UNIVERSITÀ
DEGLI STUDI
DI TORINO

ALMA UNIVERSITAS
TAURINENSIS

Immunotherapy in Lung Cancer

Giorgio V. Scagliotti
University of Torino
Department of Oncology
giorgio.scagliotti@unito.it

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Agenda

- The immune system
- Strategy to modulate/boost the immune system
- Check point inhibitors
- The clinical data
- Toxicity
- Biomarkers

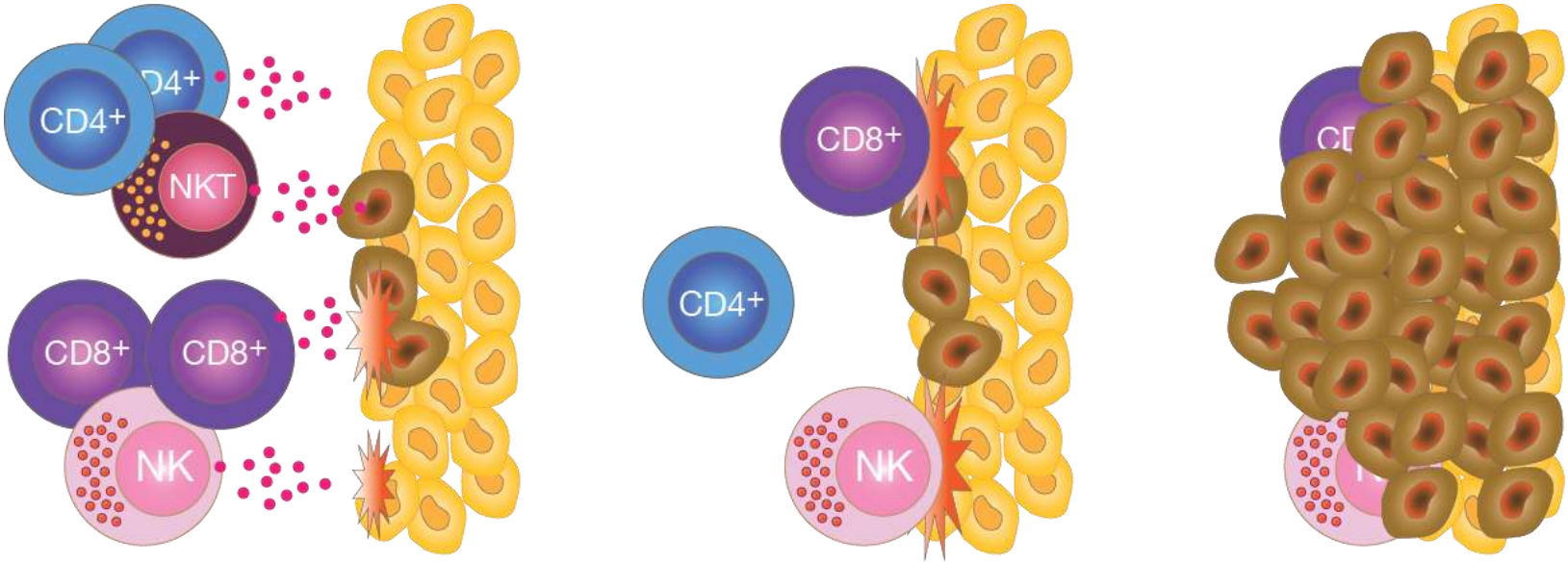
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Evidence to Suggest That an Immune Response Against Solid Tumors Exists

- Spontaneous regression of tumors without therapy
- Heterogeneity of clinical progression of disease among patients with the same histological type
- Improved survival in patients who develop empyema
- The isolation of tumor-infiltrating lymphocytes in lung cancer
- Encouraging results in patients immunized with autologous tumor cell vaccines expressing GM-CSF

The Immune Editing Hypothesis (3E's)

Elimination **Equilibrium** **Escape**



Genetic instability/tumor heterogeneity

Immune selection

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Potential Mechanisms for Immune Evasion

- Defective antigen presentation
- Checkpoint pathways
- Immunosuppressive cell infiltrates
  - Treg – high expression of CTLA-4 and TGF-B
  - MDSCs able to suppress T cell response
- Upregulation/secretion of immunosuppressive cytokines

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Potential Mechanisms for Immune Evasion

- Defective antigen presentation

  Chemotherapy, epigenetic therapy, vaccines

- Checkpoint pathways

  Checkpoint inhibitors

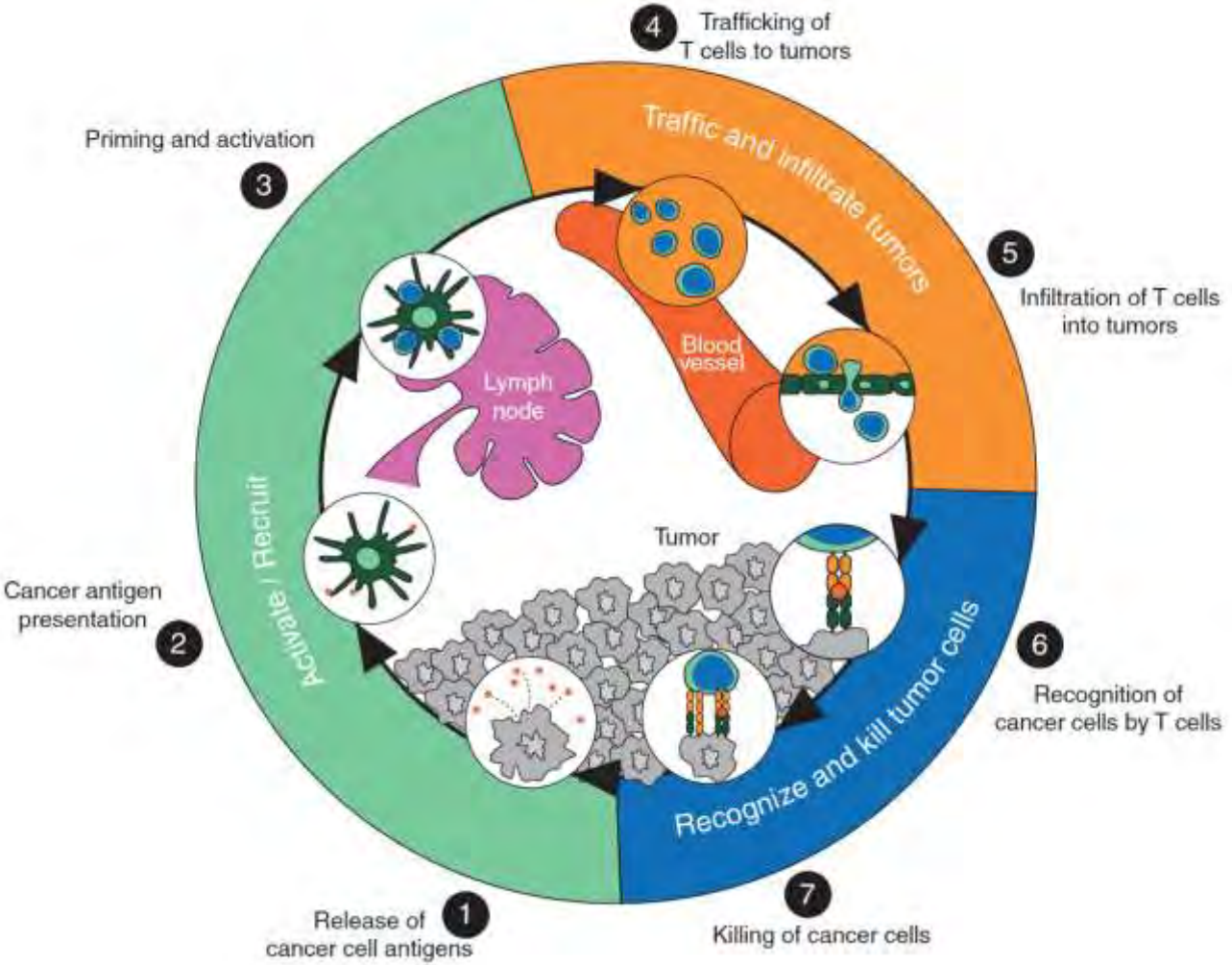
- Immunosuppressive cell infiltrates - T reg and MDSCs

  Ab or cytotoxics

- Upregulation/secretion of immunosuppressive cytokines COX-2 inhibition, TGF-B blockade and chemotherapy

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The Cancer Immunity Cycle



Chen D, Mellman I. Immunity 2013;39:1-10 modified

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Vaccines for NSCLC

- Dependent on identifying an appropriate antigen, differentially expressed between tumour and normal tissues.
- A challenging area, previous attempts unsuccessful
  - ✓ *Advanced stage patients with poor immune function*
  - ✓ *Little consideration of type of immune response and antigen presentation*
  - ✓ *No approved therapeutic vaccines (but there are preventive vaccines, e.g. HPV vaccine)*
- Most extended phase III studies are on LBLP25 (Stimuvax) and recMAGE-A3 and both were negative.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Lung cancer vaccination
Ongoing & planned studies

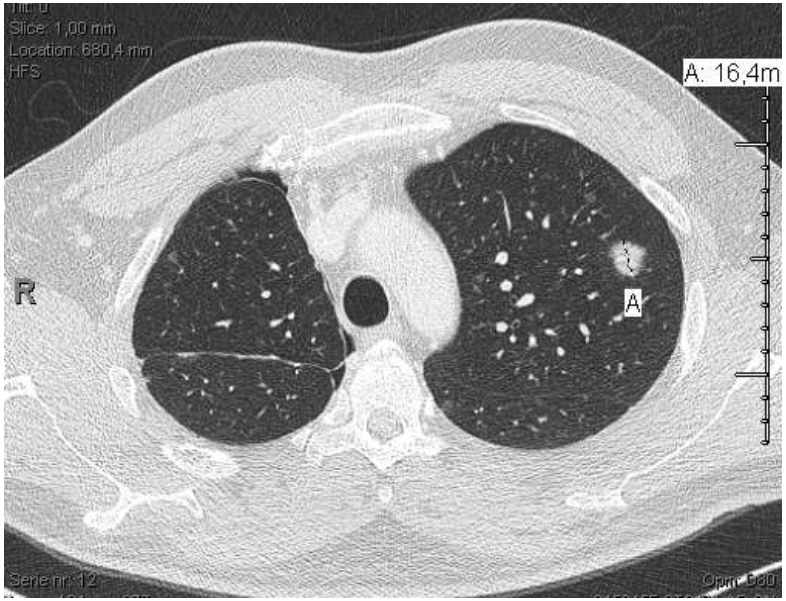
	MAGE-A3	BLP25	Lucanix	rHU-EGF	TG4010
Class	full protein	peptide in liposome	allogeneic cells	full protein	peptide by viral vector
Disease setting	post-surgery	post-CTRT	advanced	advanced	advanced
Specificity	++	+	?	+	+
Expression	+/-	+	?	++	+
Immuno-activity	++	++	++	++	++
Phase II	RCT/placebo	RCT/BSC	Open/dose	RCT/BSC	RCT/BSC
Phase III	2270 Negative	1322 Negative	532 **Negative**	ongoing – target 230	planned – target 1000

UNIVERSITÀ DEGLI STUDI DI TORINO

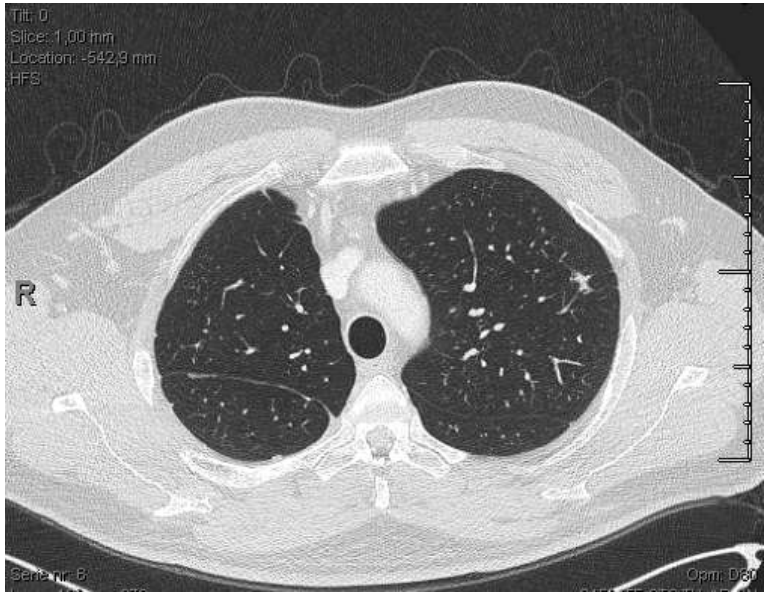
ALMA UNIVERSITAS TAURINENSIS

Immune checkpoints
An active NEW class of agents

December 2014

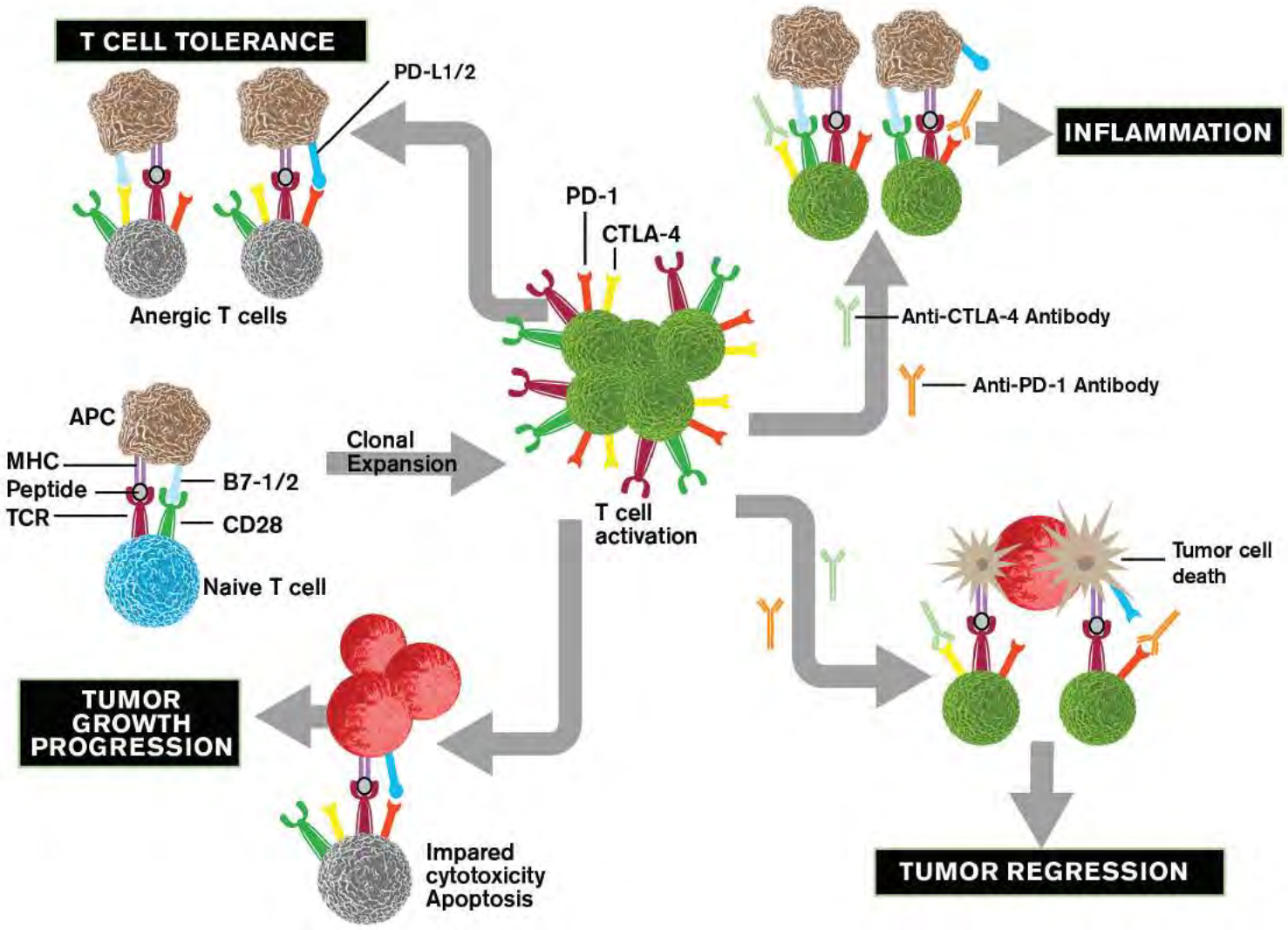


December 2016



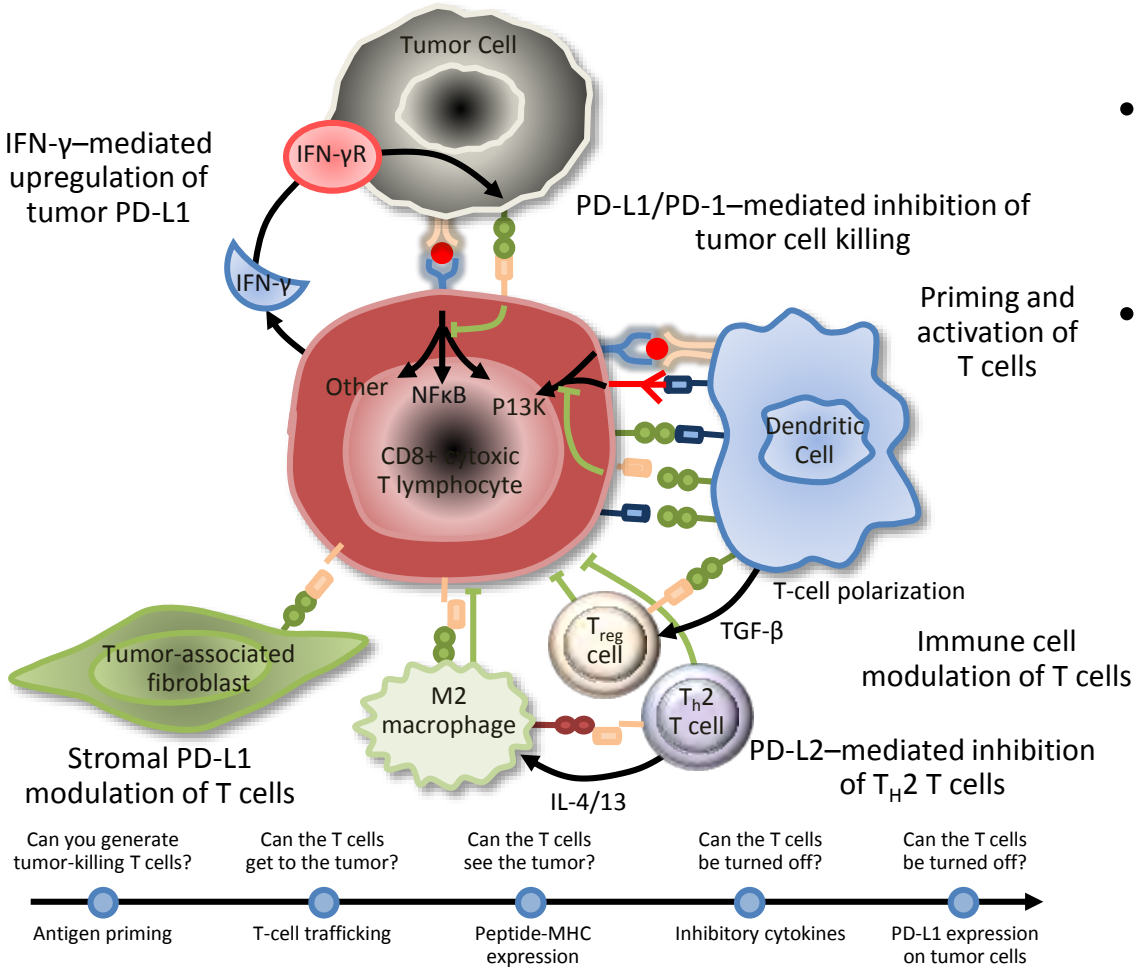
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The role of checkpoint pathways in chronic inflammation and cancer

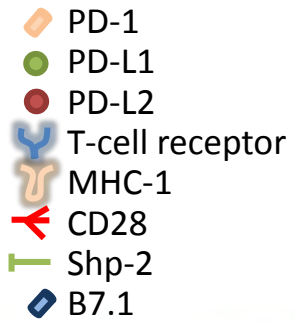


Wang D & DuBois RN Carcinogenesis, 2015, 36: 1085–1093

PD-1 Blockade: Binding to PD-L1 (B7-H1) and PD-L2 (B7-DC) Revives T Cells



- PD-L1 expression on tumor cells induced by interferon-γ
- Activated T cells that could kill tumors are specifically disabled



Sznol M, et al. Clin Cancer Res. 2013;19:1021-1034.

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

What are the data on PD-1/PD-L1

- **Second line treatment**
  - ✓ Nivolumab
  - ✓ Pembrolizumab
  - ✓ Atezolizumab

- **First line treatment**
  - ✓ Pembrolizumab
  - ✓ Nivolumab

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Status of Key Checkpoint Inhibitors for Advanced NSCLC (≥2nd-line)

Agent / Study	Phase	Design	Histology	Approval Status
Nivolumab, anti-PD-1				
NCT01642004 (CheckMate 017)	3	Nivo vs. doc, pretreated NSCLC	Squamous	Approved: US and EU
NCT01673867 (CheckMate 057)	3	Nivo vs. doc, pretreated NSCLC	Non-squamous	Approved: US and EU
Pembrolizumab, anti-PD-1 NCT01905657 (KEYNOTE-010)	2 / 3	Pembro vs. doc, post-platinum	All	Approved: US Approved: EU
Atezolizumab (MPDL3280A), anti-PD-L1				FDA breakthrough therapy designation and priority review CHMP positive opinion
NCT02008227 (OAK)	3	Atezolizumab vs. doc, post-platinum	All	
Durvalumab (MEDI4736), anti-PD-L1				-
NCT02154490 (Lung-MAP)	2 / 3	Biomarker-targeted 2nd-line therapy	Squamous	
NCT02352948 (ARCTIC)	3	Durvalumab + / - tremelimumab (anti-CTLA-4) by PD-L1 expression, pretreated NSCLC	All	
Avelumab, anti-PD-L1 NCT02395172 (JAVELIN Lung 200)	3	Avelumab vs. doc, post-platinum	All	-
Ipilimumab, anti-CTLA4 NCT02039674 (KEYNOTE-021)	1 / 2	Pembro + ipilimumab, 2nd-line	All	-

ClinicalTrials.gov
Patnaik A et al. *J Clin Oncol* 2015;33(Suppl):8011

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

What are the data, second line

Key patient inclusion criteria*

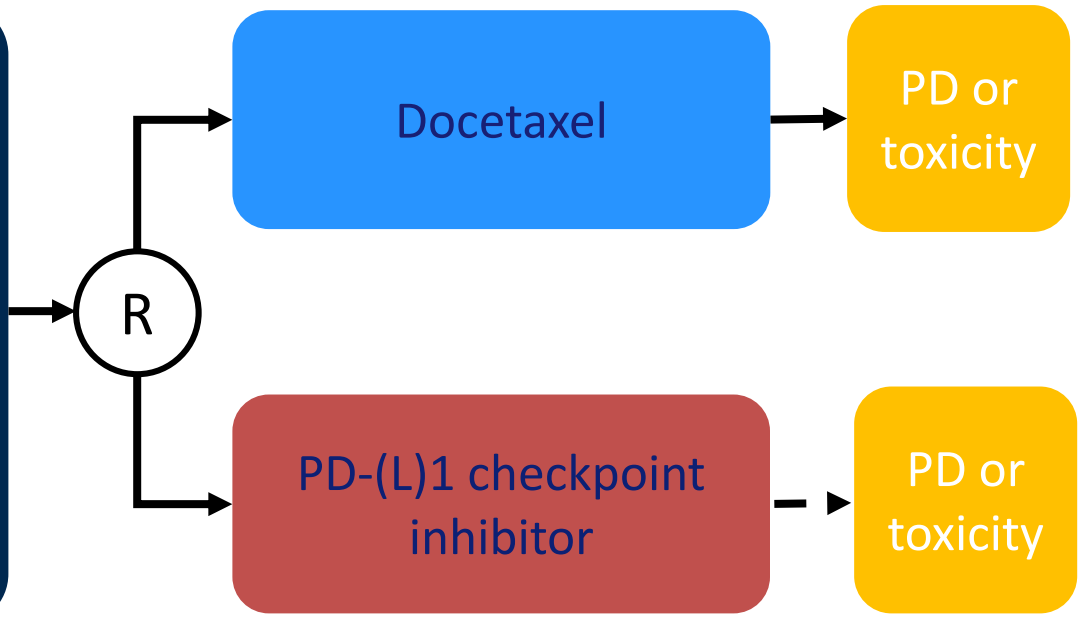
- Previously treated with a first line platinum-based regimen

Differences between studies:

PD-L1 status

PD-L1 cut-off

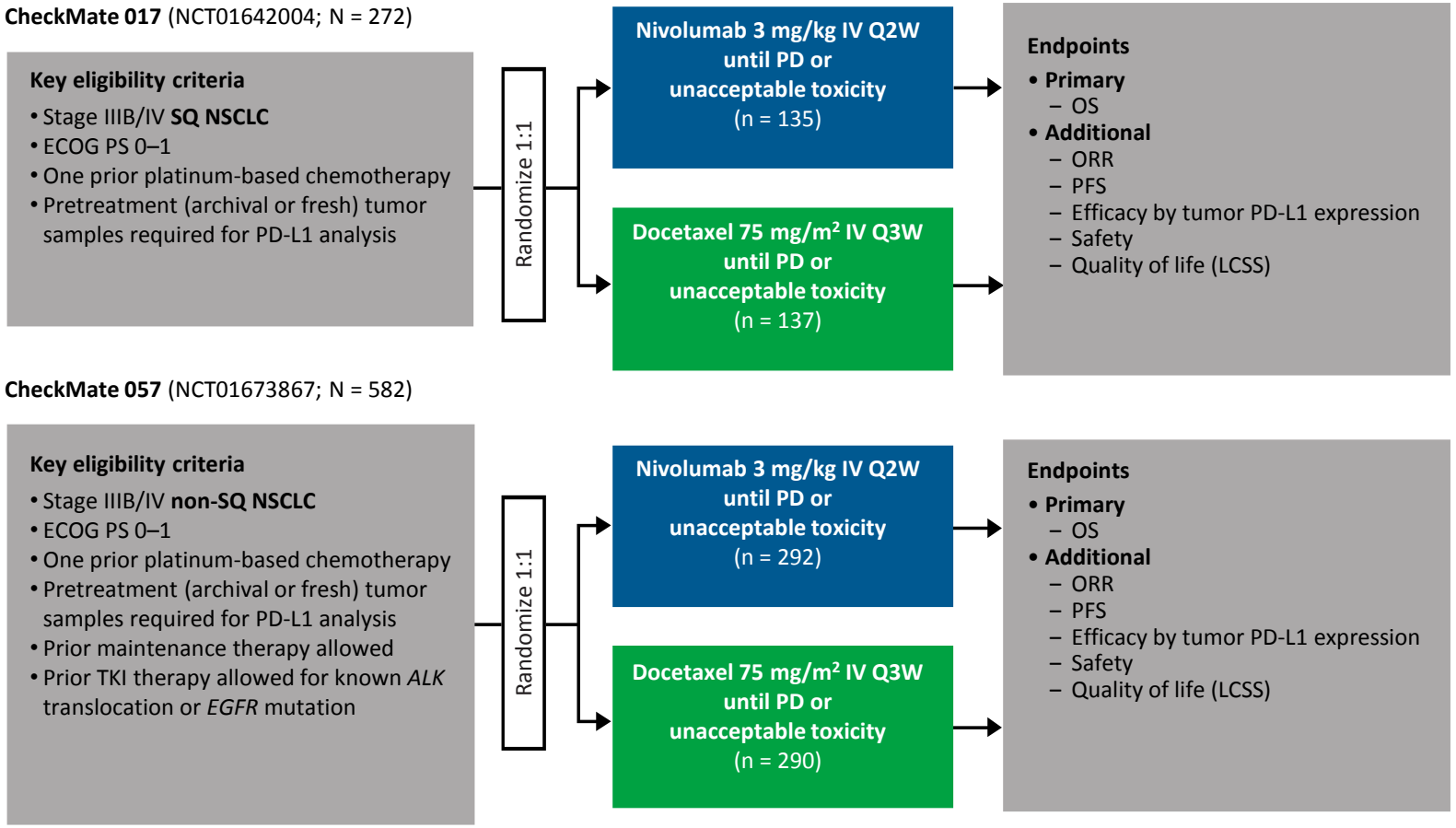
Histology



Primary endpoint: OS

Secondary endpoint: PFS, response rate, QOL

CheckMate 017 and CheckMate 057 Study Designs



LCSS = Lung Cancer Symptom Scale; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; TKI = tyrosine kinase inhibitor

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Phase 3 Efficacy Results from CheckMate 017 and 057

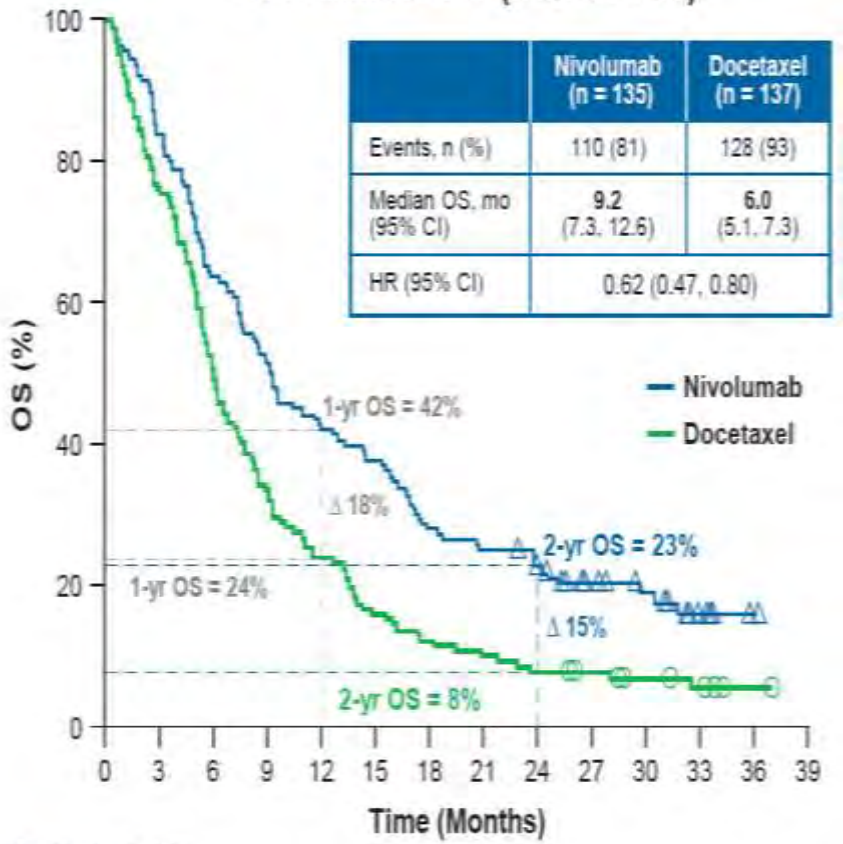
	CheckMate 017 (NCT01642004)		CheckMate 057 (NCT01673867)	
Efficacy Measure	Nivolumab (n=135)	Docetaxel (n=137)	Nivolumab (n=292)	Docetaxel (n=290)
Median OS, months (95% CI)	9.2 (7.3-13.3)	6.0 (5.1-7.3)	12.2 (9.7-15.0)	9.4 (8.1-10.7)
HR (95% CI)	0.59 (0.44-0.79) p<.001		0.73 (0.59-0.89) p=.002	
1-year OS, % (95% CI)	42 (34-50)	24 (17-31)	51 (45-56)	39 (33-45)
Median PFS, months (95% CI)	3.5 (2.1-4.9)	2.8 (2.1-3.5)	2.3 (2.2-3.3)	4.2 (3.5-4.9)
HR (95% CI)	0.62 (0.47-0.81) p<.001		0.92 (0.77-1.11) p=.39	
1-year PFS, % (95% CI)	21 (14-28)	6 (3-12)	19 (14-23)	8 (5-12)
Investigator-assessed ORR, %	20	9	19	12
	p=.008		p=.02	

Brahmer J et al. *N Engl J Med* 2015;373:123-35
Borghaei H et al. *N Engl J Med* 2015;Epub ahead of print

Checkmate 017 & 057: OS at minimum follow up of 2 years

)

CheckMate 017 (SQ NSCLC)

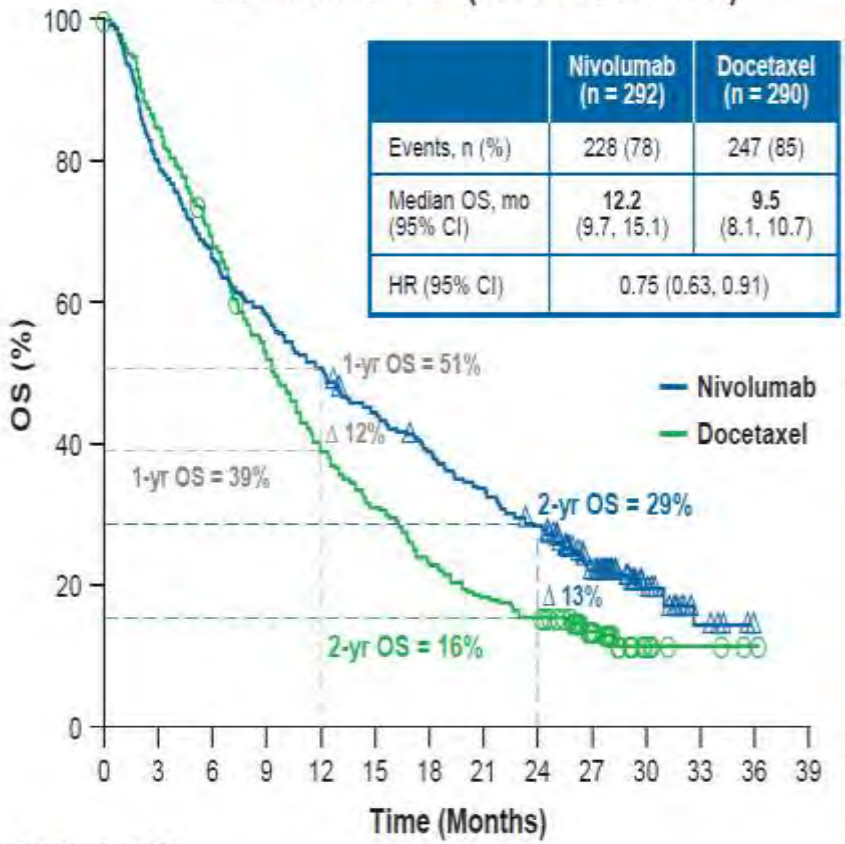


	Nivolumab (n = 135)	Docetaxel (n = 137)
Events, n (%)	110 (81)	128 (93)
Median OS, mo (95% CI)	**9.2** (7.3, 12.6)	**6.0** (5.1, 7.3)
HR (95% CI)	0.62 (0.47, 0.80)	

No. of patients at risk:

Nivolumab	135	113	86	69	57	51	38	34	29	19	14	7	1	0
Docetaxel	137	104	69	46	33	22	17	14	11	9	6	4	1	0

CheckMate 057 (non-SQ NSCLC)



	Nivolumab (n = 292)	Docetaxel (n = 290)
Events, n (%)	228 (78)	247 (85)
Median OS, mo (95% CI)	**12.2** (9.7, 15.1)	**9.5** (8.1, 10.7)
HR (95% CI)	0.75 (0.63, 0.91)	

No. of patients at risk:

