m	1-y OS: 79%
DETERRED [74]	CRT CT + A A	10	18.6 m	22.8 m
	A + CRTCT + A A	30	13.2 m	NR

In SCLC

STIMULI: A randomised open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after standard of care chemo-radiotherapy conducted by ETOP and IFCT

Trial design: STIMULI is an open-label, randomised, two-arm, phase II clinical trial. Inclusion is restricted to stage I-IIIB untreated LD-SCLC patients (pts) with adequate organ and pulmonary function, and no history of auto-immune disease. Hyper- or conventionally fractionated chest RT is administered concomitantly to 4 cycles of Cis-/carboplatin plus etoposide, followed by PCI. After completion of this standard treatment, non-progressing pts are randomised 1:1 to consolidation (induction and maintenance) or observation. Induction consists of four 3-week cycles of ipilimumab 3mg/kg plus nivolumab 1mg/kg, and is followed by maximally 12 months of nivolumab 240mg every 2 weeks. OS and progression-free survival (PFS) are co-primary endpoints. ORR, time to treatment failure and tolerability are secondary endpoints. A total of 325 pts are expected to be enrolled in the standard treatment

Conclusion

- ICI have proven role in metastastic advanced disease
- Currently data is supportive only for stage III NSCLC as consolidation therapy
- Need more RCT