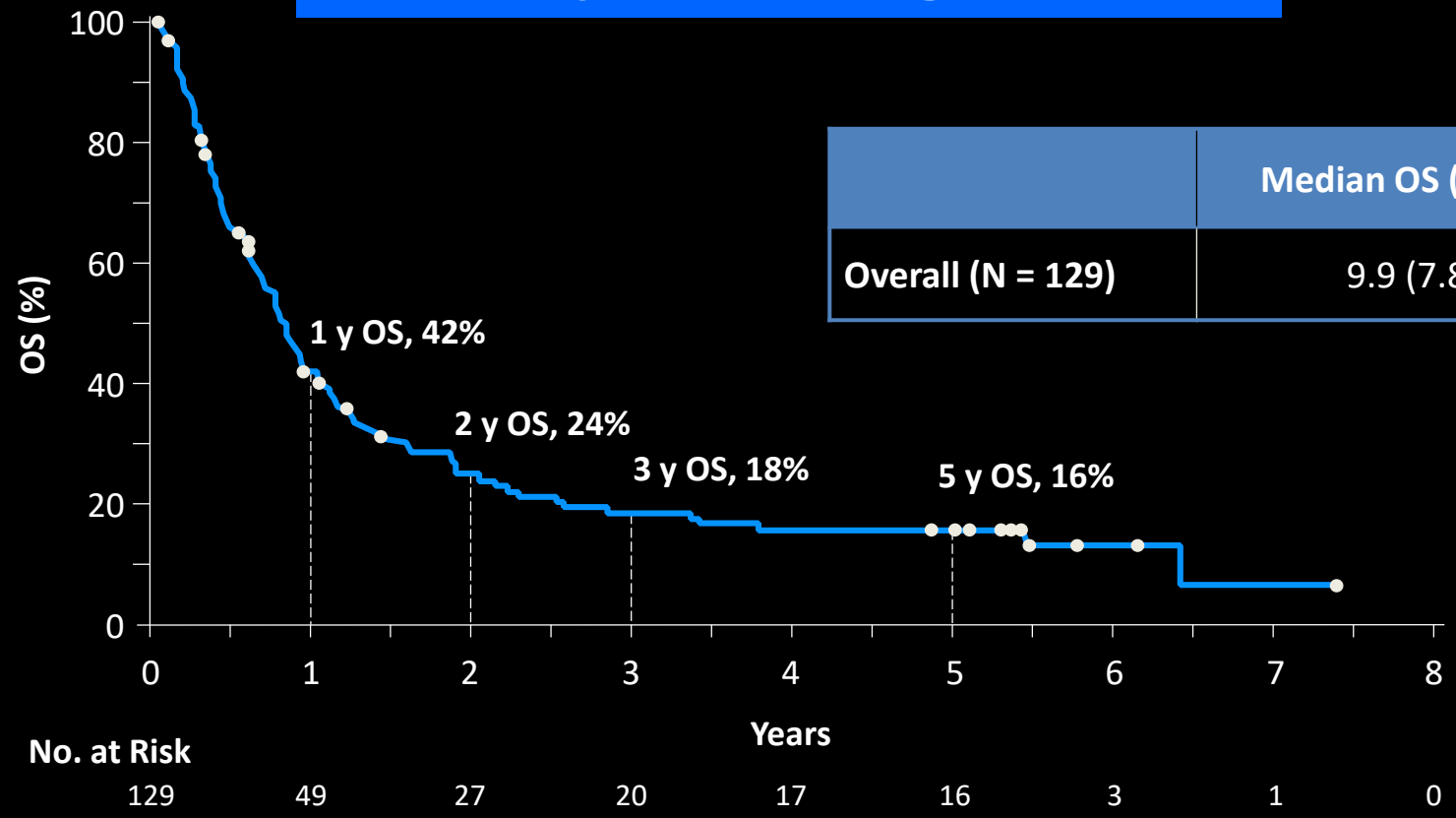
The immune-modulatory effects of non-immunotherapies

何肇基醫師

台大醫院胸腔內科

Immunotherapy in Lung Cander
Phase 1 Nivolumab (CA209-003): 5-Year Estimates of OS

The surprise: Long term OS



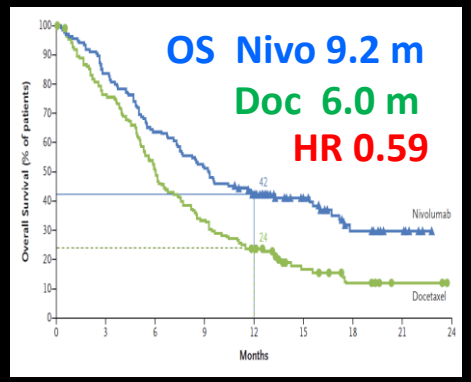
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

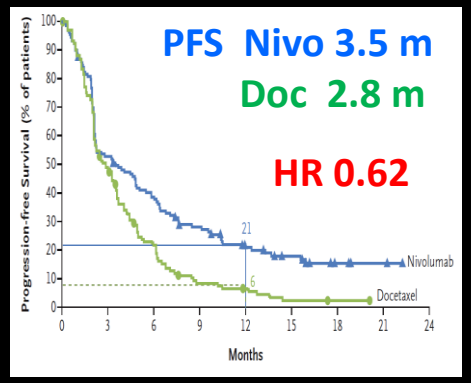
[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Gettinger, S et al. J Clin Oncol 36:1675-1684, 2018

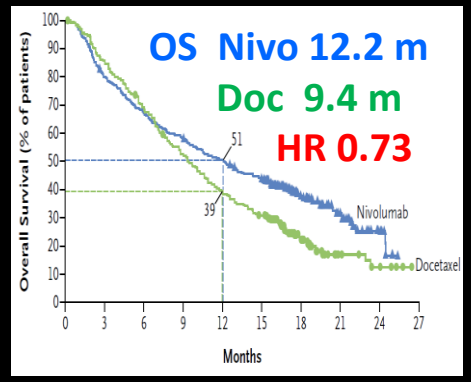
Not all patients benefit in IO monotherapy ≥ 2nd Line Phase III Trial: OS & PFS

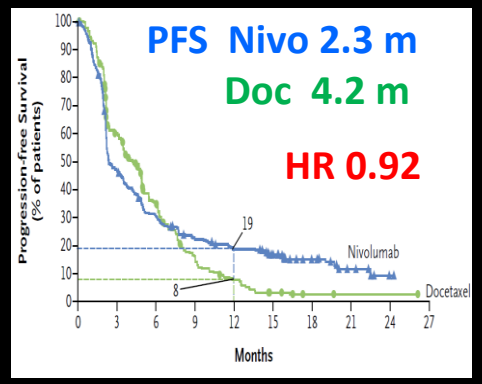
CM 017 Nivo Sq CC



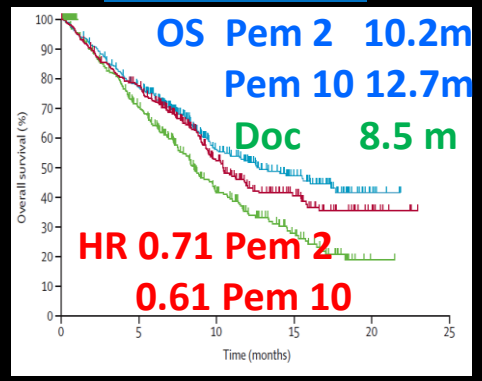


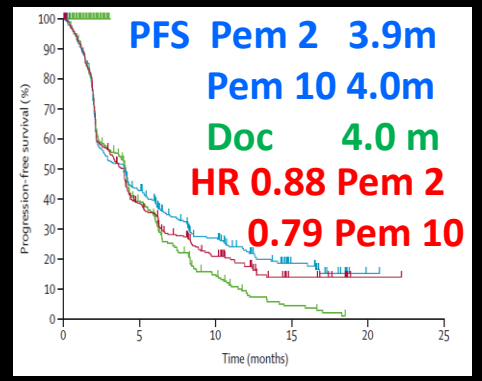
CM 057 Nivo Adeno



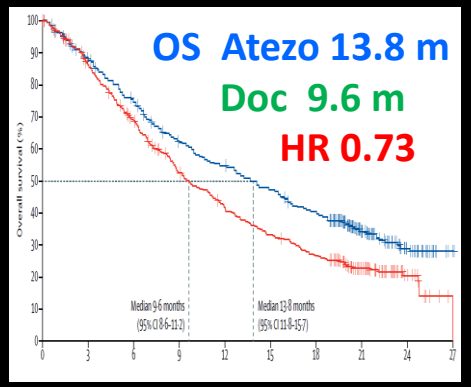


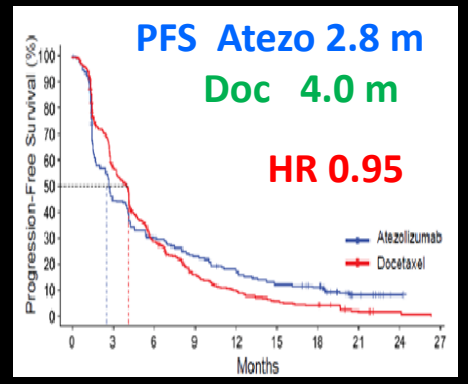
KN 010 Pem NSCLC PD-L1 ≥ 1%





OAK Atezo NSCLC





Brahmer J et al. N Engl J Med 2015; 373:123-135
Borghaei H et al. N Engl J Med 2015; 373:1627-1639
Herbst RS et al. **Lancet**. 2016;387:1540-50
Rittmeyer A,Lancet 2017; 389(10066): 255–265.

Summary: phase III studies of anti-PDL1 and anti-PD1 therapies in previously treated NSCLC

	CheckMate 017[1] (n=272)	CheckMate 057[1] (n=582)	KEYNOTE-010[2] (n=1033)	OAK[3] (n=850)
	Squamous	Non-squamous	All comers	All comers
PD-L1 selected	No	No	PD-L1 ≥1%	No
	HR 0.62	HR 0.75	HR 0.72	HR 0.73
Median OS (months)	9.2 vs 6.0	12.2 vs 9.5	10.5 vs 8.6	13.8 vs 9.6
	Nivo vs Doc	Nivo vs Doc	Pembro 2mg/kg vs Doc	Atezo vs Doc
ORR, %	20% vs 9%	19% vs 12%	19% vs 10%	14% vs 13%
Follow-up	Minimum follow-up 24.2 months	Minimum follow-up 24.2 months	Median follow-up 19.2 months	Minimum follow-up 19 months

Non-selected Pts

Response Rate around 20%

2.3 vs 4.2

3.9 vs 4.0

2.8 vs 4.0

Frontline IO monotherapy: Pembrolizumab in TPS ≥ 50%

KN 024

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

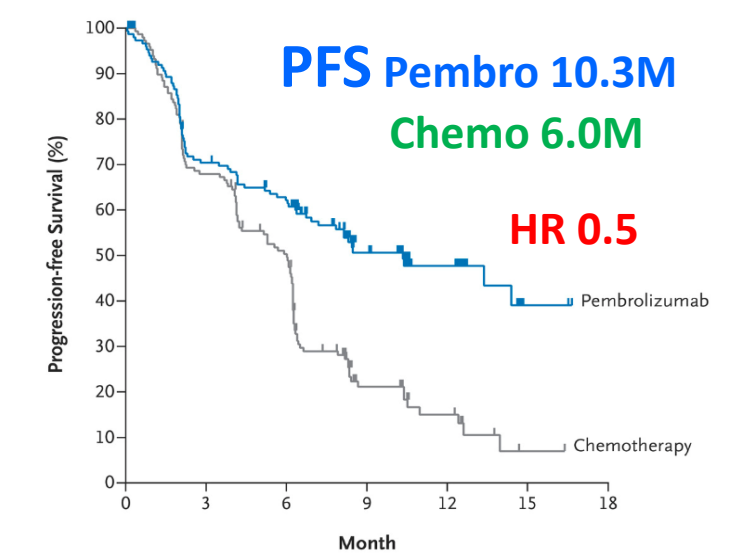
R (1:1)
N = 305

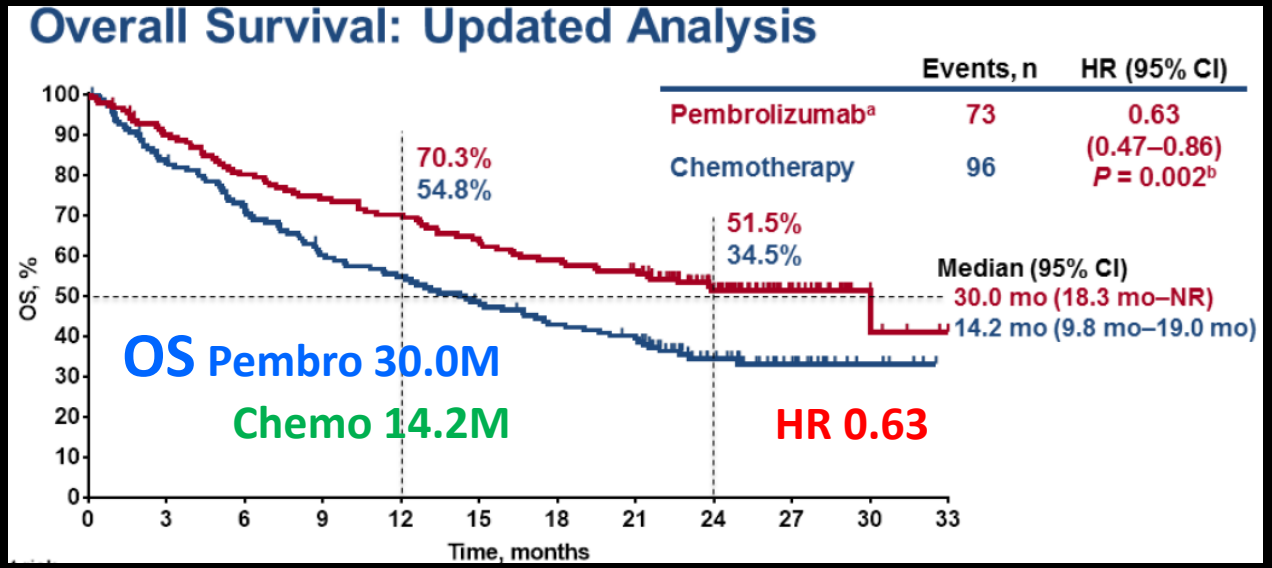
Pembrolizumab
200 mg IV Q3W
(2 years)

Platinum-Doublet Chemotherapy
(4-6 cycles)

PD[a]