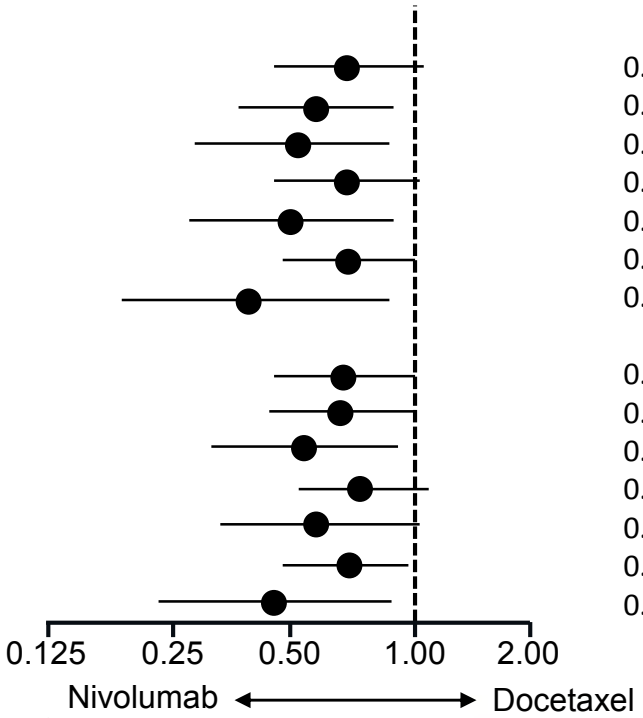
Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Does Tumour PD-L1 Expression Affect Nivolumab Efficacy? CheckMate 017

- Across the prespecified expression levels (1%, 5% and 10%), PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints in patients with squamous NSCLC

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified HR (95% CI)
OS	**No. patients**		
≥1%	63	56	0.69 (0.45-1.05)
<1%	54	52	0.58 (0.37-0.92)
≥5%	42	39	0.53 (0.31-0.89)
<5%	75	69	0.70 (0.47-1.02)
≥10%	36	33	0.50 (0.28-0.89)
<10%	81	75	0.70 (0.48-1.01)
Not quantifiable at baseline	18	29	0.39 (0.19-0.82)
PFS			
≥1%	63	56	0.67 (0.44-1.01)
<1%	54	52	0.66 (0.43-1.00)
≥5%	42	39	0.54 (0.32-0.90)
<5%	75	69	0.75 (0.52-1.08)
≥10%	36	33	0.58 (0.33-1.02)
<10%	81	75	0.70 (0.49-0.99)
Not quantifiable at baseline	18	29	0.45 (0.23-0.89)



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

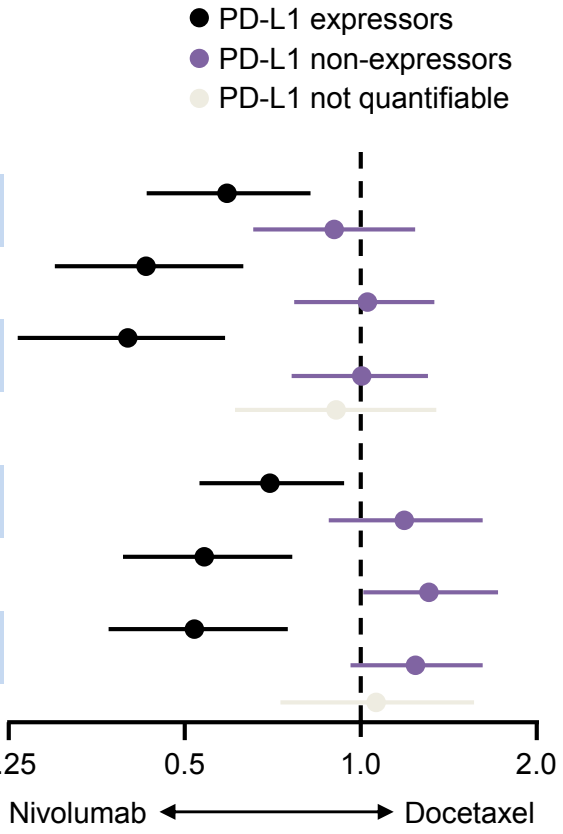
Brahmer J et al. *N Engl J Med* 2015;373:123-35

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Does Tumor PD-L1 Expression Affect Nivolumab Efficacy? CheckMate 057

- Higher PD-L1 expression was associated with greater benefit from nivolumab in patients with nonsquamous NSCLC[1]
- Similar results found after 2 years of follow up[2]

PD-L1 Expression Level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction p value[a]
OS				
≥1%	123	123	0.59 (0.43-0.82)	.06
<1%	108	101	0.90 (0.66-1.24)	
≥5%	95	86	0.43 (0.30-0.63)	<.001
<5%	136	138	1.01 (0.77-1.34)	
≥10%	86	79	0.40 (0.26-0.59)	<.001
<10%	145	145	1.00 (0.76-1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61-1.35)	
PFS				
≥1%	123	123	0.70 (0.53-0.94)	.02
<1%	108	101	1.19 (0.88-1.61)	
≥5%	95	86	0.54 (0.39-0.76)	<.001
<5%	136	138	1.31 (1.01-1.71)	
≥10%	86	79	0.52 (0.37-0.75)	<.001
<10%	145	145	1.24 (0.96-1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73-1.56)	

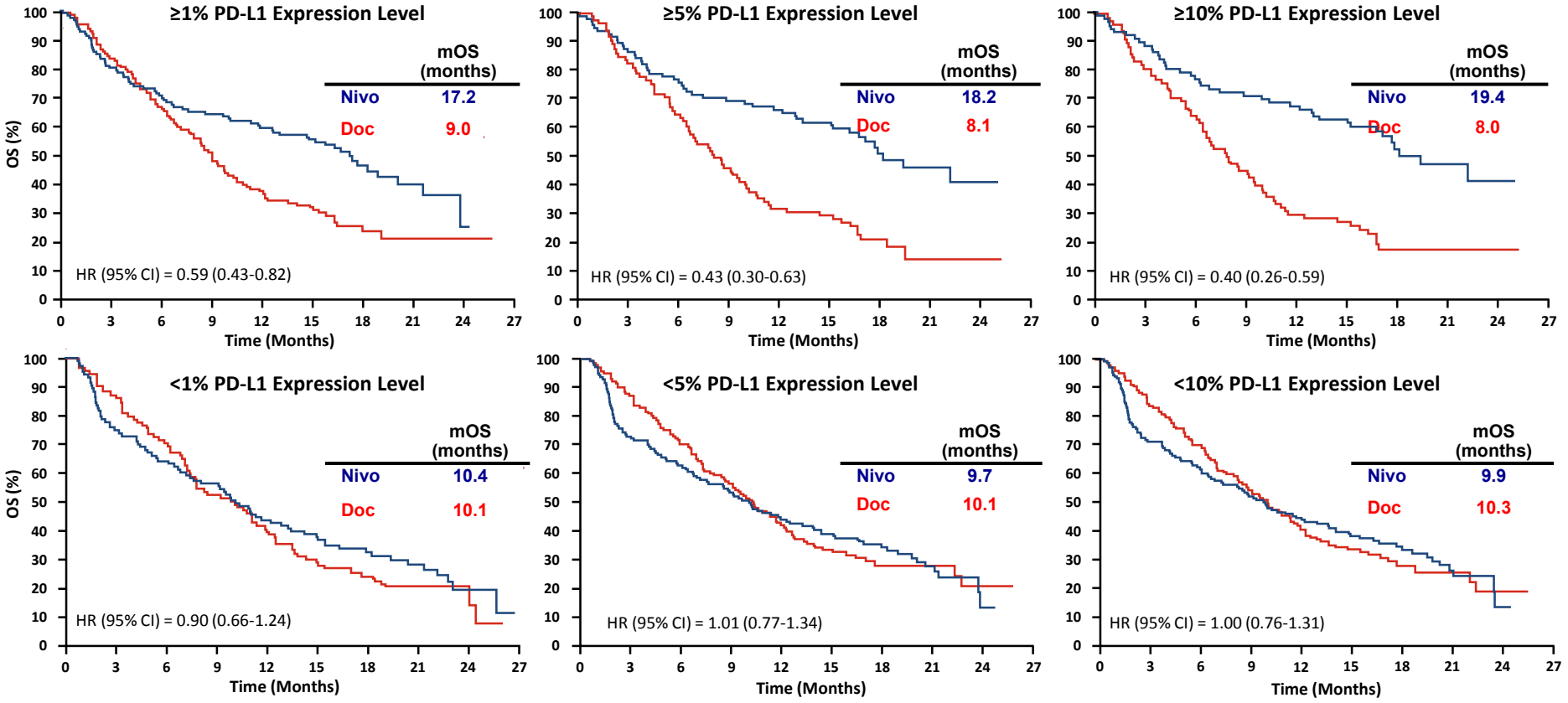


1. Borghaei H et al. *N Engl J Med* 2015;373:1627-39
2. Borghaei H et al. *J Clin Oncol* 2016;34 (suppl):abstr 9025

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

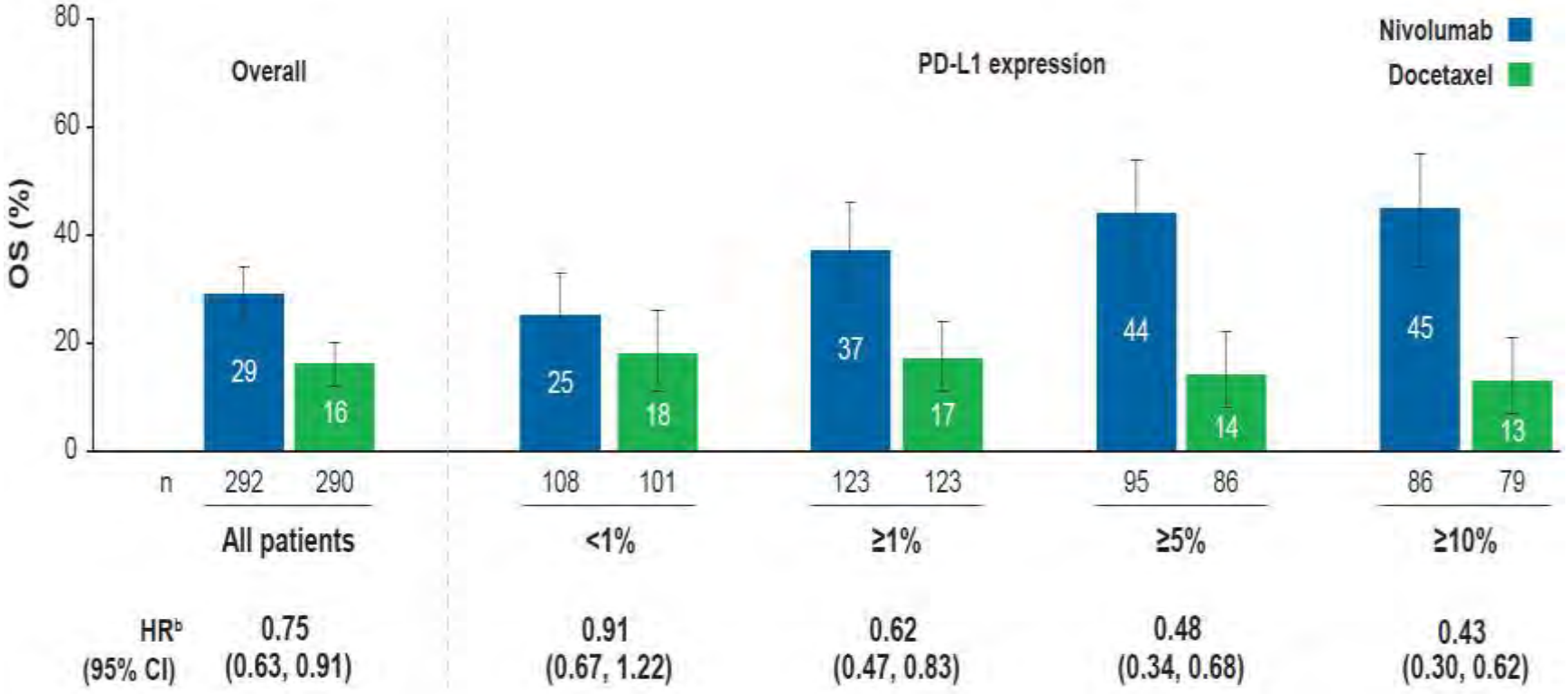
Does Tumour PD-L1 Expression Affect Nivolumab Efficacy? CheckMate 057

OS by PD-L1 Expression



Paz-Ares L et al. *J Clin Oncol* 2015;33(Suppl):LBA109; Slides presented at ASCO 2015

2-Year OS Rates[a] Overall and by PD-L1 Expression Level in CheckMate 057 (Non-SQ NSCLC)

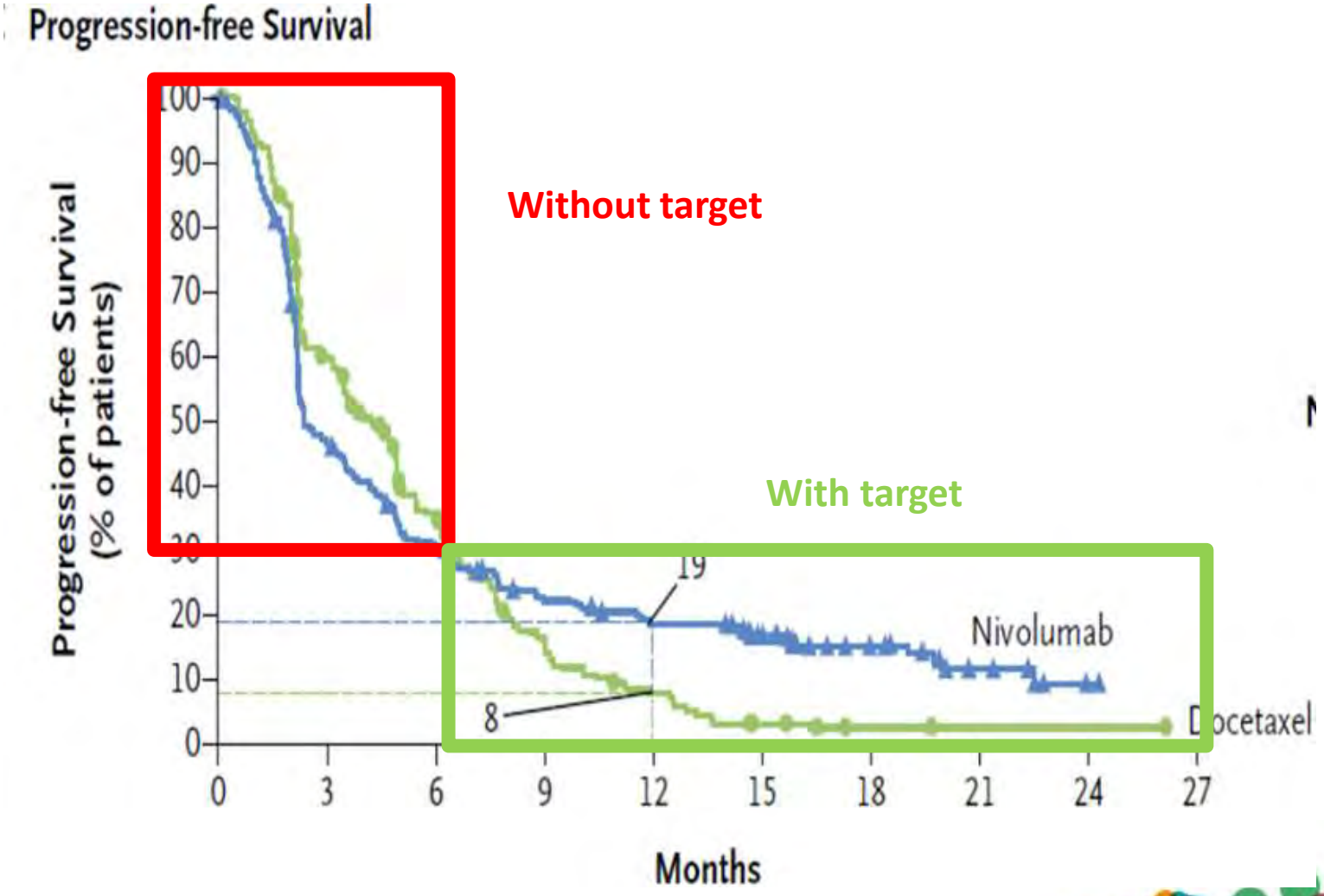


- In CheckMate 057, consistent with the primary analysis,[2] PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)

[a]Kaplan–Meier estimates, with error bars indicating 95% CIs
[b]For the comparison of the full Kaplan–Meier survival curves for each treatment group

PD-1/PD-L1 is targeted treatment

Nivolumab – Checkmate 057



1. Borghaei H et al. *N Engl J Med* 2015;373:1627-39

Borghaei et al, *NEJM* 2015

Pembrolizumab in NSCLC
Phase 1 KEYNOTE-001 Trial

Inclusion criteria
- Locally advanced or metastatic NSCLC
- ECOG PS 0/1
- Adequate organ function
- Biopsy sample required to assess PD-L1 expression

Multiple expansion cohorts

TRAINING OR VALIDATION GROUP

Pembrolizumab monotherapy (10 mg/kg IV every 2 or 3 weeks)

Treatment until disease progression or discontinuation due to toxicity / other reasons

Pembrolizumab monotherapy (2 mg/kg IV every 3 weeks)

Primary endpoint	Safety, side-effect profile, antitumour activity (response rate)
Secondary endpoints	Pharmacokinetic parameters, PFS, OS, duration of response

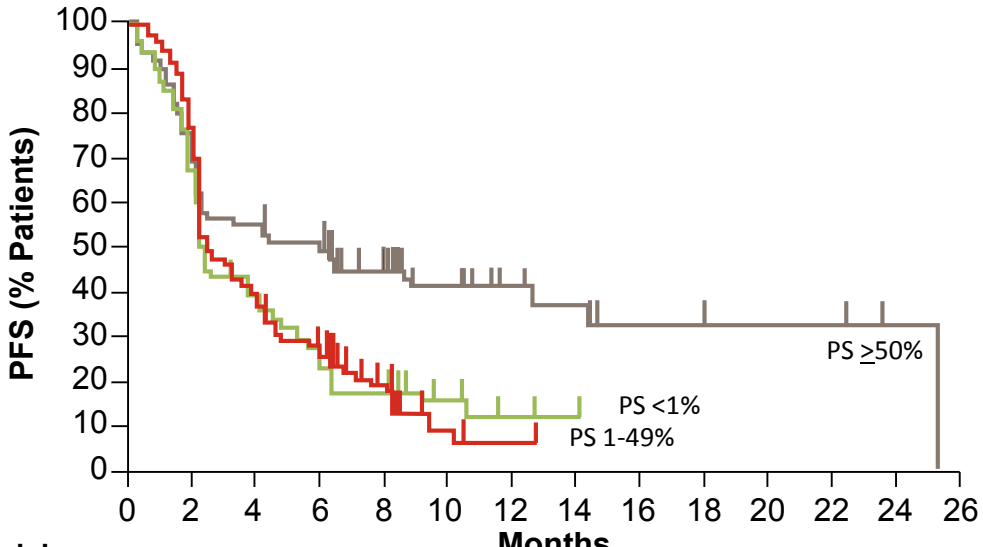
Garon EB et al. *N Engl J Med* 2015;372:2018-28

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab in NSCLC: PD-L1 Status (Phase 1 Results)

- Pembrolizumab, a humanised monoclonal antibody against PD-1, has been evaluated in 495 patients with advanced NSCLC (untreated [n=101] and pretreated [n=394]) in a Phase 1 study (KEYNOTE-001, NCT01295827)

- In previously treated patients
  - ORR was 18%, median PFS 3.0 months, and median OS 9.3 months
  - PFS and OS were longer in patients with PD-L1 expression in ≥50% of tumour cells



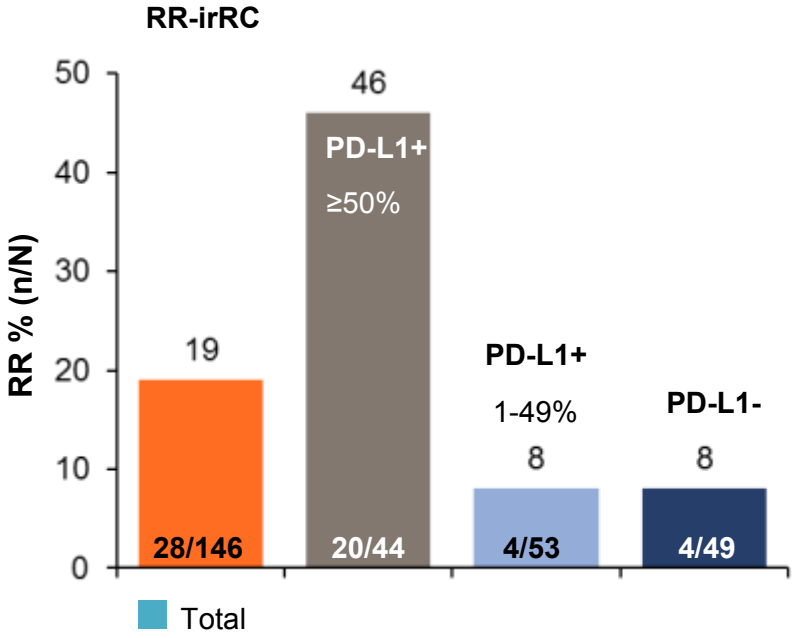
No. at risk														
PS ≥50%	99	67	53	47	30	19	12	8	4	3	3	3	1	0
PS 1-49%	127	93	48	31	15	3	1	0	0	0	0	0	0	0
PS <1%	68	44	26	16	11	6	2	0	0	0	0	0	0	0

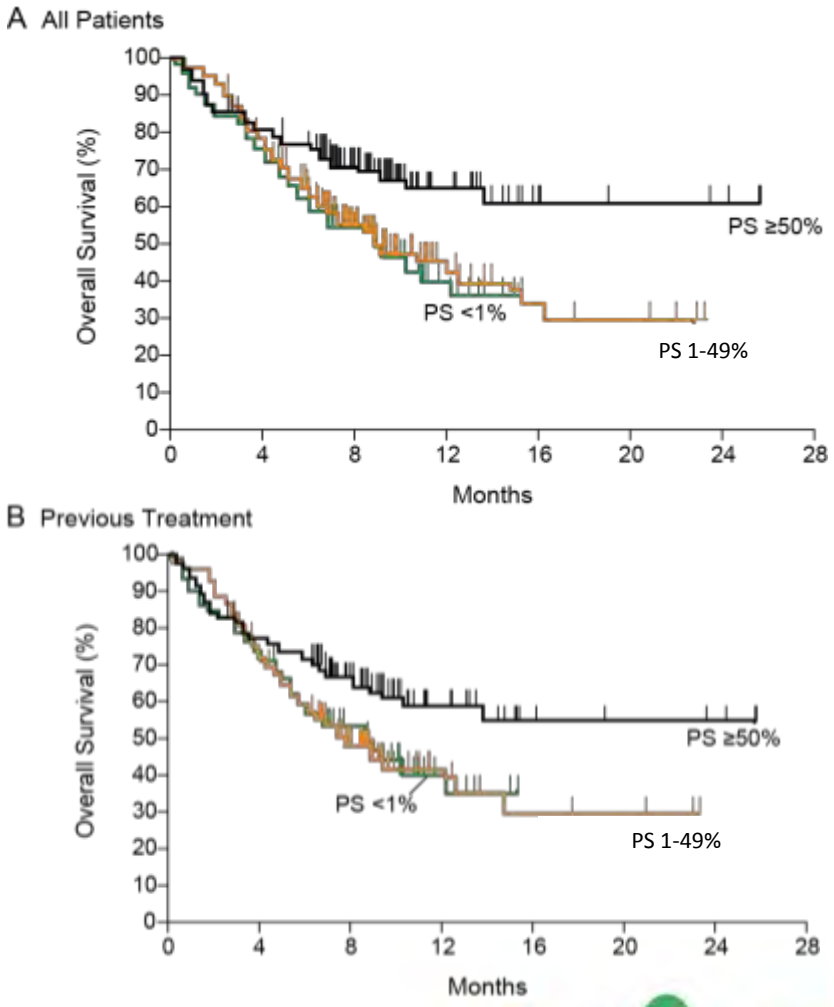
Garon EB et al. *N Engl J Med* 2015;372:2018-28

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab in NSCLC: PD-L1 Status (Phase 1 Results)

Pembrolizumab in NSCLC: OS per Proportional Scores (TPS)





Gandhi L et al. AACR 2014. Abstract CT105
Garon EB et al. *N Engl J Med* 2015;372:2018-28

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab Improves OS in Pretreated, PD-L1-Positive NSCLC - Keynote 10

	Total population			PD-L1 ≥50%		
Efficacy Measure	Pembro 2 mg/kg (n=345)	Pembro 10 mg/kg (n=346)	Doc (n=343)	Pembro 2 mg/kg	Pembro 10 mg/kg	Doc
Median OS, months	10.4	12.7	8.5	14.9	17.3	8.2
HR vs. doc (95% CI)	0.71 (0.58-0.88) p=.0008	0.61 (0.49-0.75) p<.0001		0.54 (0.38-0.77) p=.0002	0.50 (0.36-0.70) p<.0001	
Median PFS, months	3.9	4.0	4.0	5.0	5.2	4.1
HR vs. doc (95% CI)	0.88 (0.74-1.05) p=.07	0.79 (0.66-0.94) p=.004		0.59 (0.44-0.78) p=.0001	0.59 (0.45-0.78) p<.0001	

- In a post-hoc analysis, pembrolizumab improved OS vs. docetaxel in patients with PD-L1 1-49%, despite a lack of PFS and ORR benefit in this group[2]

1. Herbst RS et al. *Lancet* 2016;387:1540-50
2. Garon EB et al. *J Clin Oncol* 2016;34 (suppl):abstr 9024

OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC

- **Study objective**
  - To evaluate the efficacy and safety of atezolizumab vs. docetaxel in patients with previously treated NSCLC

Key patient inclusion criteria
- Locally advanced or metastatic NSCLC
- 1–2 prior lines of chemotherapy including at least 1 platinum based
- Any PD-L1 status

(n=1225)

R

Atezolizumab 1200 mg IV q3w (n=425) → PD / loss of benefit

Stratification
- PD-L1 status
- Prior chemotherapy regimens (1 vs. 2)
- Histology

Docetaxel 75 mg/m² IV q3w (n=425) → PD

Primary endpoint
- OS in ITT and PD-L1-expression on ≥1% TC or IC

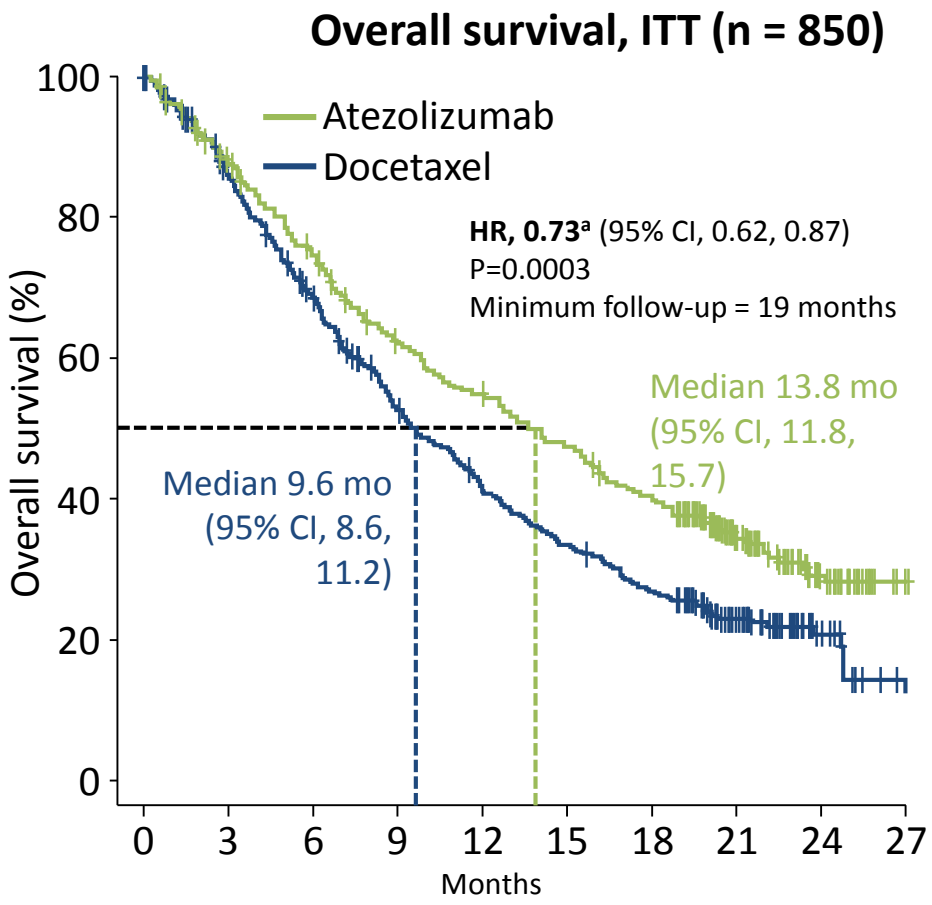
Secondary endpoints
- ORR, PFS, DoR, safety

Barlesi et al. Ann Oncol 2016;27(suppl 6):abstr LBA44_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

OAK, a randomized Phase 3 study comparing atezolizumab with docetaxel in 2L/3L NSCLC

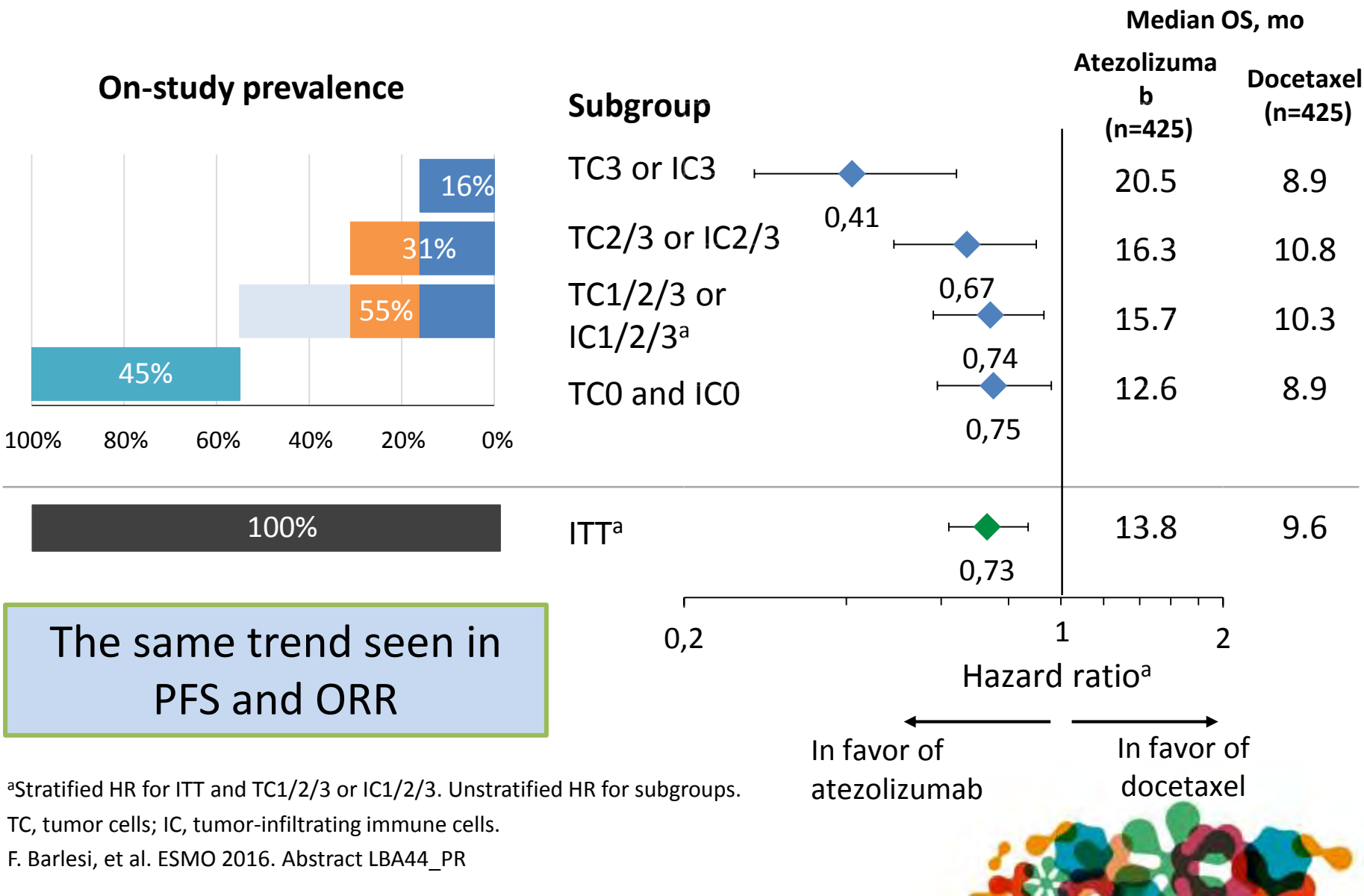
Characteristics	Atezolizumab n = 425	Docetaxel n = 425
Median age, y	63	64
≥65 y	45%	49%
Male	61%	61%
Nonsquamous	74%	74%
Squamous	26%	26%
ECOG PS, 0/1	37%/64%	38%/62%
No. of prior therapies, 1/2	75%/25%	75%/25%
History of tobacco use		
Never	20%	17%
Current/previous	14% / 66%	16% / 67%
Known EGFR status, %		
Mutant/WT	10% / 75%	10% / 73%



F. Barlesi, et al. ESMO 2016. Abstract LBA44_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Primary analysis from OAK, a Phase 3 study of atezolizumab vs. docetaxel in 2L/3L NSCLC



The same trend seen in PFS and ORR

[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells.
F. Barlesi, et al. ESMO 2016. Abstract LBA44_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Anti-PD-L1 agents compared to platinum CT in 1st-Line advanced NSCLC (PD-L1+)

Only PD-L1+ are eligible: marker positive design in both trials

Nivolumab (PD-L1 ≥5%)

CheckMate 026: Phase 3 trial
Stage IIIB/IV NSCLC
N=495

- **Platinum Doublet Q3W**
- **Nivolumab 3 mg/kg IV Q2W**

NEGATIVE

Progression-free survival (PFS)

Pembrolizumab (PD-L1 ≥50%)

KeyNote 024: Phase 3 trial
Stage IIIB/IV NSCLC
N=300

- **Platinum Doublet Q3W**
- **Pembro 200 mg IV Q3W**

POSITIVE

Progression-free survival (PFS)

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

KEYNOTE-024: advanced NSCLC with a PD-L1 tumor proportion score (TPS) ≥50%

Key Eligibility Criteria

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

R (1:1) N = 305

- Pembrolizumab 200 mg IV Q3W (2 years)
- Platinum-Doublet Chemotherapy (4-6 cycles) → PD → Pembrolizumab 200 mg Q3W for 2 years

1934 patients entered screening

1729 submitted samples for PD-L1 assessment

1653 samples evaluable for PD-L1

- 500 TPS ≥50% (30%)
- 1153 TPS <50%

Key End Points

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

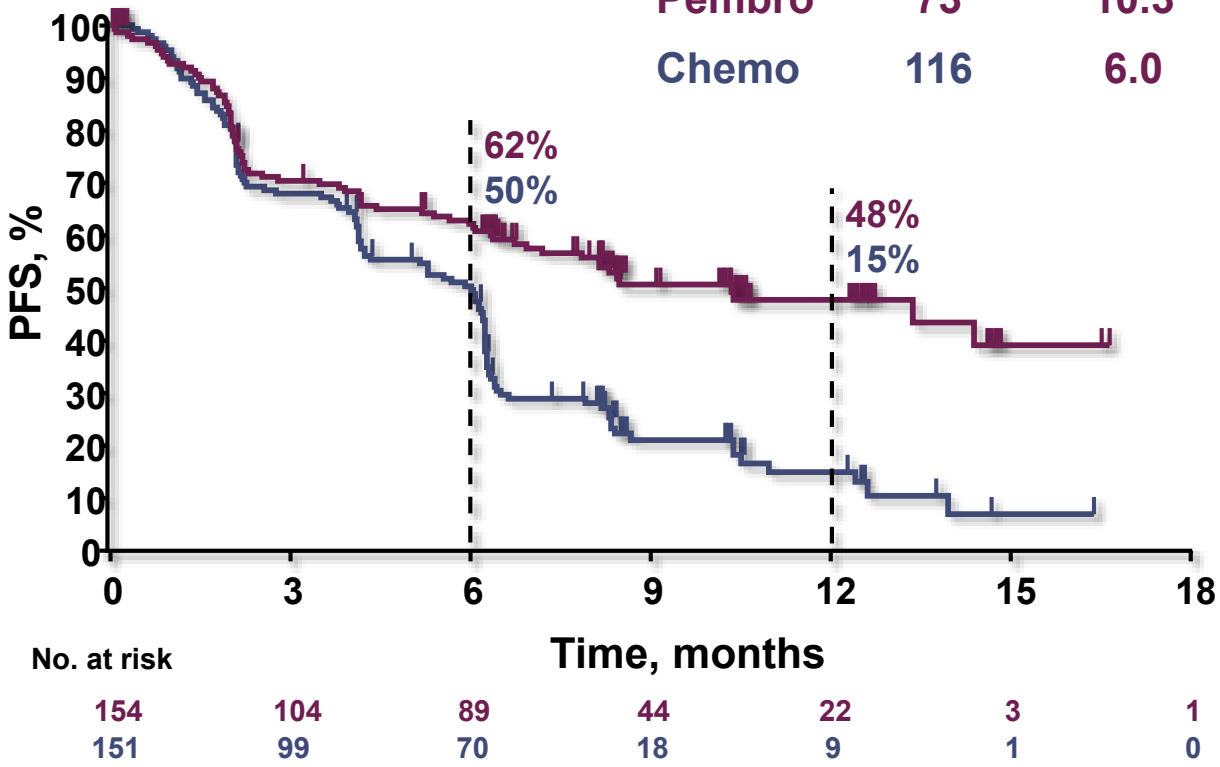
Secondary: OS, ORR, safety

Exploratory: DOR

Reck M. et al. ESMO 2016. Abstract LBA8_PR

KEYNOTE-024: Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



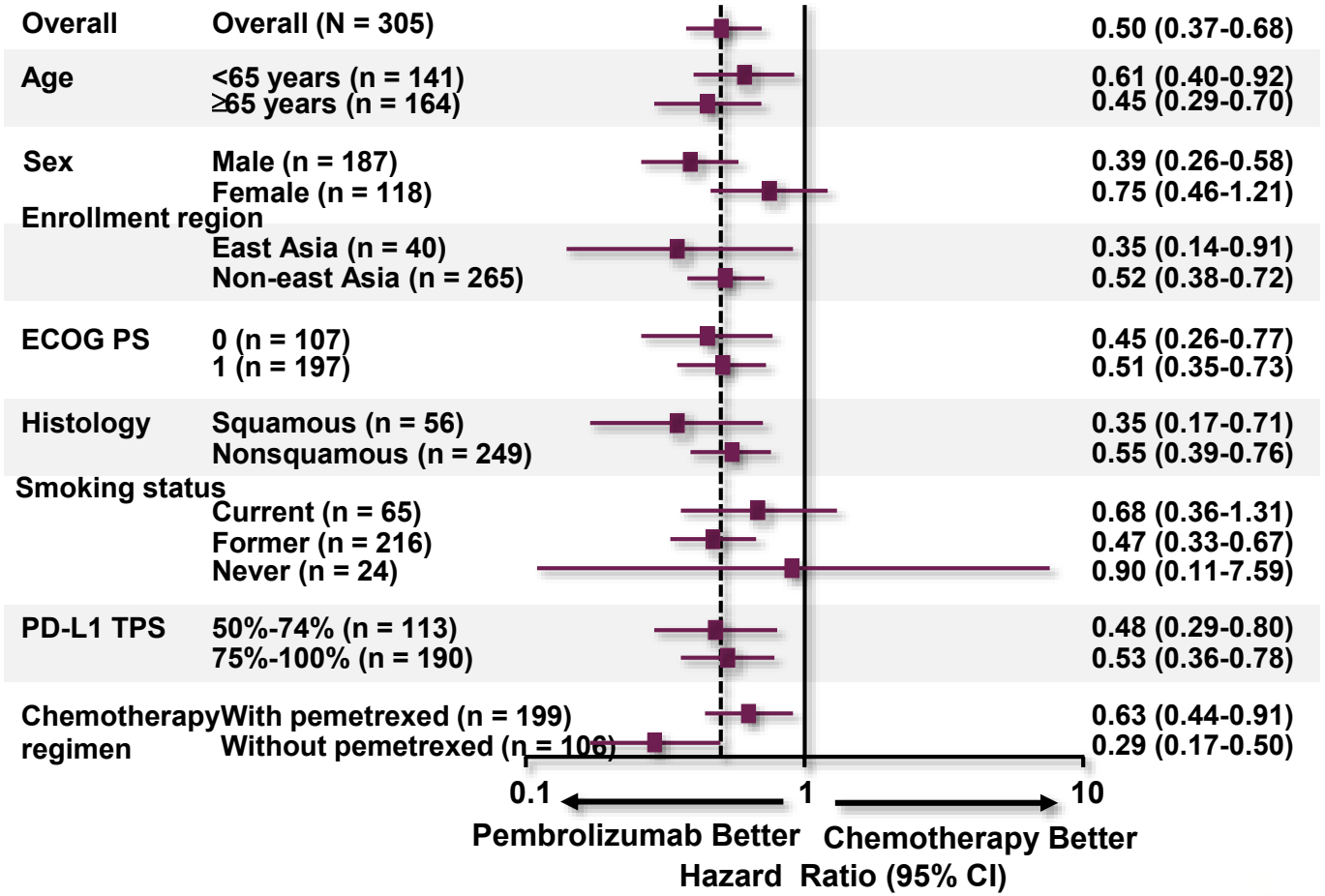
IDMC recommended the trial be stopped because of OS superior efficacy observed with pembrolizumab

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck M. et al. ESMO 2016. Abstract LBA8_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

KEYNOTE-024: Progression-Free Survival in Subgroups



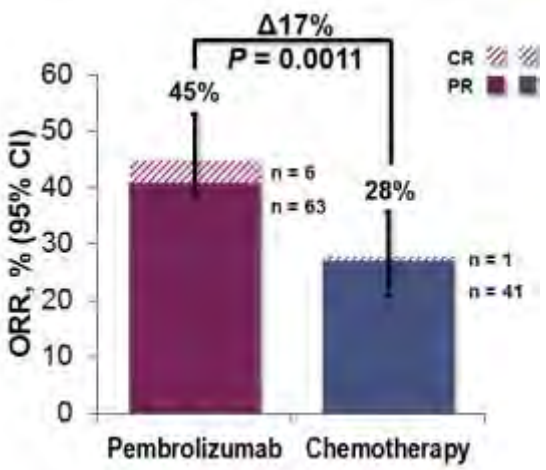
Most of the subgroups benefit from the front line treatment with Pembro when compared to cytotoxic chemotherapy

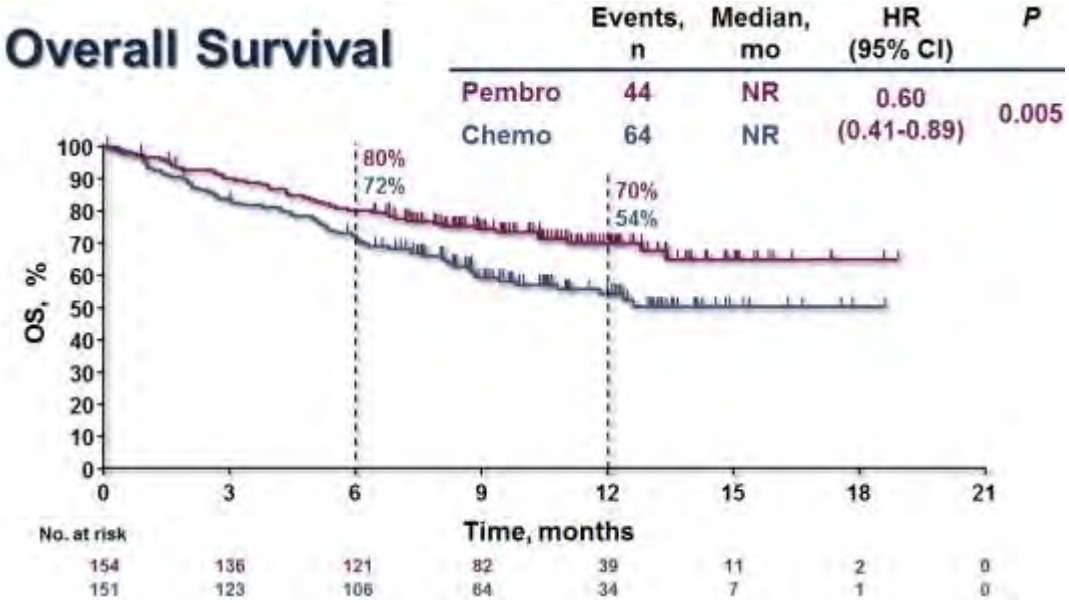
Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

Reck M. et al. ESMO 2016. Abstract LBA8_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab vs platinum-based CT as first-line therapy – OS and ORR





→ORR is improved, with a control arm that performs as expected (from other phase III trials)
→Time to Response is identical between Pembro & Ct
→**PFS is improved by 4.3 months** (**HR of 0.50**)
→**Strongest signal of PFS benefit observed in SCC** (HR of 0.35)
→Cross-over **was limited to 50% of the patients**

Reck M. et al NEJM 2016; DOI: 10.1056/NEJMoa1606774; Reck M, et al. ESMO 2016. Abstract LBA8_PR.
Soria JC – Discussion Plenary Session at ESMO 2016

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

CheckMate 026: nivo vs investigator's choice (IC) of platinum-based doublet chemotherapy as first-line therapy for Stage IV/recurrent PD-L1-positive NSCLC

Key eligibility criteria:

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

R (1:1)

Nivolumab
3 mg/kg IV Q2W
n=271

→ **Disease progression or unacceptable toxicity**

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

→ **Disease progression**

Tumor scans Q6W until wk 48 then Q12W

→ **Crossover nivolumab[c] (optional)**

Stratification factors at randomization:

- PD-L1 expression (<5% vs ≥5%)[a]
- Histology (squamous vs non-squamous)

Primary endpoint: PFS (≥5% PD-L1+)[d]

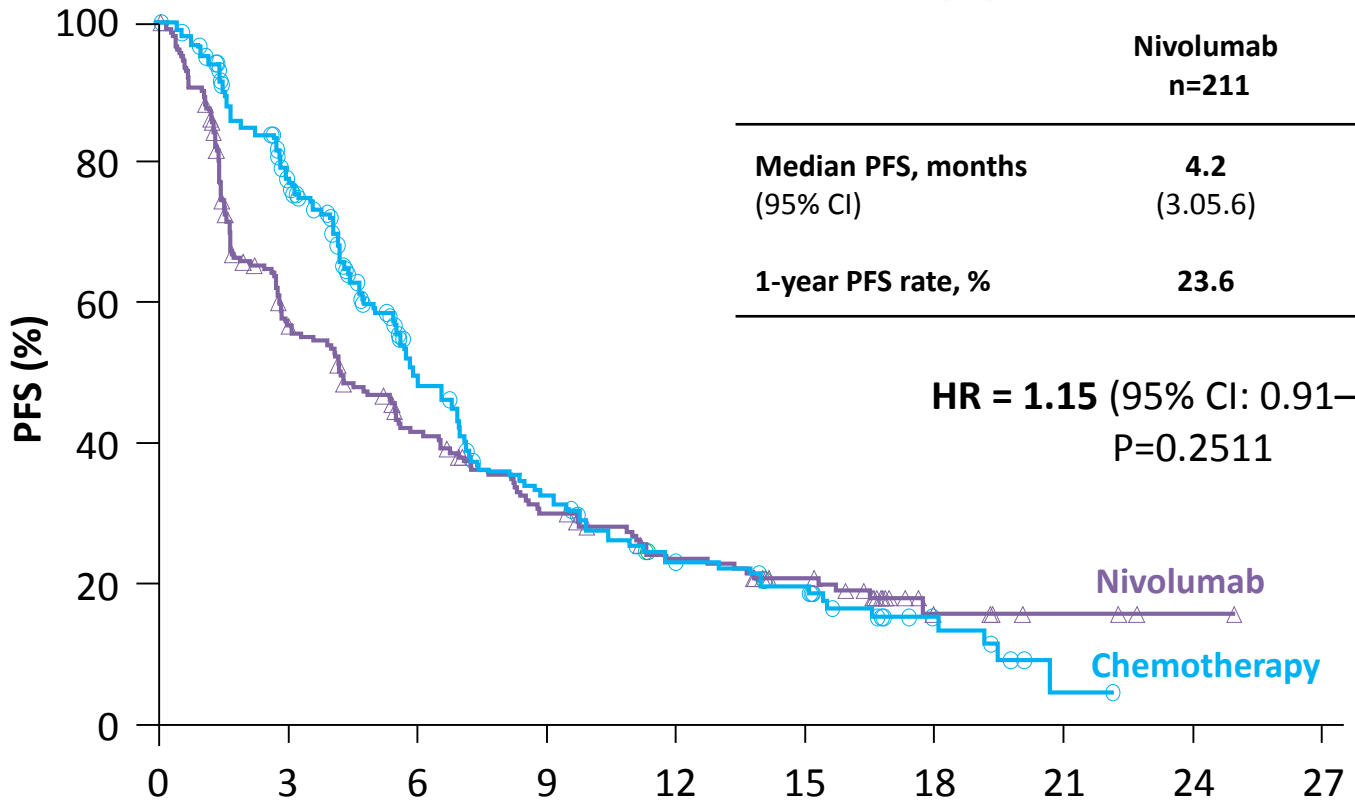
Secondary endpoints:

- PFS (≥1% PD-L1+)[d]
- OS
- ORR[d]

Socinski et al. ESMO 2016. Abstract LBA7_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

CheckMate 026: Nivolumab vs chemotherapy in first-line NSCLC



	Nivolumab n=211	Chemotherapy n=212
Median PFS, months (95% CI)	**4.2** (3.05.6)	**5.9** (5.46.9)
1-year PFS rate, %	**23.6**	**23.2**

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

No. of patients at risk: **Months**

Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)
All randomized patients (≥1% PD-L1+): HR 1.17 (95% CI: 0.95–1.43)

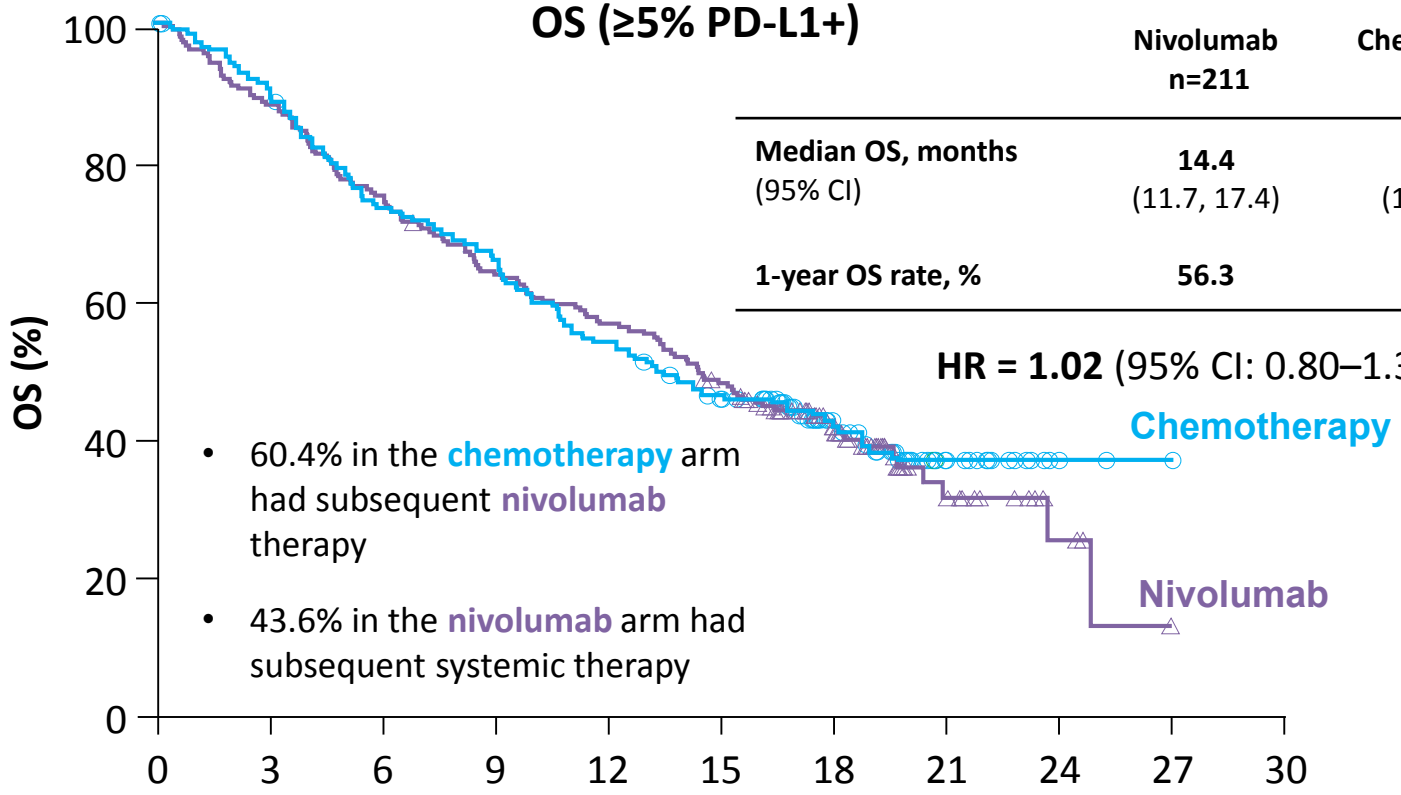
M. Socinski, et al. ESMO 2016. Abstract LBA7_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

CheckMate 026: Nivolumab vs chemotherapy in first-line NSCLC

OS (≥5% PD-L1+)

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



No. of patients at risk:

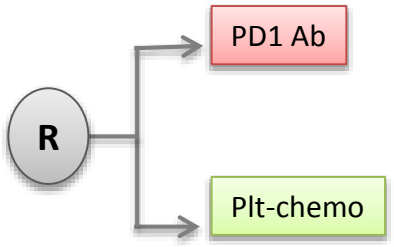
Nivolumab	211	186	156	133	118	98	49	14	4	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1

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

M. Socinski, et al. ESMO 2016. Abstract LBA7_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Impact of PDL1 threshold (performance)

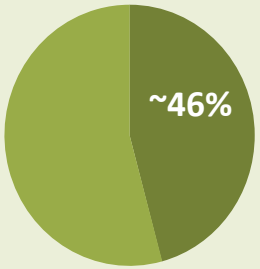
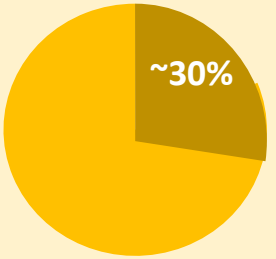


CHECKMATE 026

HR 1.15; 95% CI 0.91–1.45; *P*=0.25
Median PFS 4.2 vs 5.9 months

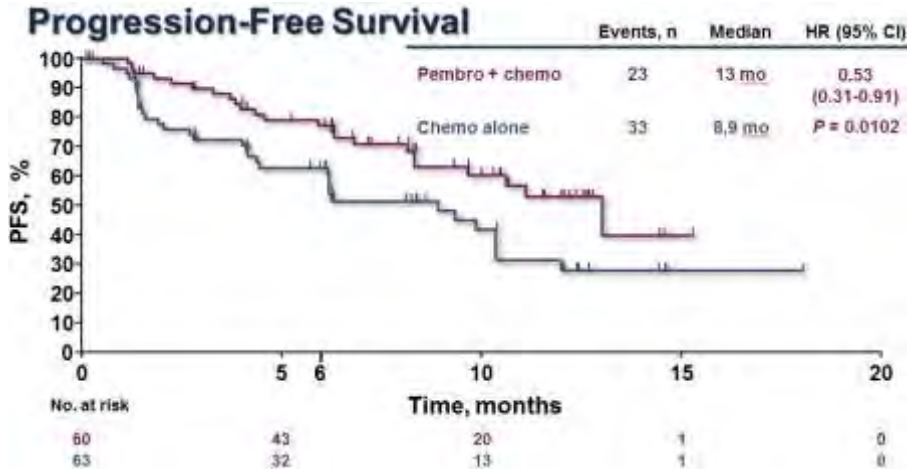
KEYNOTE 024

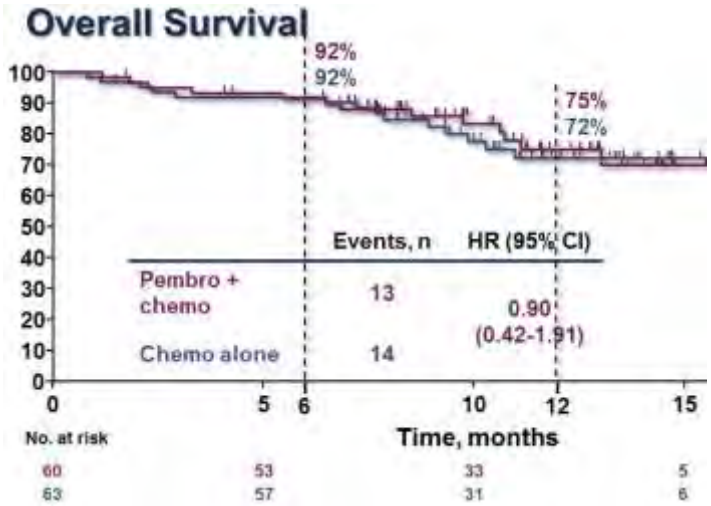
HR 0.50; 95% CI 0.37–0.68; *P*<0.001
Median PFS 10.3 vs 6 months

Drug	Nivolumab 3 mg/kg every 2 wks	Pembrolizumab 200 mg every 3 wks
Detection antibody	28–8 (Dako)	22C3 (Dako)
Criteria	≥5% on tumor cells	≥50% on tumor cells
Estimated PD-L1 prevalence in NSCLC	*PD-L1+ as ≥5% of TCs* 	*PD-L1+ as ≥50% of TCs* 
No. of patients in final analysis	N=415/541 (PD-L1 ≥1%)	N=305/1934 (all comers)

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Keynote 21 cohort G – Phase II study of frontline Pembrolizumab +CT vs. CT





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

Langer C. et al. Ann. Oncol. Proccedings ESMO 2016

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Advanced NSCLC , PS 0-1, cytology or histology

TTF-1, p63 (p40), PDL-1

EGFR, ALK, ROS1, (NGS)

Diagnostic box

NS-NSCLC

SQ-NSCLC*

Molecular tests positive

Appropriate targeted agent until progression

≈ 20%

NS-NSCLC PDL-1 + < 50%

Cis/carbo/pem for 4-6 cycles (± Bevacizumab)

Pemetrexed maintenance until progression

≈ 40%

NS & SQ NSCLC PDL-1 + > 50%

Pembrolizumab until progression**

≈ 15-20%

SQ NSCLC PDL-1 + < 50%

Cis/carbo doublets for 4-6 cycles or Necitumumab plus Cis/gem

≈ 25%

Progression of the disease

*Consider molecular tests if SQ-NSCLC is diagnosed in a never smoker or ≤ 40 years

** according to the eligibility criteria of KEYNOTE 024

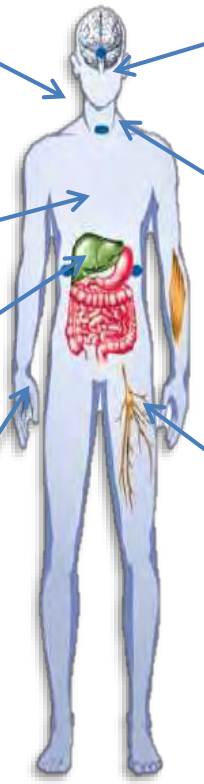
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

irAEs with Immunotherapy

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens Johnson Syndrome
- Toxic Epidermal Necrolysis
- Vitiligo
- Alopecia

Eye
- Uveitis
- Iritis

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis



Hepatic
Hepatitis, autoimmune

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

Gastrointestinal (GI)
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Neurologic
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia Gravis like syndrome

Renal
- Nephritis, autoimmune
- Renal failure

If not vigilant, may result in more serious immune-related adverse events

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

Onset:

Average is 6-12 wks after initiation of therapy
Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy

Occasional (5% to 20%)

- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Toxicity Guidelines

- TFTs, CBCs, LFTs and metabolic panels should be obtained at each treatment and q 6-12 weeks for 6 months post-treatment in all patients receiving checkpoint protein antibodies
- ACTH, cortisol should also be checked in patients with fatigue and nonspecific symptoms, plus testosterone in men
- Frequency of follow-up testing should be adjusted to individual response and AEs that occur
- Corticosteroids can reverse nearly all toxicities associated with these agents, but should be reserved for grade 3/4, or prolonged grade 2, irAEs

Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The Biomarker Questions…

- Do we need biomarkers for cancer immunotherapies?

  - ✓ Treatment options for patients with oncogenic drivers go beyond resistance
  - ✓ Responses to chemotherapy in tumors without druggable oncogenic drivers are poor from 2L on
  - ✓ Clearly 1L therapy selection is biomarker guided

    (targeted therapies vs chemotherapy vs immunetherapies)

- Do we have biomarkers for cancer immunotherapies that help to identify the patients that benefit most from treatments?

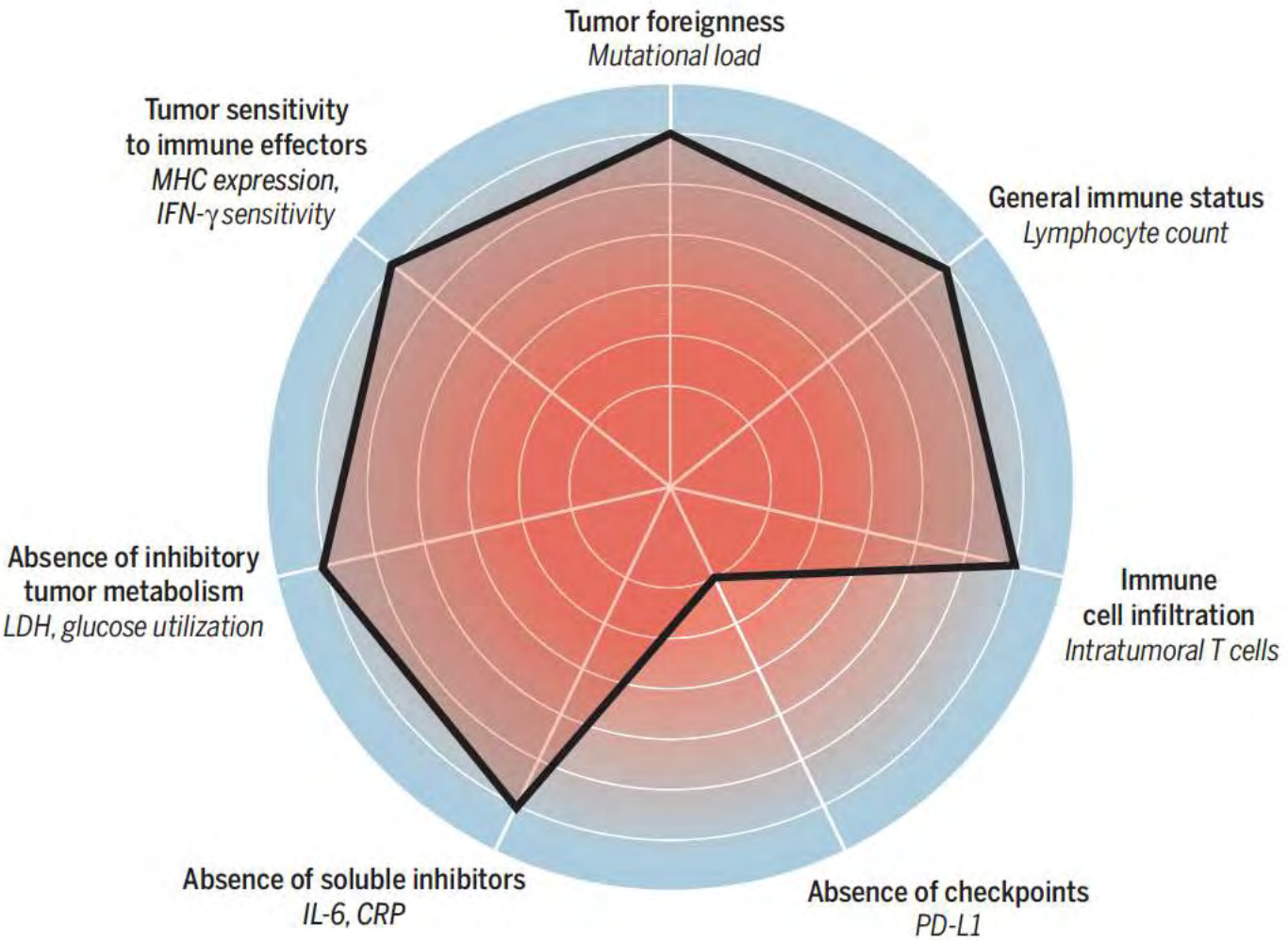
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Key Translational Questions for PD-1 Pathway Blockade

- Predictive Biomarkers
  - ✓ Which tumors to treat?
  - ✓ Which patients to treat?
- Other combinations?
- Line of therapy?
- What to do for tumors without immune infiltrates?