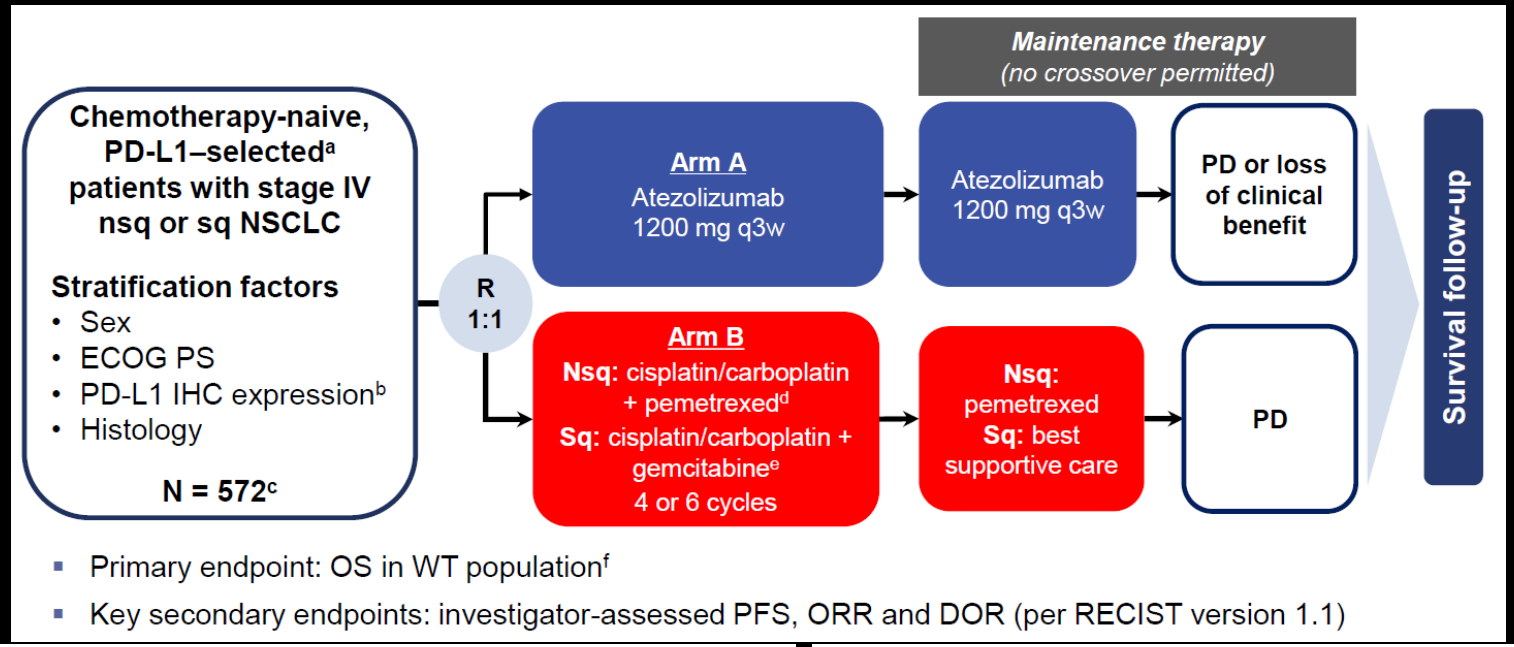
Pembrolizumab
200 mg Q3W
for 2 years



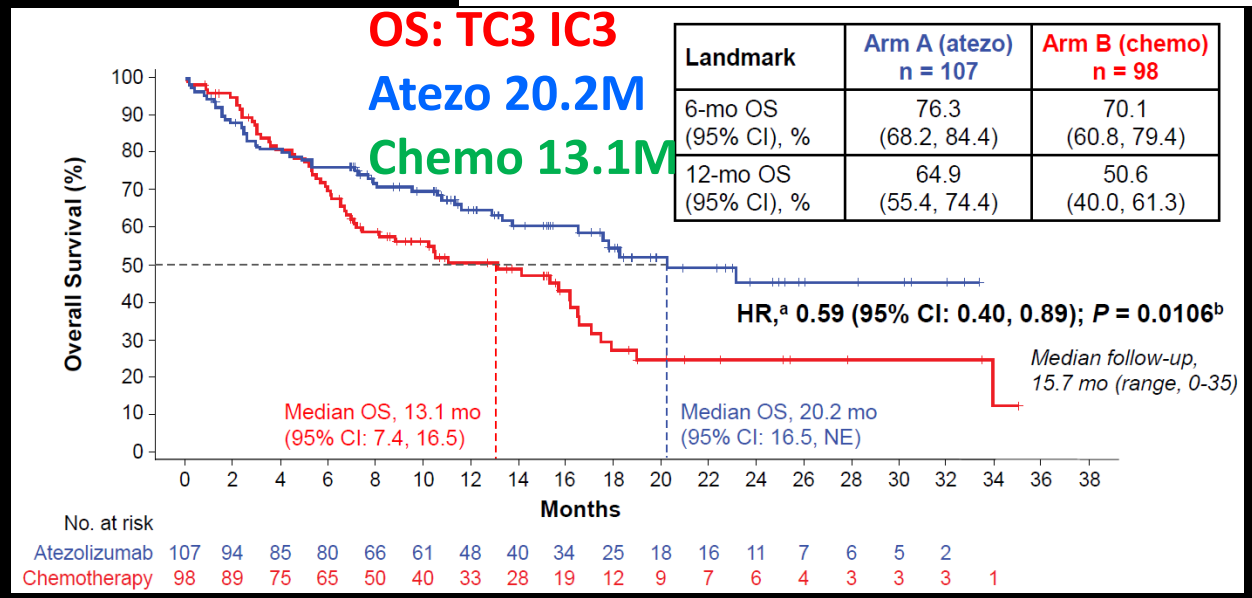


Reck M et al. N Engl J Med 2016; 375:1823-1833

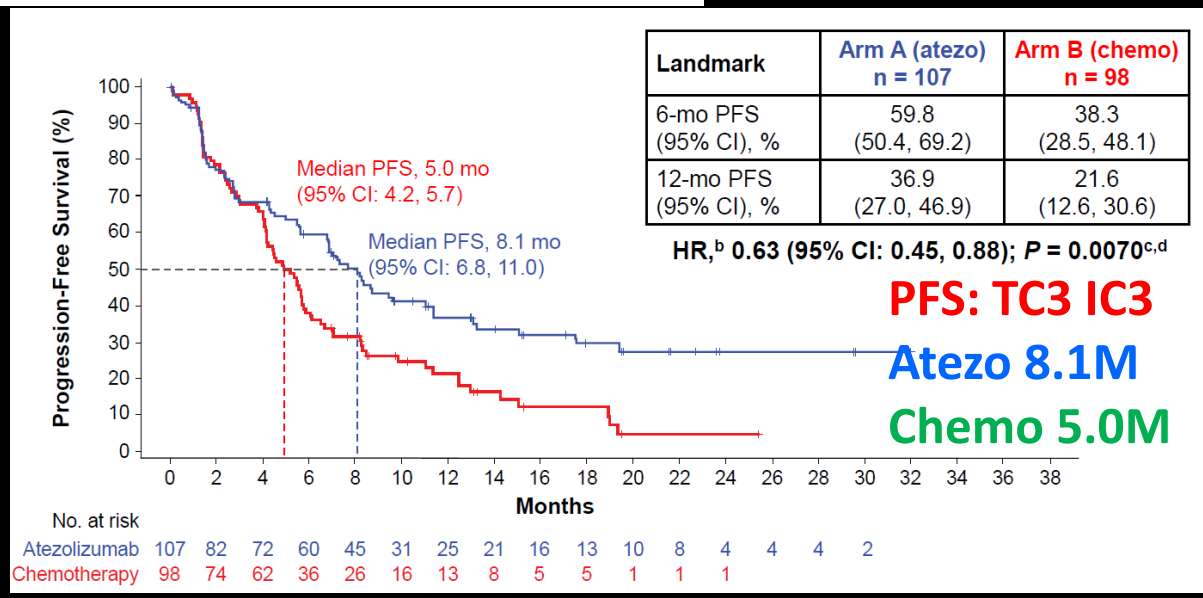
Frontline IO monotherapy: IMpower 110



Spigel DR et al ESMO2019

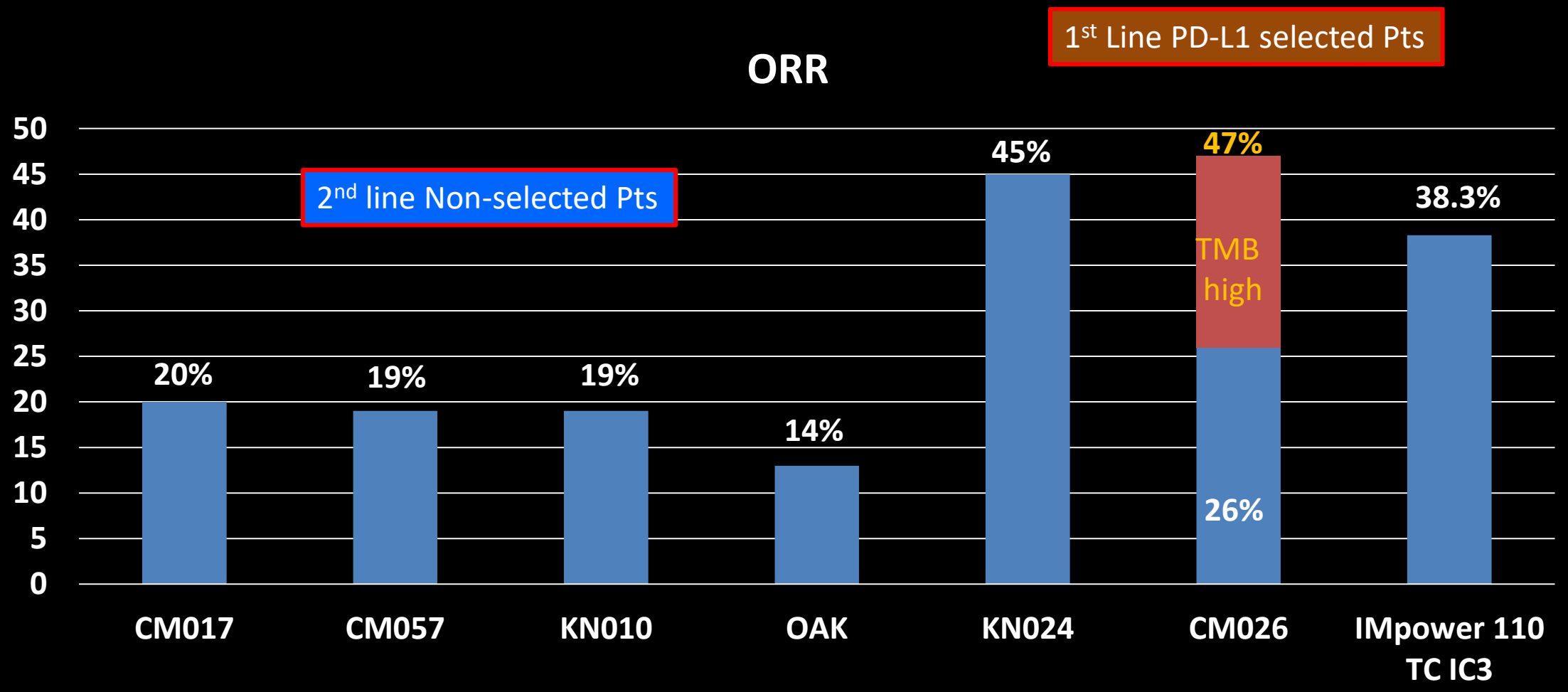


Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)

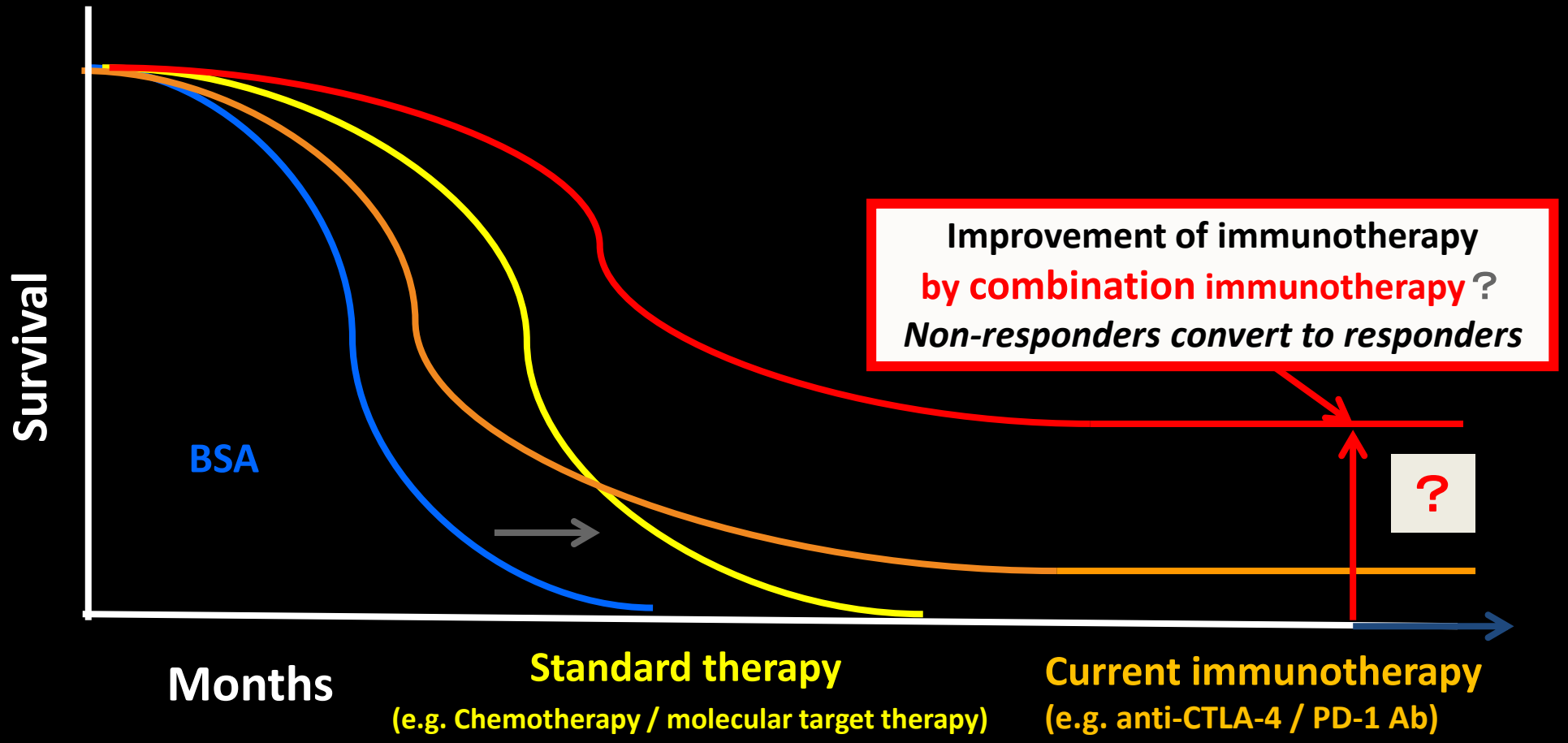


Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo PFS (95% CI), %	59.8 (50.4, 69.2)	38.3 (28.5, 48.1)
12-mo PFS (95% CI), %	36.9 (27.0, 46.9)	21.6 (12.6, 30.6)

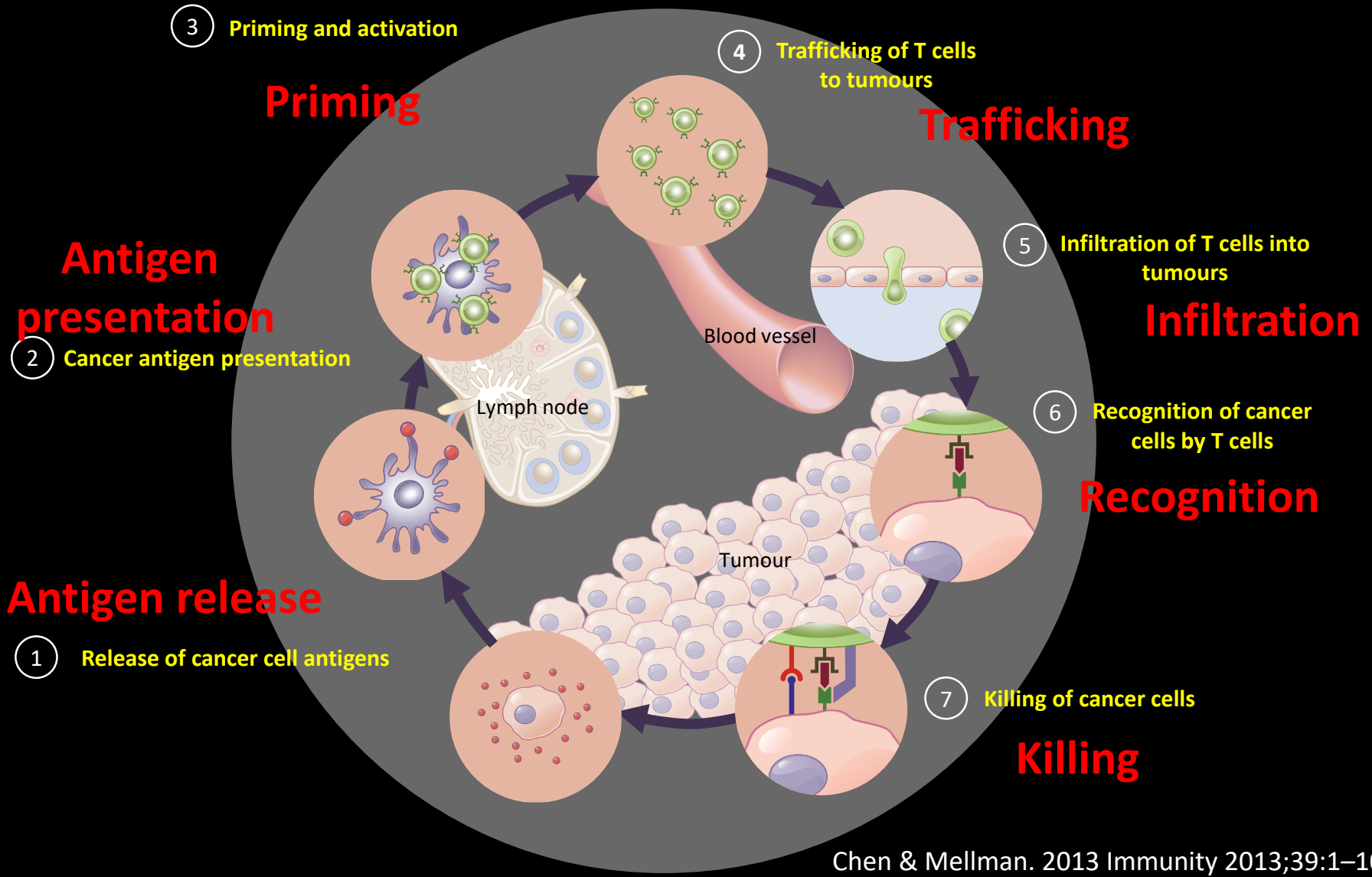
ICI monotherapy ORR



Combination immunotherapy for better OS

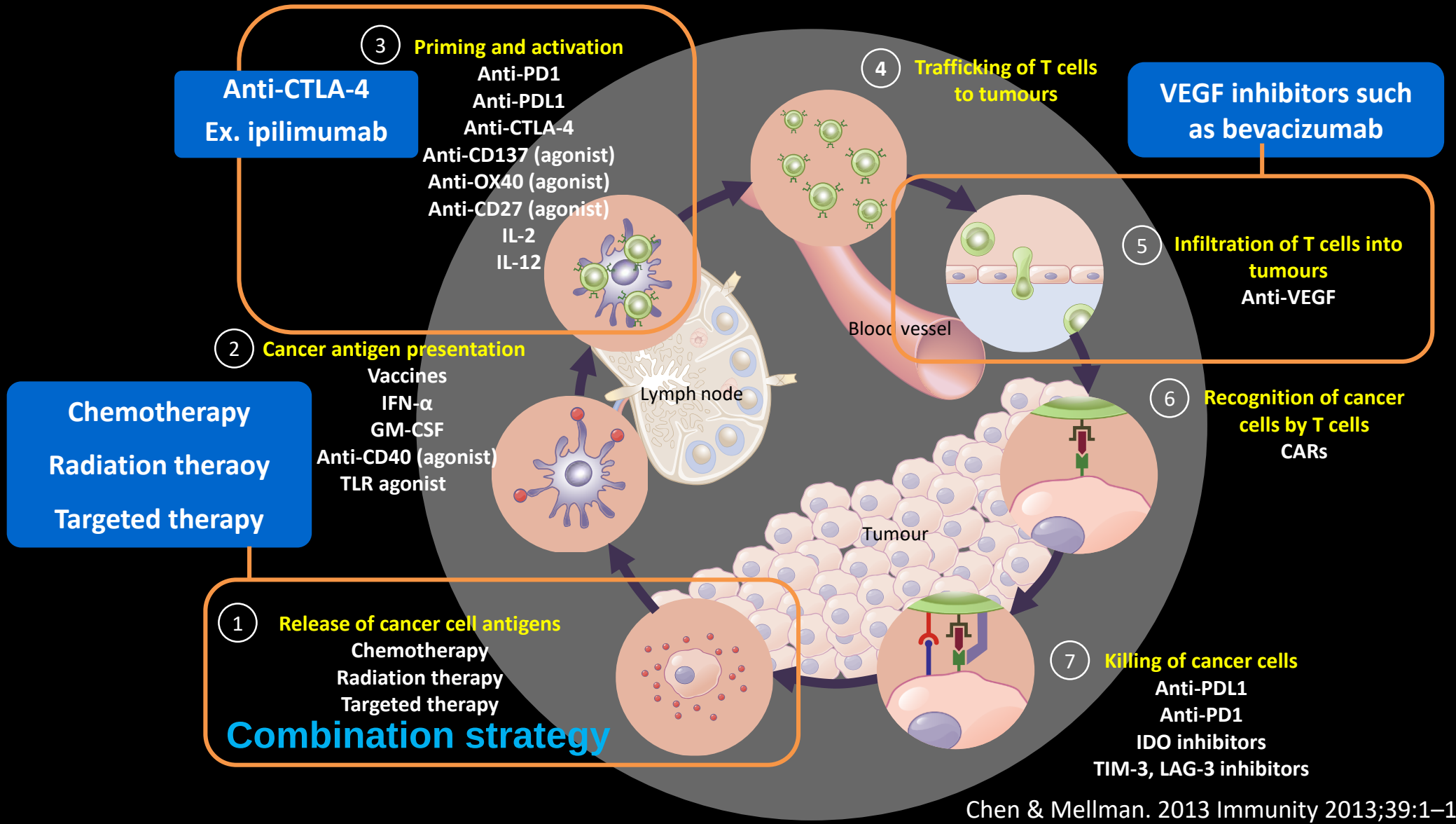


Cancer-immunity cycle

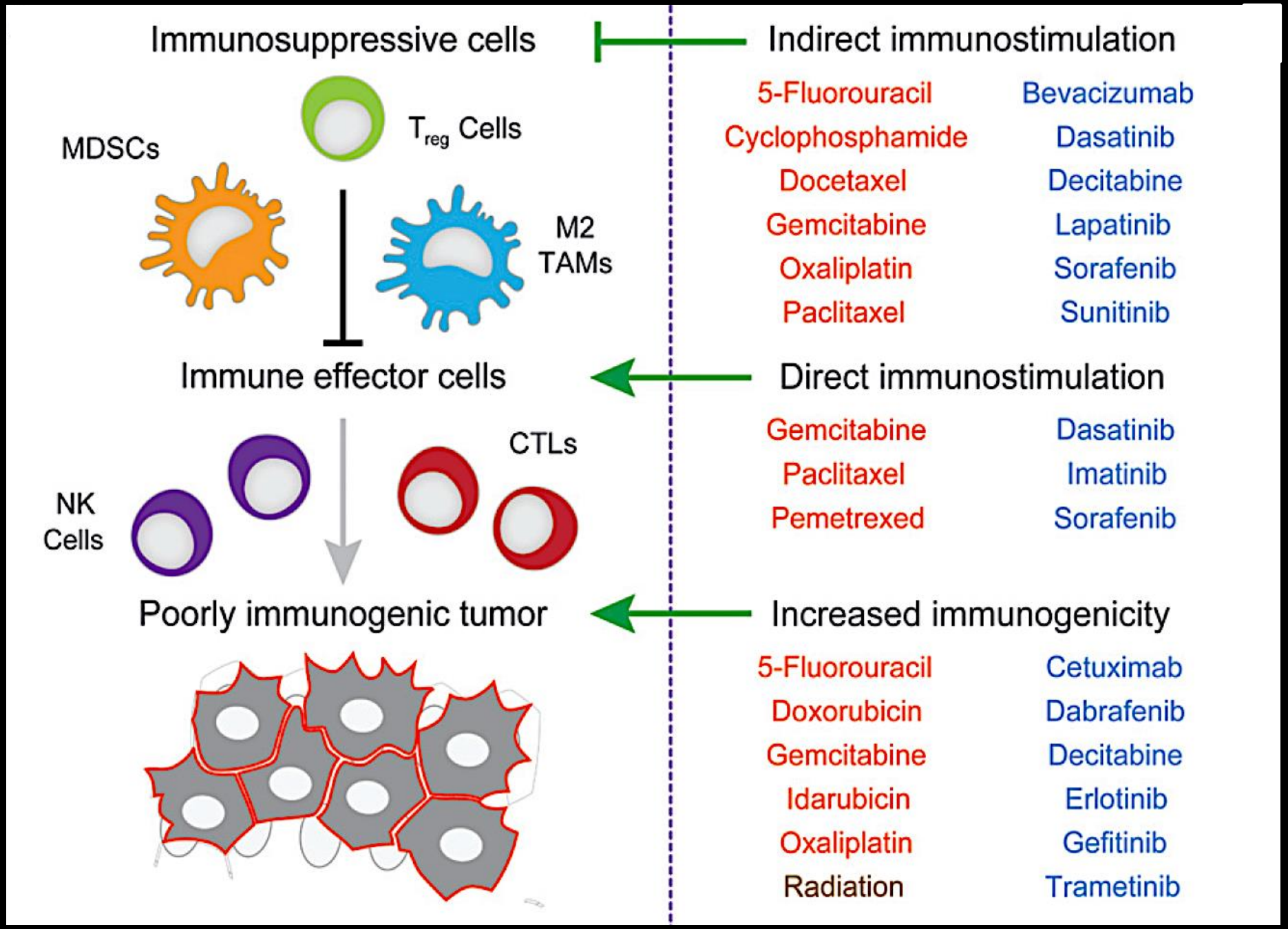


Chen & Mellman. 2013 Immunity 2013;39:1–10

Combination Strategy for immunotherapy

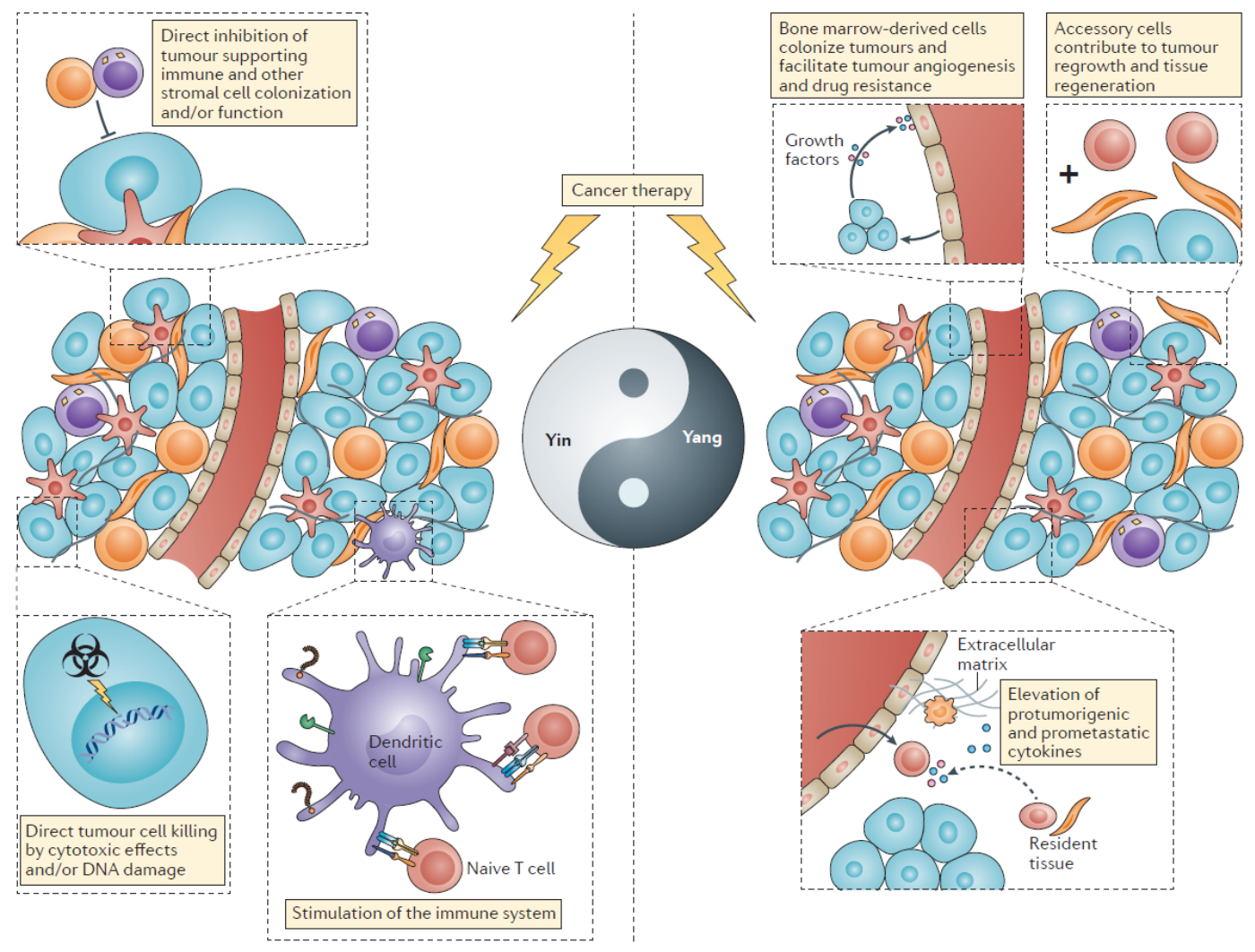


Chen & Mellman. 2013 Immunity 2013;39:1–10



Galluzzi L, et al. Cancer Immunol Res; 4(11); 895–902. 2016 AACR.