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The cancer immunogram

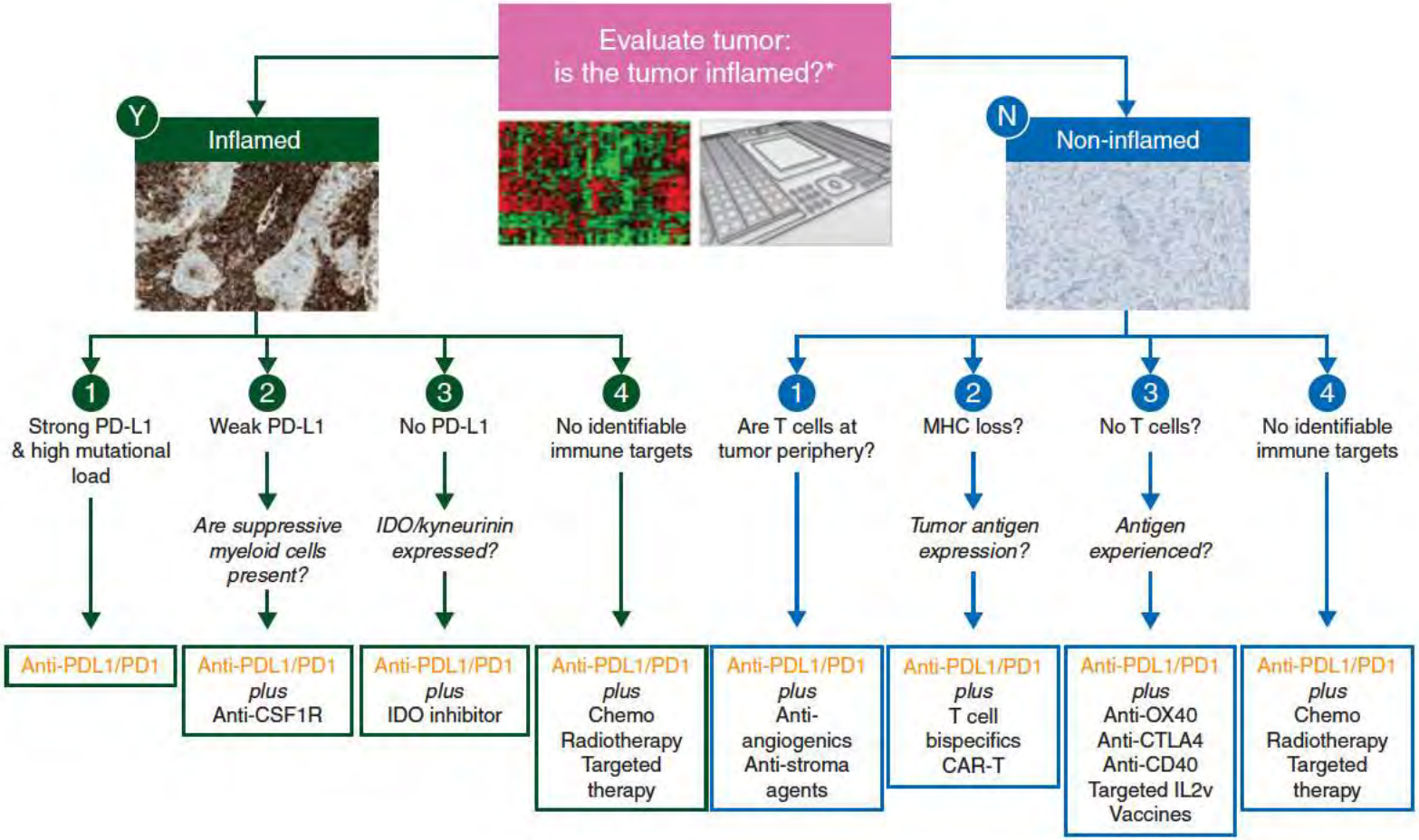


Blank CU et al. Science 2016; 352:658

UNIVERSITÀ DEGLI STUDI DI TORINO

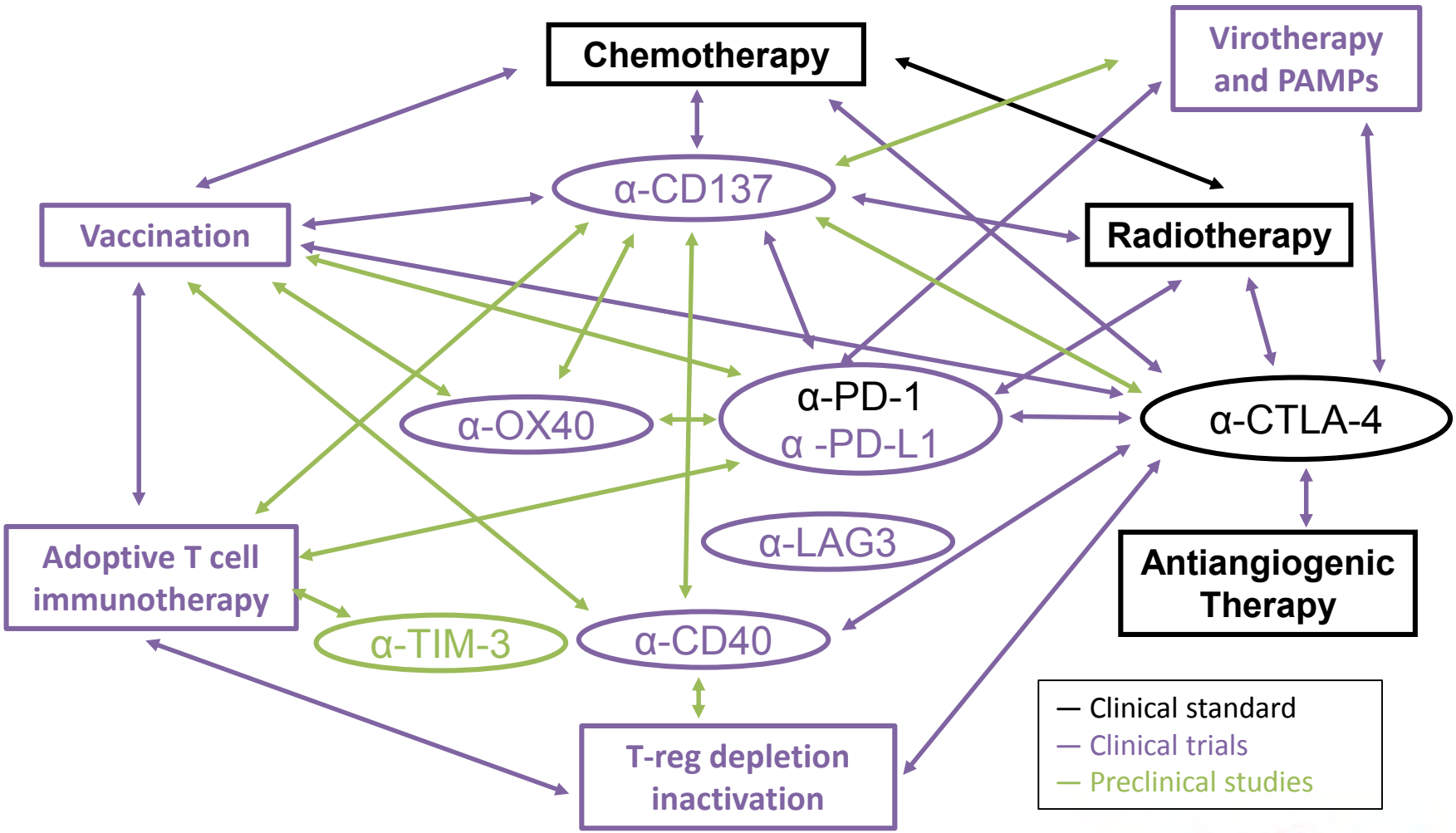
ALMA UNIVERSITAS TAURINENSIS

Personalized cancer immunotherapy paradigm



UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

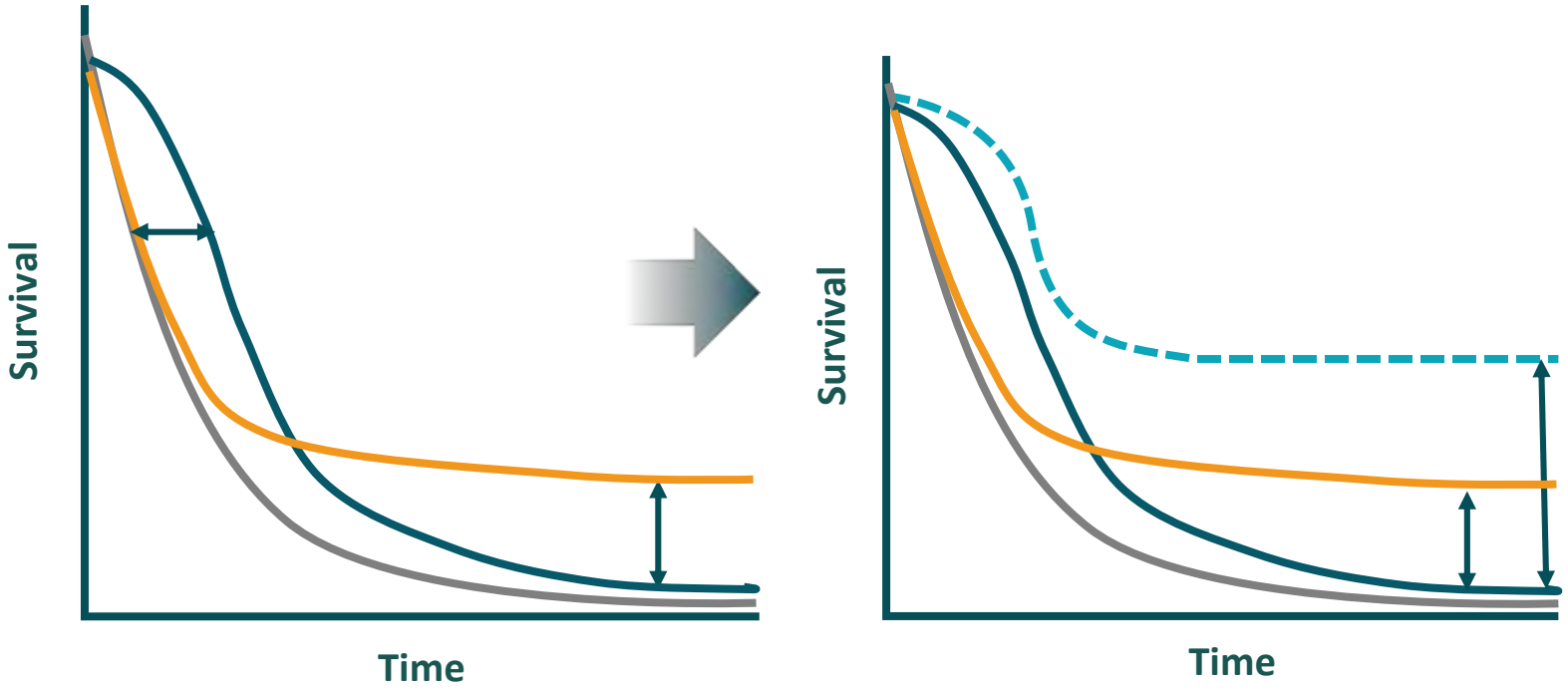
Rationale Combinations: the Way Forward



UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Where we are now

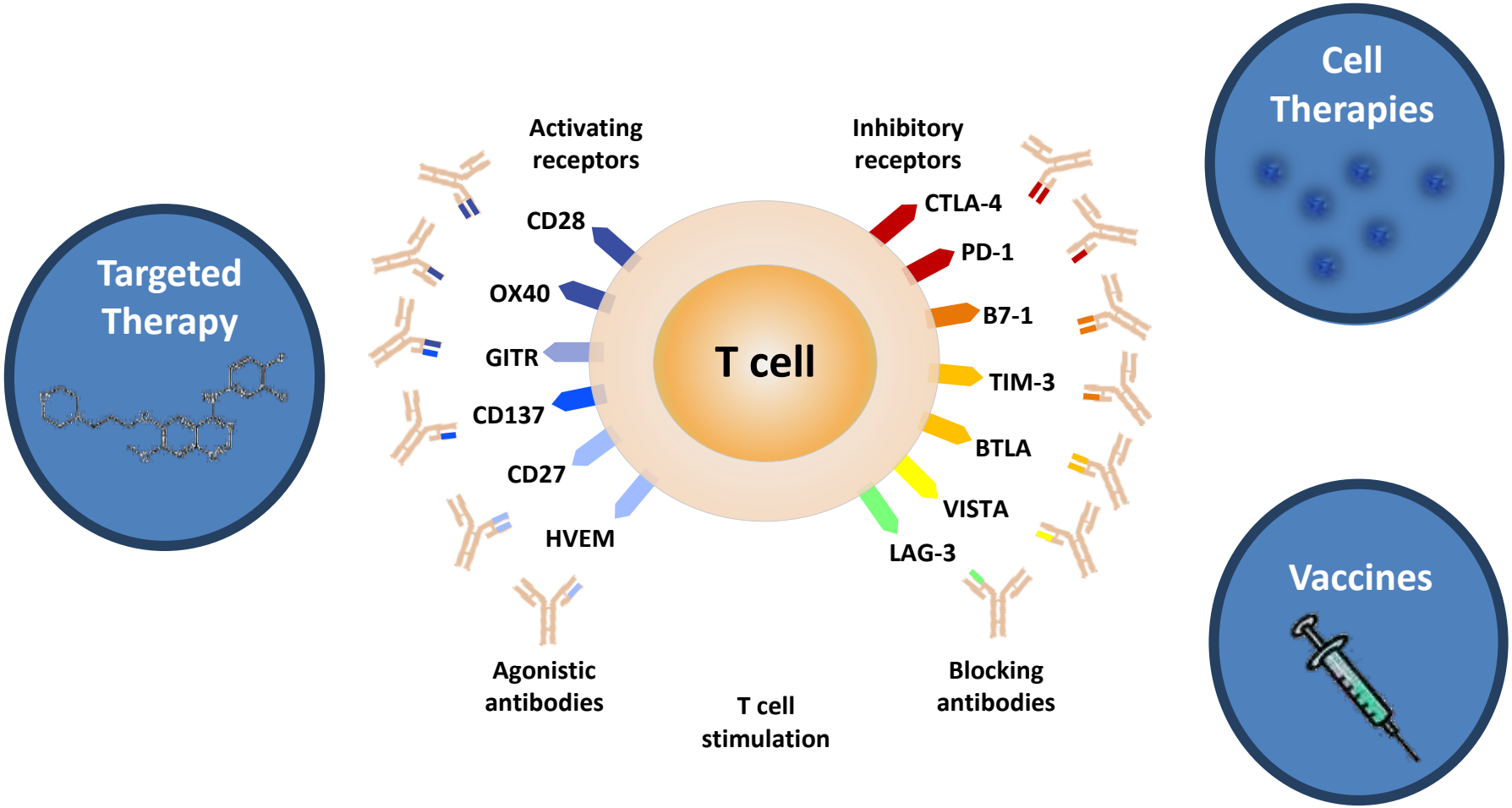
Where we want to be



Salvati M, 3rd Intl Symp in Lung Ca, 2014; Ribas A, WCM, 2013; Ribas A, et al. Clin Cancer Res 2012; Drake CG. Ann Oncol 2012

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

T-Cell Immune Checkpoints as Targets for Immunotherapy



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

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

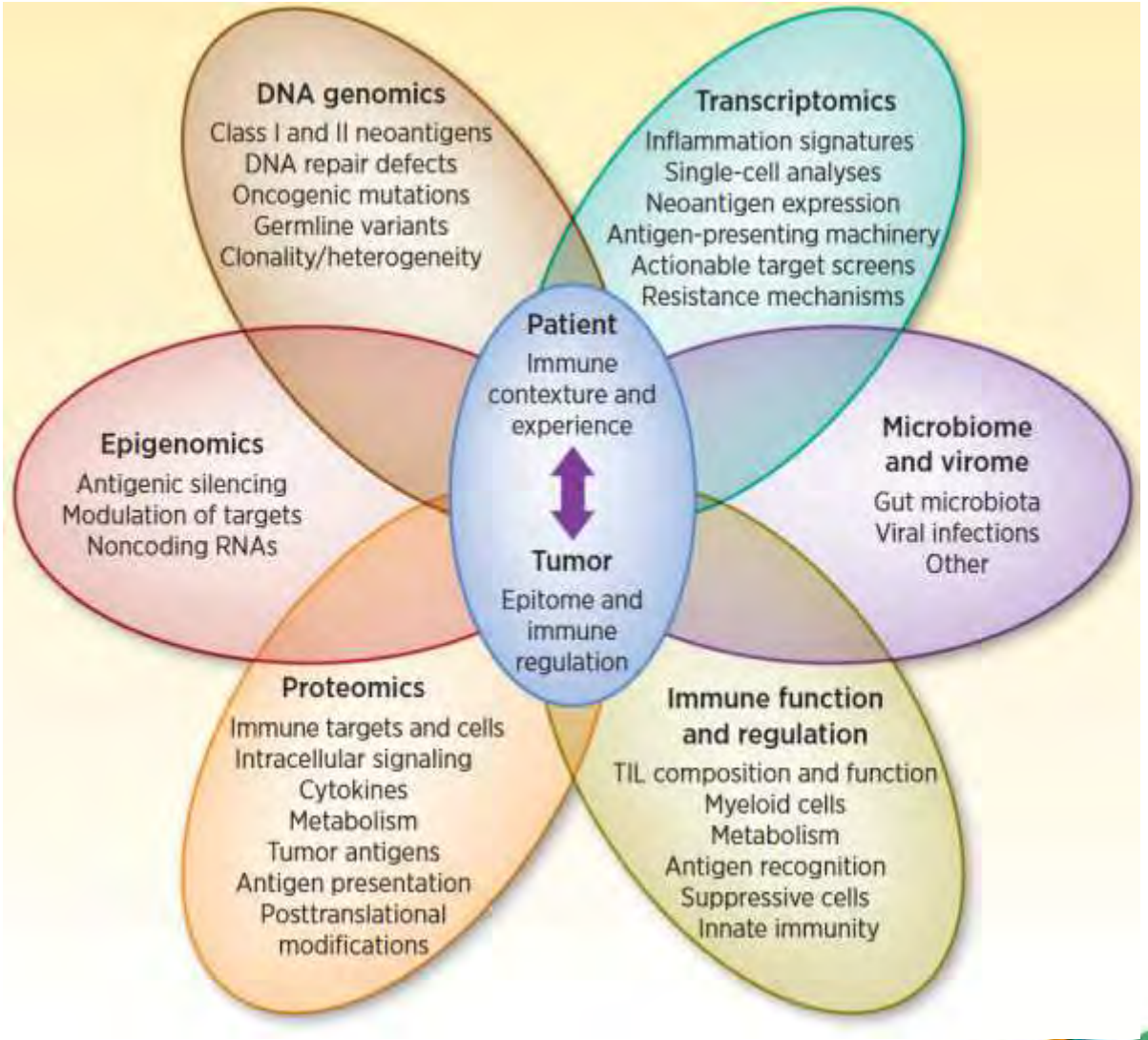
Combination treatment

	Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks (n=38)	Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (n=39)
Confirmed objective response*	18 (47% [31–64])	15 (38% [23–55])
Confirmed disease control†	30 (79% [63–90])	22 (56% [40–72])
Best overall response‡		
Complete response	0	0
Partial response	18 (47%)	15 (38%)
Stable disease	12 (32%)	7 (18%)
Stable disease for ≥6 months	6 (16%)	3 (8%)
Progressive disease	5 (13%)	11 (28%)
Unable to determine	3 (8%)	6 (15%)
Ongoing responses§	13 (72%)	12 (80%)
Median duration of response (months)¶	NR (11·3–NR)	NR (8·4–NR)
Median progression-free survival (months)	8·1 (5·6–13·6)	3·9 (2·6–13·2)
Progression-free survival at 24 weeks	68% (50–80)	47% (31–62)
1 year overall survival	NC	69% (52–81)

Hellman, Lancet Oncol 2017

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Translational view of the complex patient–tumor immune interactions



Schalper KA et al. Clin. Cancer Res. 2016; 22:2102

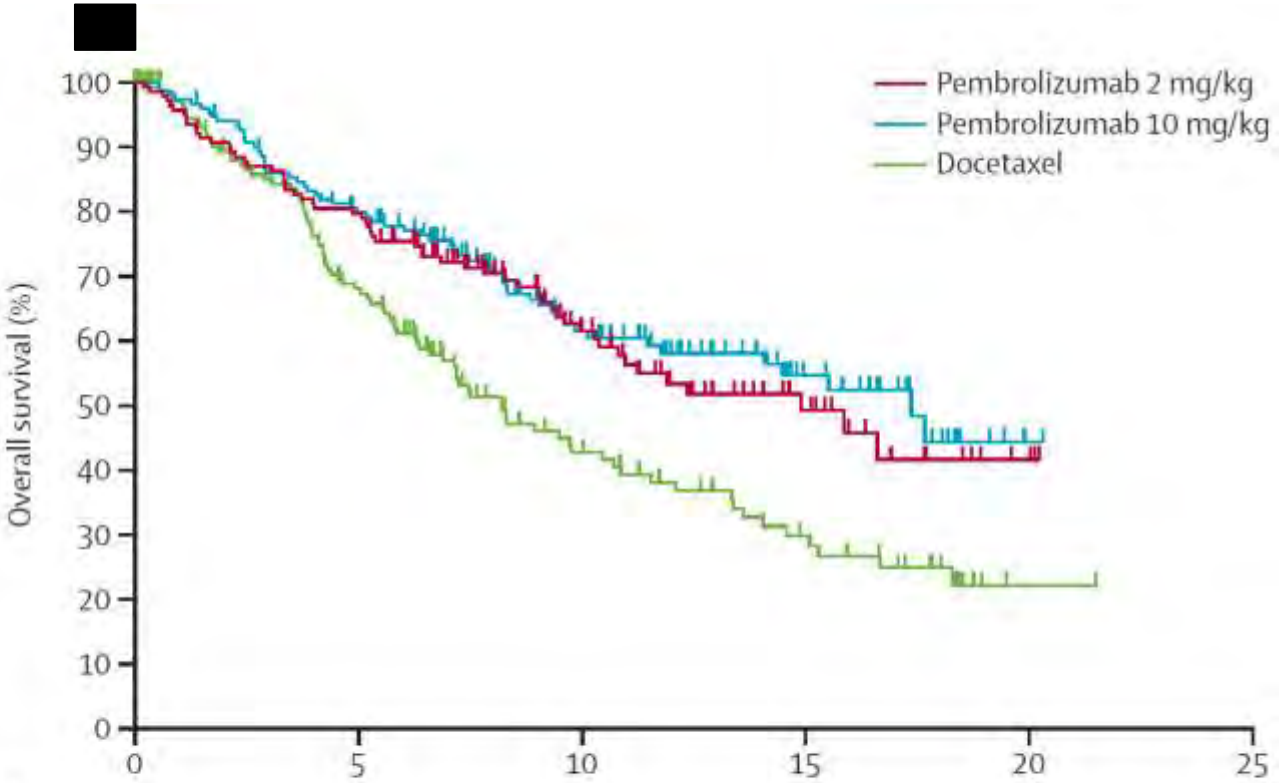
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Conclusions

- In second line both PD- 1 and PD-L1 treatment show a consistent increase in OS compared to docetaxel
- PD-1 treatment with pembrolizumab shows an increase in progression free survival compared to chemotherapy in a highly selected study population
- Still unclear
  - ✓ Patient selection
    - PD-L1 expression enriches, but far from perfect
  - ✓ Duration of treatment
  - ✓ Combination treatment
    - Combination IO
    - Combination with chemotherapy
  - ✓ Sequencing

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab – KEYNOTE 010
All histologies, PD-L1 cut off >1%



Number at risk						
Pembrolizumab 2 mg/kg	139	110	51	20	3	0
Pembrolizumab 10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

Herbst et al. Lancet 2016;387:1540-1550.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

What are the data, first line

Key patient inclusion criteria

- Untreated stage IV NSCLC

Differences between studies

PD-L1 cut-off

Histology

R

Platinum chemotherapy → Cross over

PD-(L)1 checkpoint inhibitor → Cross over

Primary endpoint: PFS

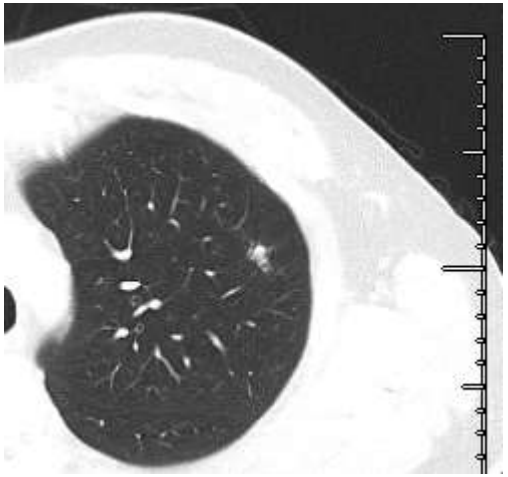
Secondary endpoint: OS, response rate, QOL

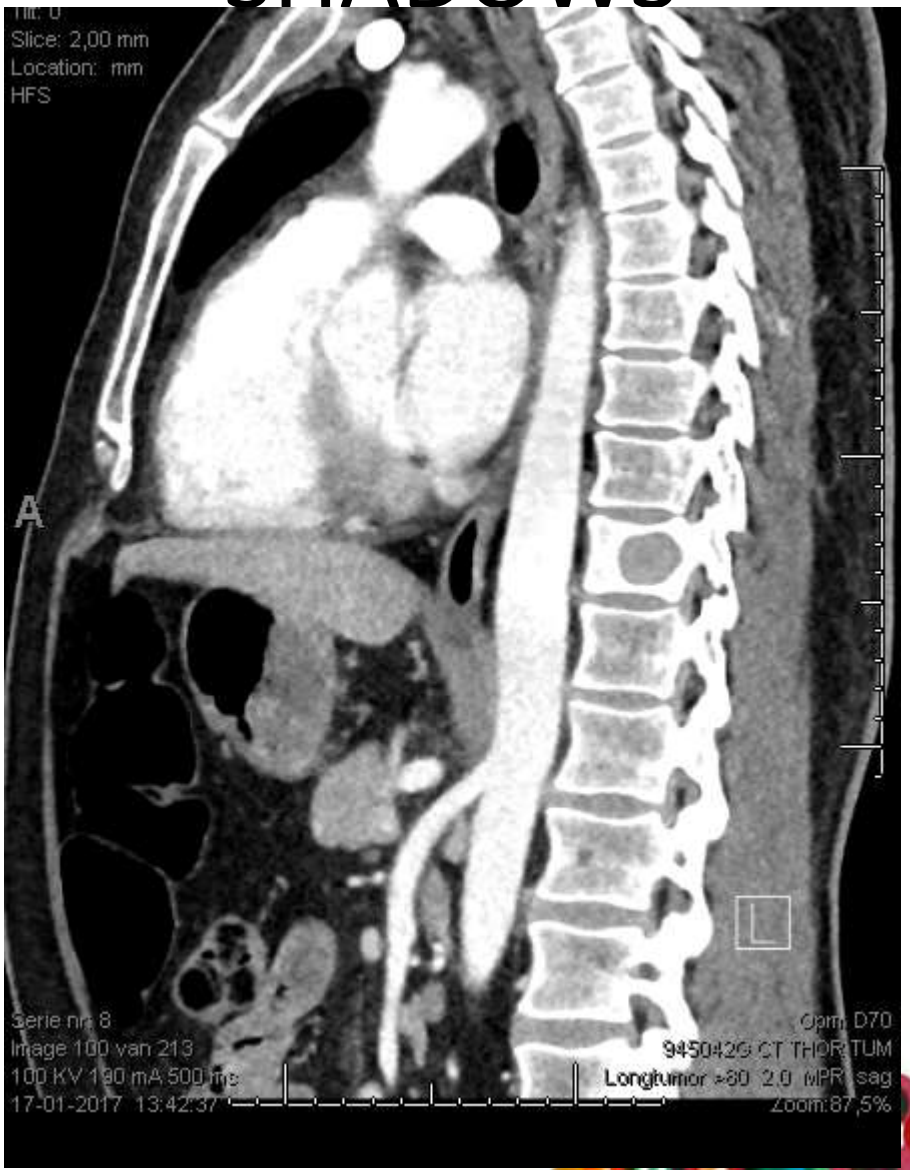
UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

Immune checkpoints SHADOWS

- January 2017

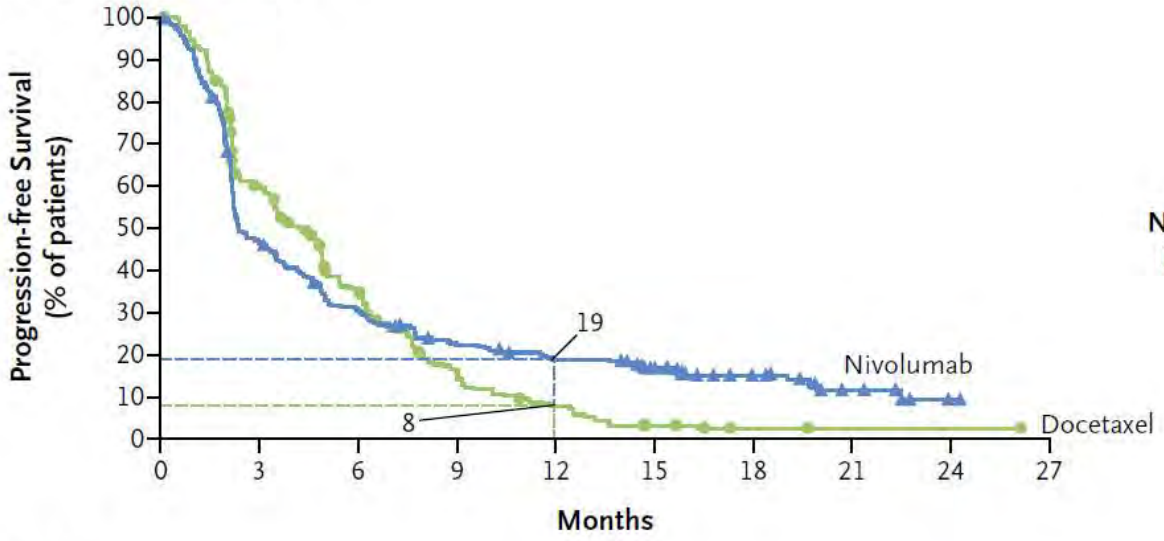




UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

PFS curve in non-squamous NSCLC

Progression-free Survival



No. at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

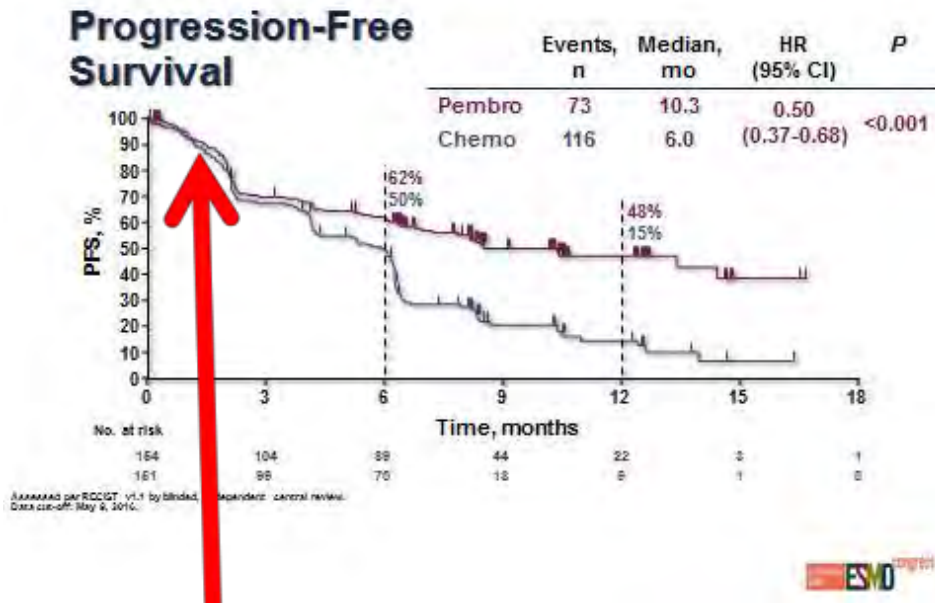
N Engl J Med 2015;373:1627

UNIVERSITÀ DEGLI STUDI DI TORINO

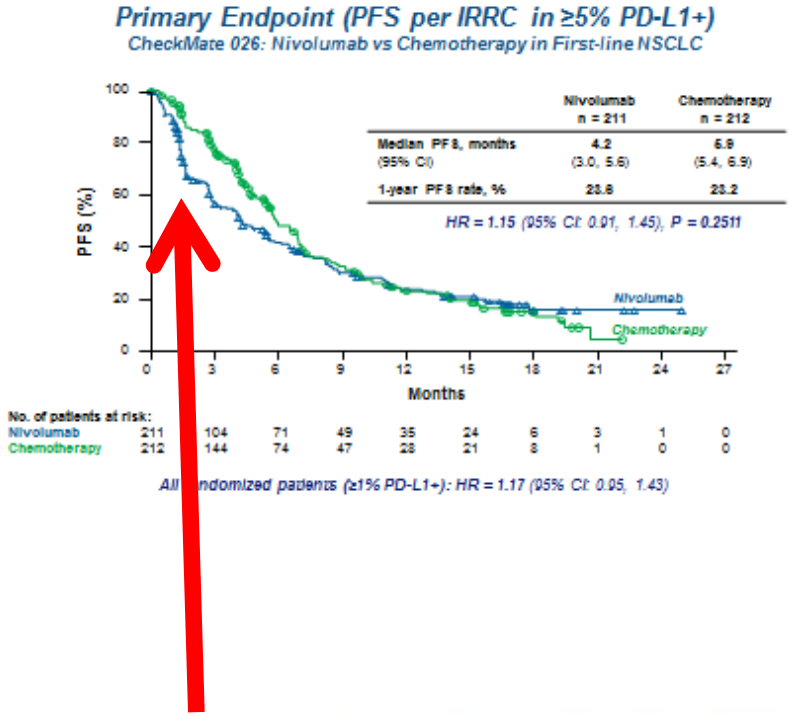
ALMA UNIVERSITAS TAURINENSIS

PD-1/PD-L1 is targeted treatment

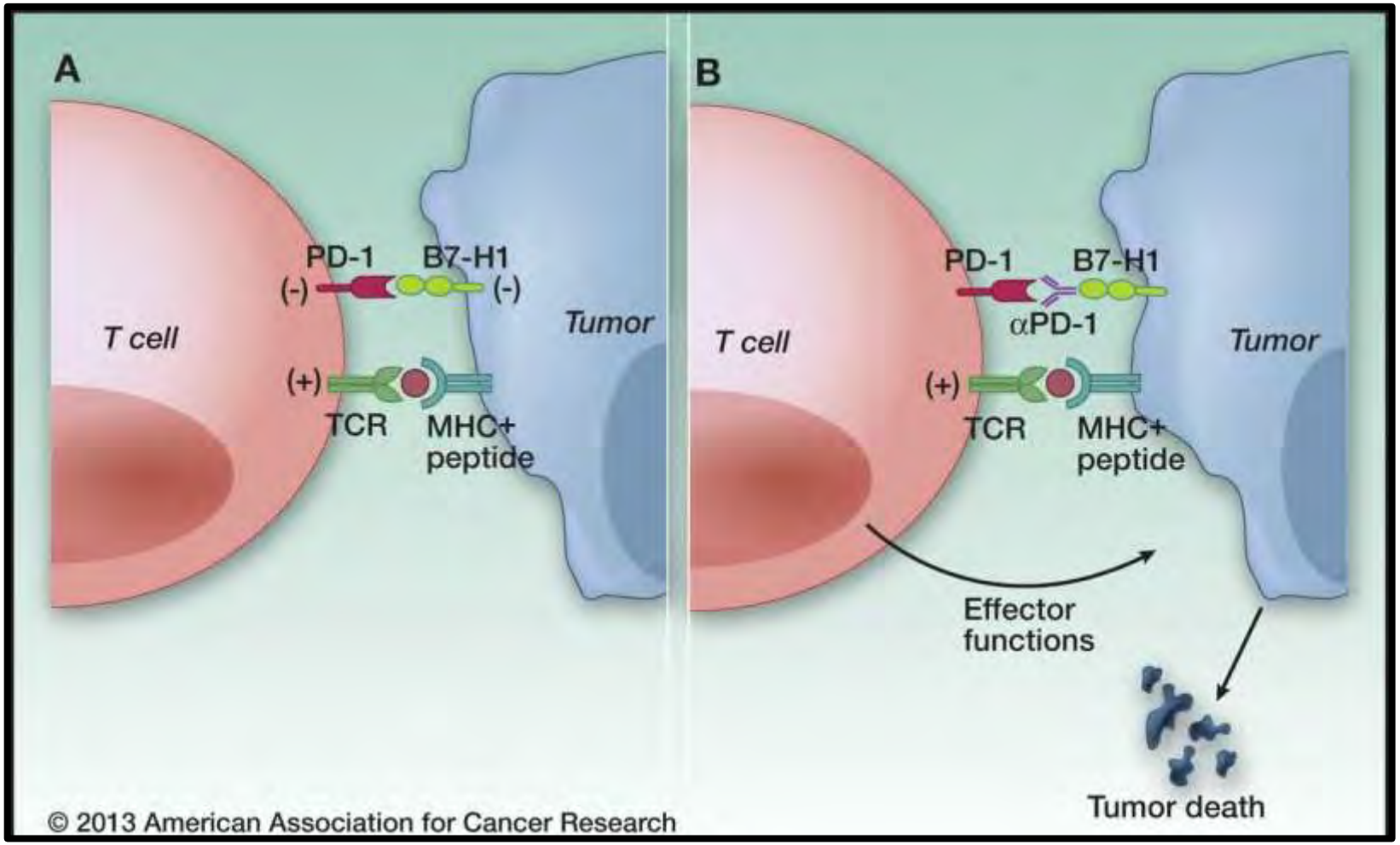
Keynote 024



Checkmate 026



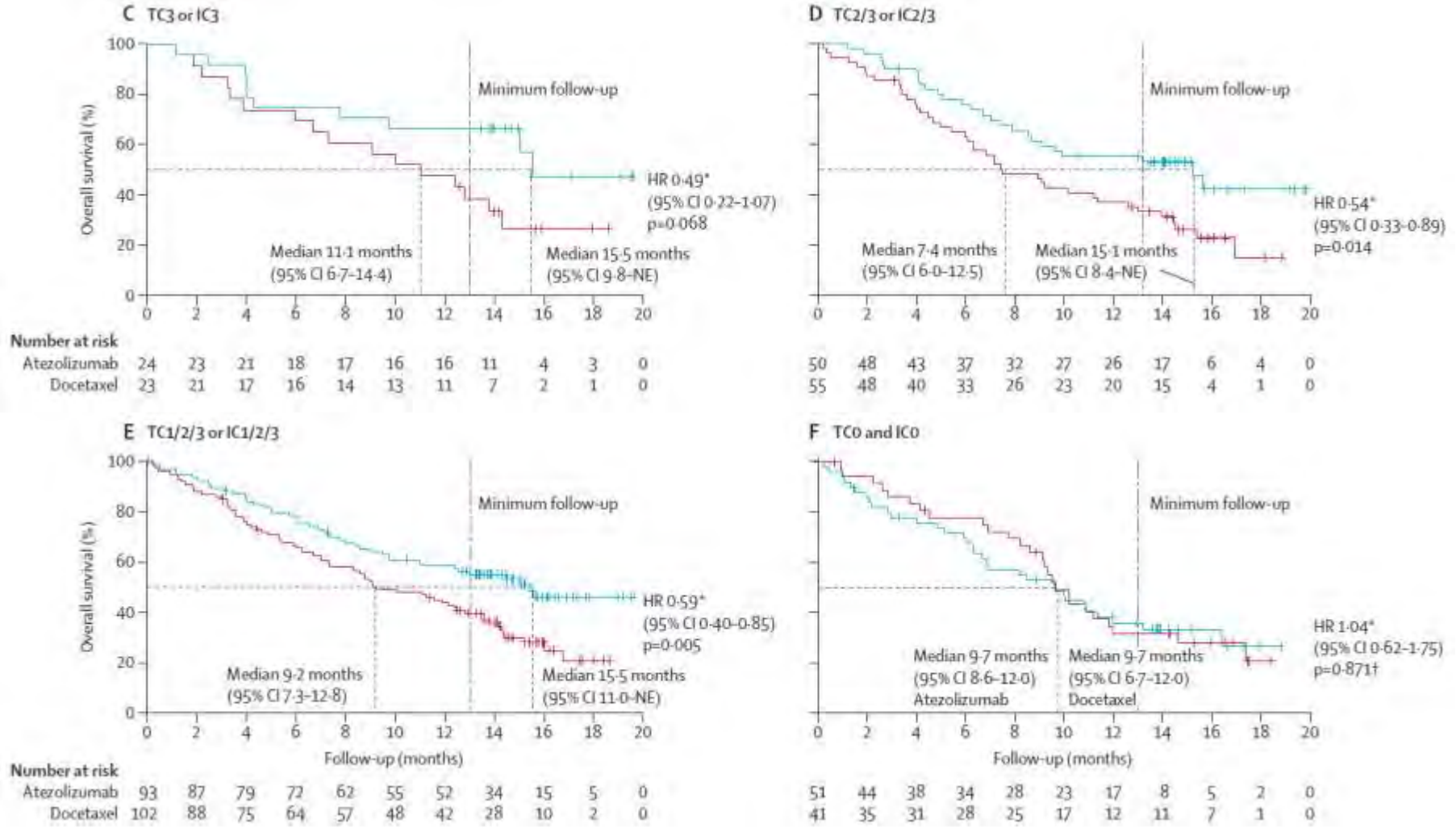
PD-1/PD-L1 targeted therapy



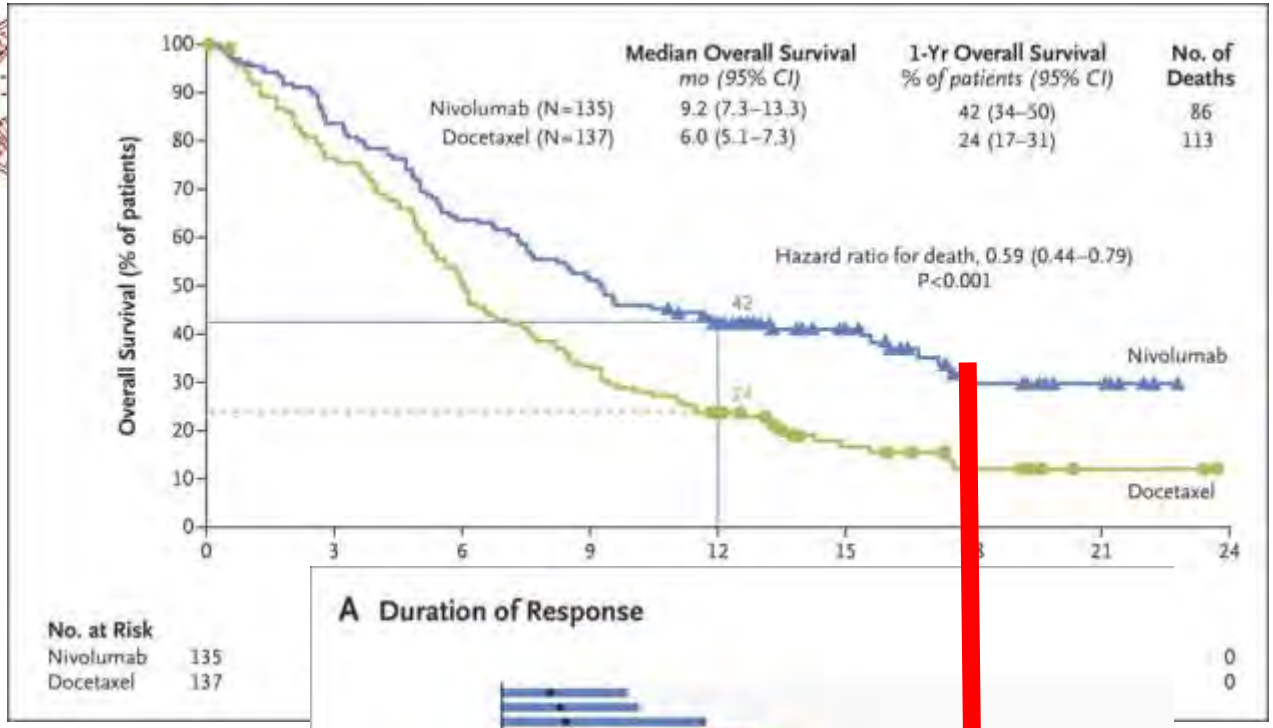
Sznol M et al. Clin Cancer Res 2013;19:1021-1034.

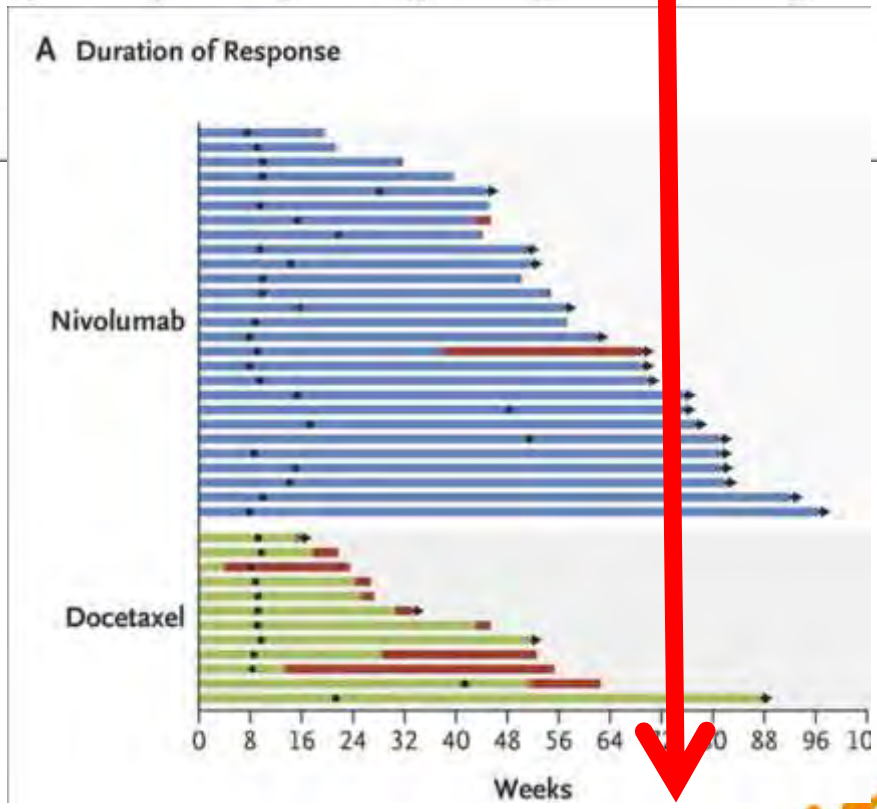
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Atezolizumab based on PD-L1 positivity



et al. Lancet 2016;387:1837–46.



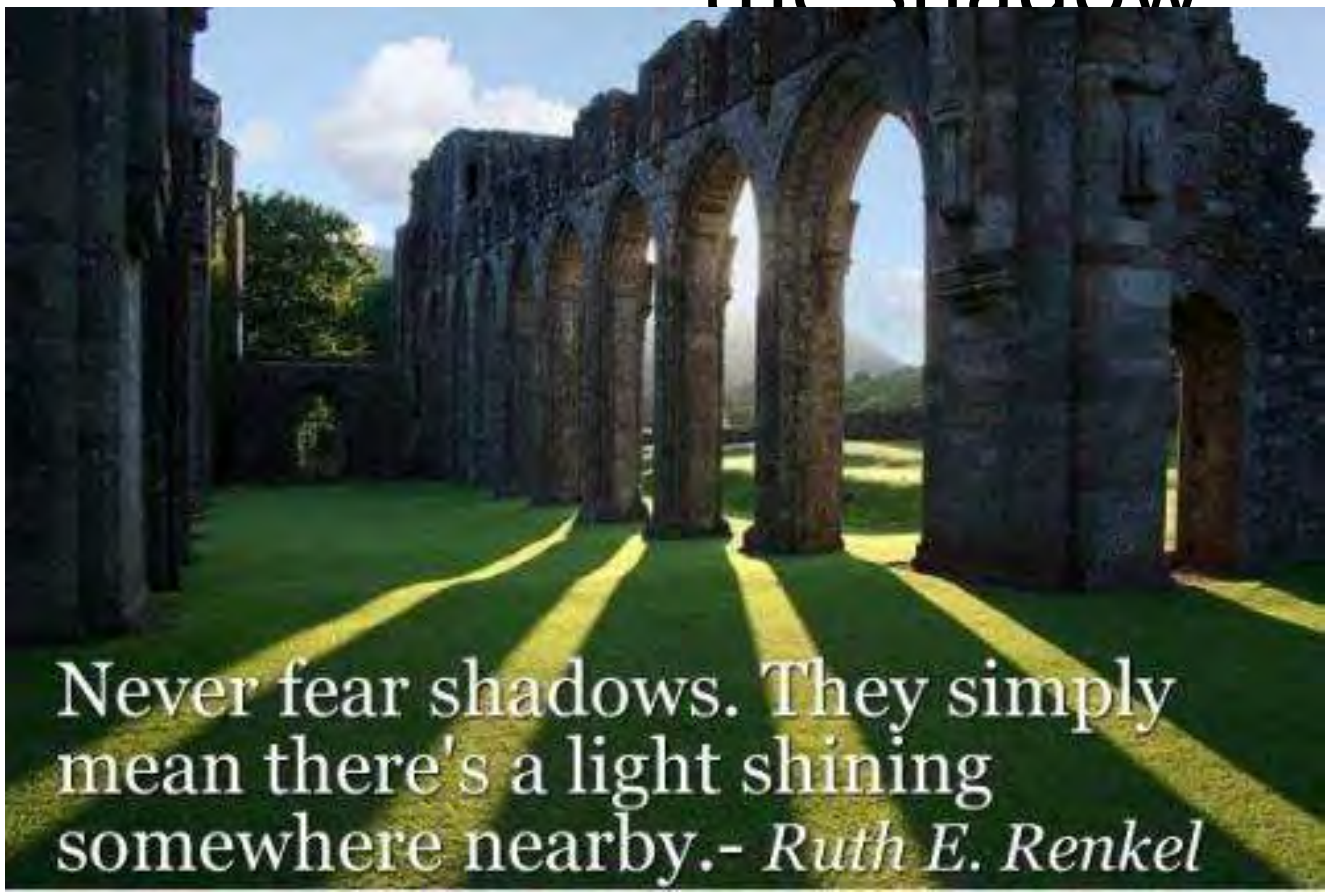


Brahmer NEJM 2015 suppl data

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

How to bring light into the shadow



UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

How to bring light into the shadow

- Patient selection
  - PD-L1 expression enriches, but far from perfect
- Combination treatment
  - Combination IO
  - Combination with chemotherapy

Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021

Pembrolizumab + chemotherapy
Pembrolizumab 200 mg q3w (2 years) + carboplatin AUC5 mg/mL/min + pemetrexed 500 mg/m^2 q3w (4 cycles)* (n=60)

R
1:1

Stratification

- PD-L1 status (TPS ≥1 vs. <1%)

Chemotherapy
Carboplatin AUC5 mg/mL/min + pemetrexed 500 mg/m^2 q3w (4 cycles)* (n=63)

PD

Pembro 200 mg q3w (2 years)

Primary endpoint

- ORR (RECIST)

Secondary endpoints

- PFS, OS, safety, relationship between anti-tumor activity and PD-L1 TPS

*Pemetrexed 500 mg/m^2 q3w permitted as maintenance therapy

Langer et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA46_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

PR:

pemetr

nd

t-line

t

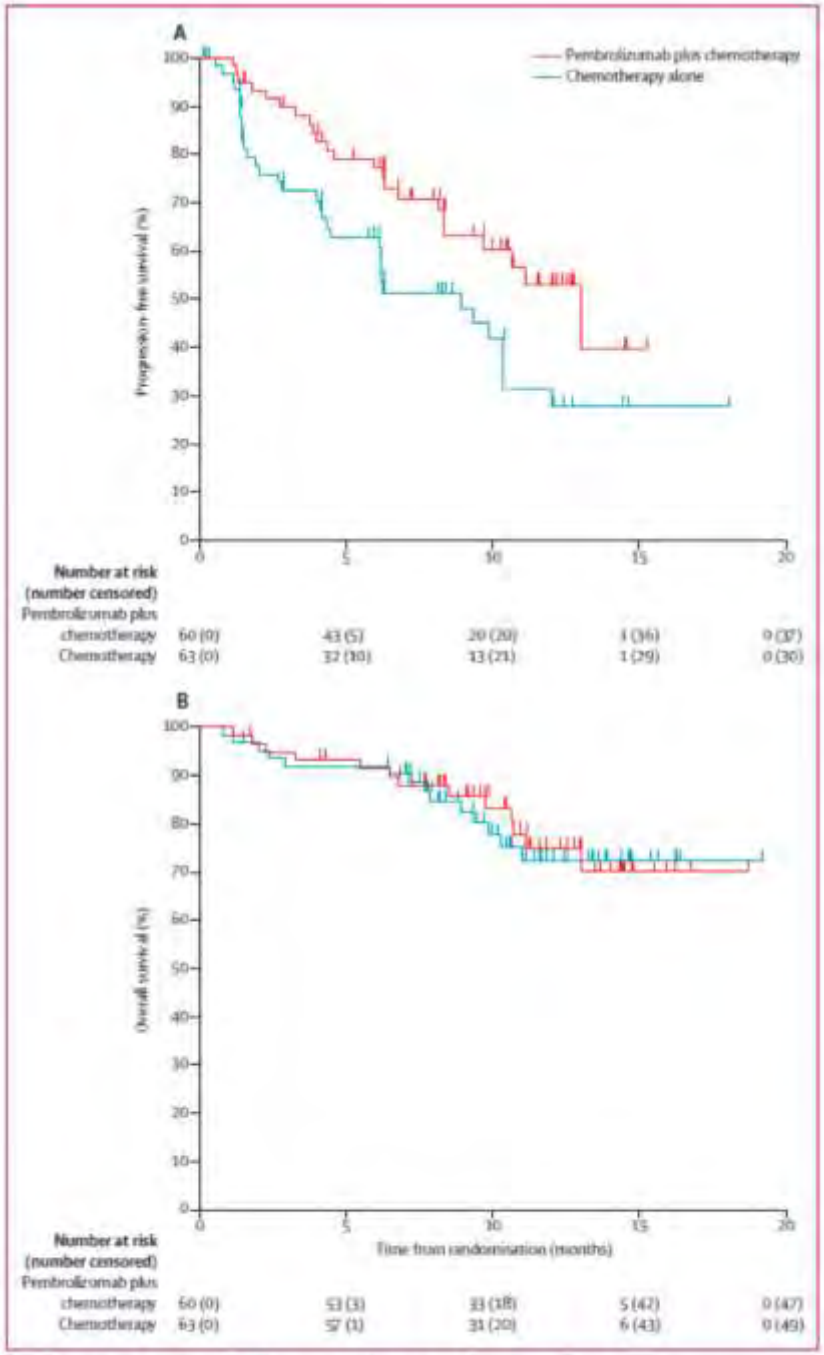


Figure 3: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)
Progression-free survival assessed per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review in the intention-to-treat population

Pembro 200 mg q3w (2 years)

Primary endpoint

- ORR (RECIST)

anti-

*Pemetrexed 500 mg/m^2 q3w permitted as maintenance th

rLBA46_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Take home message

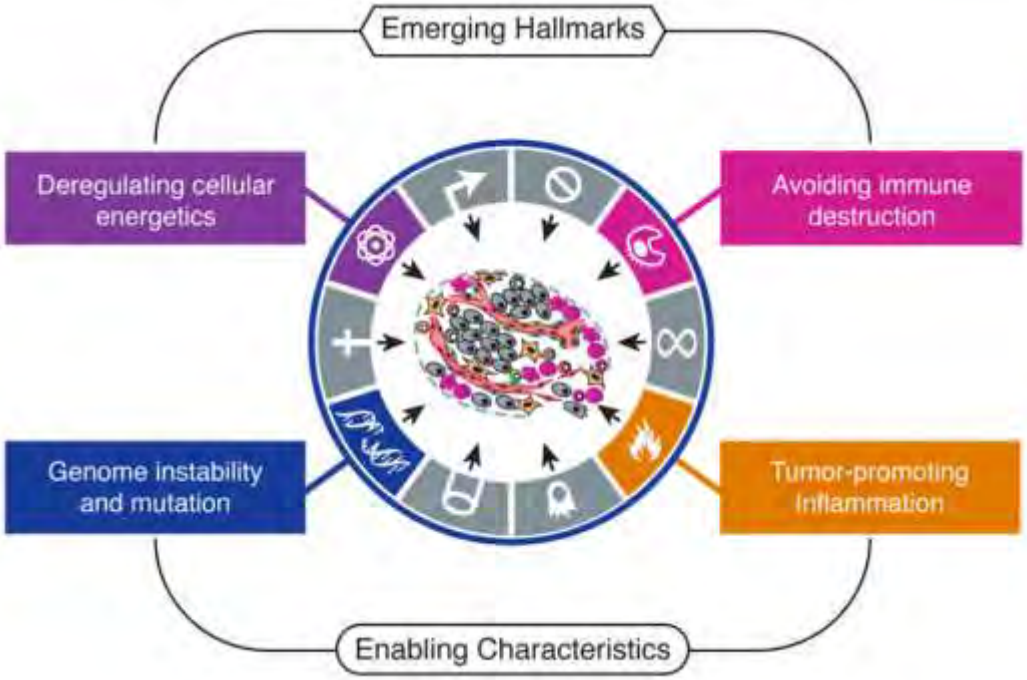
- Immunotherapy can be considered a new standard treatment in NSCLC

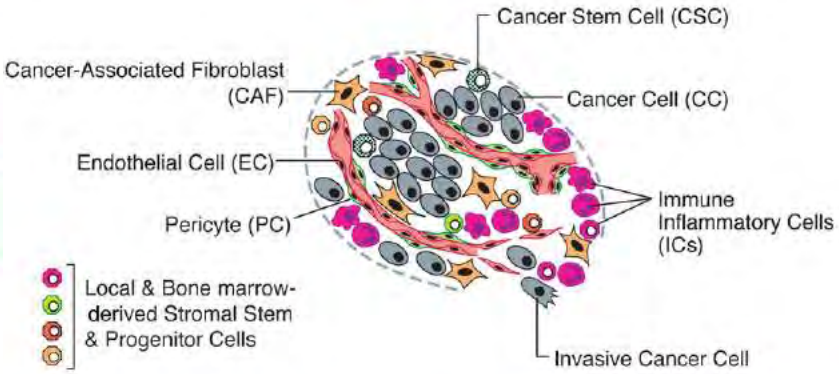
- Still unclear:
  - Patient selection
    - PD-L1 + is not the ideal marker
  - Combination treatment
    - Develop scientific logical not PHARMA-logical combinations
  - Scheduling
    - Cross over

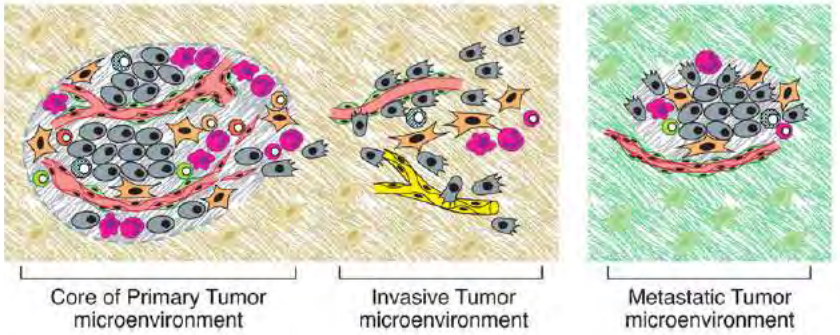
UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

Emerging hallmarks, enabling characteristics and tumor microenviroment

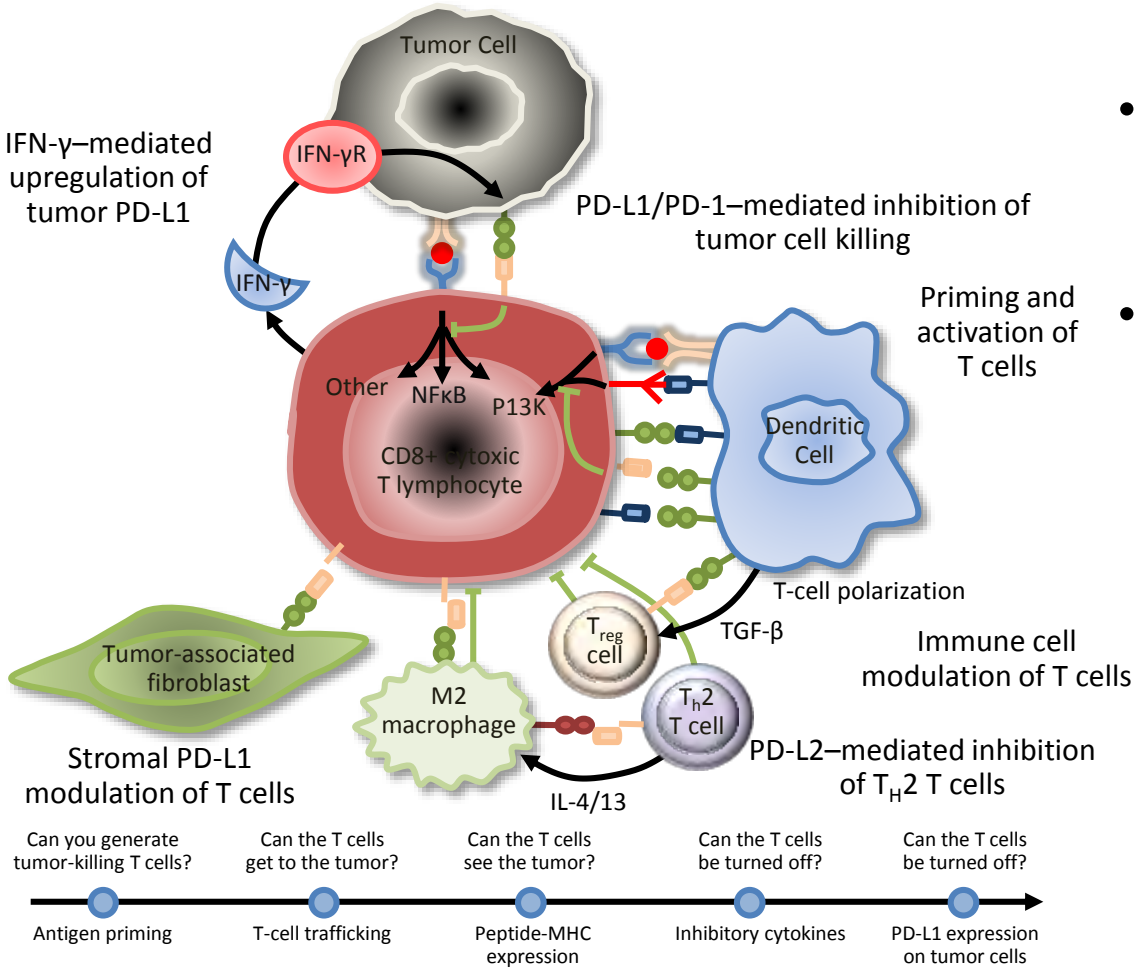




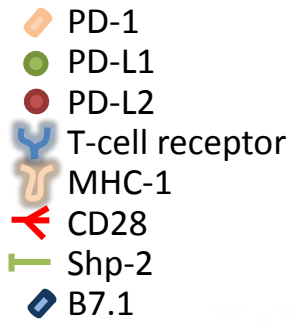


Hahahan D & Weinberg RA Cell 2011; 144: 6462

PD-1 Blockade: Binding to PD-L1 (B7-H1) and PD-L2 (B7-DC) Revives T Cells

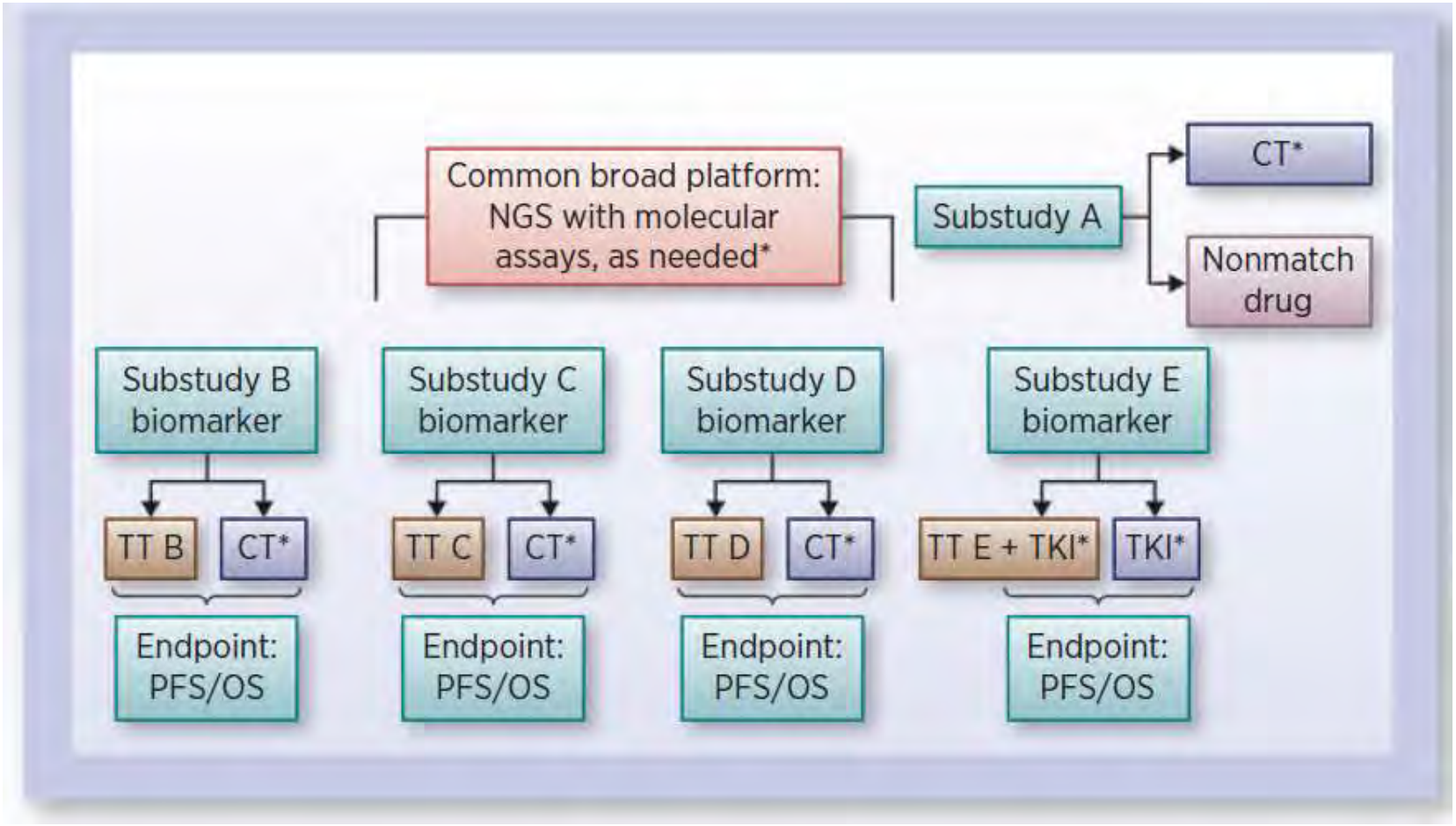


- PD-L1 expression on tumor cells induced by interferon-γ
- Activated T cells that could kill tumors are specifically disabled



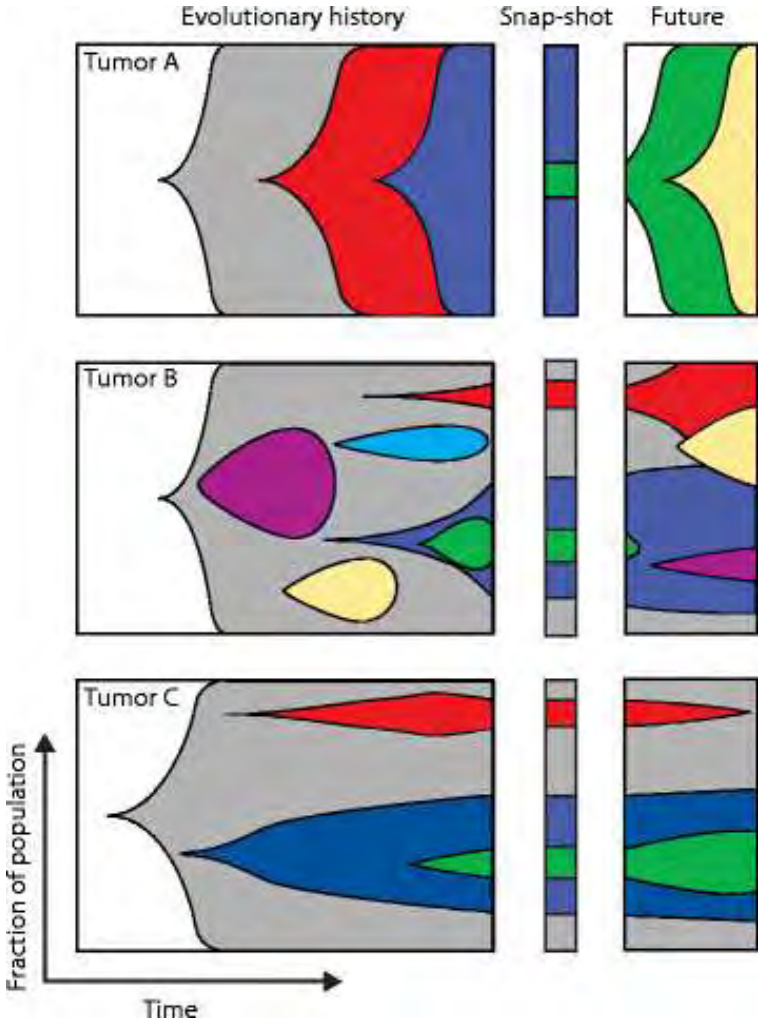
Sznol M, et al. Clin Cancer Res. 2013;19:1021-1034.

LUNG-MAP



Herbst R et al. Clin Cancer Res 2015, 21,1514

Dynamics of Cancer
Evolution of Three Tumors



Linear evolution pattern

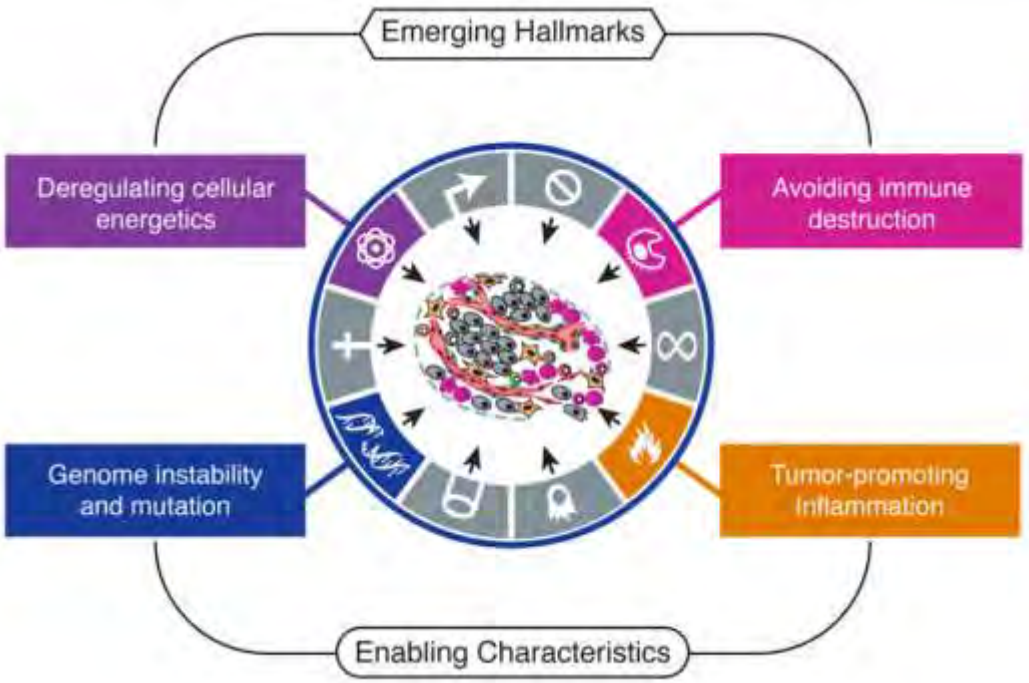
Branched evolution pattern

Hiley et al. Genome Biology 2014 15:453

UNIVERSITÀ DEGLI STUDI DI TORINO

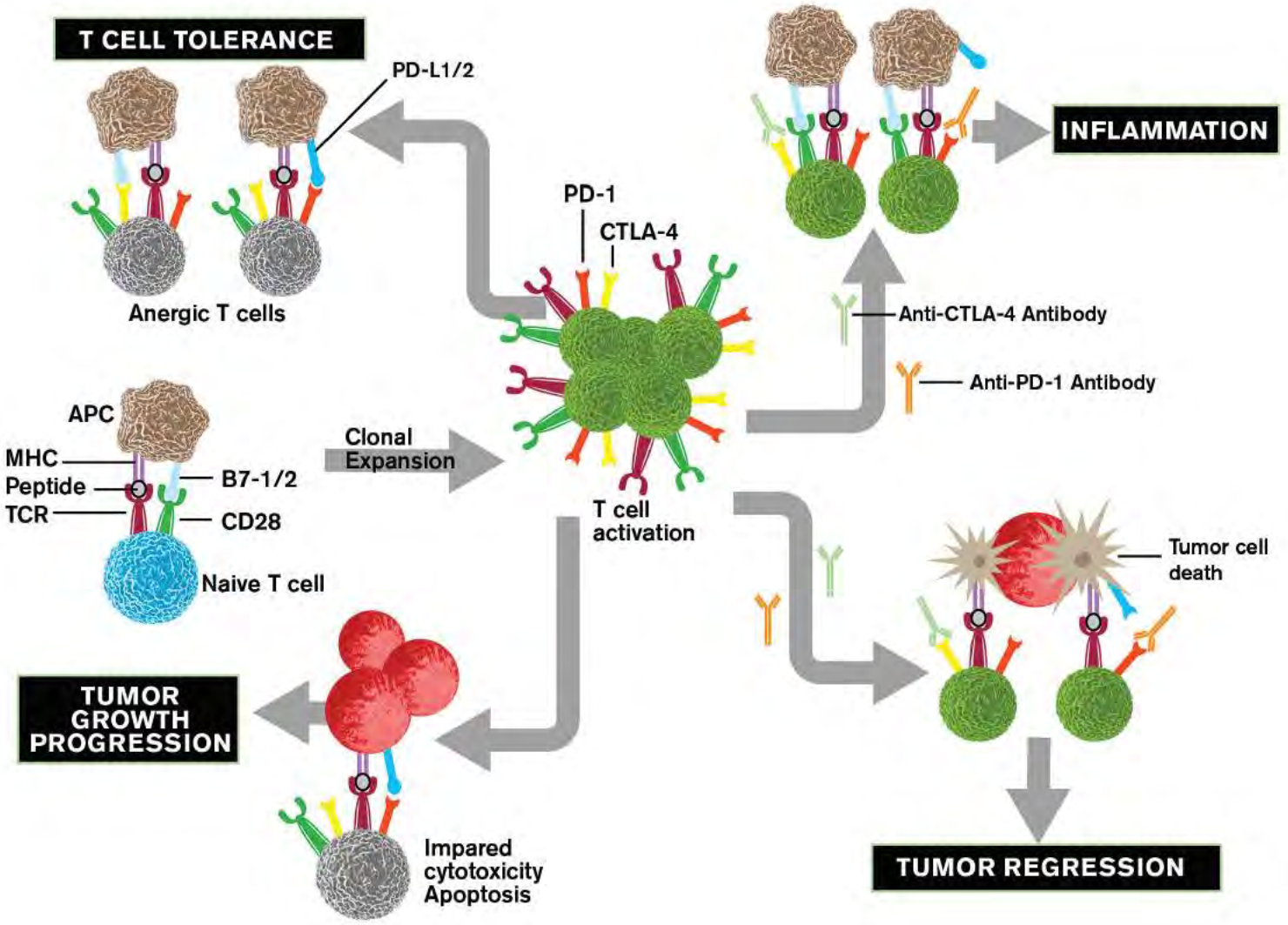
ALMA UNIVERSITAS TAURINENSIS

Emerging hallmarks, enabling characteristics and tumor micro-enviroment



Hahahan D & Weinberg RA Cell 2011; 144: 6462

Chronic inflammation and cancer



Wang D & Du Bois RN Carcinogenesis, 2015; 36: 1085–1093

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The unit in Precision Medicine is a "biomarker ensemble"

- Assumption : *"Treatment T is effective for condition C, as defined by testing positive for biomarker B, where B is determined by diagnostic assay A."*

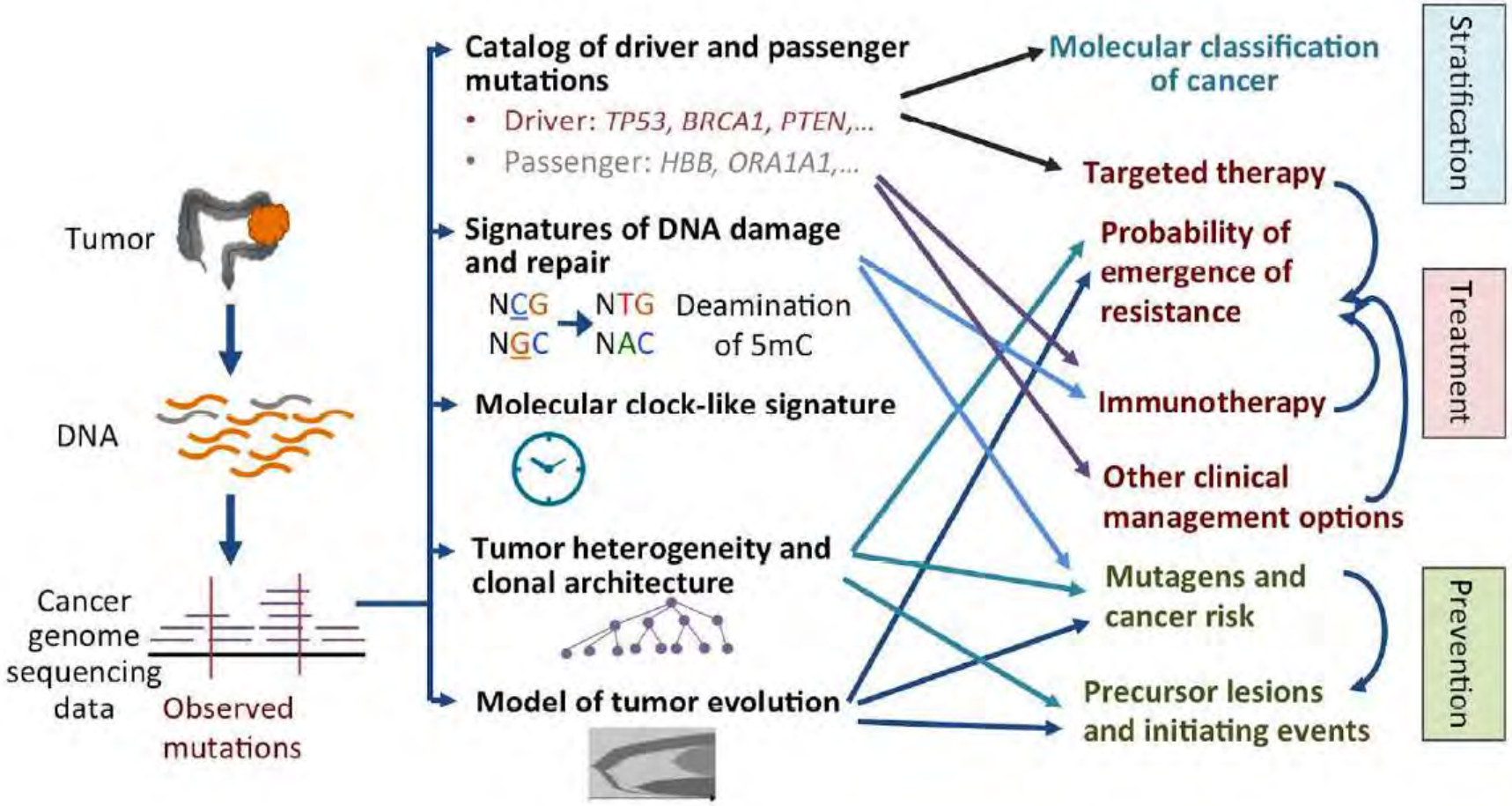
- A biomarker, hypothesized to play a crucial role in the disease pathway

- A diagnostic assay, used to determine a patient's biomarker status; and

- A therapeutic agent, intended to be more effective for patients who are "biomarker-positive."