Anticancer agents have both tumor promoting and inhibitory effects



- Chemotherapy, radiation, and molecularly targeted drugs generate host-mediated **pro-tumorigenic** and **pro-metastatic** effects
- Therapy-induced host effects support **angiogenesis**, **metastasis**, and **resistance**
- Host-derived tumor accessory cells and various secreted factors contribute to **tumor recurrence**
- Blunting these cellular and molecular host-mediated effects generated by anticancer drugs might improve overall therapeutic outcomes

Yuval Shaked *Nat. Rev. Clin. Oncol*. 13, 611–626 (2016).

Immune-modulatory effects

Chemotherapy

Targeted therapy

Anti-angiogenesis

Radiotherapy

Immune-modulatory effects

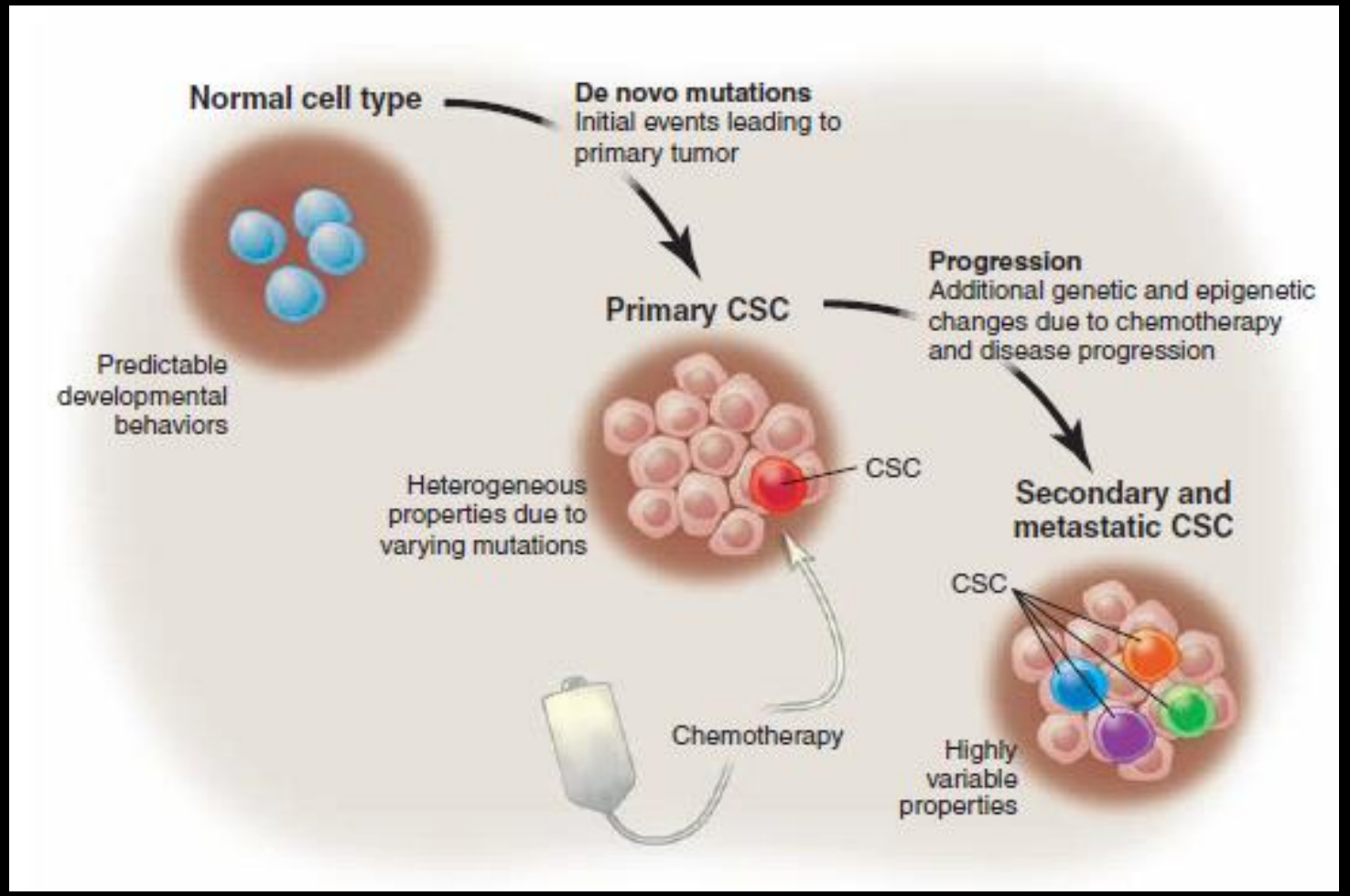
Chemotherapy

Targeted therapy

Anti-angiogenesis

Radiotherapy

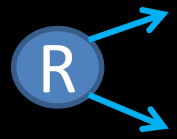
Chemotherapy induced more genetic and epigenetic change: more resistance to treatment



Science 324:1670-1673 (2009)

Immunotherapy + Chemotherapy

- To enhance chemotherapy effect

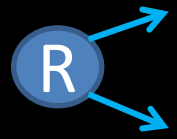


Chemotherapy + immunotherapy

Chemotherapy

Platinum doublet chemotherapy !

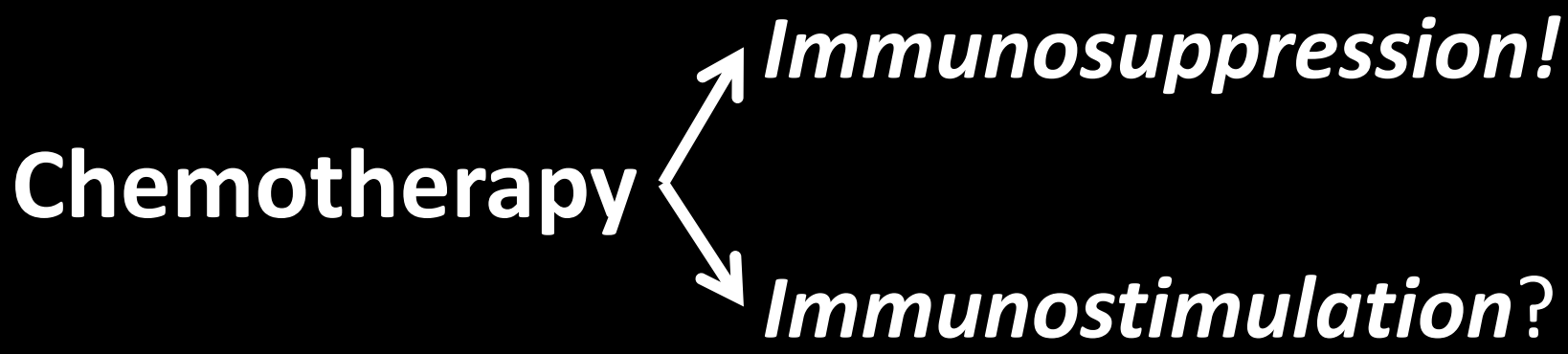
- To enhance immunotherapy effect



Immunotherapy + chemotherapy

Immunotherapy

Platinum doublet chemotherapy ?

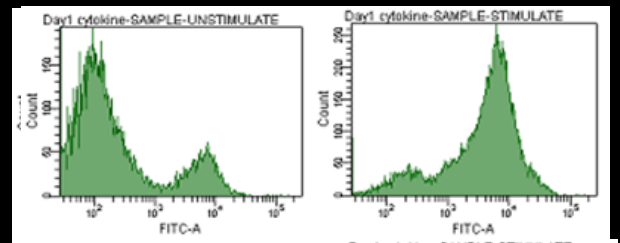
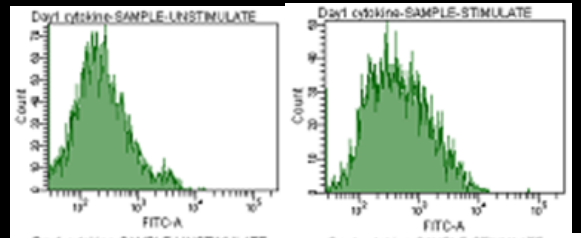
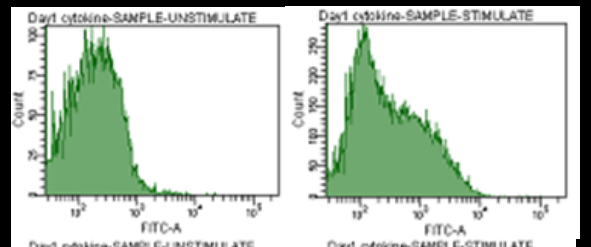
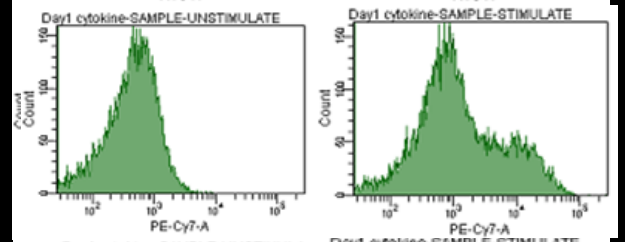
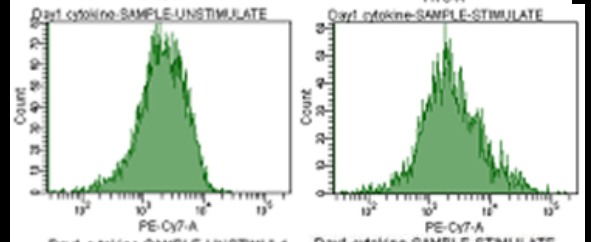
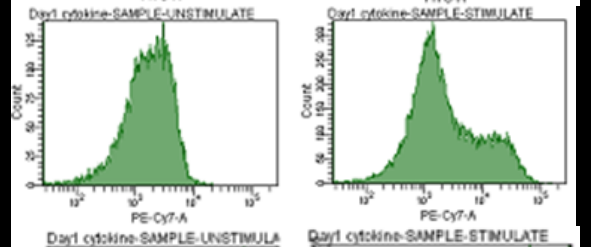
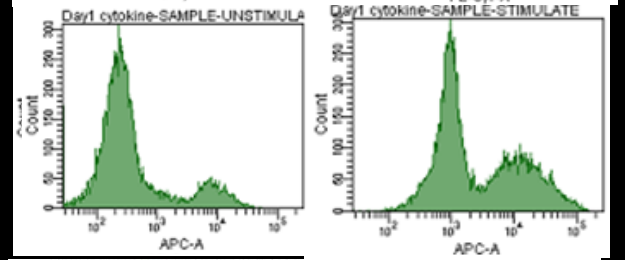
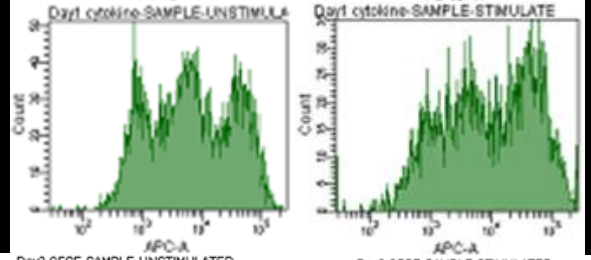
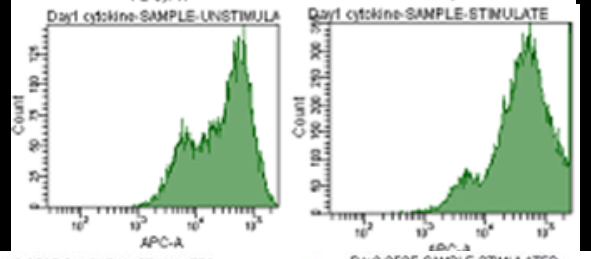
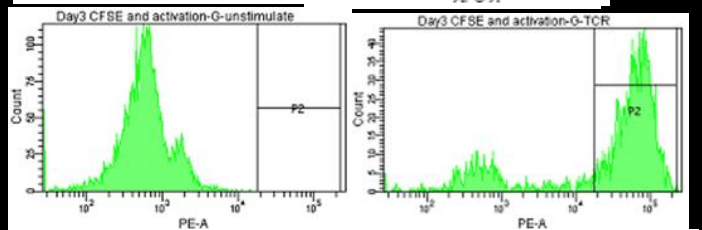
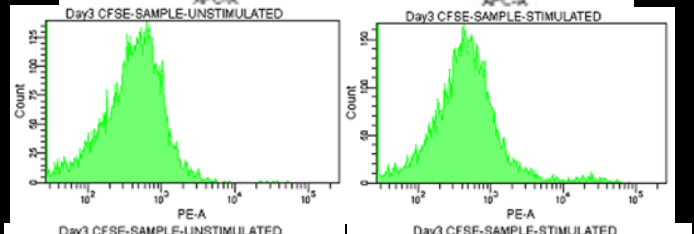
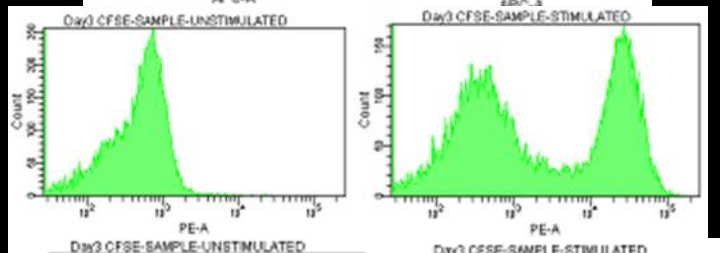
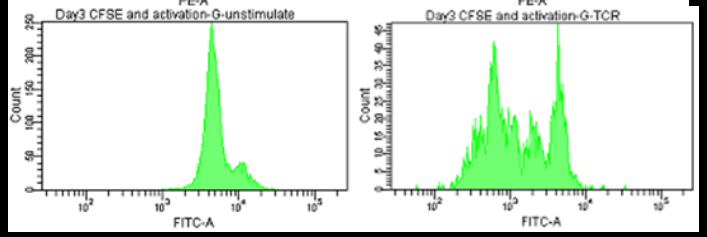
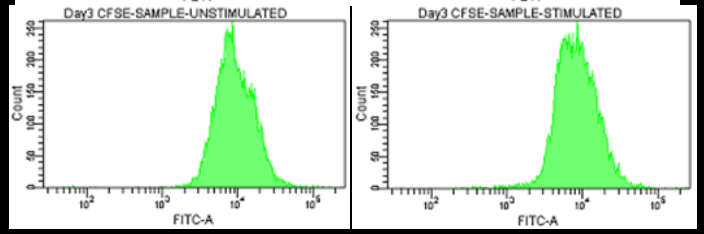
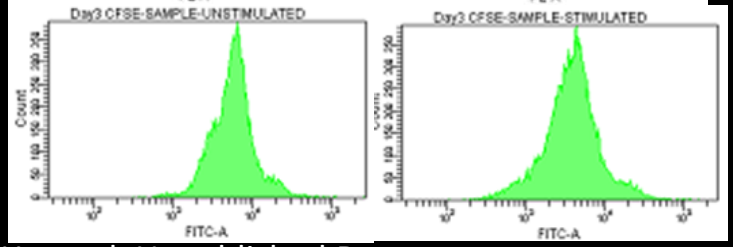

Chemotherapy
Immunosuppression!
Immunostimulation?

Cellular and molecular host factors generated in response to chemotherapy with poor immune-modulatory effects

Host cell	Accompanied factor(s)	Cytotoxic or cytotoxic-like drugs	Human/mouse (H/M)
EPCs	Not applicable	• Cyclophosphamide • Docetaxel • 5-FU • Paclitaxel • FOLFOX • Ca4-P/OXi-4503	M
EPCs/CECs	SDF-1, G-CSF	• Paclitaxel • Ca4-P/OXi-4503	H/M
EPCs/CECs	MMP-9, VEGF-A	Ca4-P/OXi-4503	M
Pulmonary ECs	VEGFR1	• Cisplatin • Paclitaxel	M
CD34+/CD133+ cells	VEGF-A/G-CSF	Ca4-P/OXi-4503	H
Thymic ECs	TIMP-1/IL-6	Doxorubicin	M
	IL-6	• Cisplatin • Doxorubicin • Epirubicin	H
TAMs (anti-inflammatory) CXCR4+ cells	VEGF-A	• Cyclophosphamide • Doxorubicin • Docetaxel • 5-FU • Paclitaxel	H/M
TAMs (M2/CD68/CD163)	Not applicable	• Cisplatin • Doxorubicin • 5-FU	H
MDSCs	IL-6/IL-8/GM-CSF	• Gemcitabine • 5-FU	M
	GM-CSF	Gemcitabine	H
Myeloid/macrophages	Cathepsins	• Doxorubicin • Paclitaxel • Etoposide	M
Myeloid/macrophages	Cathepsins	• Doxorubicin • Paclitaxel • Etoposide	H
Antigen-presenting cells	Not applicable	Epirubicin	M
BMDCs	MMP-2/MMP-9	• Paclitaxel • FOLFOX	M
MDSCs/macrophages	IL-1β	• Gemcitabine • 5-FU • Paclitaxel	M
CD4+ T cells	IL-17	• Gemcitabine • 5-FU	M
MSCs	Polyunsaturated fatty acids	Cisplatin	H/M

Yuval Shaked *Nat. Rev. Clin. Oncol*. 13, 611–626 (2016).