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

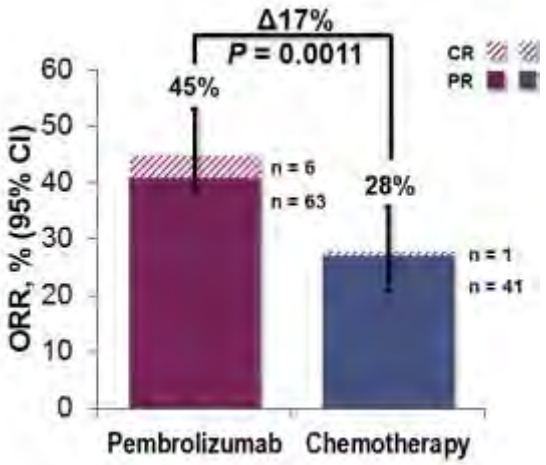
Comprehensive analyses of cancer genome sequencing data

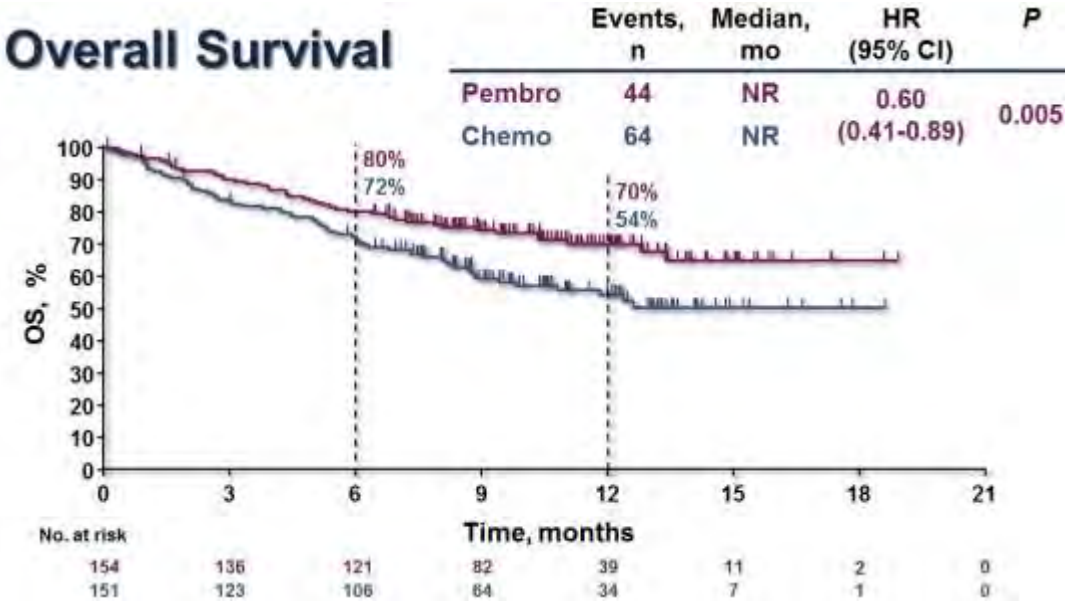


De S., Ganesan S. Ann. Oncol. 2016; ahead of print

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab vs platinum-based CT as first-line therapy – OS and ORR





→ ORR is improved, with a control arm that performs as expected (from other phase III trials)
→ Time to Response is identical between Pembro & Ct
→ PFS is improved by 4.3 months (HR of 0.50)
→ Strongest signal of PFS benefit observed in SCC (HR of 0.35)
→ Cross-over was limited to 50% of the patients

Reck M. et al NEJM 2016; DOI: 10.1056/NEJMoa1606774; Reck M, et al. ESMO 2016. Abstract LBA8_PR.
Soria JC – Discussion Plenary Session at ESMO 2016

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

Therapeutic Algorithm for Lung Cancer in 2020

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab vs platinum-based CT as first-line therapy

Key eligibility criteria

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

R (1:1)
N=305

Pembrolizumab
200 mg IV Q3W (2 years)

Platinum-doublet chemotherapy
(4–6 cycles)

PD[a]

Pembrolizumab
200 mg Q3W
for 2 years

Key endpoints

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

Secondary: OS, ORR, safety

Exploratory: DOR

1934 patients entered screening

1729 submitted samples for PD-L1 assessment

1653 samples evaluable for PD-L1

500 TPS ≥50% (30%)

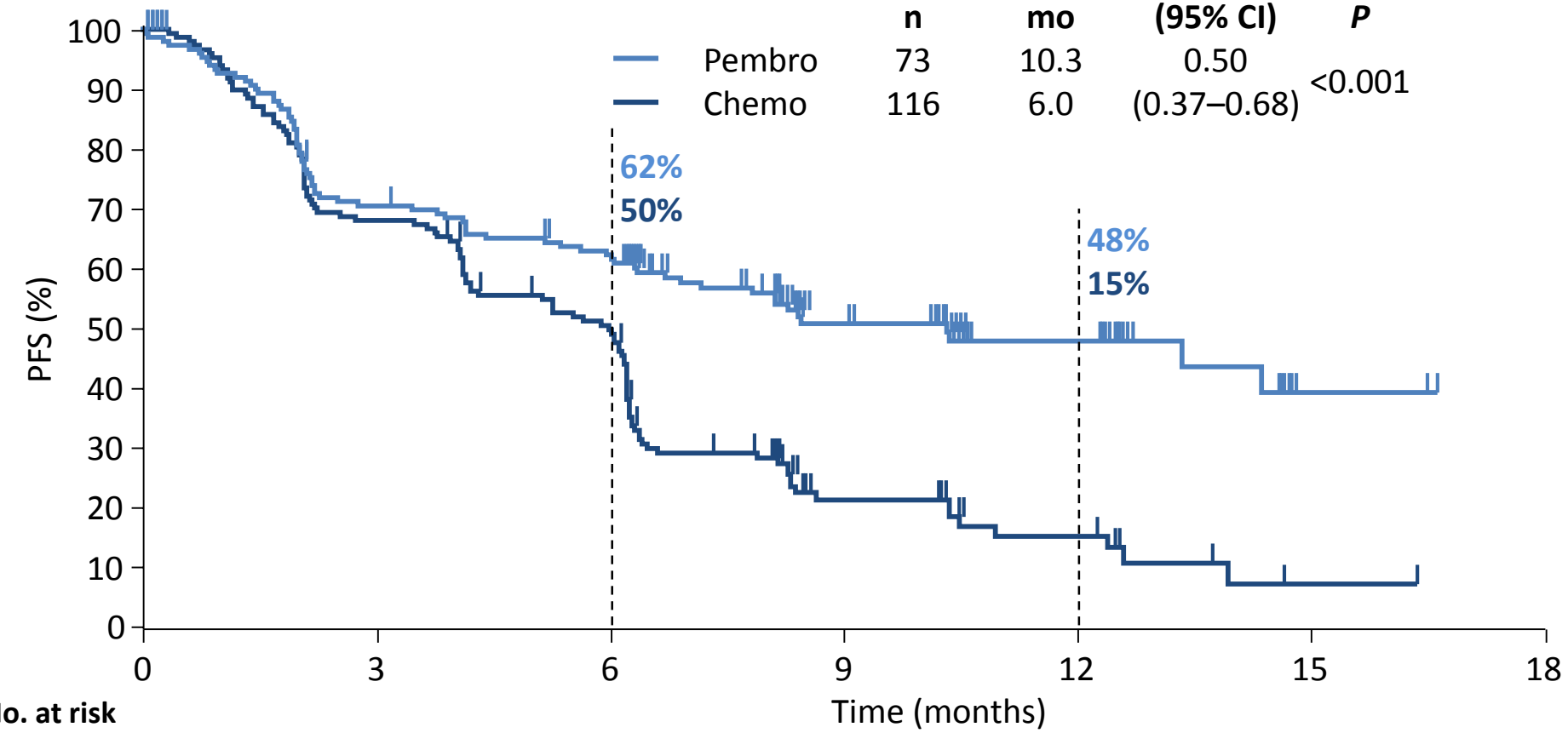
1153 TPS <50%

Reck M. et al NEJM 2016; DOI: 10.1056/NEJMoa1606774; Reck M, et al. ESMO 2016. Abstract LBA8_PR.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab vs platinum-based CT as first-line therapy - PFS

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37–0.68)	<0.001
Chemo	116	6.0		



No. at risk

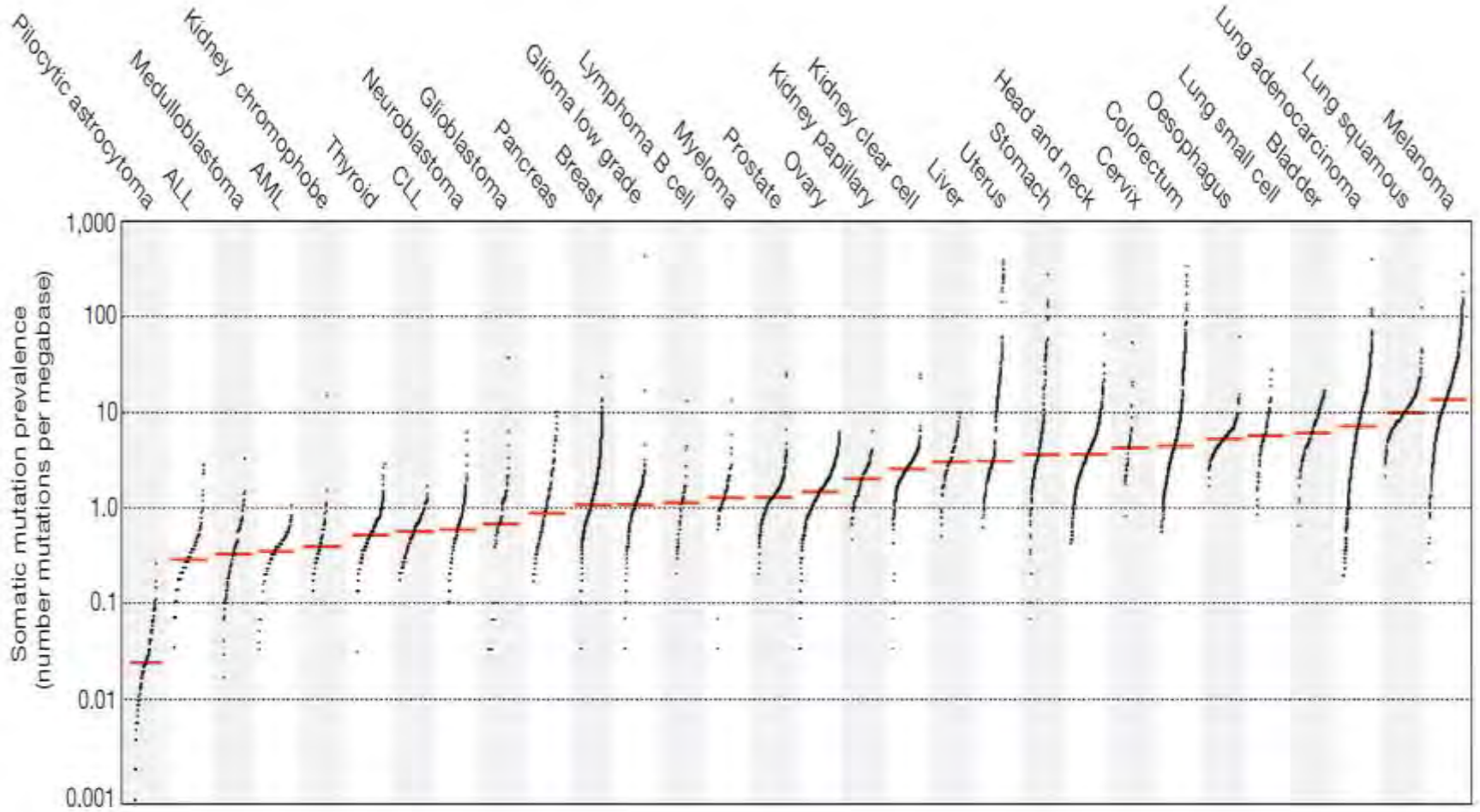
Pembro	154	104	89	44	22	3	1
Chemo	151	99	70	18	9	1	0

Reck M. et al NEJM 2016; DOI: 10.1056/NEJMoa1606774; Reck M, et al. ESMO 2016. Abstract LBA8_PR.

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

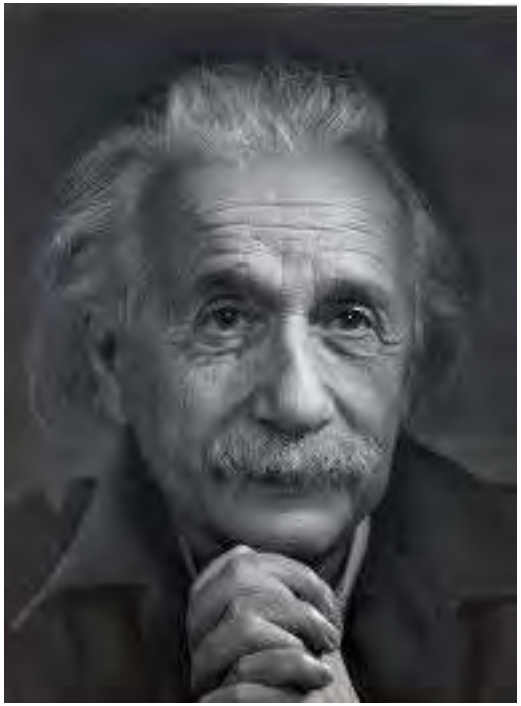
Cancer is a genetic disease: Mutational burden across cancers



Alexandrov, et al. Nature 2013

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS



Einstein Albert, 1879-1955

The crisis is the best blessing that can happen to people and countries, because the crisis brings progress. Creativity is born from the distress, as the day is born from the dark night. It is in crisis that invention, discovery and large strategies are born.Who ever overcomes crisis, outdoes himself without being overcome

UNIVERSITÀ
DEGLI STUDI
DI TORINO

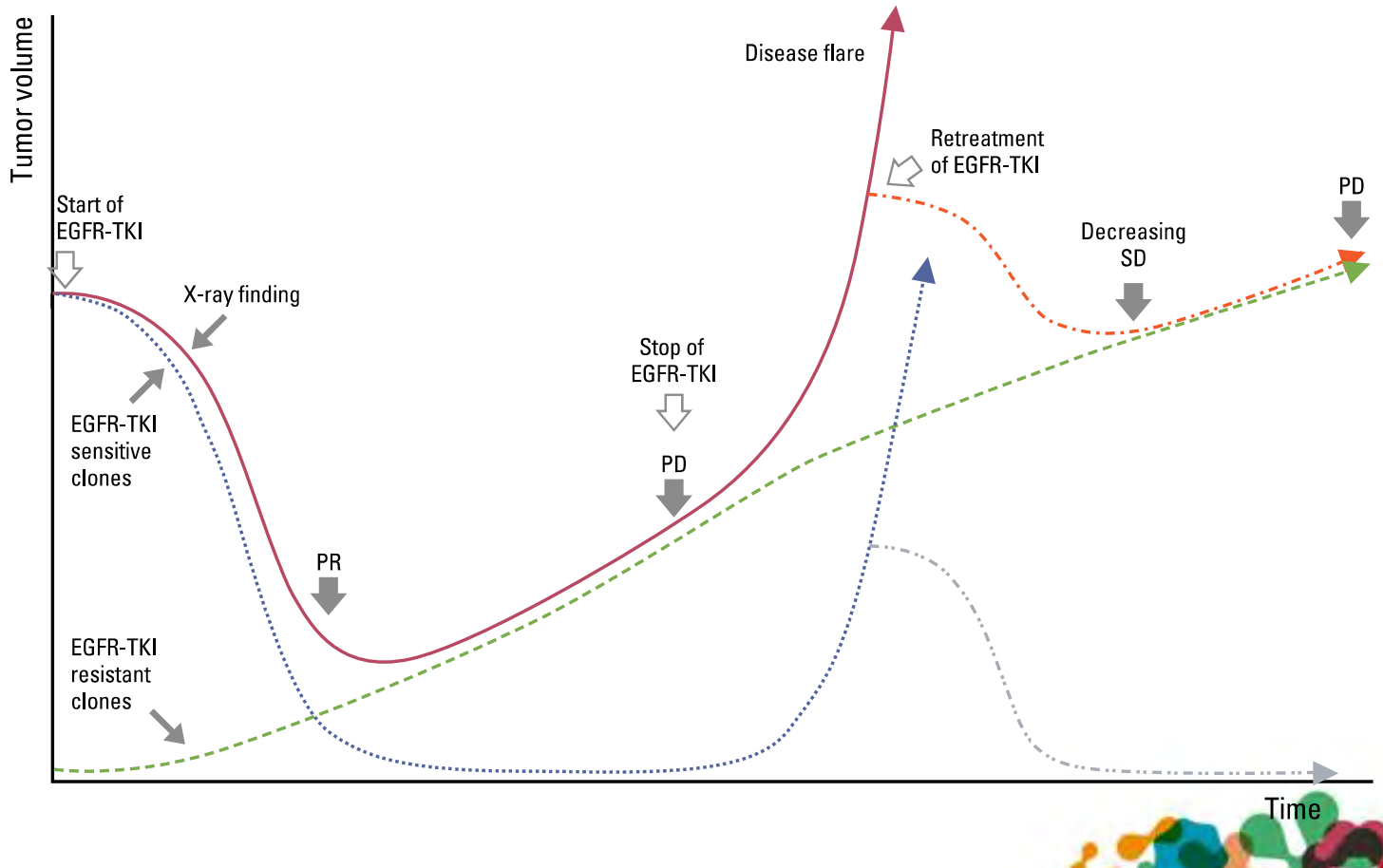
ALMA UNIVERSITAS
TAURINENSIS

"The difficulty lies not so much in developing new ideas as in escaping from the old ones".

John Maynard Keynes

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Clonal Evolution and Disease Progression in EGFR mutant NSCLC



UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

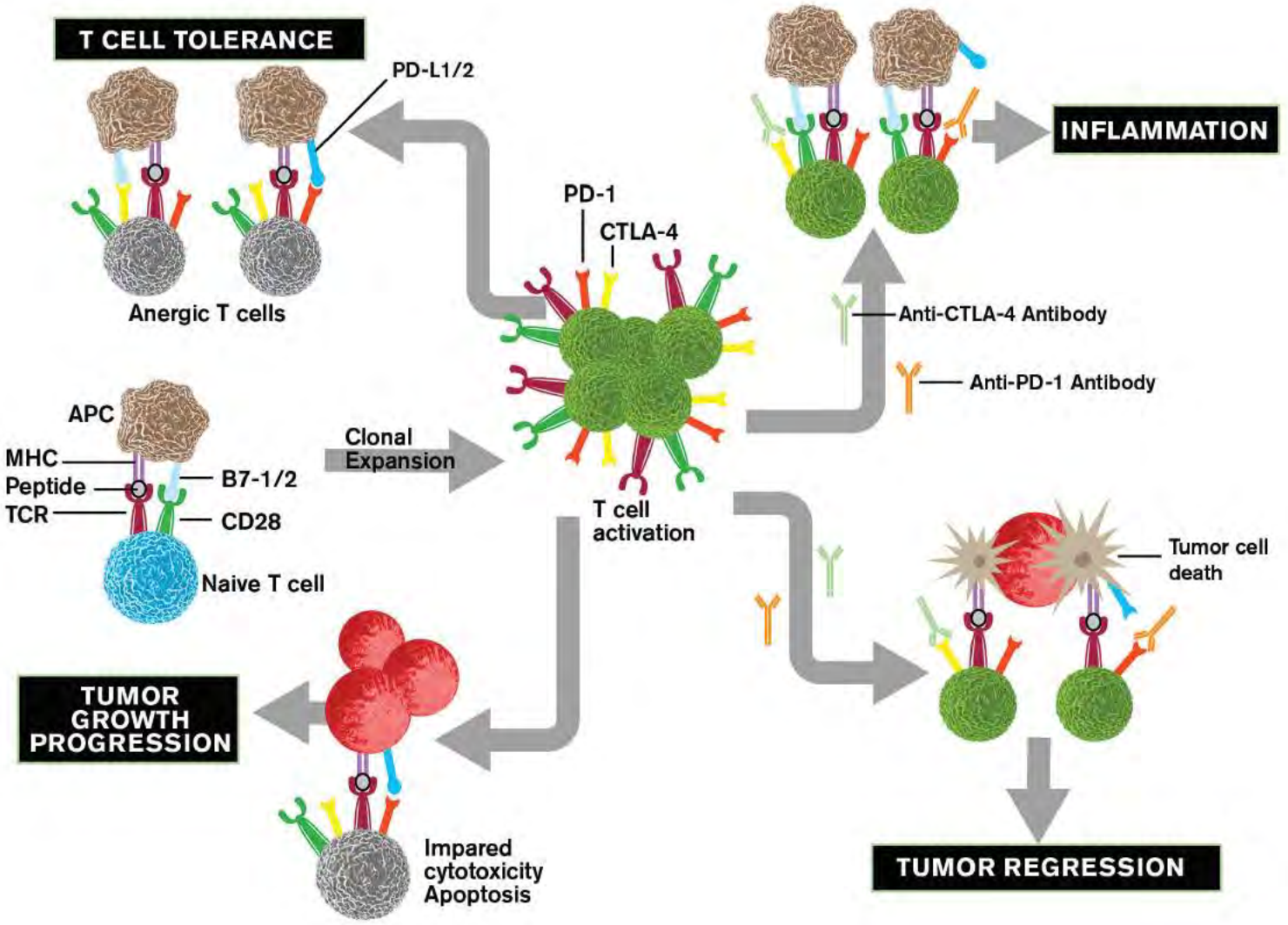
Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity

- Academicians must avoid in participating in the development of marginal therapies
- Professional societies and scientific journals must raise standards and avoid giving prominence to studies with marginal outcomes
- The value of cooperative groups must be acknowledged and they should receive support
- The Me-Too mentality that settles for incremental improvements must be addressed
- The viability of the current health care system expenditures and what we can do to address it

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

Checkpoint pathways in chronic inflammation and cancer

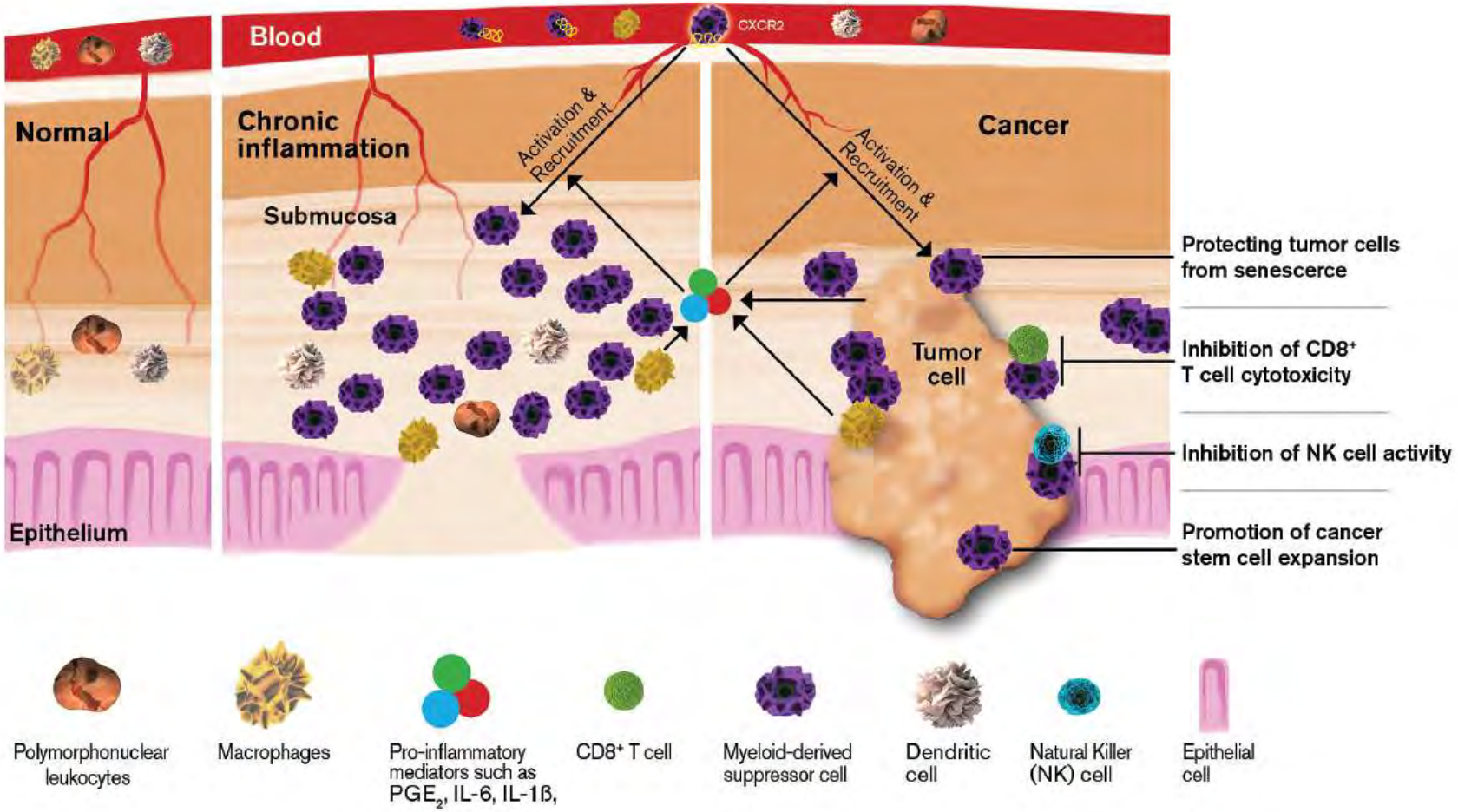


Wang D & Du Bois RN Carcinogenesis, 2015; 36: 1085–1093

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

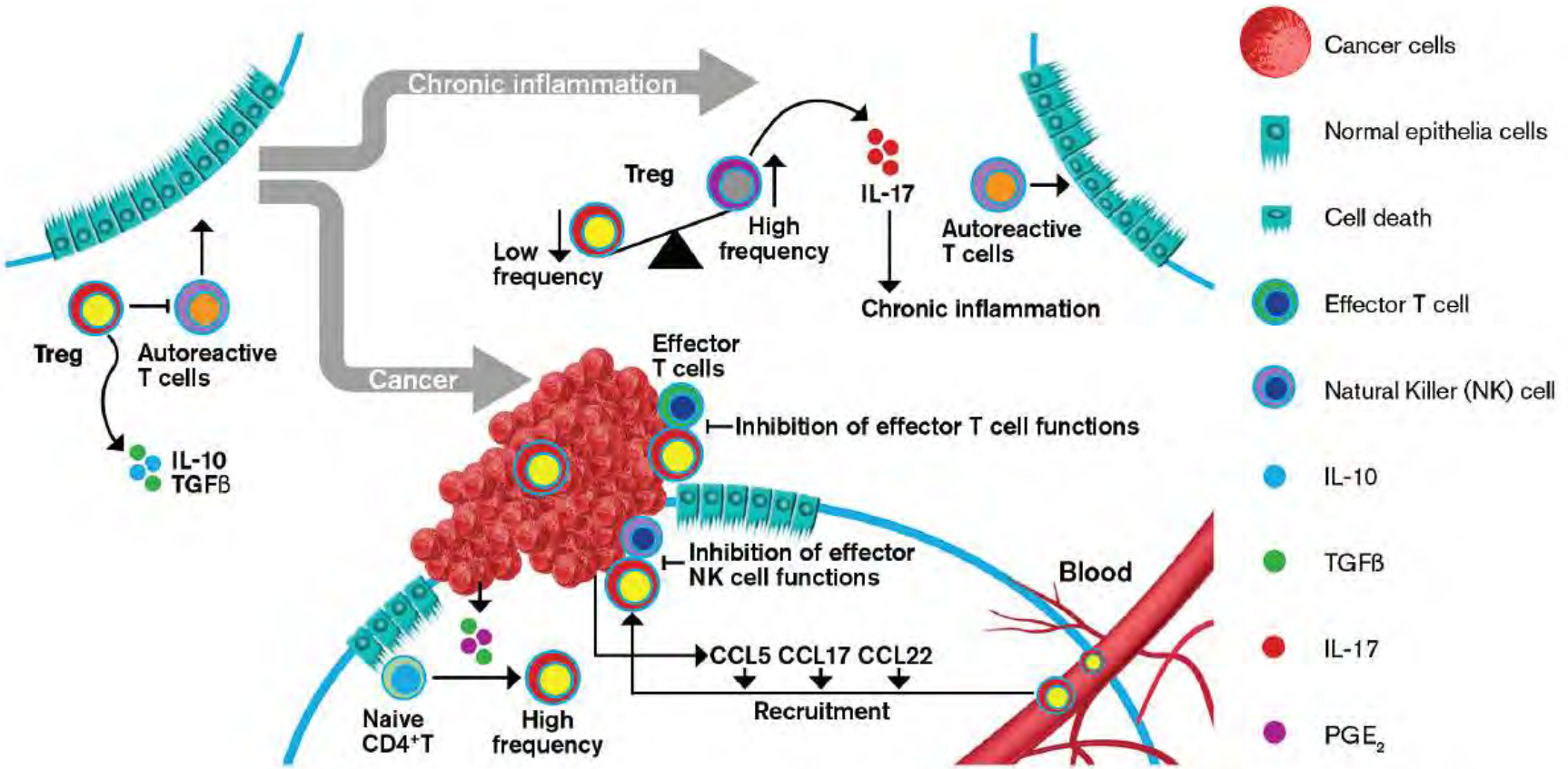
The role of MDSCs in chronic inflammation and cancer



Wang D & Du Bois RN Carcinogenesis, 2015; 36: 1085–1093

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The role of Tregs in chronic inflammation and cancer