T cell Activity: Control vs. Chemotherapy

	Control		Chemotherapy D6		Chemotherapy D21	
	Unstimulated	**Stimulated**	**Unstimulated**	**Stimulated**	**Unstimulated**	**Stimulated**
CD69 Early activation						
INF- γ Function						
Granzyme B Function						
CD25 Early activation						
CFSE Proliferation						

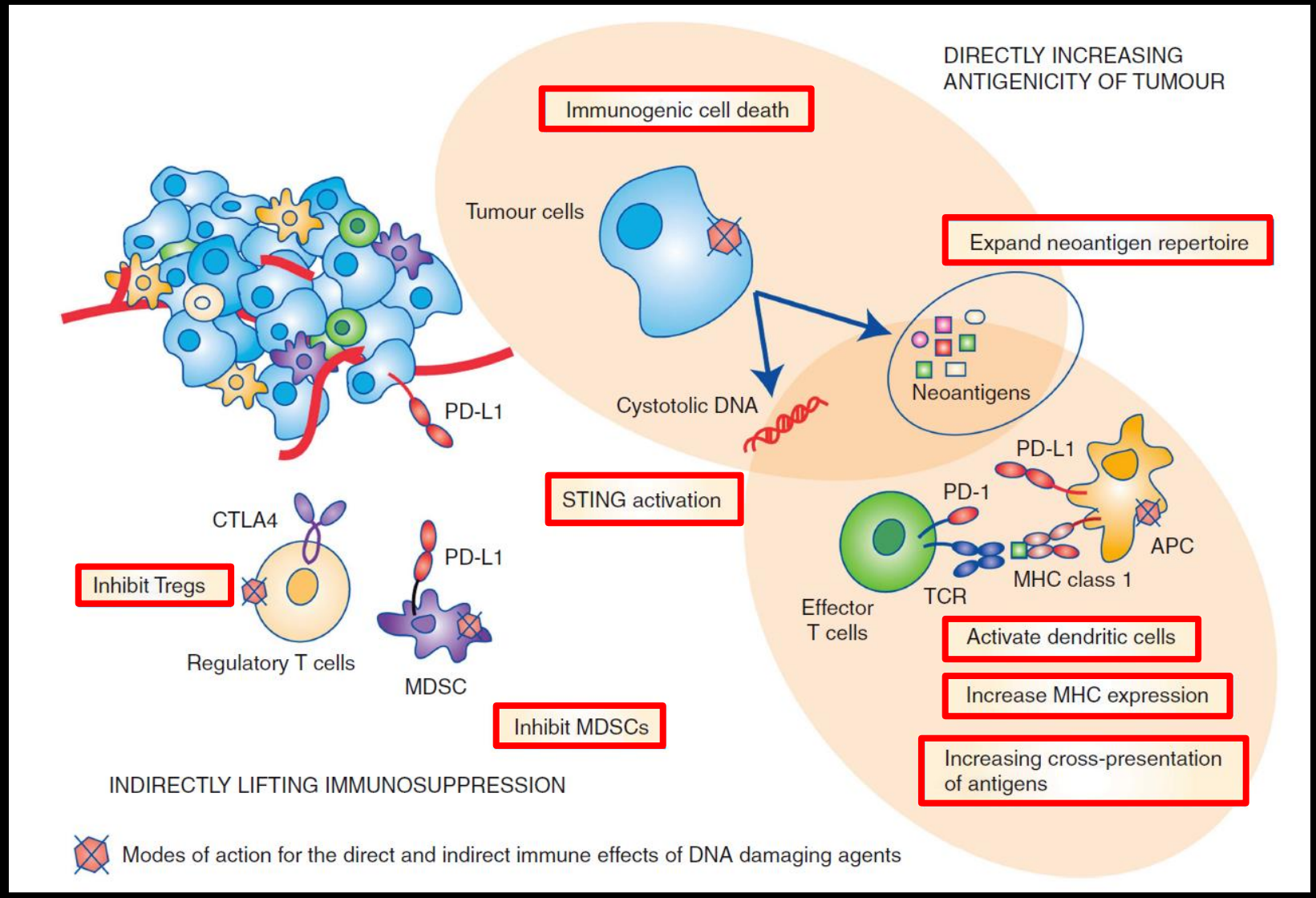
Ho et al. Unpublished Data

Chemotherapy

- In the past decades, chemotherapy was considered an immunosuppressive modality in the treatment of cancer.
- However, accumulating evidence indicates positive immunologic effects of chemotherapeutic agents.

Hato SV, et al. Clin Cancer Res 2014;20: 2831–2837.

DNA damaging agents affect the immunogenicity of tumors

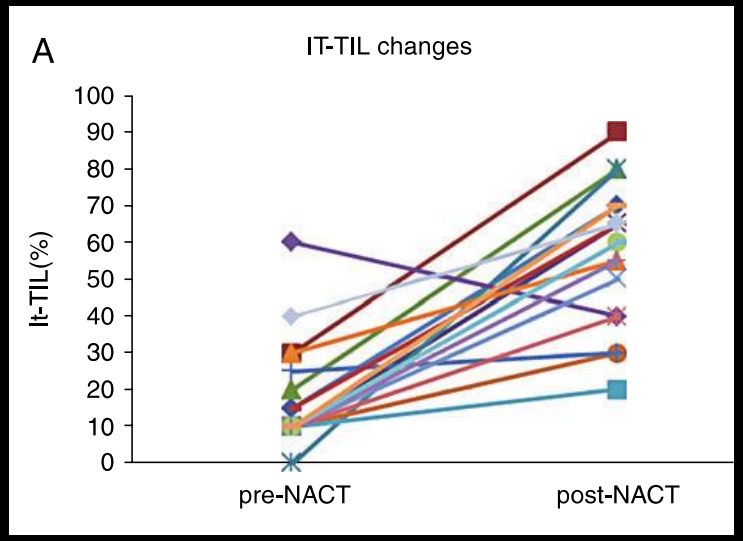


STING: stimulator of interferon genes

Brown JS et al. Br J Cancer 2018; 118, 312–324

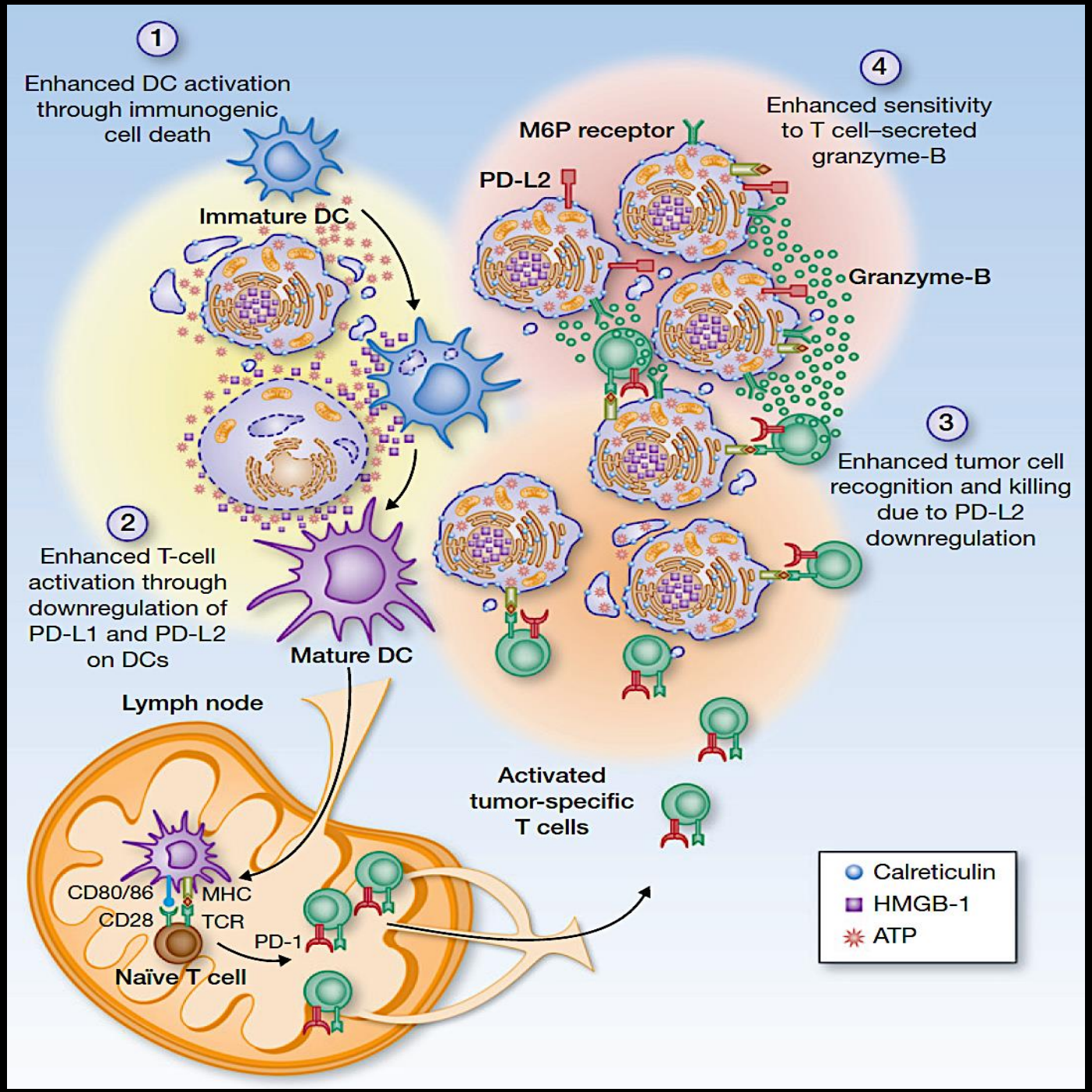
Chemotherapy stimulated immune-based anti-cancer activity

- Chemotherapy may stimulate the immune system by
  - Lysing tumor cells to release cancer cell antigen[1,2]
  - Activating dendritic cells[3]
  - Depleting immunosuppressive Tregs at low doses[4]
  - Increasing tumor-infiltrating lymphocytes (TILs)[5]



CT increased TIL number following neoadjuvant therapy in 278 patients with TNBC

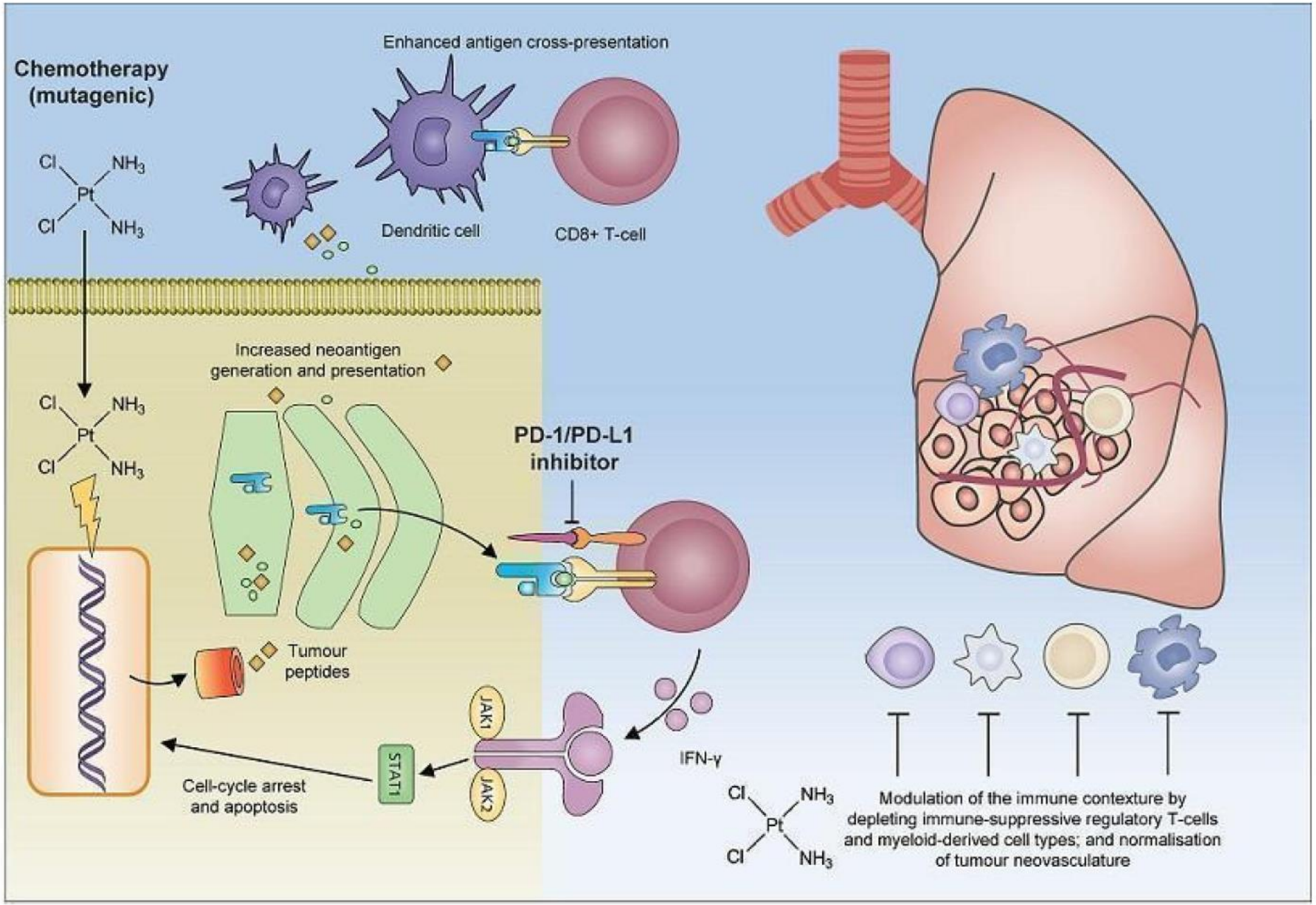
1. Bracci et al. Cell Death Differ 2014
2. Mellman et al. Nature 2011
3. Tanaka et al. Cancer Res 2009
4. Banissi et al. Cancer Imm Immunother 2009
5. Dieci et al. Ann Oncol 2014



Immunologic effects of platinum chemotherapeutics on the tumor microenvironment.

- ATP release from cells dying from platinum exposure **attracts DCs,** which take up parts of dying cells that have cell surface expression of calreticulin.
- The maturation of DCs in the presence of platinum drugs results in **downregulation of PD-L1 and PD-L2** on the DCs, increasing their T-cell activation potential.
- Platinum drugs **inactivate STAT6** in the tumor cells, leading to decreased PD-L2 expression, resulting in enhanced recognition and killing by the tumor-specific T cells.
- Platinum induces upregulation of M6P receptor on tumor cells, which leads to **enhanced tumor cell lysis by granzyme-B secreted** by the activated T cells.

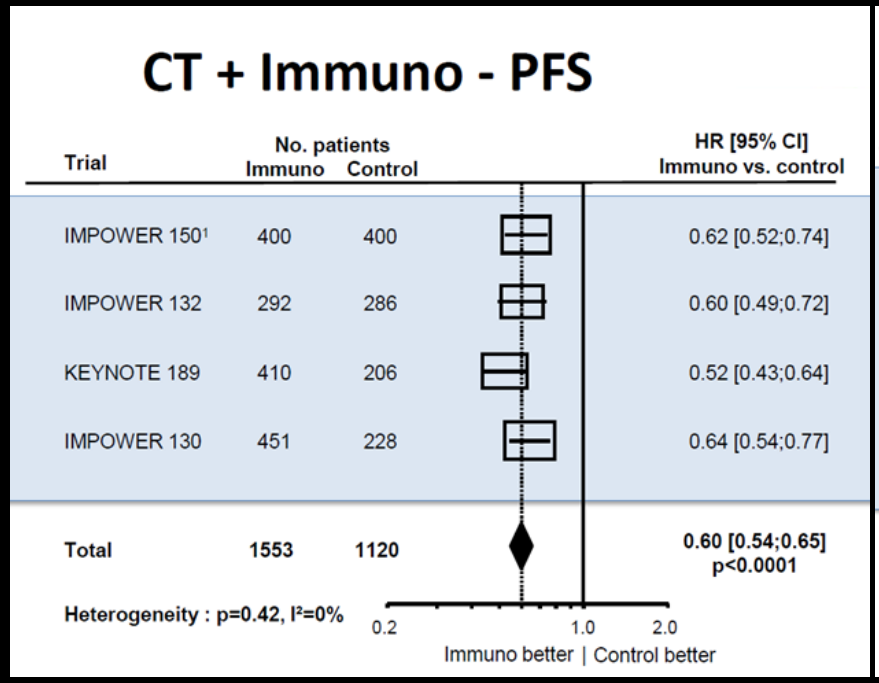
Hato SV, et al. Clin Cancer Res 2014;20: 2831–2837.

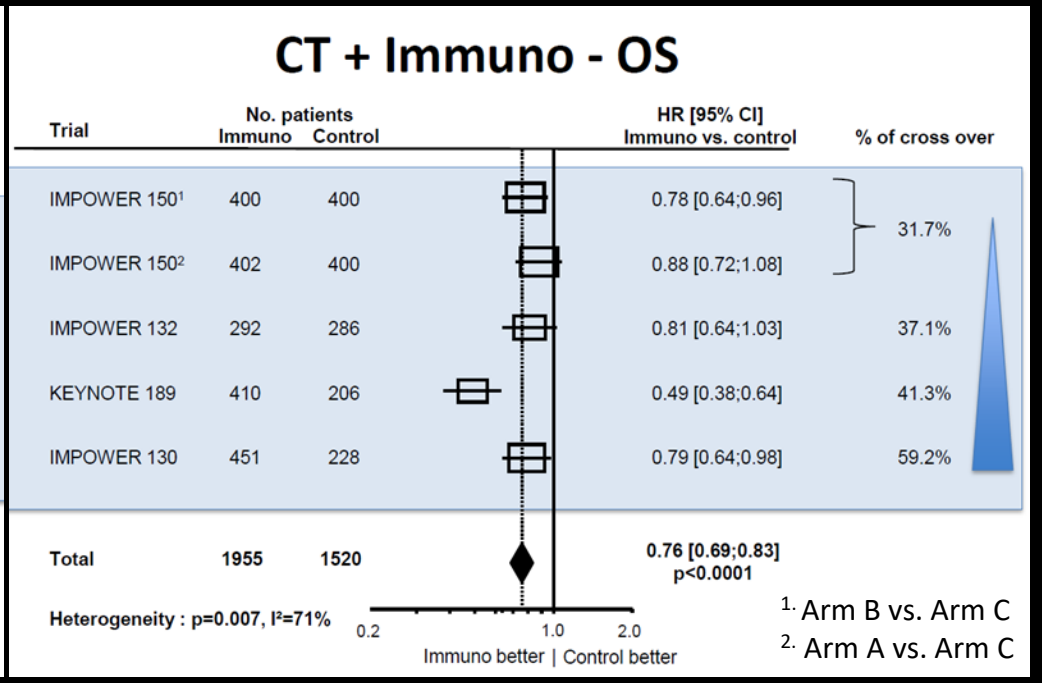


- ***Increasing the mutational load in cancer cells*** (Szikriszt 2016; McGranahan 2016; Pardoll 2012; Rizvi 2015; Snyder 2014; Syn 2017a; Van Allen 2015).
- ***Depleting or reducing the activity of immune-suppressive regulatory T-cells and myeloid-derived cell subsets*** (Kodumudi 2010; Nowak 2002; Pol 2015; Zitvogel 2008).
- ***Normalizing the tumour neo-vasculature*** **allowing** ***greater CD8+ T-cell infiltration.***(Schwartz 2009; Motz 2014).
- ***Augmenting major histocompatilibity complex class I expression*** (de Biasi 2014; Galluzzi 2012).
- ***Enhancing the cross presentation of neoantigens through inducing immunogenic forms of tumour cell death*** (Galluzzi 2017; Pfirschke 2016; Pol 2015).
- ***Increasing the sensitivity of tumour cells to interferon-gamma*** (Hato 2014).

Syn NLX, et al. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD013009.

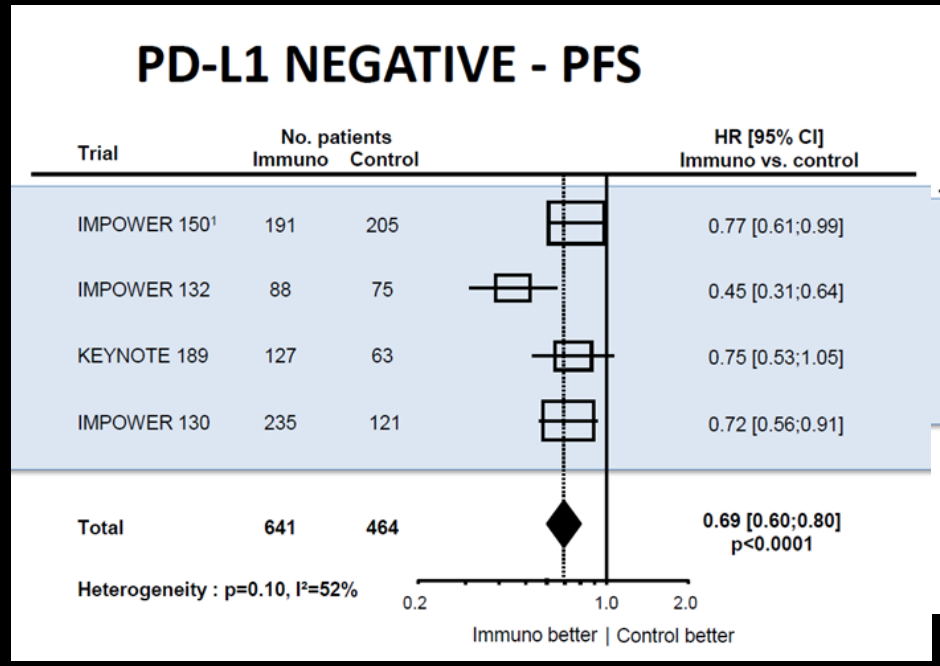
IO + CT vs. CT
Meta-analysis: ITT group

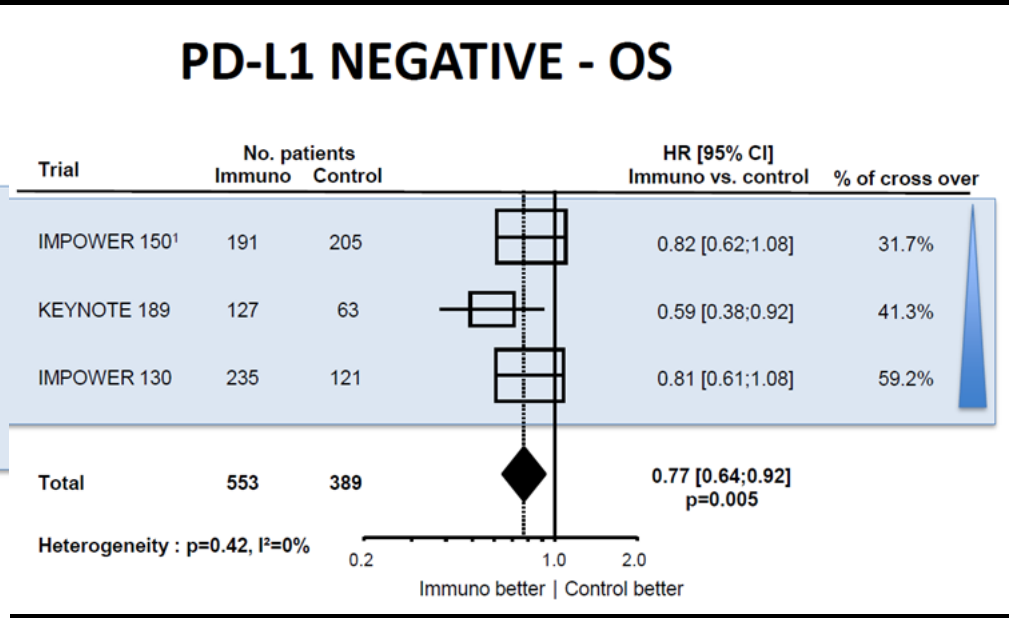




Modified from Benjamin Besse ESMO 2018

IO + CT vs. CT
Meta-analysis: PD-L1 (-) group





Modified from Benjamin Besse ESMO 2018

Immunotherapy + chemotherapy
Chemotherapy backbone?

Non-squamous cell

- Pemetrexed + platinum maintenance with pemetrexed
- Bevacizumab + paclitaxel + carboplatin maintenance with bevacizumab

Squamous cell

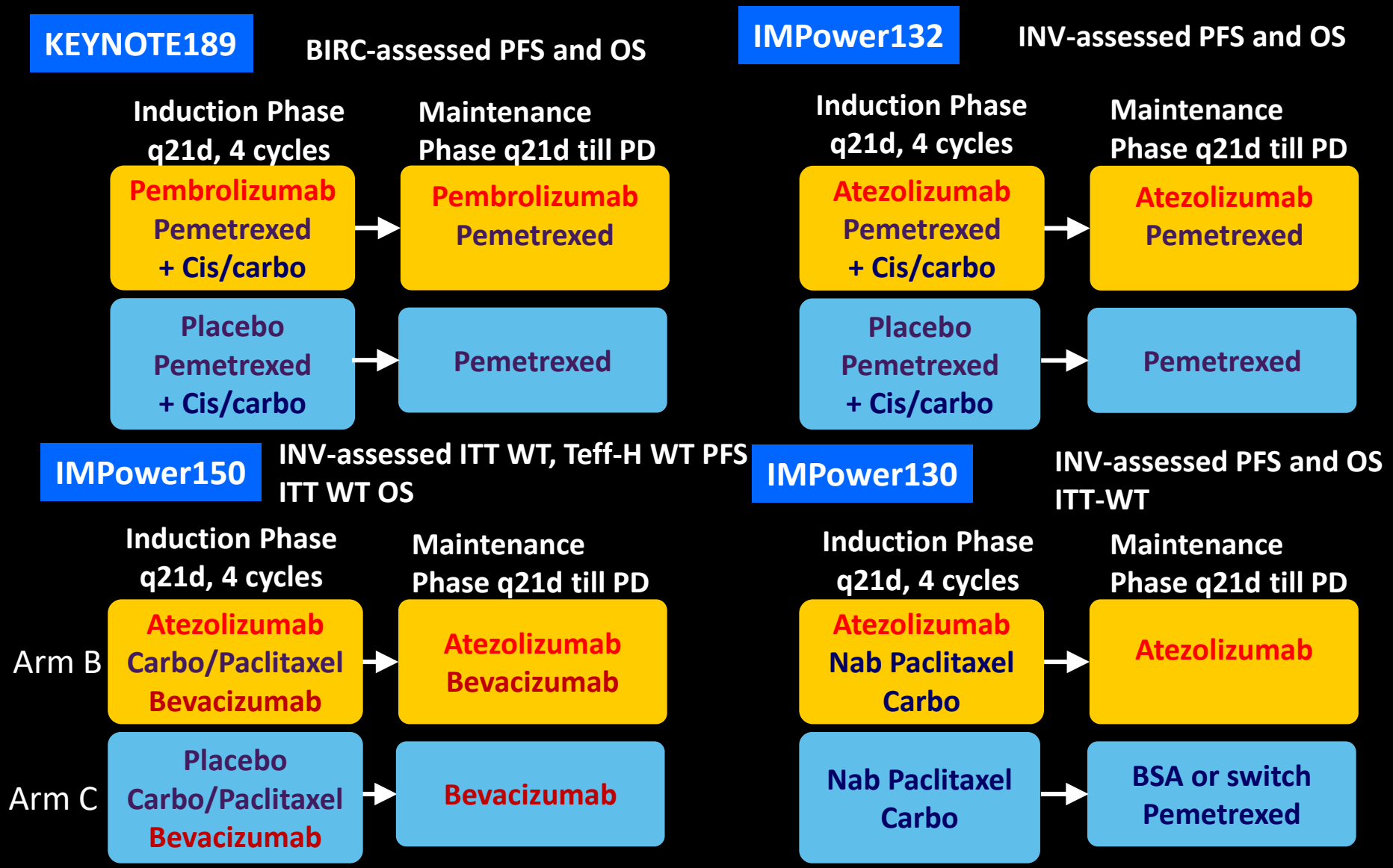
- Paclitaxel + carboplatin
- Nab-Paclitaxel + carboplatin
- Gemcitabine + platinum
- Vinorelbine + platinum

Which is better?

Immune effects of selected chemotherapy used in NSCLC

Chemotherapy	Setting	Effect	Reference
Paclitaxel	Breast carcinoma	Favours tumor infiltration by CD68 macrophages Favours tumor infiltration by NK cells and CTLs	Denardo et al. 2011 Demaria et al. 2001
	Transgenic breast carcinoma	Boosts DC maturation and cross priming	Pfannenstiel et al. 2010
	Transgenic murine melanoma	Depletes circulating MDSCs	Sevko et al. 2013
Docetaxel	NSCLC	Depletes circulating Treg	Li et al. 2014
Vinorelbine	NSCLC	Increases CTL/Treg ratio (reduced activity of Treg)	Roselli et al. 2013
Gemcitabine	Transplantable murine lung carcinoma	Depletes circulating MDSCs	Sawant et al. 2013
	NSCLC	Depletes circulating Treg	Chen et al. 2015
Pemetrexed	Pancreatic cancer	Activates IFN gamma producing NK cells, but depletes CD45RO+ memory T cells	Davis et al. 2012

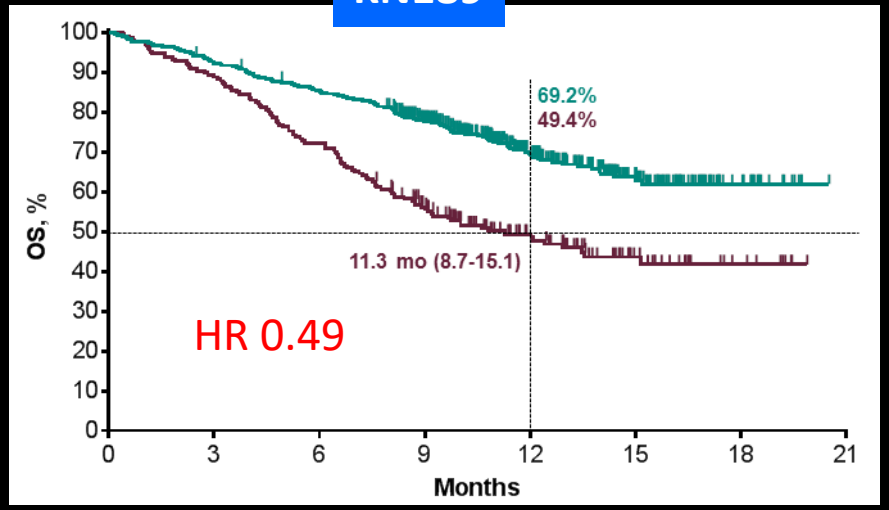
IO + Chemo Phase 3 in Non-sq



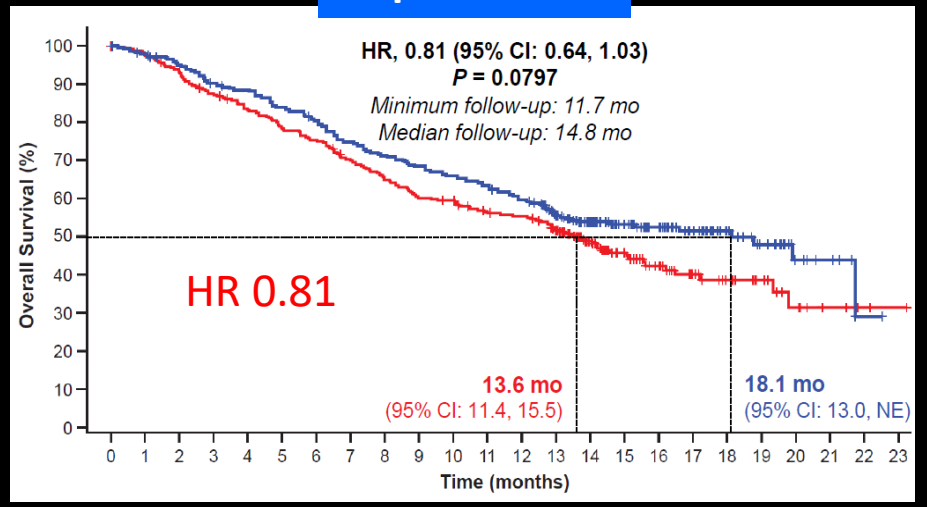
There is no intent to perform directly cross-trial comparison