Wang D & Du Bois RN Carcinogenesis, 2015; 36: 1085–1093

UNIVERSITÀ
DEGLI STUDI
DI TORINO

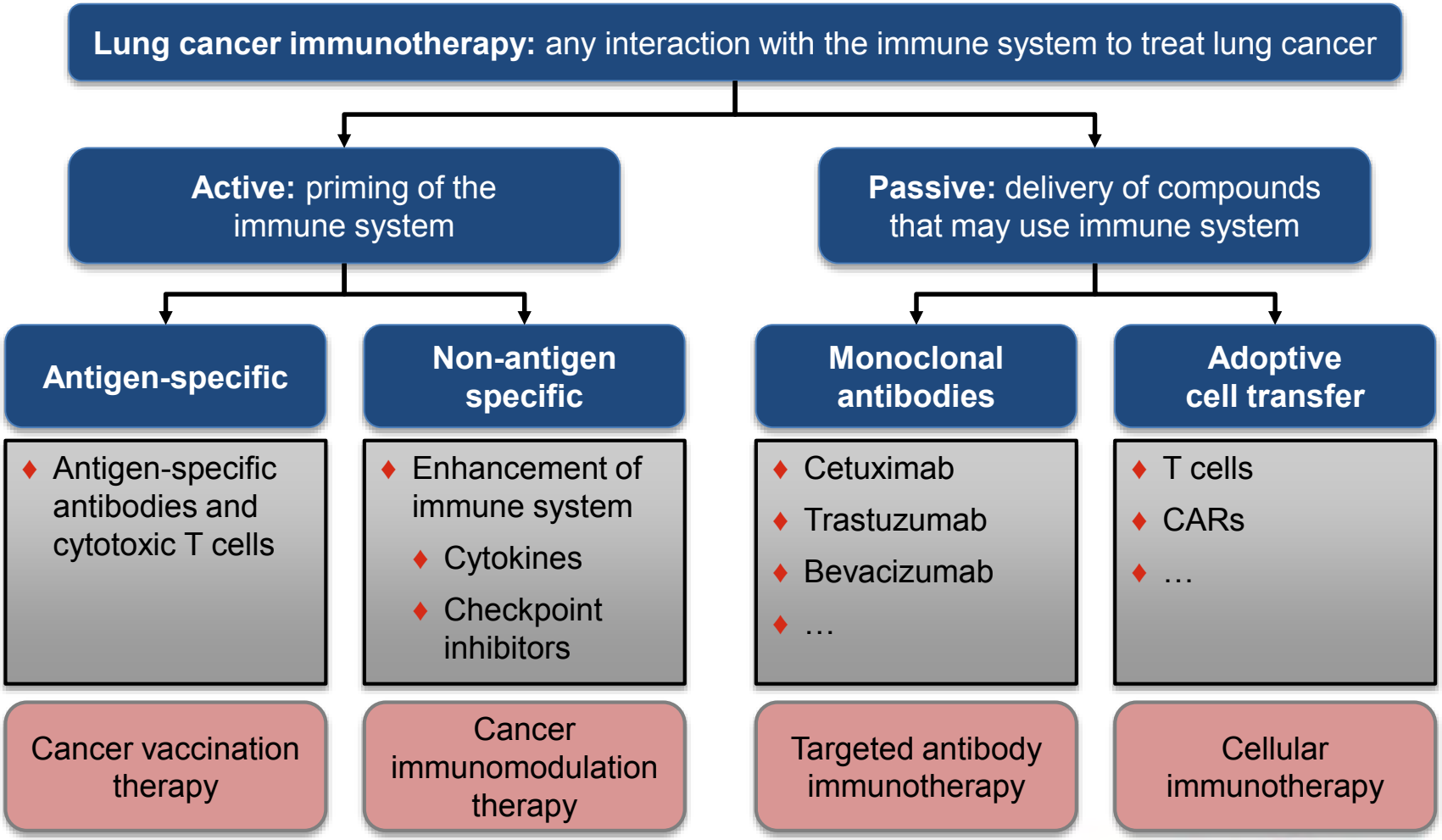
ALMA UNIVERSITAS
TAURINENSIS

1965

2015

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Lung Cancer Immunotherapy



UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Potential Mechanisms for Immune Evasion in Lung Cancer

- Defective antigen presentation
- Checkpoint pathways
- Immunosuppressive cell infiltrates - T reg and MDSCs
- Upregulation/secretion of immunosuppressive cytokines

Thomas A et al Humoral and Cellular Immune Dysregulation and Lung Cancer, 2013

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Potential Mechanisms for Immune Evasion in Lung Cancer

- Defective antigen presentation - chemotherapy, epigenetic therapy, vaccines
- Checkpoint pathways – Checkpoint inhibitors
- Immunosuppressive cell infiltrates - T reg and MDSCs – Ab or cytotoxics
- Upregulation/secretion of immunosuppressive cytokines – COX-2 inhibition, TGF-B blockade and chemotherapy

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Vaccines for NSCLC

- Dependent on identifying an appropriate antigen, differentially expressed between tumour and normal tissues.
- A challenging area, previous attempts unsuccessful
  - *Advanced stage patients with poor immune function*
  - *Little consideration of type of immune response and antigen presentation*
  - *No approved therapeutic vaccines (but there are preventive vaccines, e.g. HPV vaccine)*
- Most extended phase III studies are on LBLP25 (Stimuvax) and recMAGE-A3 and both were negative.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Lung cancer vaccination
Ongoing & planned studies

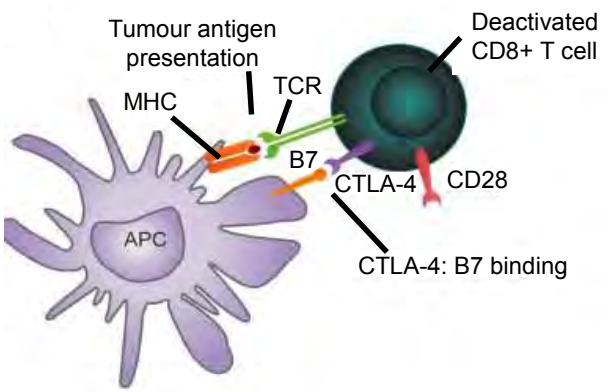
	MAGE-A3	BLP25	Lucanix	rHU-EGF	TG4010
Class	full protein	peptide in liposome	allogeneic cells	full protein	peptide by viral vector
Disease setting	post-surgery	post-CTRT	advanced	advanced	advanced
Specificity	++	+	?	+	+
Expression	+/-	+	?	++	+
Immuno-activity	++	++	++	++	++
Phase II	RCT/placebo	RCT/BSC	Open/dose	RCT/BSC	RCT/BSC
Phase III	2270 Negative	1322 Negative	532 **Negative**	ongoing – target 230	planned – target 1000

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

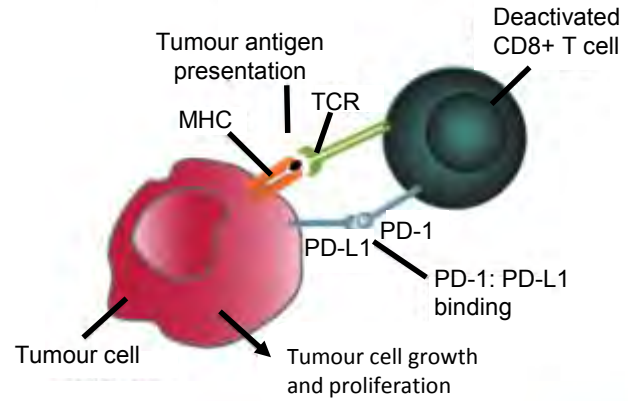
Immunotherapy Targets in NSCLC: CTLA-4 and PD-1 Pathways

- CTLA-4 and PD-1 pathways are immune checkpoint pathways that play critical roles in controlling T cell immune responses
  - Inhibitory receptors
  - Regulate immune responses at different levels
- T cells can become unresponsive after CTLA-4 binds B7 molecules on APC, or when PD-1 binds PD-L1 or PD-L2 on target cells
- CTLA-4 and PD-1 are the best characterised of the immune checkpoint receptors as targets for cancer therapy

CTLA-4 pathway



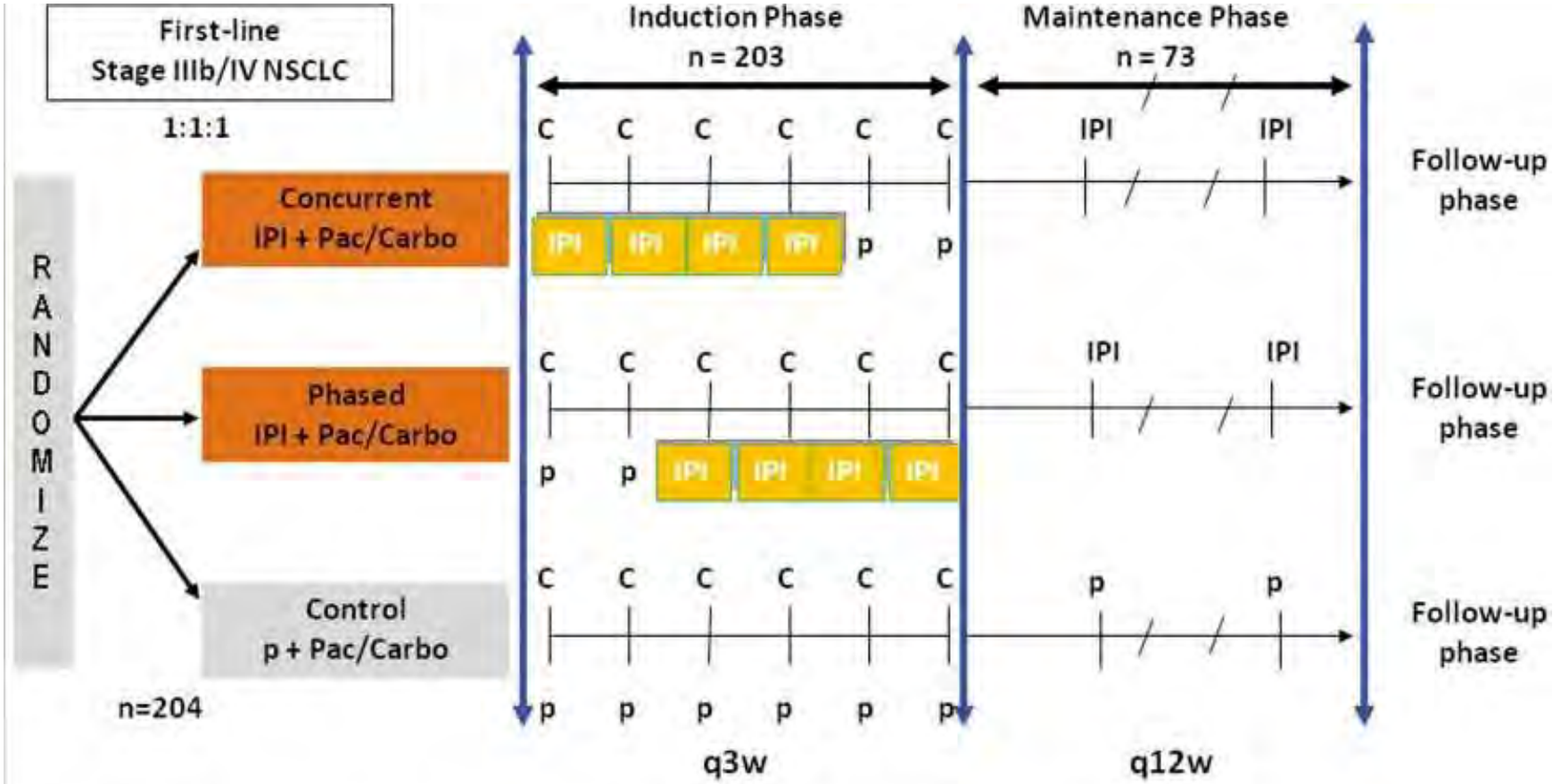
PD-1 pathway



Pardoll DM. *Nat Rev Cancer* 2012;12:252-64
Davies M. *Cancer Manag Res* 2014;6:63-75

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Randomized phase II study of ipilimumab and chemotherapy in advanced NSCLC



IPI, Ipilimumab (10 mg IV) ; C, Chemotherapy (Pac /Carbo); p, Placebo

Cx regimen: Pac (175 mg/m²)/Carbo (AUC=6) prior to start of ipilimumab

Primary endpoint: Immune-related PFS

Lynch T et al. J.Clin.Oncol 2012

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

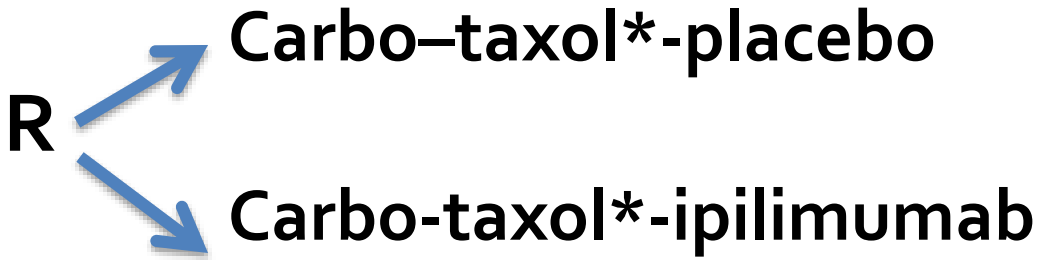
Randomized phase II of ipilimumab and chemotherapy in advanced NSCLC – results by histology

irPFS	All	Squamous	Non-squamous
Carbo-taxol	4.6		
Phased ipi	5.7 (HR 0.72)	HR 0.55	HR 0.82
Concurrent ipi	5.5 (HR 0.81)	HR 0.85	HR 0.77
Survival			
Carbo-taxol	8.3		
Phased ipi	12.2 (HR 0.87)	HR 0.48	HR 1.17
Concurrent ipi	9.7 (HR 0.99)	HR 1.02	HR 0.96

Lynch T et al. J. Clin. Oncol 2012

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Phase III of ipilimumab in squamous cell lung cancer



- Double-blind
- Overall survival primary endpoint
- Secondary: OS in patients who receive one dose of ipi/placebo, PFS, RR
- 920 patients – started Aug 2011

*Carboplatin (AUC 6); paclitaxel (175 mg/m2); ipilimumab (10 mg/kg q3w)

http:// clinical trials.gov/NCT01285609

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Status of Key Checkpoint Inhibitors for Advanced NSCLC (≥2nd-line)

Agent / Study	Phase	Design	Histology	Approval Status
Nivolumab, anti-PD-1				
NCT01642004 (CheckMate 017)	3	Nivo vs. doc, pretreated NSCLC	Squamous	Approved: US and EU
NCT01673867 (CheckMate 057)	3	Nivo vs. doc, pretreated NSCLC	Non-squamous	Approved: US and EU
Pembrolizumab, anti-PD-1 NCT01905657 (KEYNOTE-010)	2 / 3	Pembro vs. doc, post-platinum	All	Approved: US Approved: EU
Atezolizumab (MPDL3280A), anti-PD-L1				FDA breakthrough therapy designation and priority review CHMP positive opinion
NCT02008227 (OAK)	3	Atezolizumab vs. doc, post-platinum	All	
Durvalumab (MEDI4736), anti-PD-L1				-
NCT02154490 (Lung-MAP)	2 / 3	Biomarker-targeted 2nd-line therapy	Squamous	
NCT02352948 (ARCTIC)	3	Durvalumab + / - tremelimumab (anti-CTLA-4) by PD-L1 expression, pretreated NSCLC	All	
Avelumab, anti-PD-L1 NCT02395172 (JAVELIN Lung 200)	3	Avelumab vs. doc, post-platinum	All	-
Ipilimumab, anti-CTLA4 NCT02039674 (KEYNOTE-021)	1 / 2	Pembro + ipilimumab, 2nd-line	All	-

ClinicalTrials.gov
Patnaik A et al. *J Clin Oncol* 2015;33(Suppl):8011

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Pembrolizumab in Pretreated, PD-L1-Positive NSCLC in the Phase 2/3 KEYNOTE-010 Trial

Inclusion criteria

- Advanced NSCLC; progression after ≥2 cycles of platinum-doublet chemotherapy
- ≥18 years
- ECOG PS 0/1
- Provision of a tumor sample
- PD-L1 expression on ≥1% of tumor cells

Stratification

- ECOG PS: 0 vs 1
- Region: East Asia vs not East Asia
- PD-L1 expression: tumor proportion score ≥50% vs 1-49%

RANDOMIZE

1:1:1

- Pembrolizumab monotherapy (2 mg/kg IV every 3 weeks) n=345
- Pembrolizumab monotherapy (10 mg/kg IV every 3 weeks) n=346
- Docetaxel monotherapy (75 mg/m^2 IV every 3 weeks) n=343

Treatment for 24 months or until disease progression or discontinuation due to toxicity / other reasons

Primary endpoints	OS, PFS in total population and patients with tumor proportion score ≥50%
Secondary endpoints	Safety, response rate (as per RECIST version 1.1), duration of response

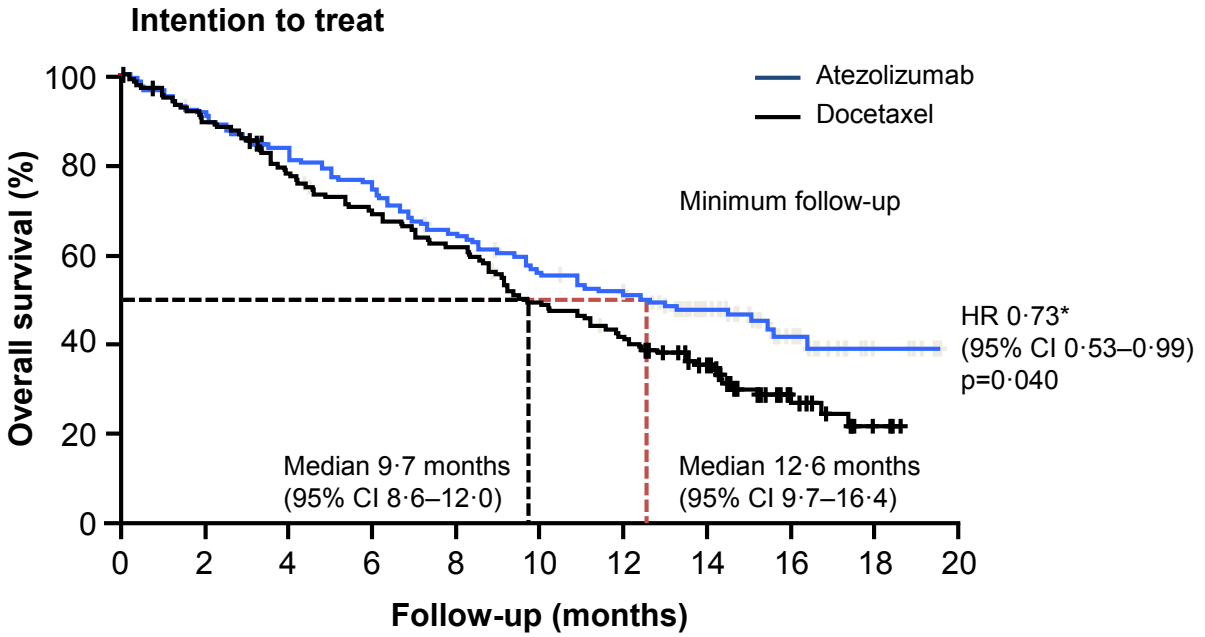
Herbst RS et al. *Lancet* 2016;387:1540-50

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Atezolizumab in NSCLC: Phase 2 Results

- Atezolizumab, an anti-PD-L1 monoclonal antibody, has been evaluated in a randomized Phase 2 study vs. docetaxel in pretreated patients with squamous and nonsquamous NSCLC (POPLAR, NCT01903993; N=287 randomized patients)[1]

- Atezolizumab improved OS vs docetaxel, 12.6 vs 9.7 months[1]
- With longer follow-up (min 20 months), further separation in survival curves and improvement in OS HR were seen for atezolizumab over docetaxel[2]



1. Fehrenbacher L et al. *Lancet* 2016;387:1837-46
2. Smith DA et al. *J Clin Oncol* 2016;34(Suppl):9028 ASCO abstract.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Atezolizumab in NSCLC: Phase 2 Results by PD-L1 Expression

- Improved efficacy was observed with increasing PD-L1 expression on tumor-infiltrating immune cells (IC) or tumor cells (TC)

PD-L1 Expression	TC3 or IC3		TC0 and IC0		ITT	
	A (n=24)	D (n=23)	A (n=51)	D (n=41)	A (n=144)	D (n=143)
OS (Primary analysis)[1]						
Median, months	15.5	11.1	9.7	9.7	12.6	9.7
HR[a] 95% CI	0.49 0.22-1.07		1.04 0.62-1.75		0.73 0.53-0.99	
p value	.068		.871		.040	
OS (Updated analysis)[2]						
Median, months	NR	11.1	9.7	9.7	12.6	9.7
HR[a] 95% CI	0.45 0.22-0.95		0.88 0.55-1.42		0.69 0.52-0.92	
p[b] value	.033		.601		.011	

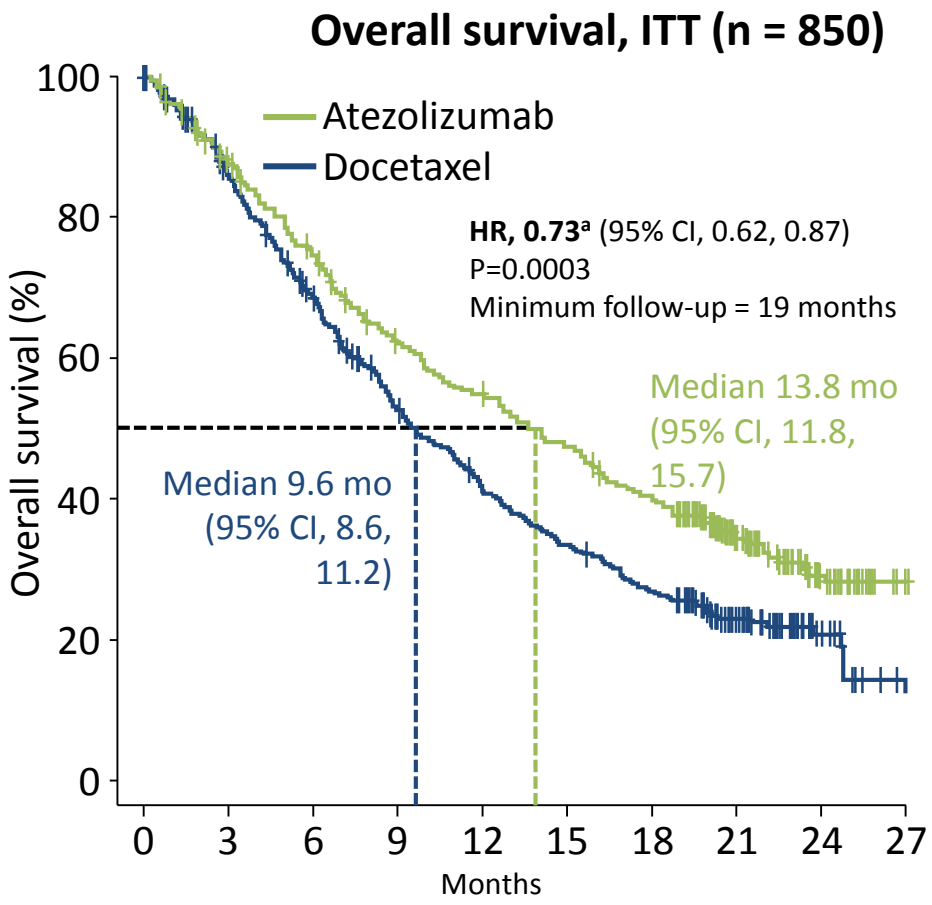
[a]Stratified HR for ITT and unstratified HR for subgroups; ; [b]Descriptive only

1. Fehrenbacher L et al. *Lancet* 2016;387:1837-46
2. Smith DA et al. *J Clin Oncol* 2016;34(Suppl):9028 ASCO abstract.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

OAK, a randomized Phase 3 study comparing atezolizumab with docetaxel in 2L/3L NSCLC

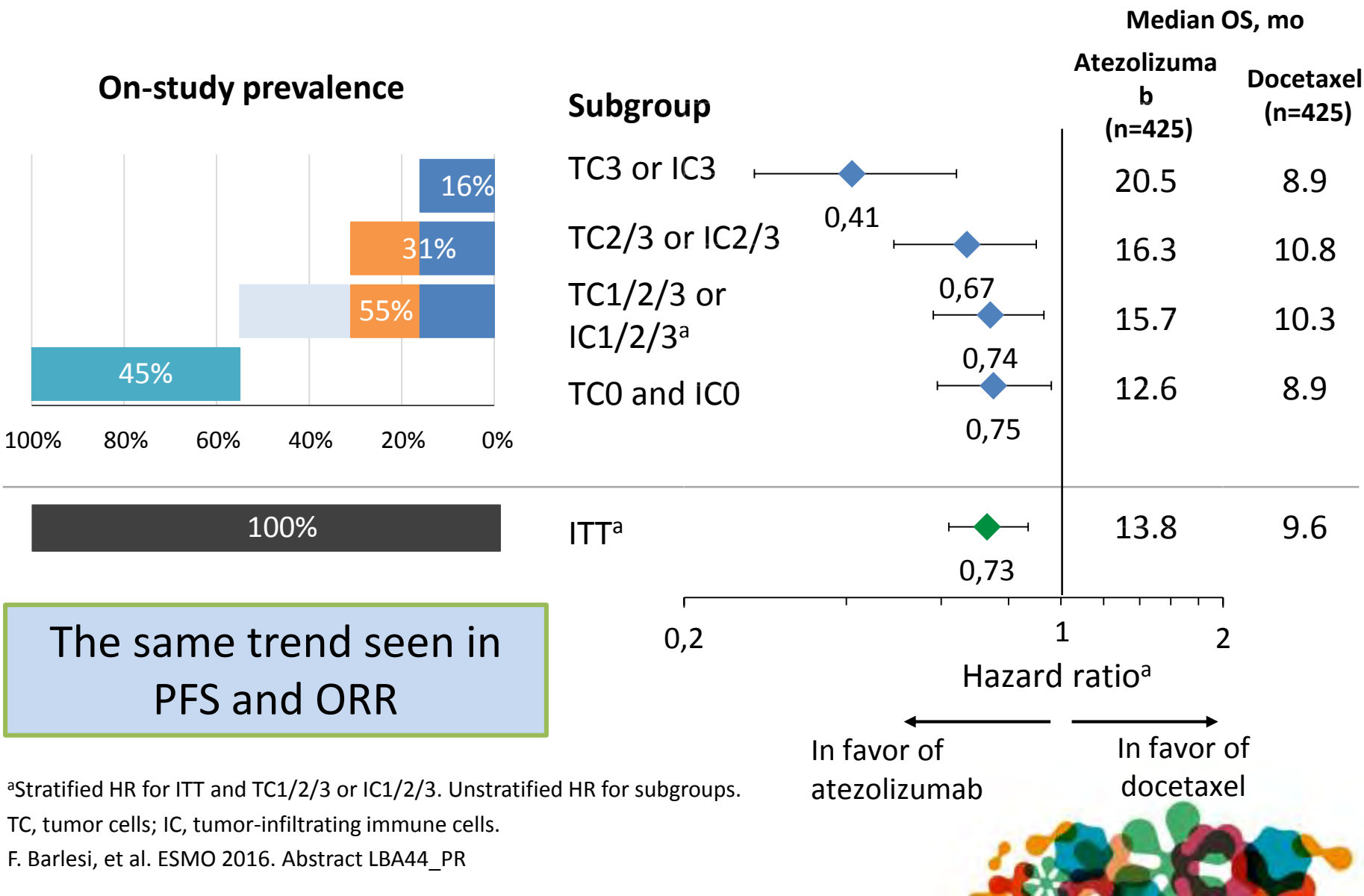
Characteristics	Atezolizumab n = 425	Docetaxel n = 425
Median age, y	63	64
≥65 y	45%	49%
Male	61%	61%
Nonsquamous	74%	74%
Squamous	26%	26%
ECOG PS, 0/1	37%/64%	38%/62%
No. of prior therapies, 1/2	75%/25%	75%/25%
History of tobacco use		
Never	20%	17%
Current/previous	14% / 66%	16% / 67%
Known EGFR status, %		
Mutant/WT	10% / 75%	10% / 73%



F. Barlesi, et al. ESMO 2016. Abstract LBA44_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Primary analysis from OAK, a Phase 3 study of atezolizumab vs. docetaxel in 2L/3L NSCLC



The same trend seen in PFS and ORR

[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells.
F. Barlesi, et al. ESMO 2016. Abstract LBA44_PR

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Is Immunotherapy the Future of Lung Cancer Treatment?

- Answer – It's complicated …. as multiple mechanisms are used to thwart the immune system
- Personalization of therapy will depend on further understanding of what mechanisms are being used by each person's cancer to evade immune surveillance
- Targeting those mechanisms in combination therapies

UNIVERSITÀ DEGLI STUDI DI TORINO

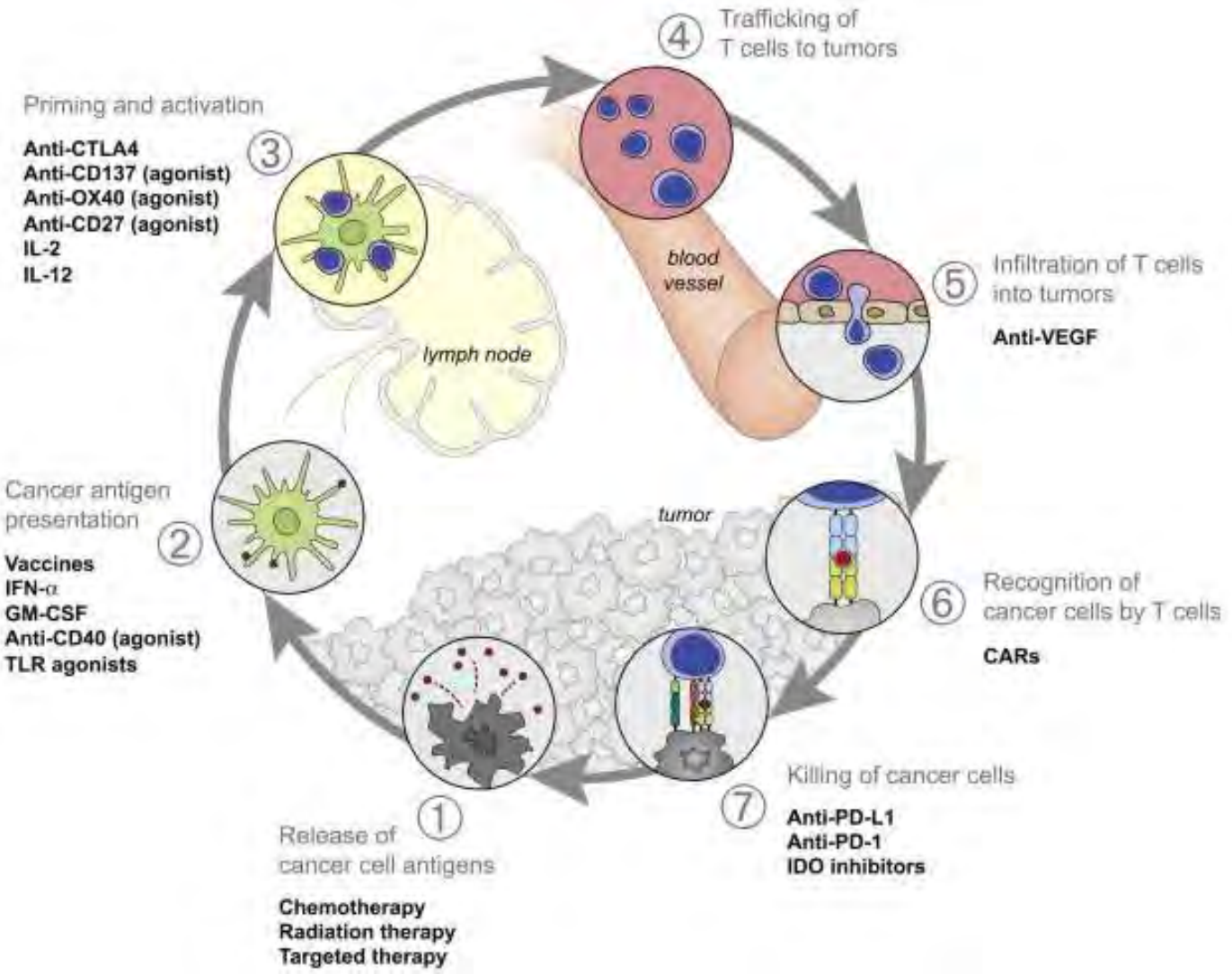
ALMA UNIVERSITAS TAURINENSIS

"The difficulty lies not so much in developing new ideas as in escaping from the old ones".