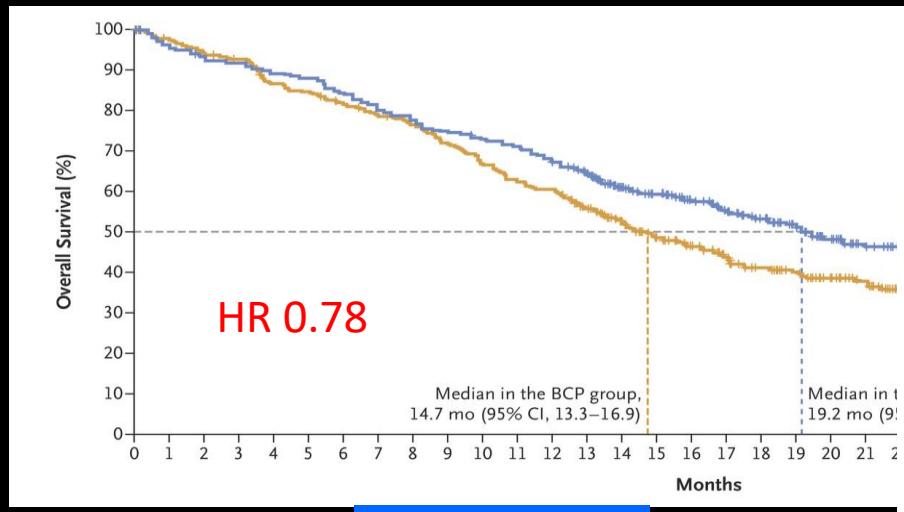
IO + Chemo in Non-sq: All regimens work

KN189

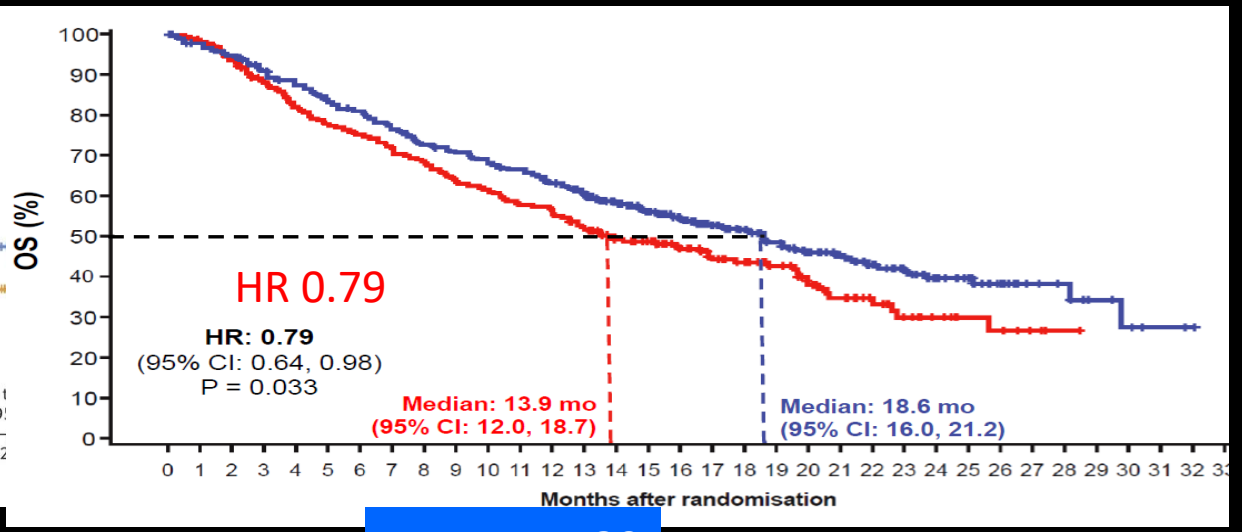


IMpower132





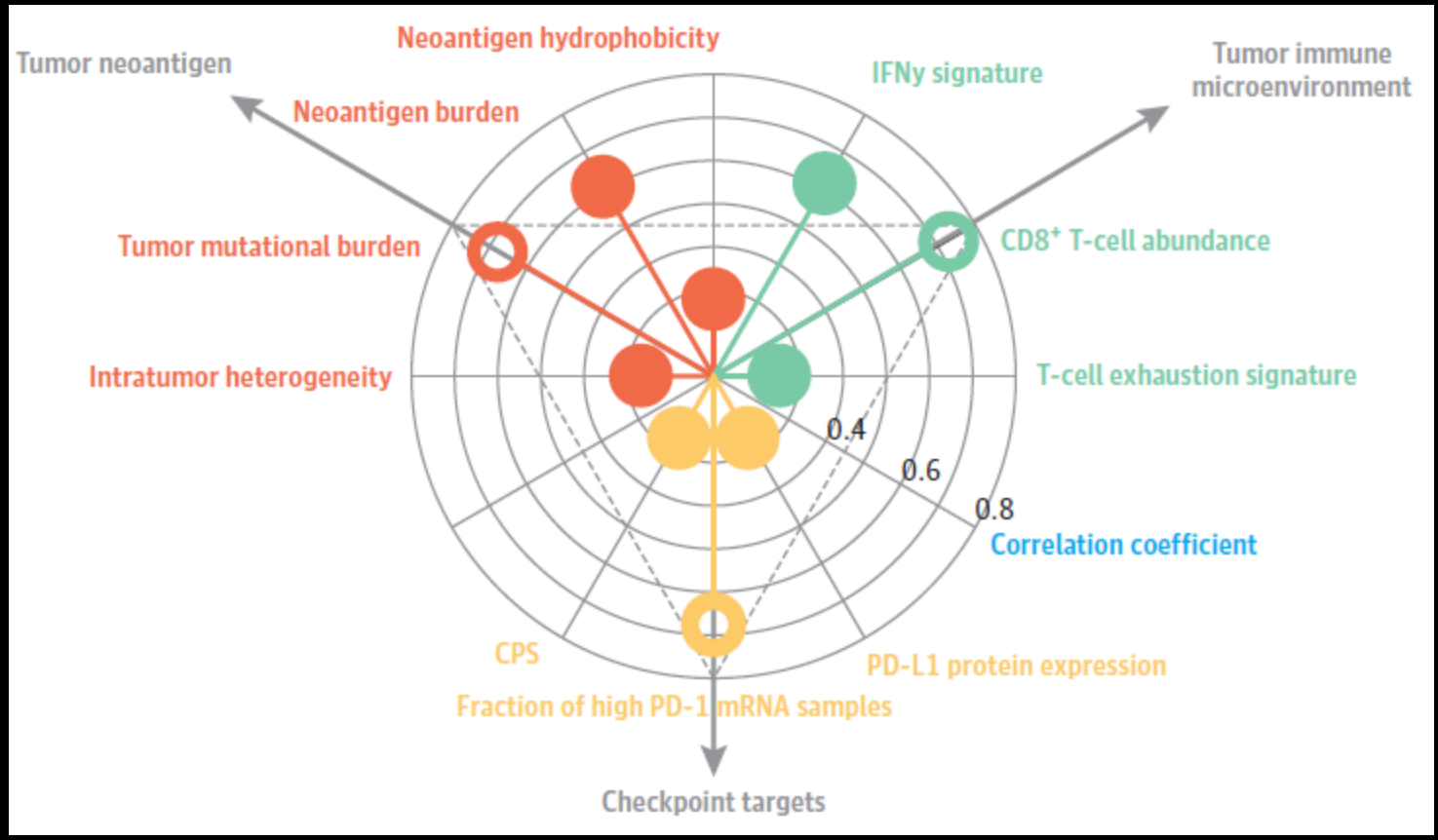
IMpower150



IMpower130

Chemotherapy immune-modulatory effects

Increase Tumor neoantigen



Turn to hot tumor:
Direct or indirect stimulatory effects on immune effectors

T cell function:
Induce a transient lymphodepletion
Refresh T cell

Modified from JAMA Oncol. 2019;5(11):1614-1618

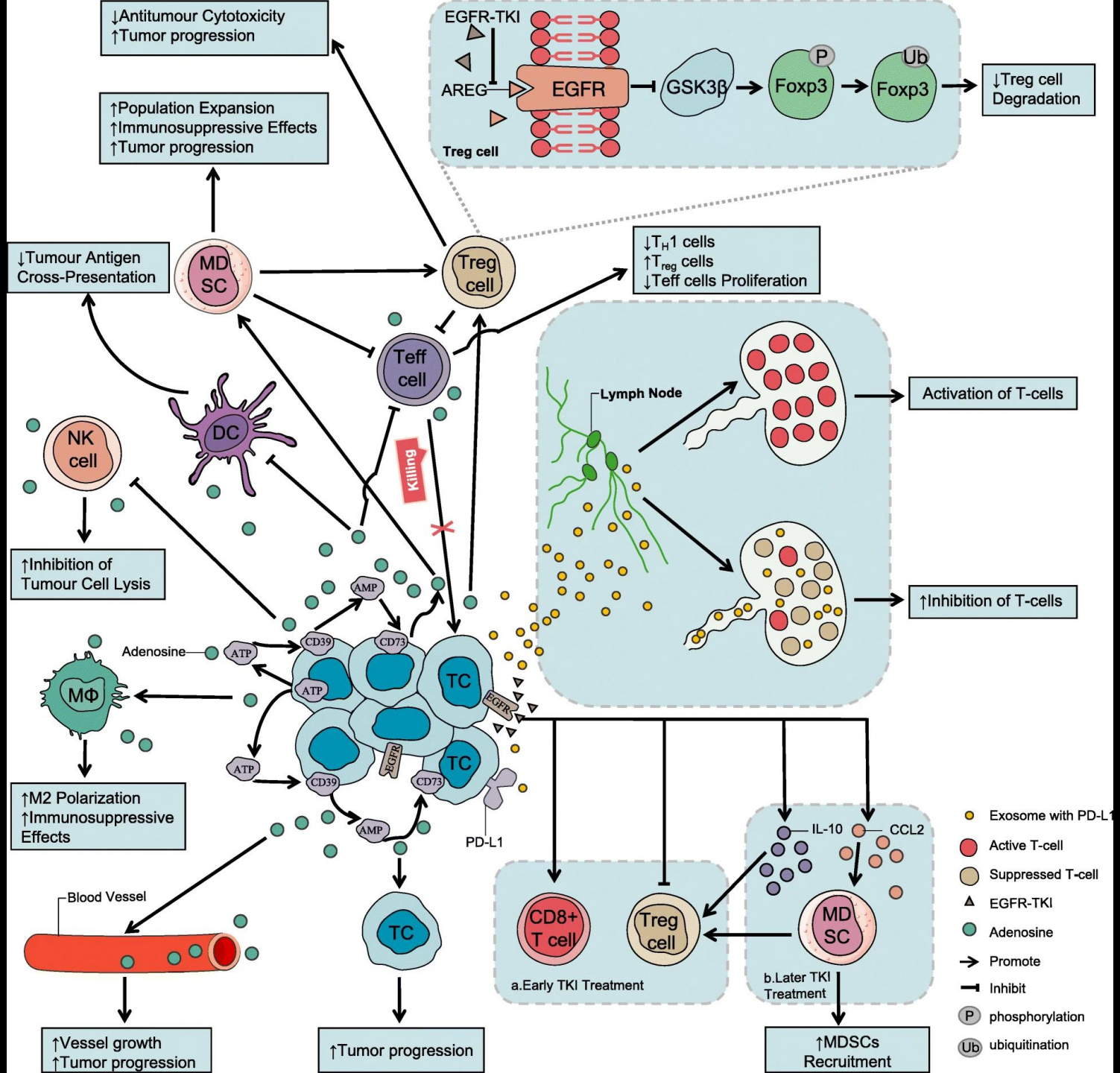
Immune-modulatory effects

Chemotherapy

Targeted therapy

Anti-angiogenesis

Radiotherapy

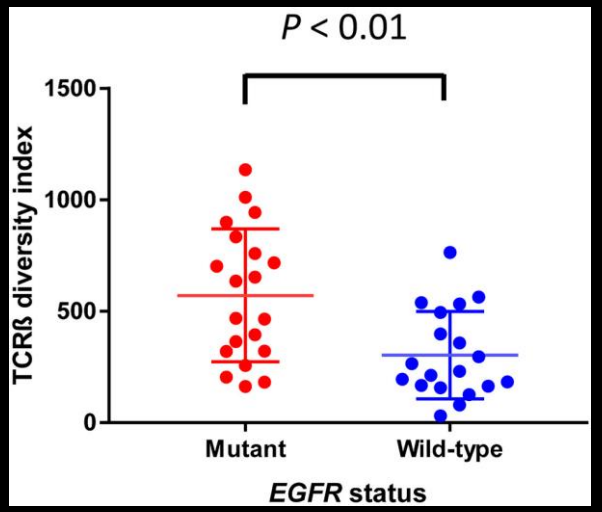


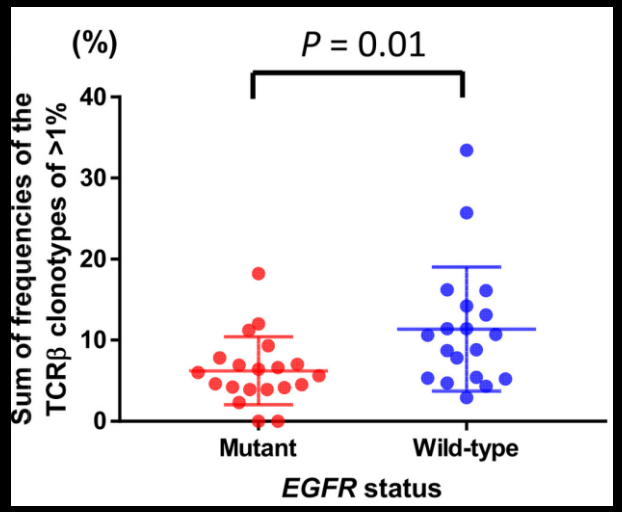
EGFR mutant TME

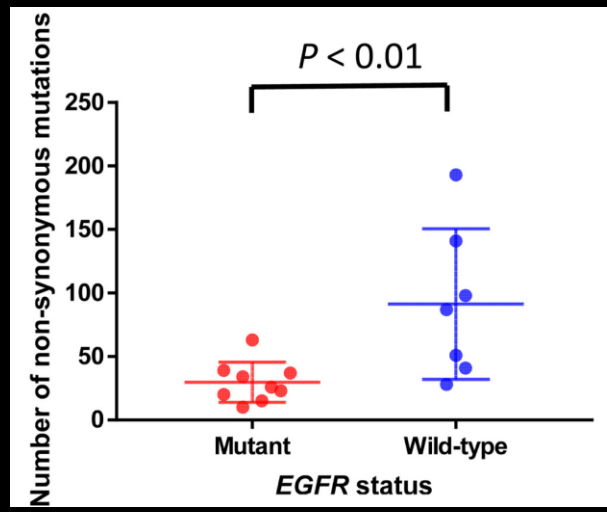
- Immune suppression environment:
- Low tumor-infiltrating lymphocytes (TILs)
- High Tregs
- High MDSCs
- High tumor-associated macrophages (TAMs)
- Immunoregulatory cytokines (immunosuppressive soluble factors, such as TGF-β, IL-10 and adenosine)
- Lower levels of human leukocyte antigen (HLA)-B expression
- Low TMB

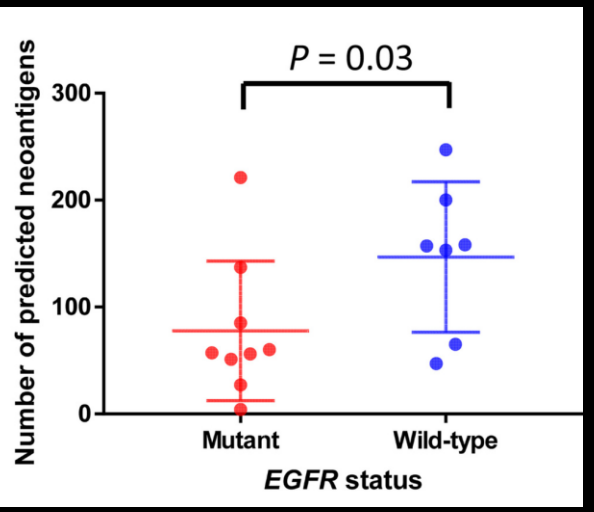
Lin A et al. Molecular Cancer (2019) 18:139

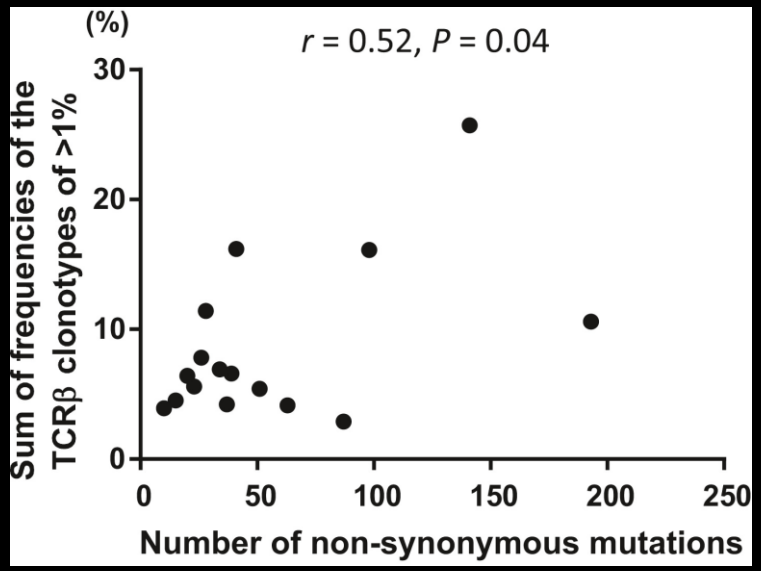
T cell receptor repertoires in EGFR + vs wild type
Less clonal expansion



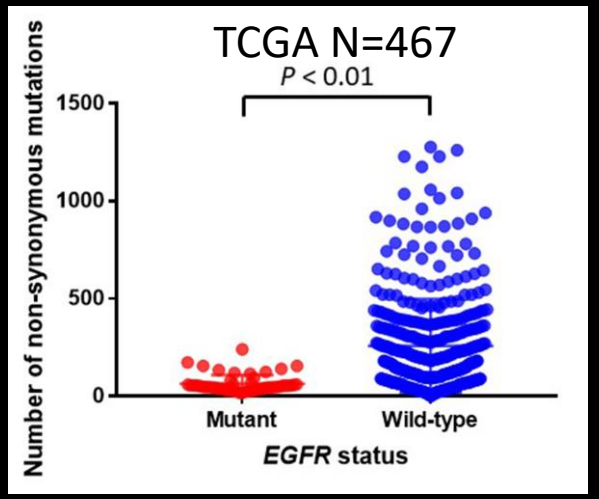








EGFR mutations have a higher TCRβ diversity and significantly lower numbers of predicted neoantigens than those without *EGFR* mutations (median: 57 [4-221] vs. 157 [47-247]; *P* = .03;
Low clonal T cell expansion in tumors with *EGFR* mutations might be a critical factor related to the unfavorable response to ICI



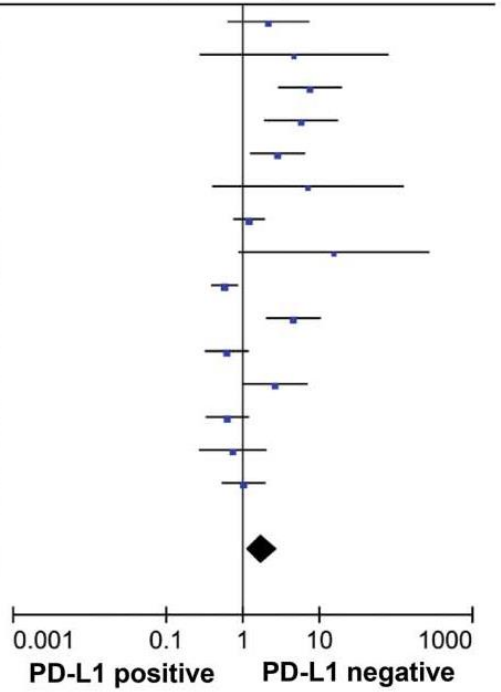
Miyauchi E et al. Cancer Sci. 2019; 110: 867-874

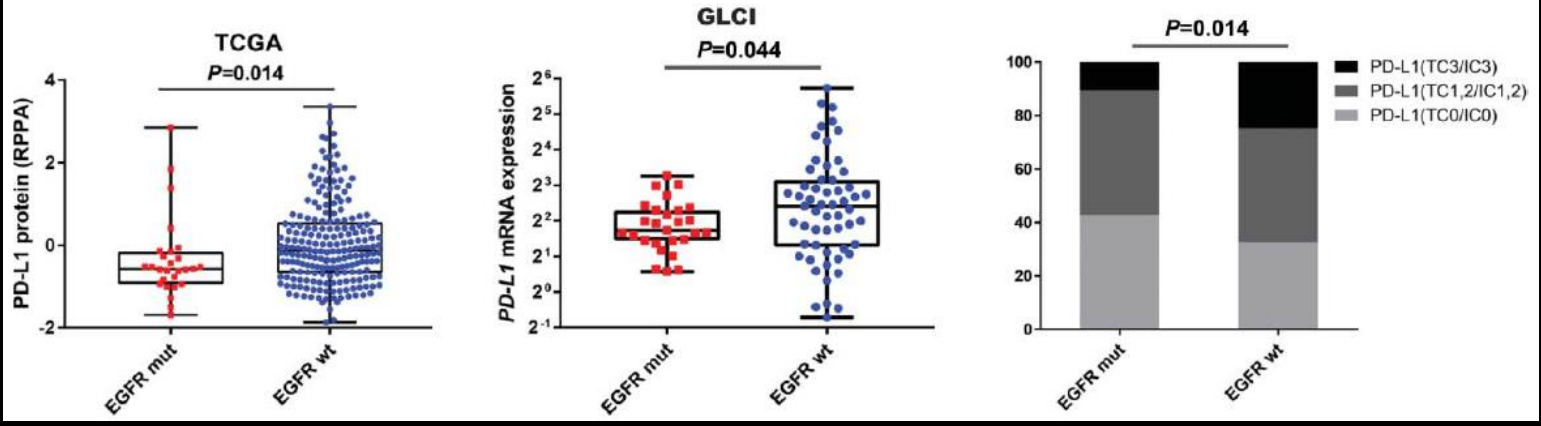
EGFR mutation with low PD-L1 expression

Study or Subgroup	*EGFR* WT Events	Total	*EGFR* MUT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ameratunga 2015	97	397	3	23	6.1%	2.16 [0.63, 7.41]
Cooper 2015	15	237	0	33	2.3%	4.67 [0.27, 79.85]
Huynh 2016	90	207	5	54	7.2%	7.54 [2.89, 19.69]
Inamura 2016	20	97	4	93	6.6%	5.78 [1.89, 17.64]
Ji 2016	22	40	18	60	7.7%	2.85 [1.24, 6.56]
Kim 2015	57	178	0	7	2.2%	7.10 [0.40, 126.44]
Mori 2017	61	160	46	136	9.1%	1.21 [0.75, 1.94]
Rangachari 2016	21	58	0	13	2.3%	15.48 [0.88, 273.58]
Song 2016	74	180	112	205	9.3%	0.58 [0.39, 0.87]
Takada 2016	32	123	8	112	7.8%	4.57 [2.00, 10.42]
Tang 2015	42	71	61	87	8.4%	0.62 [0.32, 1.19]
Tsao 2017	79	265	5	36	7.1%	2.63 [0.99, 7.02]
Yang 2014	22	66	43	97	8.5%	0.63 [0.33, 1.20]
Yang 2015	37	87	9	18	7.0%	0.74 [0.27, 2.05]
Zhang 2014	33	67	37	76	8.4%	1.02 [0.53, 1.97]
Total (95% CI)		**2233**		**1050**	**100.0%**	**1.79 [1.10, 2.93]**
Total events	702		351			

Heterogeneity: Tau² = 0.63; Chi² = 67.29, df = 14 (P < 0.00001); I² = 79%

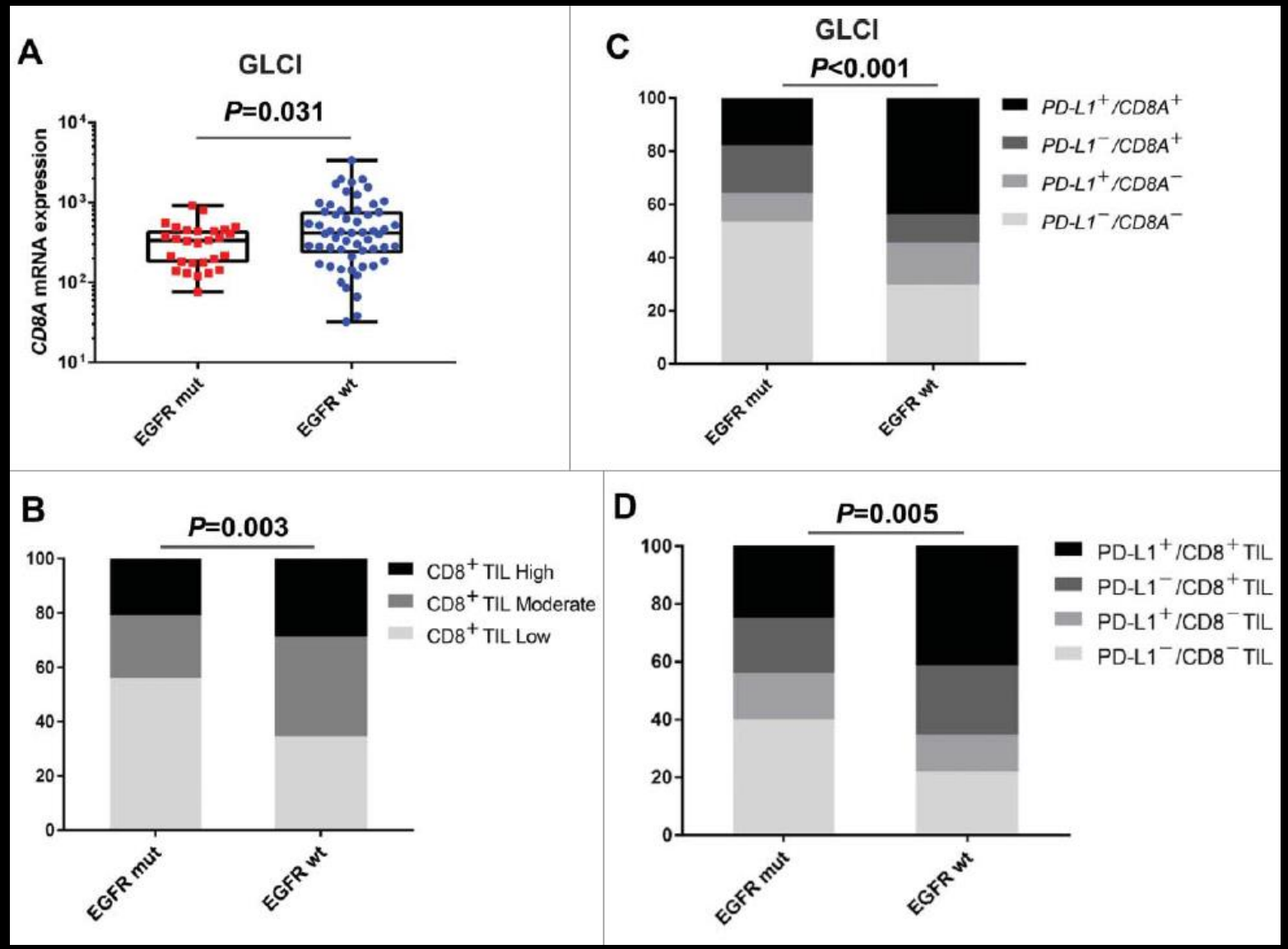
Test for overall effect: Z = 2.33 (P = 0.02)





Dong ZY et al. Oncoimmunology 2017; 6(11): e1356145

EGFR mutant tumors: a lack of T-cell infiltration and low shrink proportion of PD-L1C/CD8C TILs



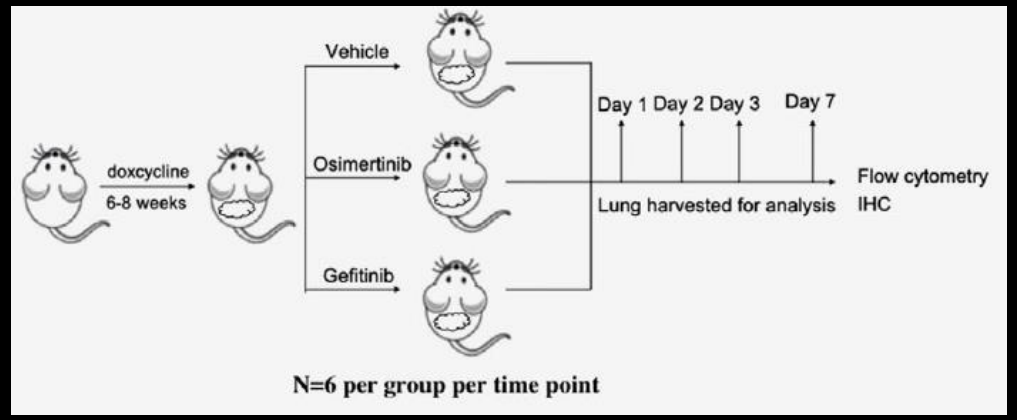
Dong ZY et al. Oncoimmunology 2017; 6(11): e1356145

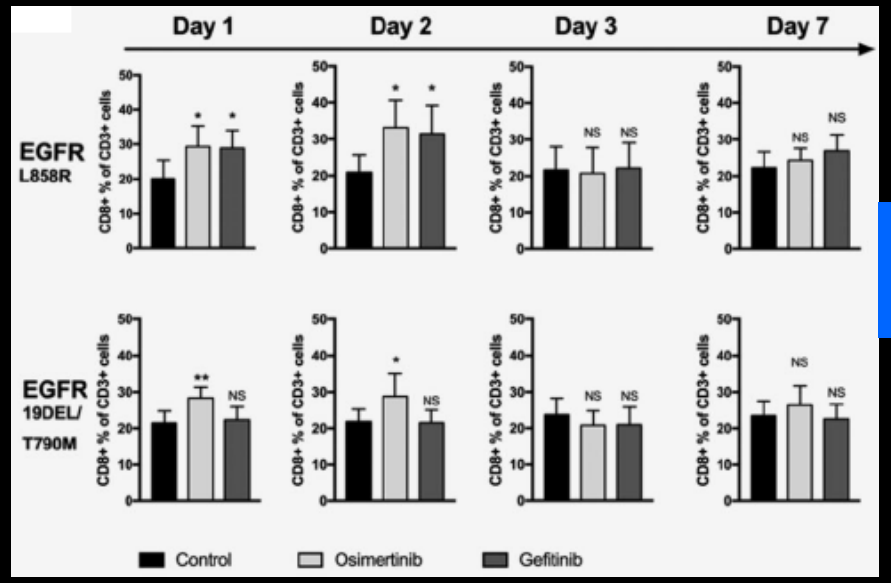
EGFR-TKIs affect the TME in NSCLC in Pre-clinical model: Immunostimulatory effect

- Induction of class I (MHCI) and II (MHCII) molecules
- Promoting Foxp3 degradation to attenuate the inhibitory function of Tregs
- Reducing the infiltration of Tregs in the TME and inhibiting tumor growth
- Enhancing the cytotoxicity of cytotoxic T lymphocytes (CTLs)
- Reduce T cell apoptosis, and increase IFN-γ secretion

Lin A et al. Molecular Cancer (2019) 18:139

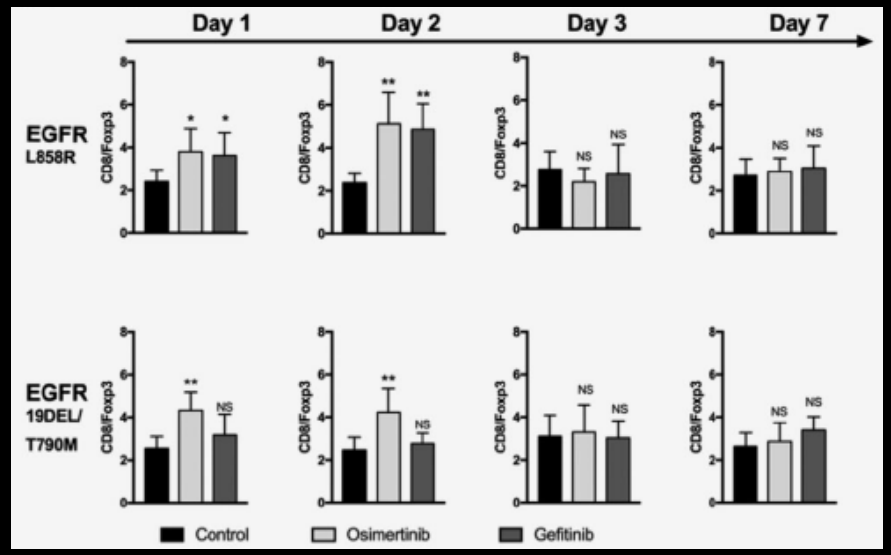
EGFR TKI altered TME toward immunosuppression : animal model

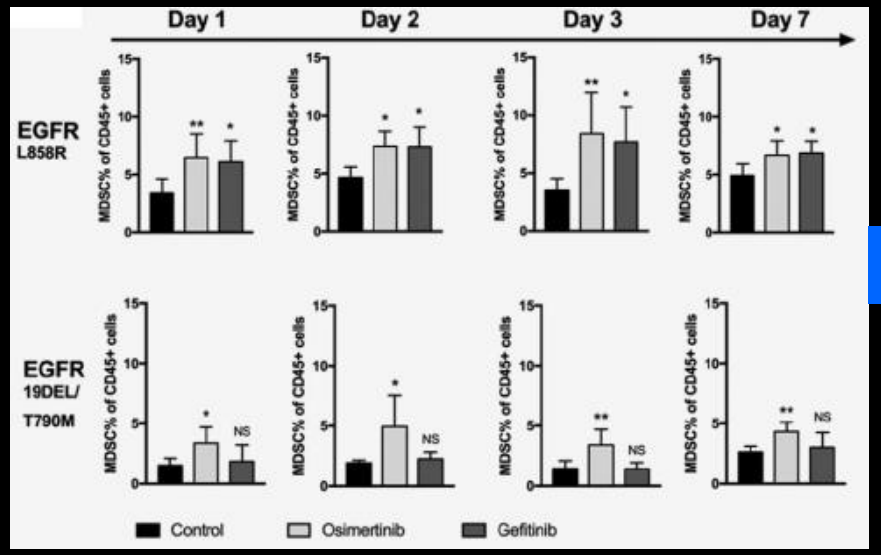




CD8 initial increase then decrease

Treg ratio increase

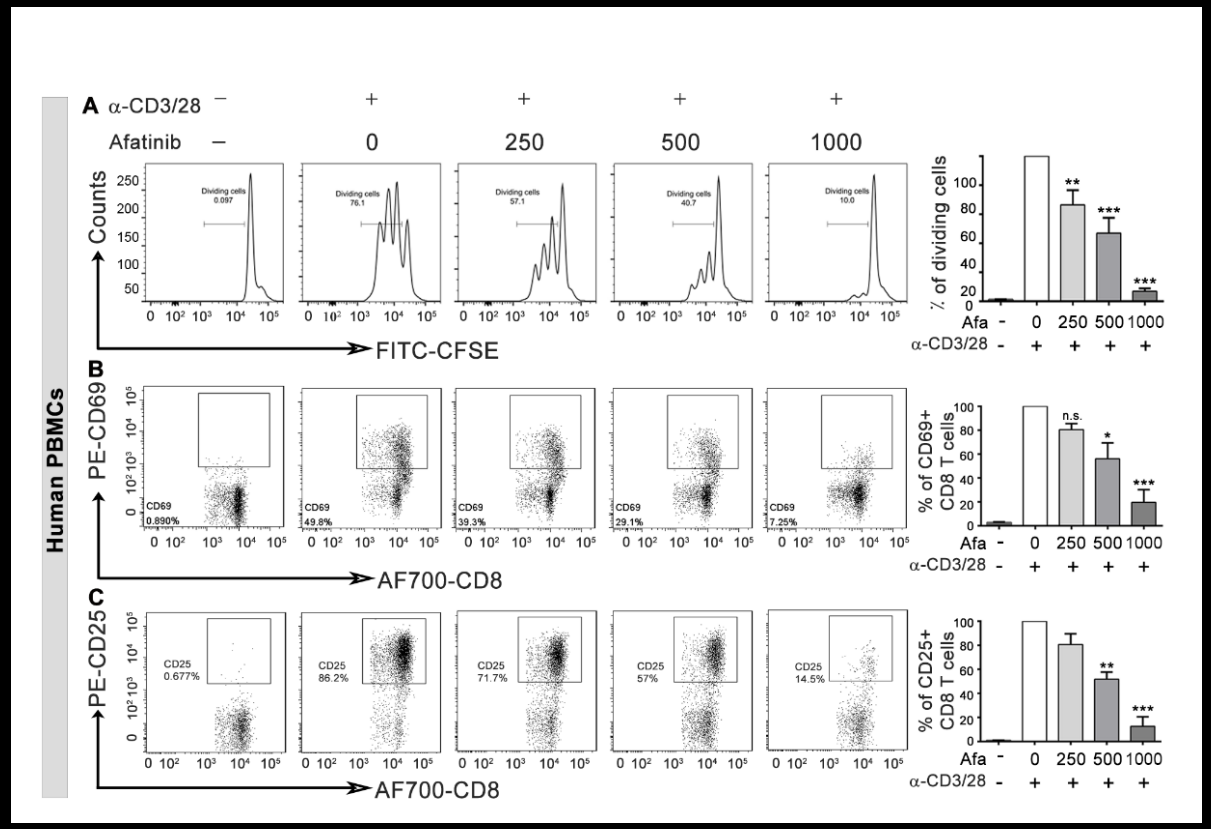




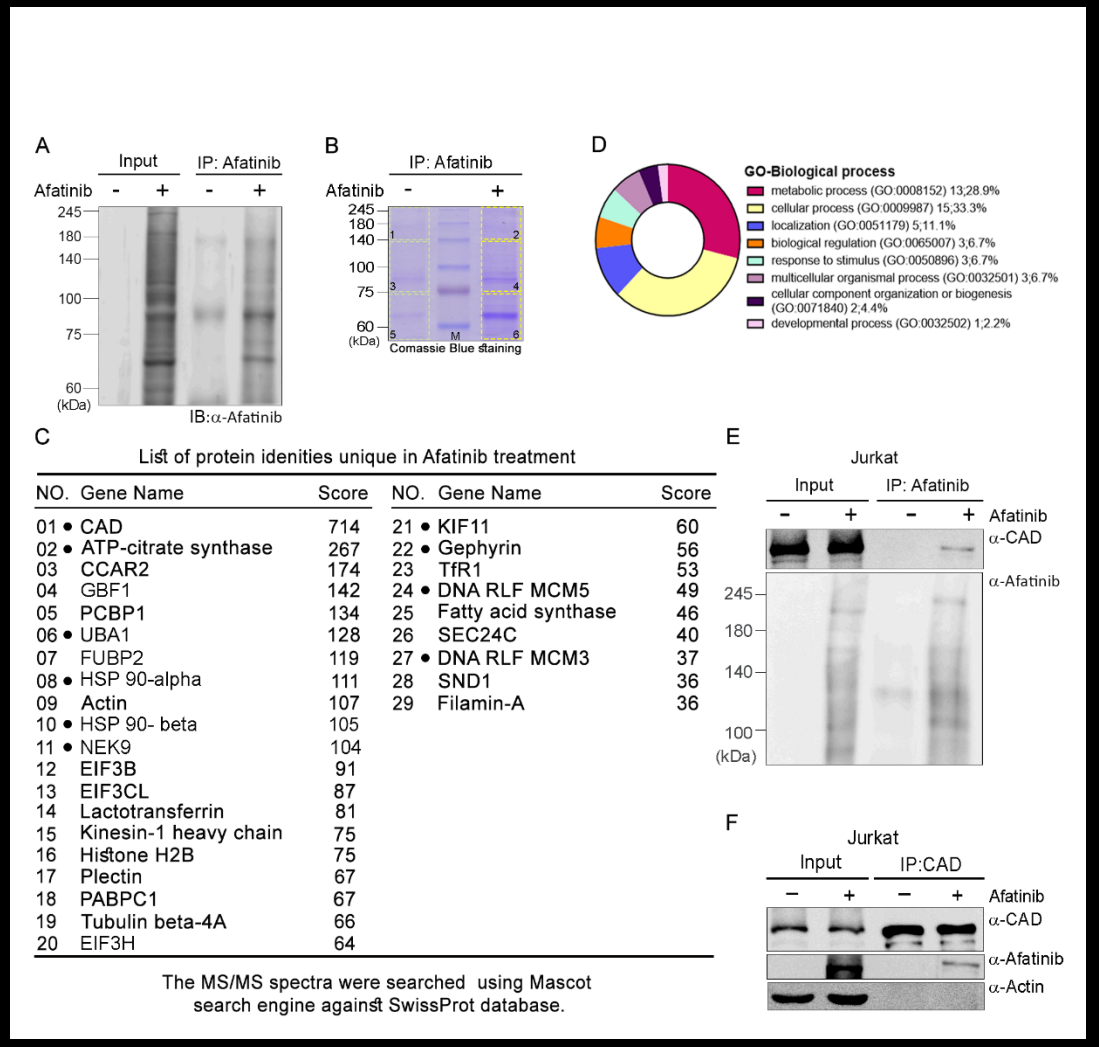
MDSC increase

Jia Y et al. Int. J. Cancer: 145, 1432–1444 (2019)

Afatinib decrease CD8 T cell proliferation



Afatinib effect on human CD8⁺ T cell proliferation and activation



C

List of protein idenities unique in Afatinib treatment

NO.	Gene Name	Score	NO.	Gene Name	Score
01 •	CAD	714	21 •	KIF11	60
02 •	ATP-citrate synthase	267	22 •	Gephyrin	56
03	CCAR2	174	23	TfR1	53
04	GBF1	142	24 •	DNA RLF MCM5	49
05	PCBP1	134	25	Fatty acid synthase	46
06 •	UBA1	128	26	SEC24C	40
07	FUBP2	119	27 •	DNA RLF MCM3	37
08 •	HSP 90-alpha	111	28	SND1	36
09	Actin	107	29	Filamin-A	36
10 •	HSP 90- beta	105			
11 •	NEK9	104			
12	EIF3B	91			
13	EIF3CL	87			
14	Lactotransferrin	81			
15	Kinesin-1 heavy chain	75			
16	Histone H2B	75			
17	Plectin	67			
18	PABPC1	67			
19	Tubulin beta-4A	66			
20	EIF3H	64			

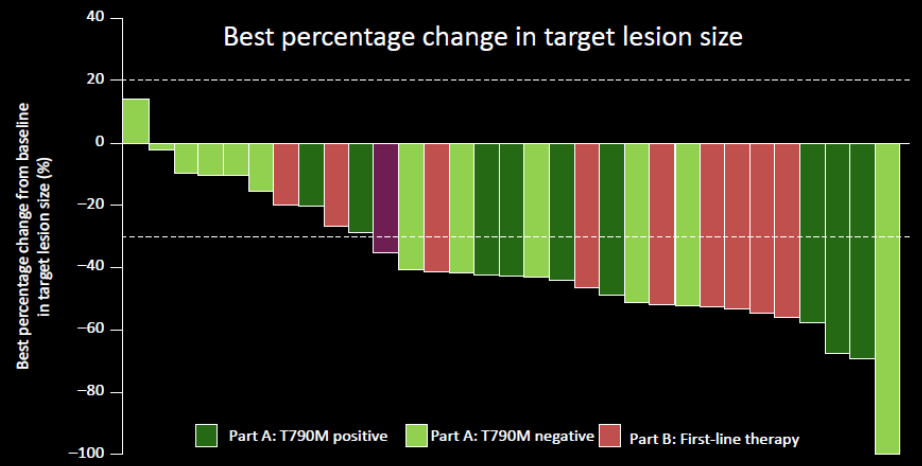
The MS/MS spectra were searched using Mascot search engine against SwissProt database.

Identification of CAD as an afatinib-targeted protein in Jurkat T cells

Tu et al. unpublished data

Clinical trials: Targeted therapy + immunotherapy more toxicities without better response

Clinical trial number	Agent	Grade 3/4 side effects
NCT02088112	Gefitinib plus durvalumab	alanine aminotransferase (ALT) elevation (65%) aspartate aminotransferase (AST) elevation (45%)
NCT02143466	Osimertinib plus durvalumab	Interstitial lung disease (38%)
NCT02013219	Erlotinib plus atezolizumab	ALT elevation (7%) Pyrexia (7%) Rash (7%)



Population: evaluable for response set; data cut off: 13 Nov 2015

TATTON trial subgroup
Osimertinib plus durvalumab
RR no increase

Ahn MJ, et al. ELCC 2016
Ahn MJ et al. Expert Opin Drug Saf. 2017 Apr;16(4):465-469

Studies of EGFR TKI + Immune checkpoint inhibitor

	Gettinger[1] n= 21	Ma/ Rudin[2, 6] n=28	Gibbons[3] n=20	Ahn[4] n=34	Planchard[5] n=26	Yang [7] n=19	Yang [8] n=14
Key patient criteria	EGFR+, TKI treated or naïve	EGFR+, TKI naïve or 1 prior non EGFR TKI tx	EGFR TKI naïve, n=20	EGFR+, TKI treated or naïve	EGFR+, TKI treated	EGFR TKI naïve	EGFR+, TKI treated
TKI treatment	Erlotinib 150mg qd	Erlotinib 150mg qd 1w run in	Gefitinib 250mg qd: concurrent or 4w lead-in	Osimertinib 80mg qd	Gefitinib 250mg qd 2 week run in	Erlotinib 150mg n=12 Or Gefitinib 250mg n=9	Osimertinib 80mg qd
IO treatment	Nivolumab 3mg/kg q2w	Atezolizumab 1200mg q3w	Durvalumab 10mg/kg q2w	Durvalumab 3-10mg/kg q2w	Tremelimumab 3-10mg/kg q4w	pembrolizumab 2 mg/kg q3w	Durvalumab 10mg/kg q2w
Gr 3-4 TRAE	10% diarrhea	7% ALT, 7% Rash, 7% fever	55% Hepatic	16% ILD	27% diarrhea	8% skin rash in erlotinib, 71.4% liver toxicity in gefitinib,	8%
ORR	15%	75%[6]	79%	70% (in TKI naïve)	0%	Erlotinib 41.7% Gefitinib 14.3% (4/7 not evaluable)	64%
Other	PFS 5.1m OS 18.7m	PFS 15m[6] DoR: 19m[6]	PFS 21.7m DoR 20.3m	DoR: 7.4m	NA	Erlotinib PFS 19.5m OS NR Gefitinib PFS 1.4 m OS 13m	DoR 21.2m

1. Gettinger JTO 2018, 2. Ma ESMO Asia 2016 , 3. Gibbons ELCC 2016, 4. Ahn ELCC 2016, 5. Planchard ESMO 2016, 6. Rudin WCLC 2018. 7. Yang JTO 2019;14::553-9. 8. Yang JTO 2019;14:933-9

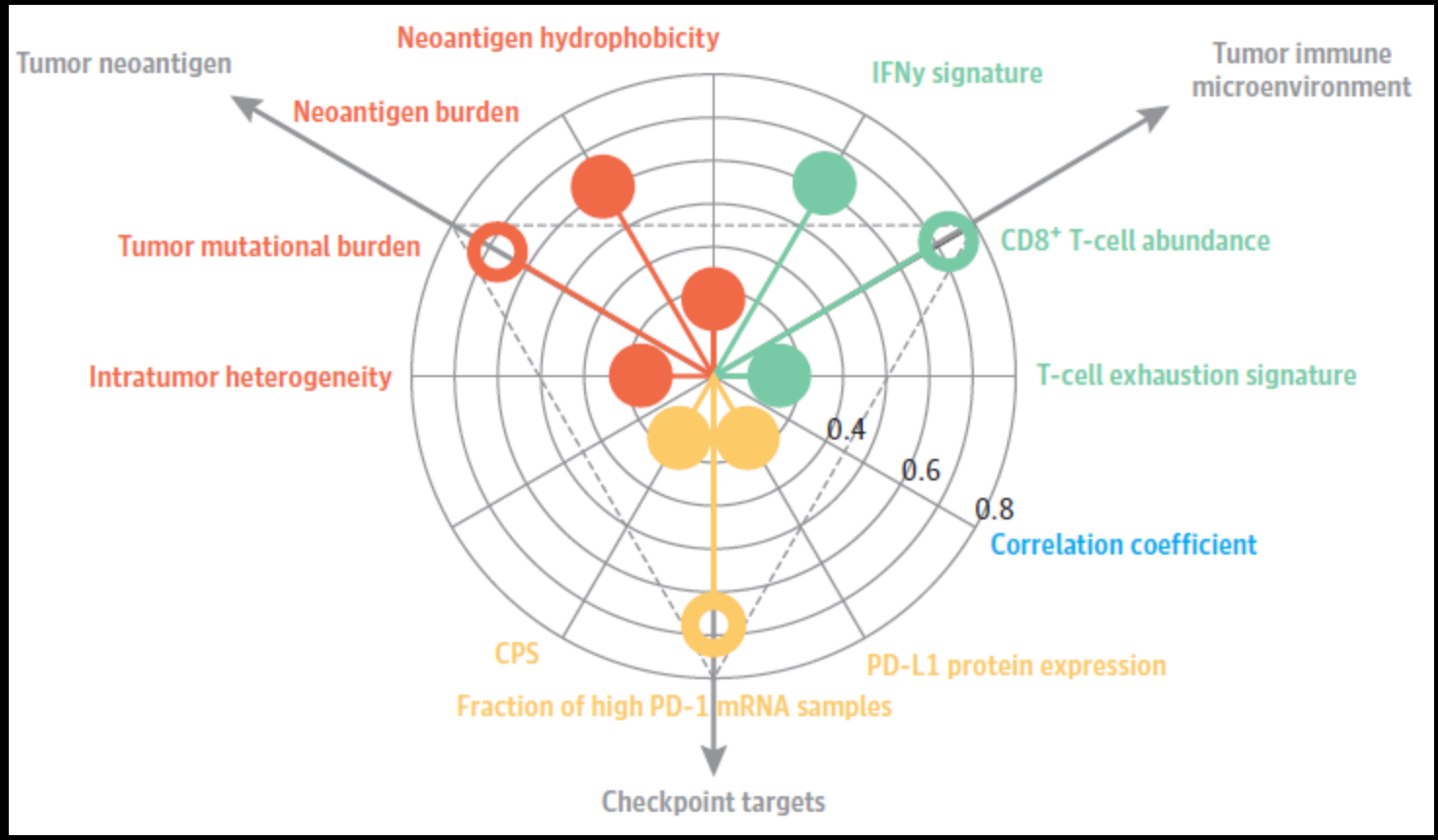
Studies of ALK TKI + Immune checkpoint inhibitor

	Spigel[1] n=13	Felip[2] n=36	Kim[3] n=21	Shaw[4] n=28	Shaw[4] n=12
Key patient criteria	ALK+, treatment naïve	ALK+, treatment naïve/ prior Tx	ALK+, treatment naïve	ALK+, treatment naïve	ALK/ ROS1/ MET-ve, ≥1 treatment
TKI treatment	Crizotinib 250mg bd	Ceritinib 450mg bd or 300mg bd	Alectinib 600mg bd (C1: 7 day lead-in)	Lorlatinib 100mg qd	Crizotinib 250mg bd
IO treatment	nivolumab 240mg q2w	nivolumab 240mg q2w	Atezolizumab 1200mg q3w	Avelumab 10mg/kg q2w	Avelumab 10mg/kg q2w
Gr 3-4 TRAE	38% Hepatic	25% ALT 22% GGT	18.9% Rash 9.5% ALT	18.9% Rash 9.5% ALT	16.7% ALT
ORR	38%	68.8%	85.7%	85.7%	16.7%
Other	NR		PFS 21.7m DoR 20.3m	DoR: 7.4m	DoR: 4.1m