John Maynard Keynes

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Therapies that Might Affect the Cancer-Immunity Cycle

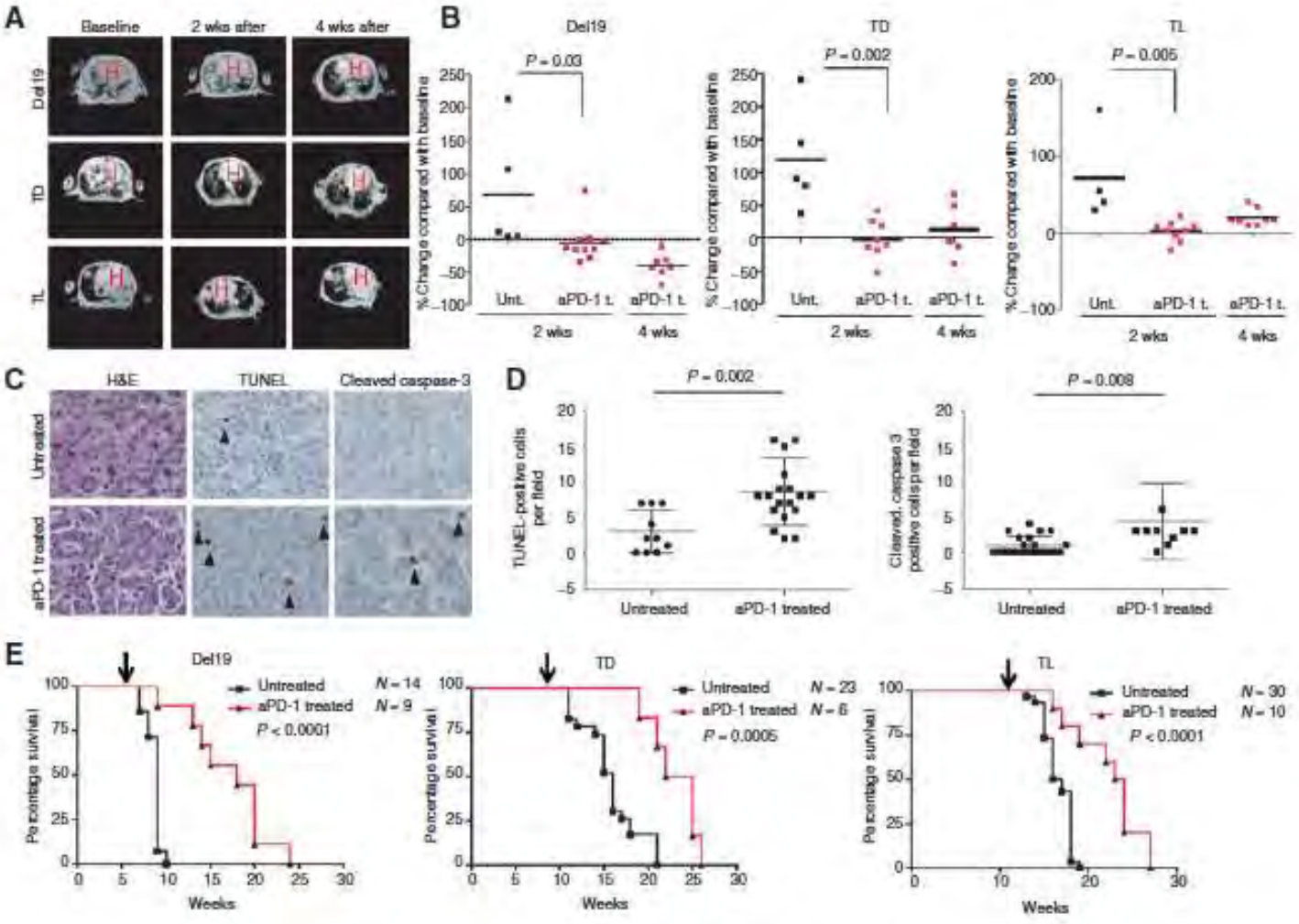


Chen D, Mellman I. Immunity 2013;39:1-10

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

PD-1 Activation leads to Immune Escape in EGFR-Driven Tumors



Akbay EA et al. Cancer Discovery 2013; 1355-1363

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Issues with PD-L1 as a Biomarker

- PD-L1 negativity an unreliable biomarker
  - Assays are technically difficult, imperfect; results may differ depending on the antibody/assay (tumor vs immune cells)
  - 5% expression, tumor heterogeneity, and inducible gene = sampling error (false negative)
  - Archived tissue different than recent biopsy
- May be more useful in determining which tumors rather than which patients to treat
- PD-L1 expression may be less relevant for combination therapies
- PD-L1 expression might be constitutive (no immune infiltrate)

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

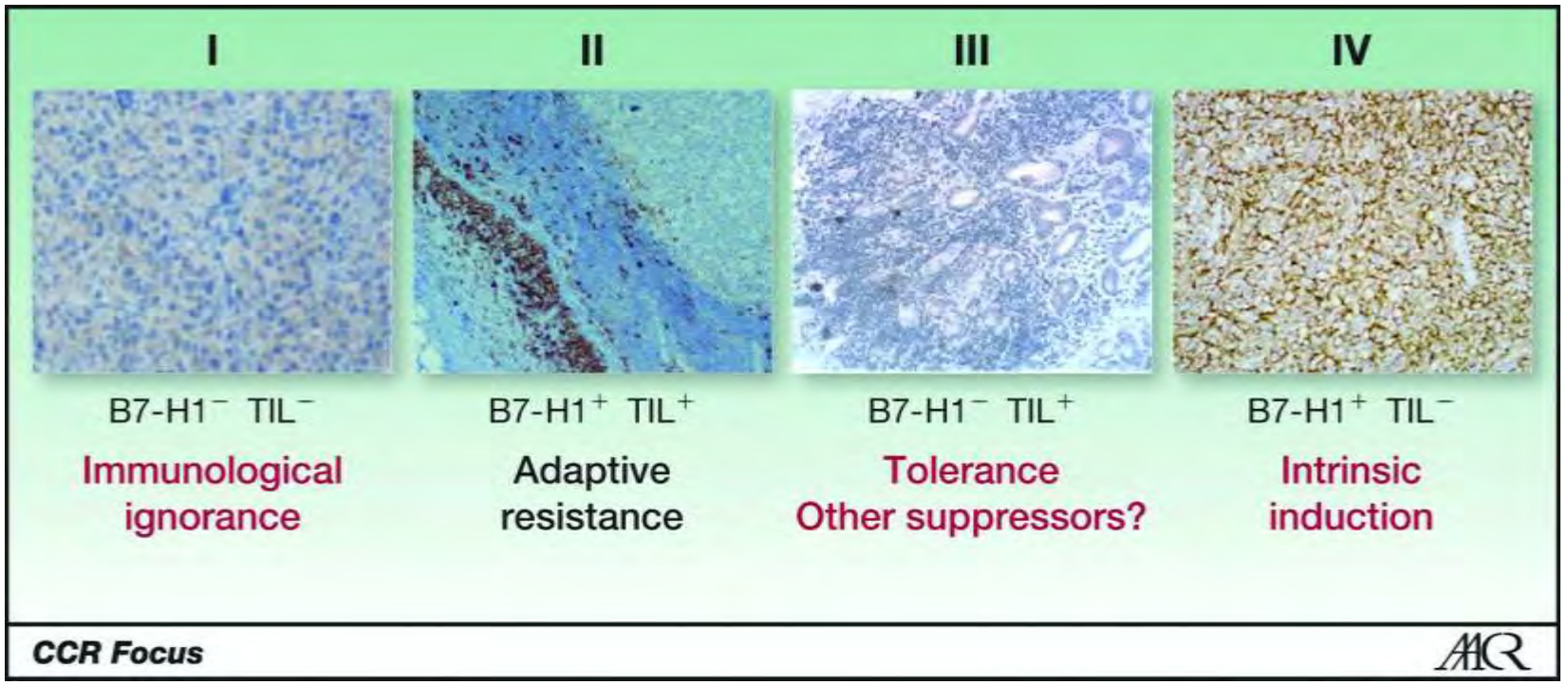
ORR by PD-L1 Expression in Patients with Solid Tumors

Rx Antibody	Testing Method	N	PD-L1 + RR	PD-L1 - RR
Nivolumab[1]	Manual staining – 5H1 5% cutoff Tumor staining	49	13/31 42%	0/18 0%
Nivolumab[2]	Dako automated 5% cutoff Tumor staining	38	7/17 41%	3/21 14%
MPDL3280A[3]	Automated Roche Dx IHC 1% cutoff Tumor immune cell staining	103	13/36 36%	9/67 13%
Ipi/Nivo[4]	Dako automated 5% cutoff Tumor staining	56	8/14 57%	17/42 40%

1.Topalian SL, et al. N Engl J Med. 2012;366:2443-2454.
2. Grosso J, et al. ASCO 2013. Abstract 3016. 3. Herbst RS, et al. ASCO 2013. Abstract 3000. 4. Sznol M, et al. ASCO 2014. LBA9003

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

PD-L1 (B7-H1) Expression and Inflammation: Implications for Mechanisms and Therapy



*Implications for combination therapy with other checkpoint inhibitors, chemotherapy, targeted therapy, and vaccines

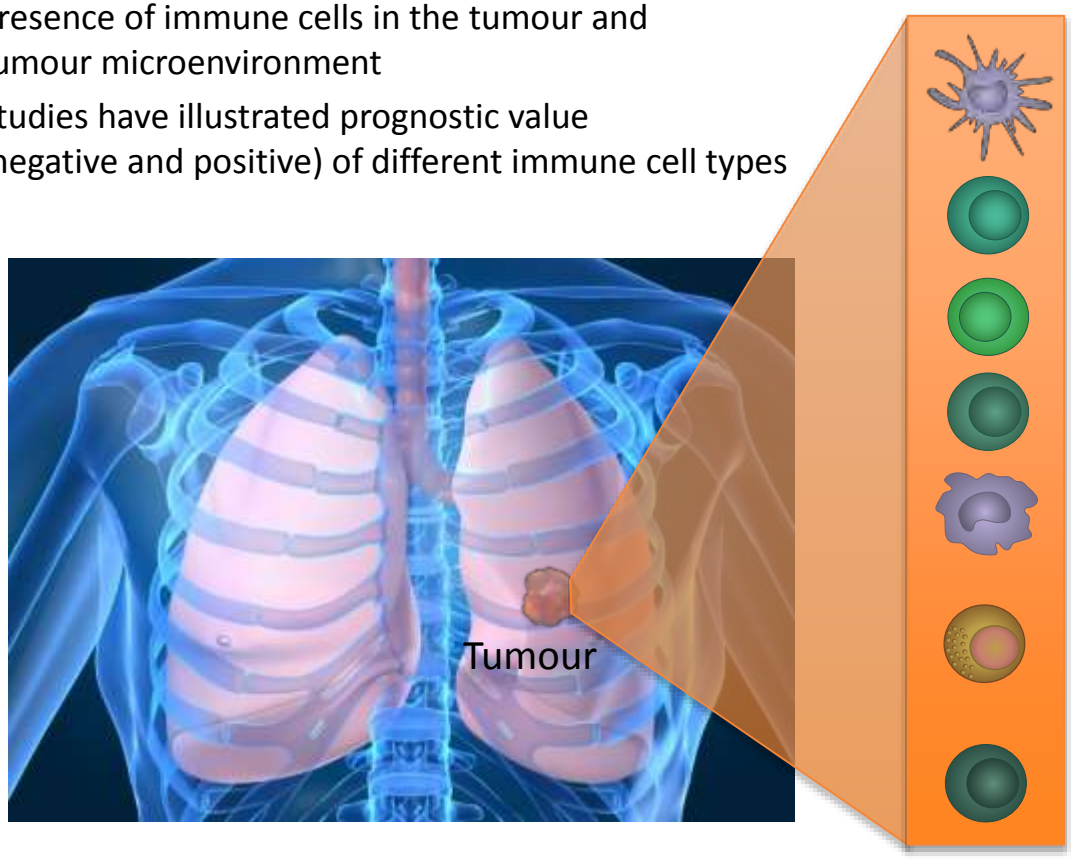
Sznol M , and Chen L Clin Cancer Res 2013;19:1021-1034

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

The Immune Response in Lung Cancer: Prognostic Implications of Infiltrating Immune Cells

There is evidence of an immune response in lung cancer:

- Presence of immune cells in the tumour and tumour microenvironment
- Studies have illustrated prognostic value (negative and positive) of different immune cell types



↑ **Dendritic Cells**
Favourable prognosis[1]: Overall survival, disease-specific survival, and disease-free survival

↑ **CD3+ Cells**
Favourable prognosis[2-4]: Disease-specific survival and lower risk of disease recurrence

↑ **CD8+ Cells**
Favourable prognosis[5-8]: Overall survival

↑ **CD4+ Cells**
Favourable prognosis[6,9]: Overall survival

↑ **Macrophages**
Favourable prognosis[7]: Overall survival

↑ **NK Cells**
Favourable prognosis[10]: Disease-specific survival

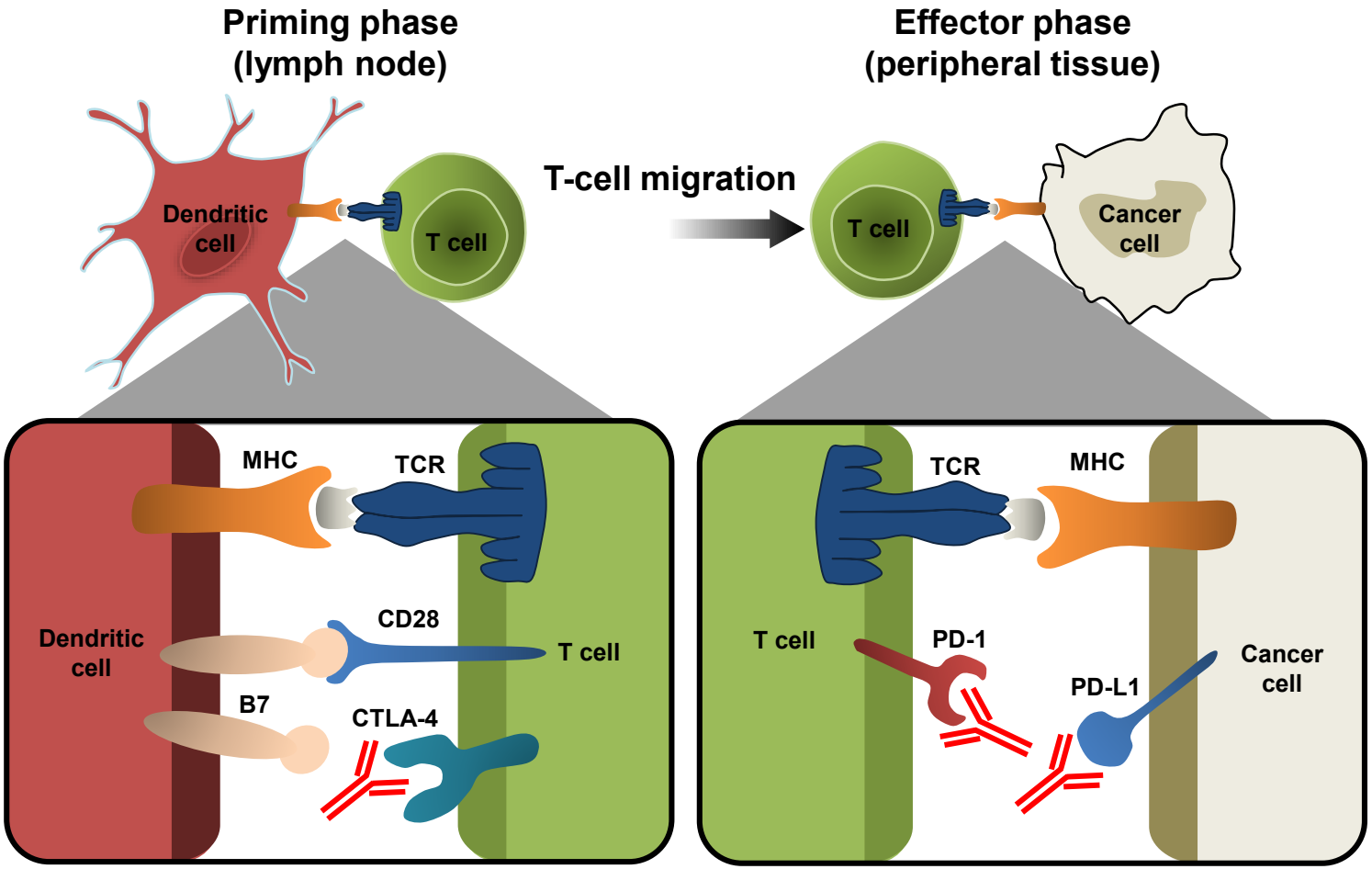
↑ **NK Cells (immature / impaired)**
Unfavourable prognosis[11]: Disease progression

↑ **T-regs**
Unfavourable prognosis[12,13]: Overall survival, relapse- and recurrence-free survival

1. Dieu-Nosjean MC et al. *J Clin Oncol* 2008;26:4410-7
2. Petersen RP et al. *Cancer* 2006;107:2866-72
3. Al-Shibli K et al. *APMIS* 2010;118:371-82
4. Ruffini E et al. *Ann Thorac Surg* 2009;87:365-71
5. Zhuang X et al. *Appl Immunohistochem Mol Morphol* 2010;18:24-8
6. Hiraoka K et al. *Br J Cancer* 2006;94:275-80
7. Kawai O et al. *Cancer* 2008;113:1387-95
8. McCoy MJ et al. *Br J Cancer* 2012;107:1107-15
9. Wakabayashi O et al. *Cancer Sci* 2003;94:1003-9
10. Al-Shibli K et al. *Histopathology* 2009;55:301-12
11. Jin J et al. *PLoS One* 2013;8:e61024
12. Tao H et al. *Lung Cancer* 2012;75:95-101
13. Shimizu K et al. *J Thorac Oncol* 2010;5:585-90

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

CTLA-4 and PD-1/L1 Checkpoint Blockade for Cancer Treatment

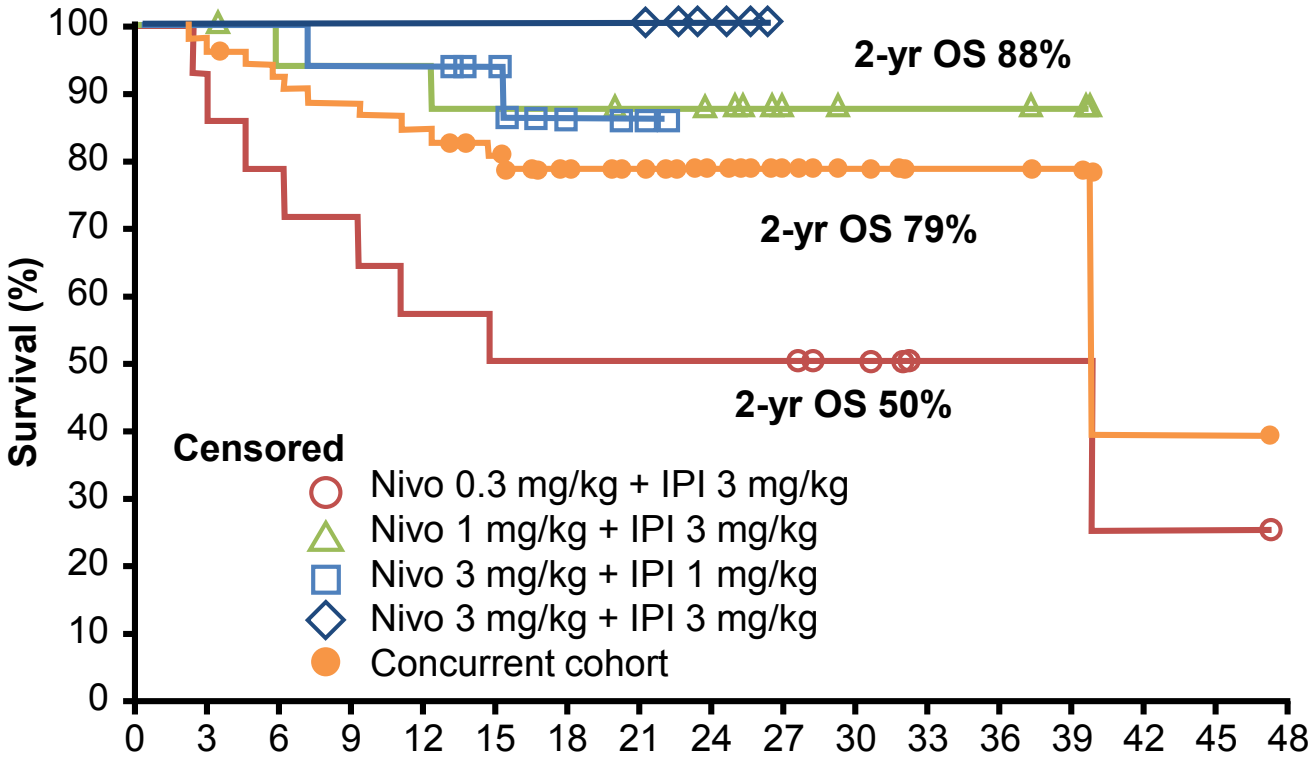


CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T cell receptor.

Ribas A. N Engl J Med. 2012;366:2517-2519.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Phase I Study of Nivolumab + Ipilimumab in Melanoma: OS for Concurrent Tx



Sznol M, et al. ASCO 2014. LBA9003

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Other Combinations with PD-1 Checkpoint Inhibitors

- Other coinhibitory pathways
  - TIM-3, LAG-3, IDO
- Co- or immunostimulatory pathways
  - OX40, 4-1BB, GITR, IL-2, IFN, IL-21
- Standard of care
  - Chemotherapy, TKI, VEGF inhibitor, XRT
- Cancer vaccines
- Epigenetic therapy

GITR, glucocorticoid-induced TNFR family related gene; IDO, indoleamine,3-dioxygenase; IFN, interferon; IL-2, interleukin-2; IL-21, interleukin-21; LAG-3, lymphocyte activation gene 3; PD-1, programmed death-1; TIM-3, T cell immunoglobulin and mucin protein 3; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

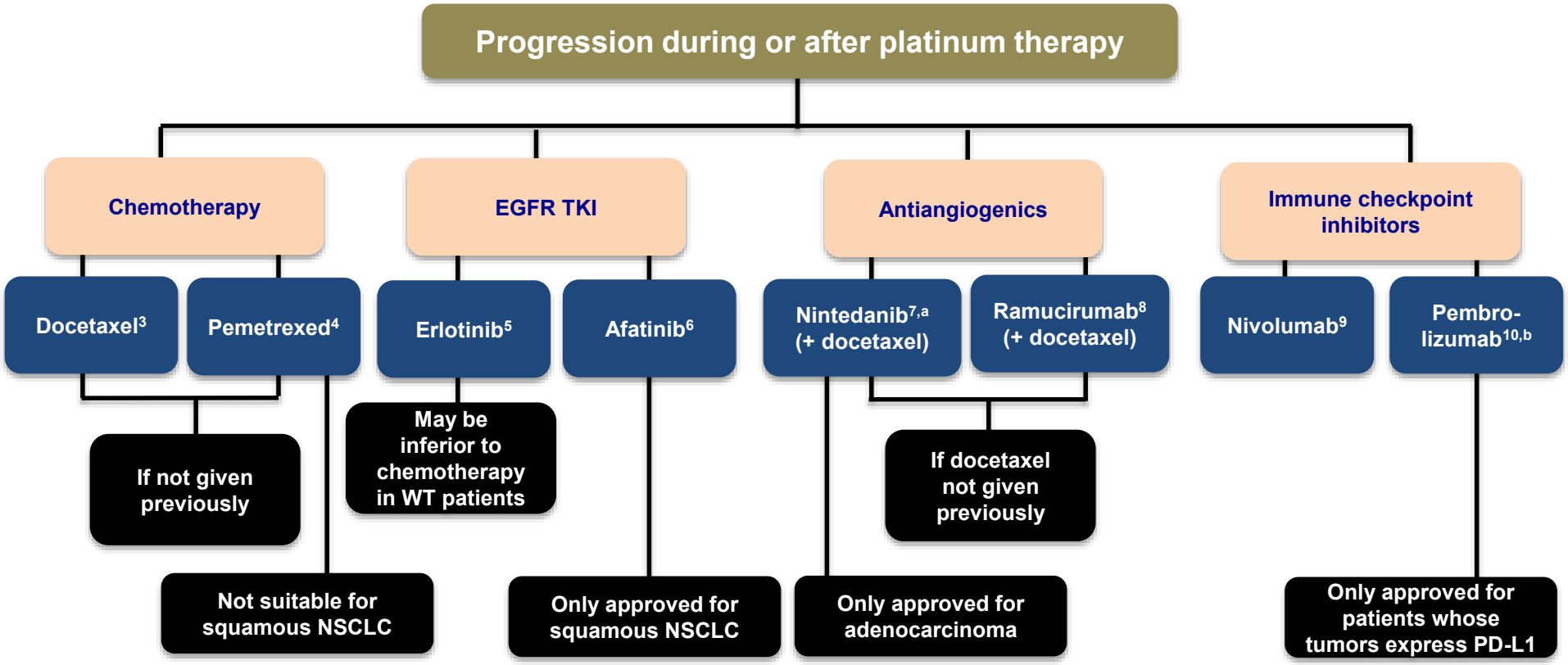
How to Approach Tumors Without Immune Infiltrates

- Combination immunotherapies
  - 4-1BB, IL-2, OX40, others
- Adoptive Cellular Therapy (ACT)
  - Genetically manipulated cells
  - CAR T cells
    - Professional killers. Don't need to have pre-existing immunity
    - CAR T cells are not HLA restricted
  - Issue is finding antigens expressed only on the tumor

ACT, adoptive cell therapy; CAR, chimeric antigen receptor; HLA, human leukocyte antigen.

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Treatment Options in Second Line: Overview



[a]Approved in EU only; [b]Approved in US only

1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.4.2016
2. Reck M et al. *Ann Oncol* 2014;25(Suppl 3):27-39

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Front-line Immuno-checkpoints in PDL-1 positive NSCLC

June 2016

Merck's Pembrolizumab Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

August 2016

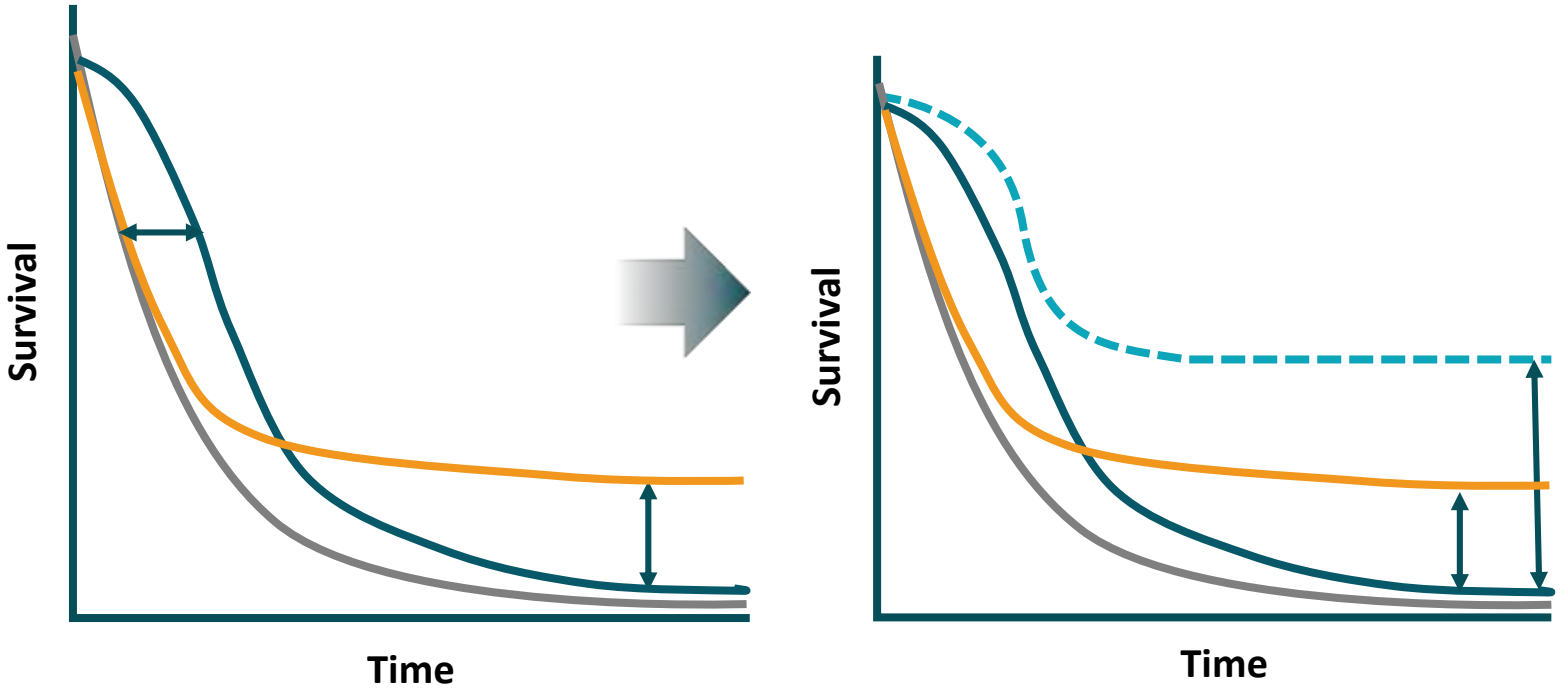
Bristol-Myers Squibb Announces Top-Line Results from CheckMate -026, a Phase 3 Study of Opdivo (nivolumab) in Treatment-Naïve Patients with Advanced Non-Small Cell Lung Cancer

Opdivo *did not meet trial primary endpoint of progression-free survival in patients expressing PD-L1 = 5%*

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Where we are now

Where we want to be

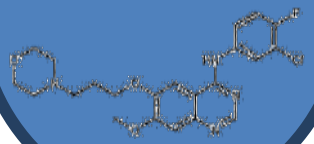


Salvati M, 3rd Intl Symp in Lung Ca, 2014; Ribas A, WCM, 2013; Ribas A, et al. Clin Cancer Res 2012; Drake CG. Ann Oncol 2012

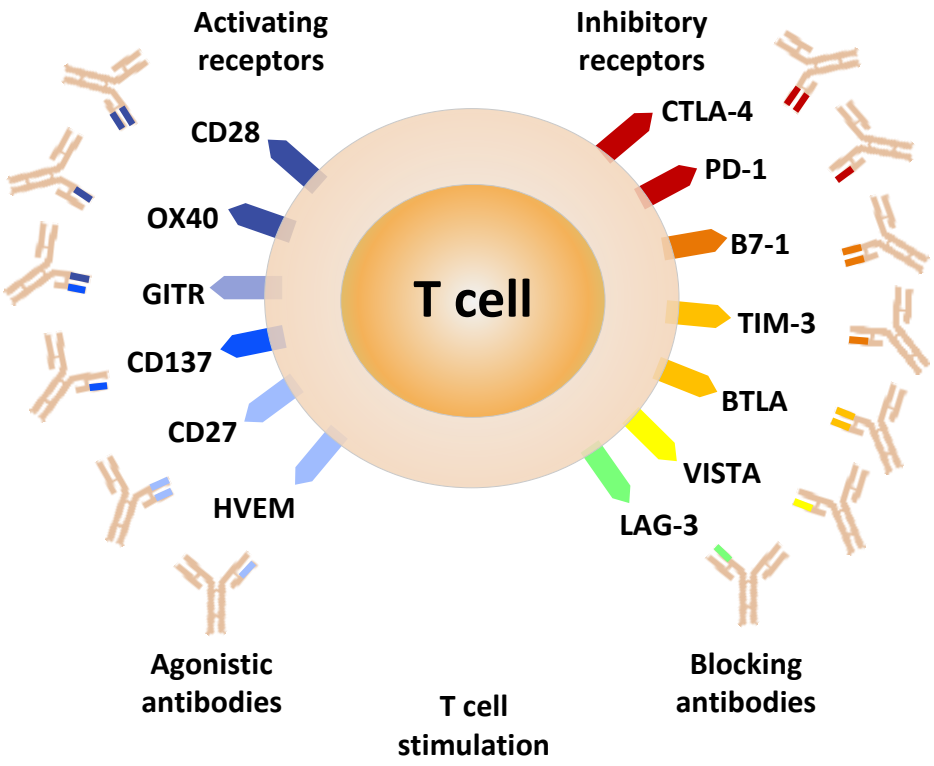
UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

T-Cell Immune Checkpoints as Targets for Immunotherapy

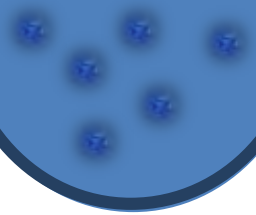
Targeted Therapy



Chemo-therapy



Cell Therapies

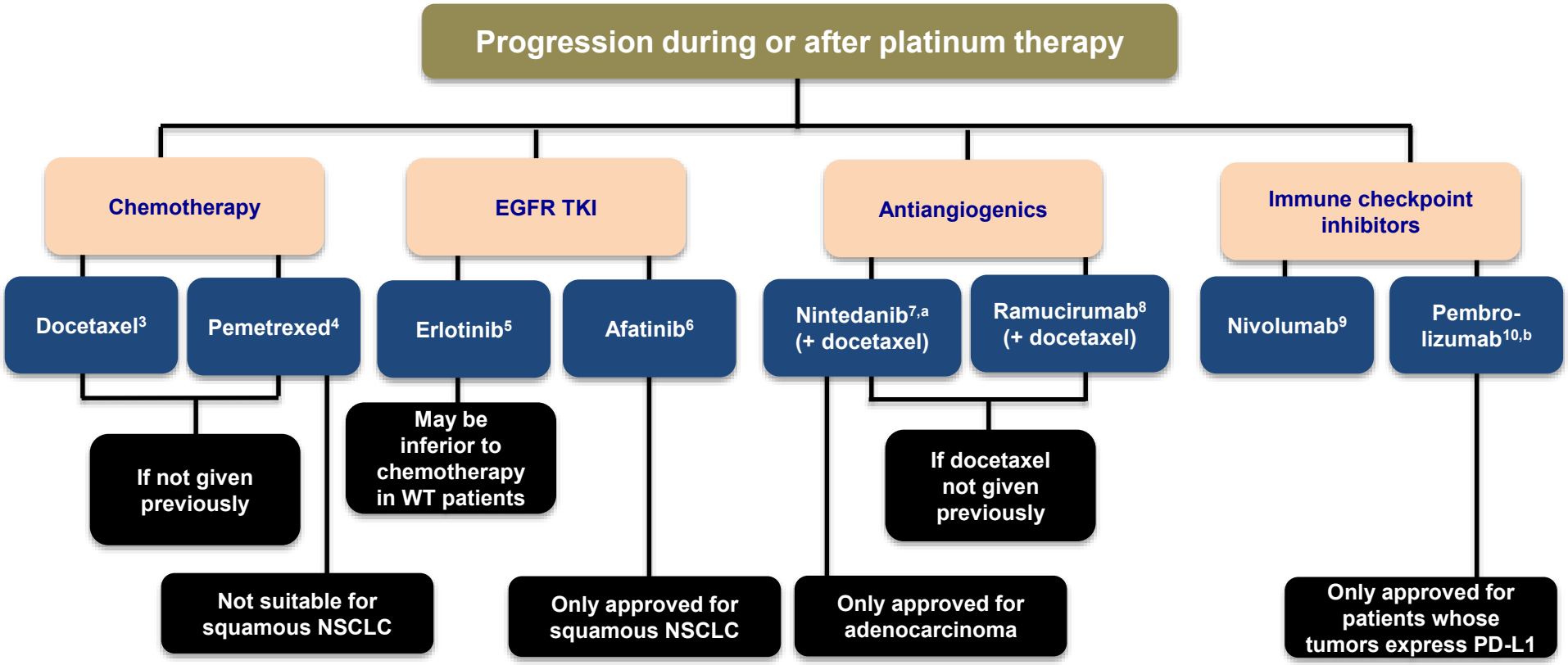


Vaccines

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

UNIVERSITÀ DEGLI STUDI DI TORINO
ALMA UNIVERSITAS TAURINENSIS

Treatment Options in Second Line: Overview



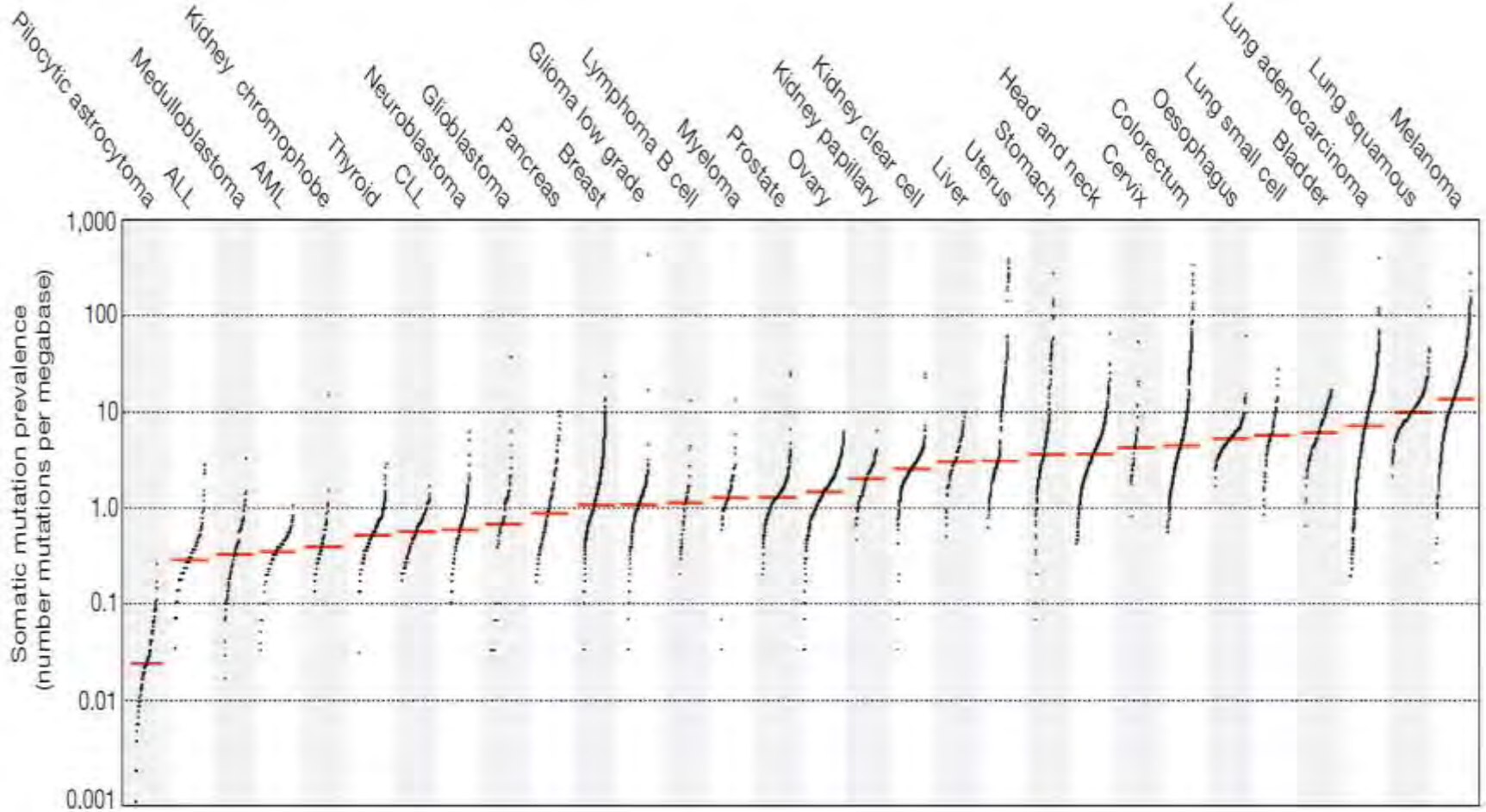
[a]Approved in EU only; [b]Approved in US only

1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.4.2016
2. Reck M et al. *Ann Oncol* 2014;25(Suppl 3):27-39

UNIVERSITÀ DEGLI STUDI DI TORINO

ALMA UNIVERSITAS TAURINENSIS

Cancer is a genetic disease: Mutational burden across cancers



Alexandrov, et al. Nature 2013