1. Spigel JTO 2018, 2. Felip ASCO 2017 , 3. Kim ASCO 2018, 4. Shaw ASCO 2018

EGFR TKI immune-modulatory effects

Increase Tumor neoantigen



Immune suppression microenvironment

T cell function

Our unpublished data

Modified from JAMA Oncol. 2019;5(11):1614-1618

Immune-modulatory effects

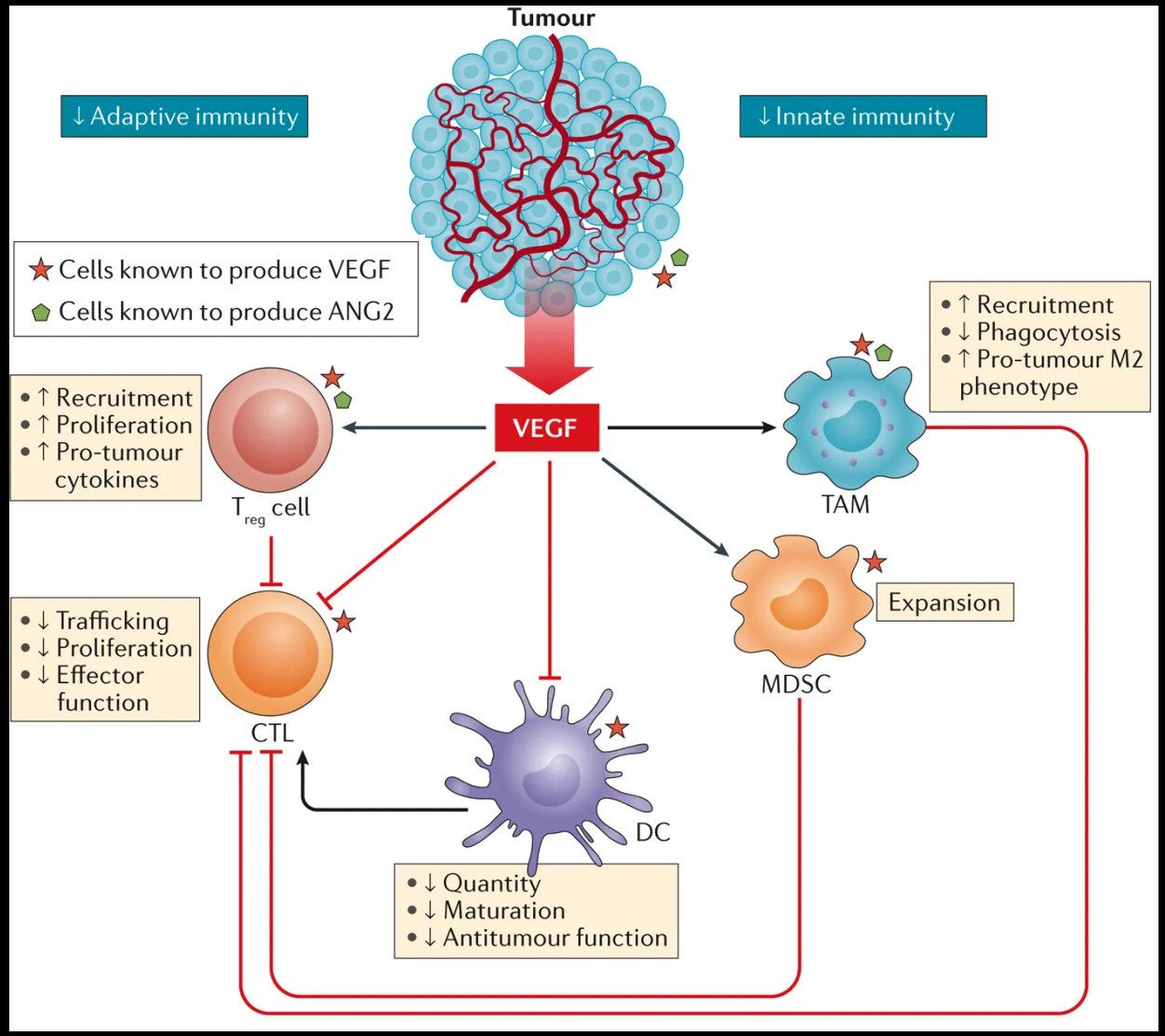
Chemotherapy

Targeted therapy

Anti-angiogenesis

Radiotherapy

Angiogenic Factors and Immune Cells

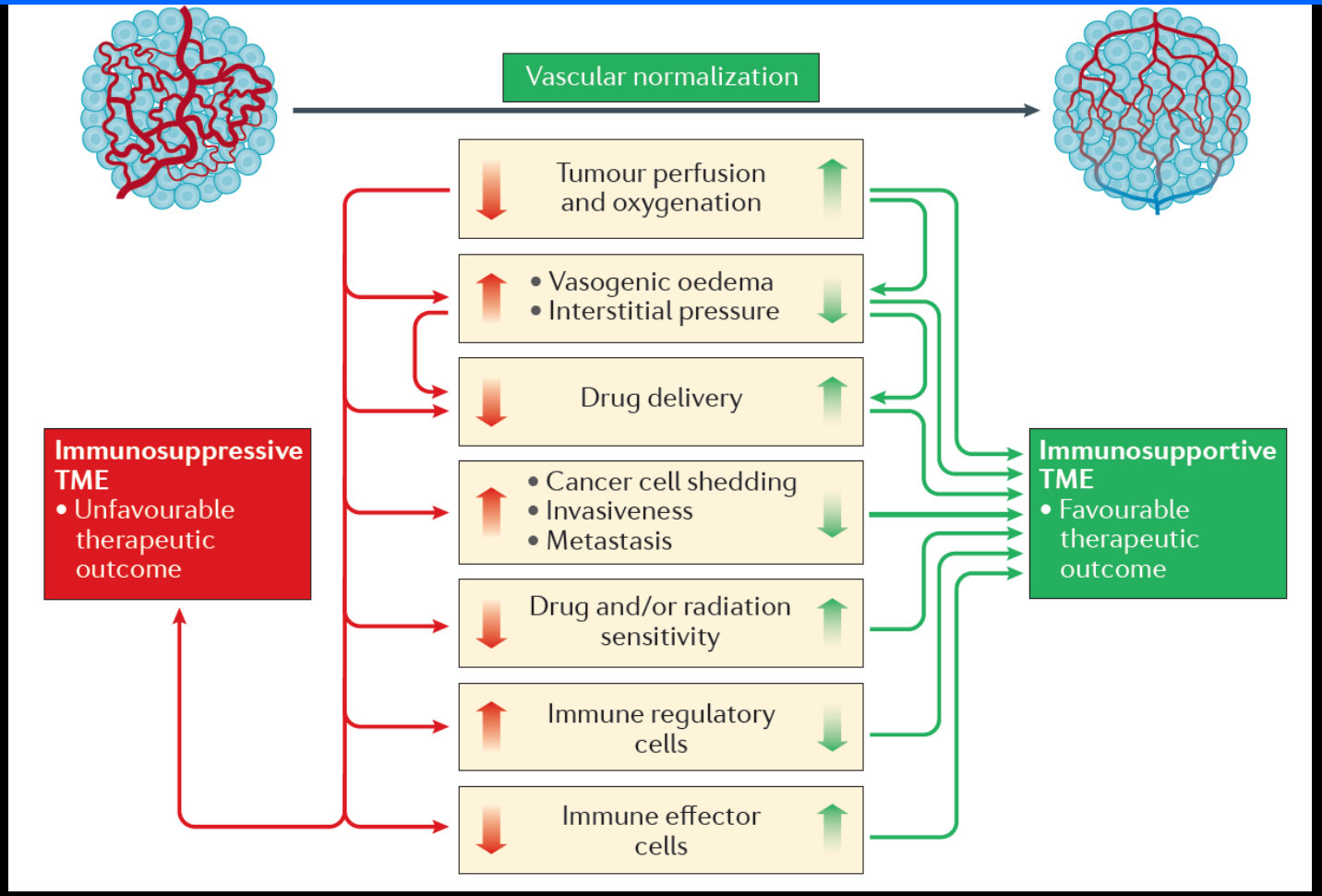


- Immunosuppression by modulating the functions of innate and adaptive immune cells
- Increasing the number and enhancing the suppressive functions of Treg cells and TAMs
- Dendritic cells lose their ability to mature and present antigens
- CTLs have a decreased capacity to traffic to the tumor, proliferate, and produce cytokines

Fukumura D et al. Nat Rev Clin Oncol 15 (5), 325-340.

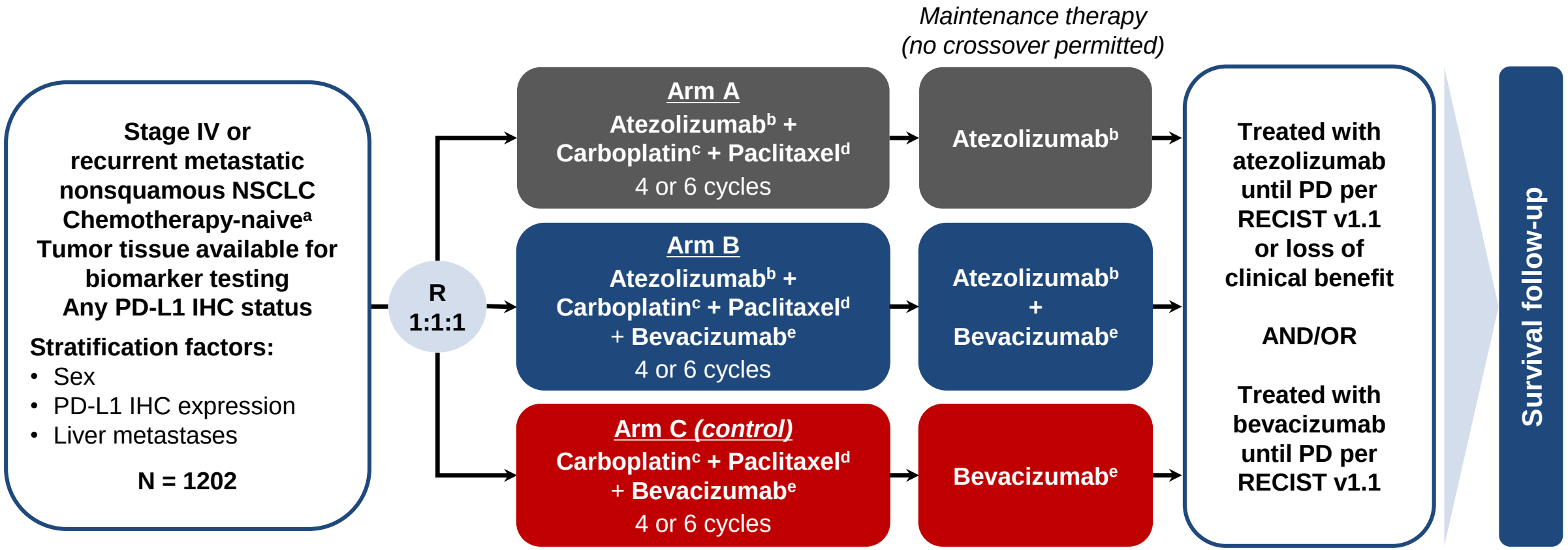
Anti-angiogenesis reprogramme the immunosuppressive TME

Antiangiogenic drugs offer only a modest survival benefit of a few weeks to months, with rare durable responses.



Fukumura D et al. Nat Rev Clin Oncol 15 (5), 325-340.

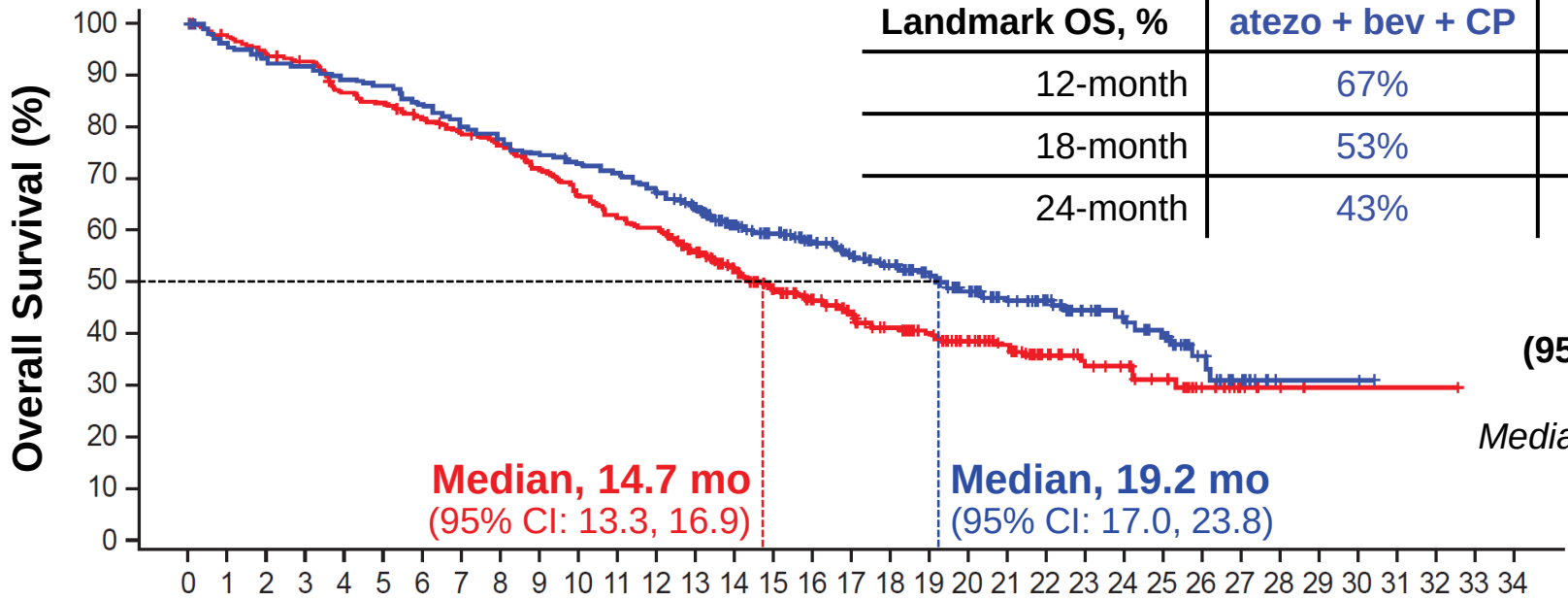
IMpower150 Study Design



[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

OS in the ITT-WT (Arm B vs Arm C)

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%



HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

No. at Risk

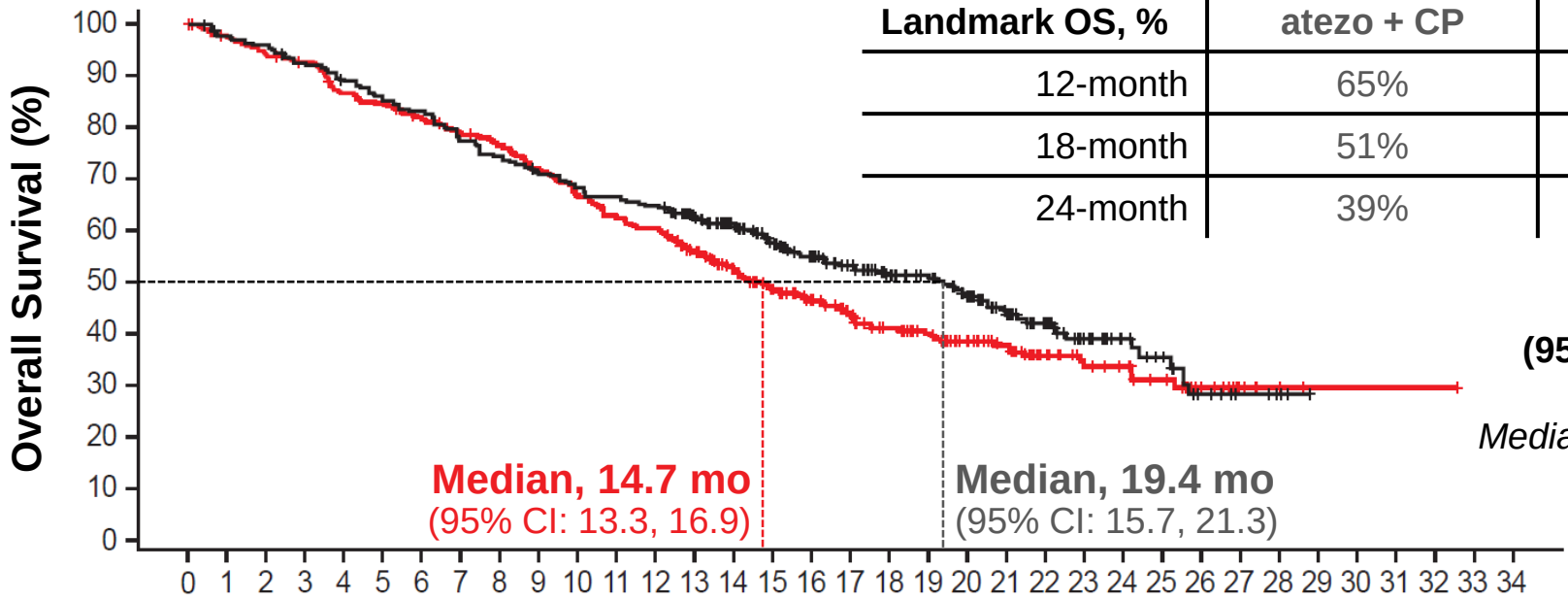
Atezo+Bev+CP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

[a] Stratified HR.
Data cutoff: January 22, 2018

OS in the ITT-WT (Arm A vs Arm C)

Landmark OS, %	Arm A: atezo + CP	Arm C: bev + CP
12-month	65%	61%
18-month	51%	41%
24-month	39%	34%



HR[a], 0.88
(95% CI: 0.72, 1.08)
***P* = 0.2041**
Median follow-up: ~20 mo

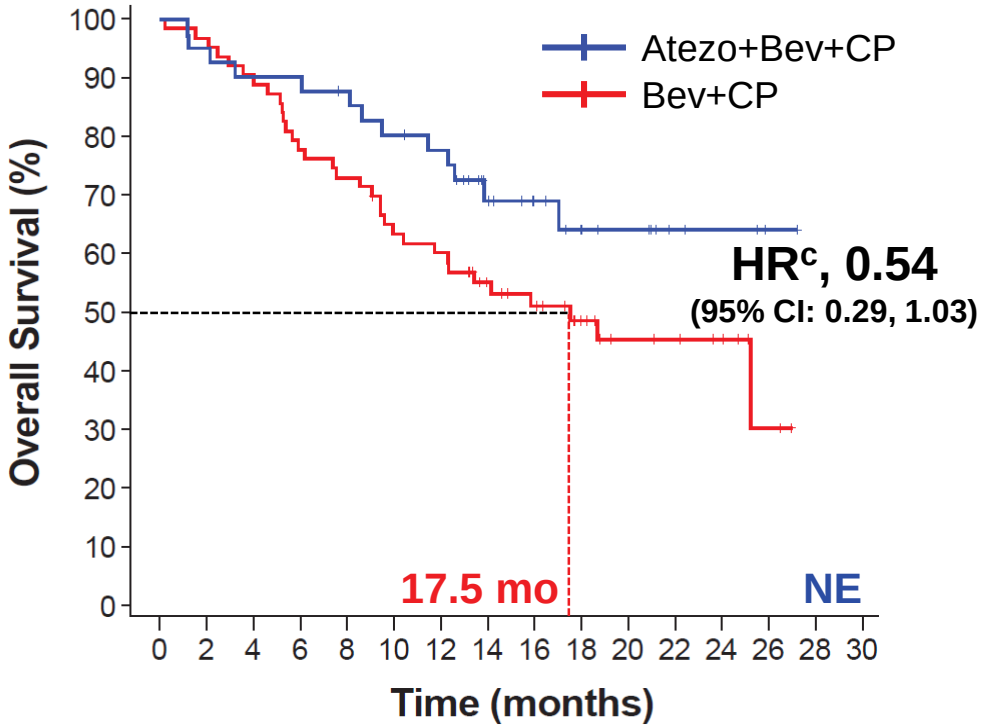
No. at Risk																																
Atezo+CP	349	339	331	319	307	294	284	266	255	244	234	227	221	203	180	153	131	115	100	91	77	60	46	33	23	18	9	5	3			
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

- A trend toward OS benefit was observed with atezolizumab + chemotherapy vs bevacizumab + chemotherapy, but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis

[a] Stratified HR.
Data cutoff: January 22, 2018

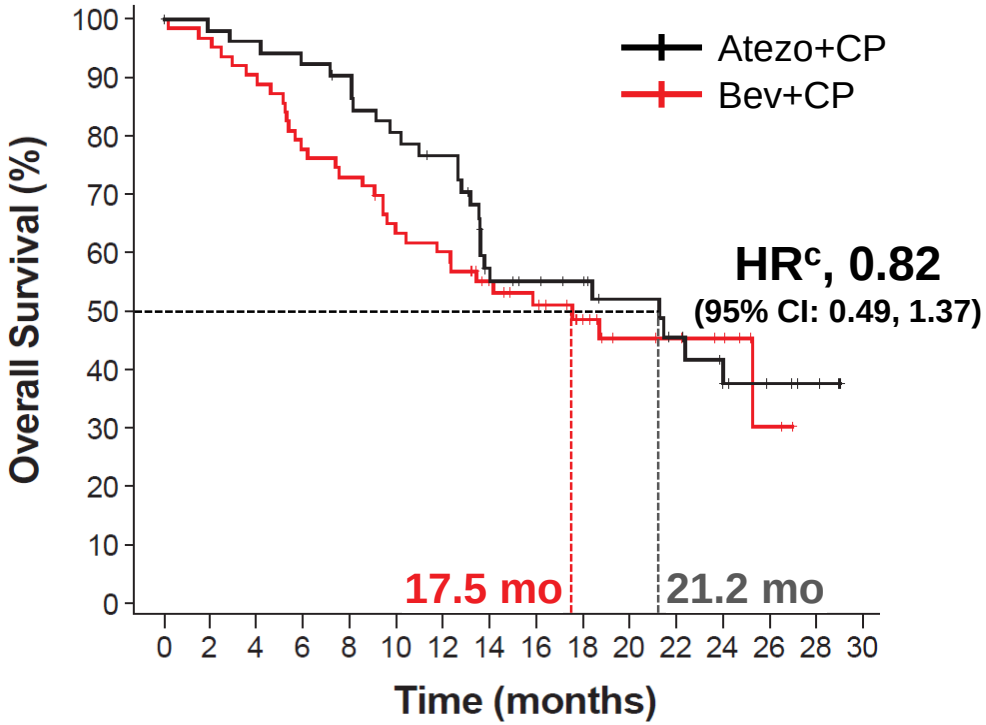
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

Arm B[b] vs Arm C



No. at Risk														
Atezo+Bev+CP	41	39	37	37	35	32	30	20	15	11	9	5	4	2
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

Arm A vs Arm C



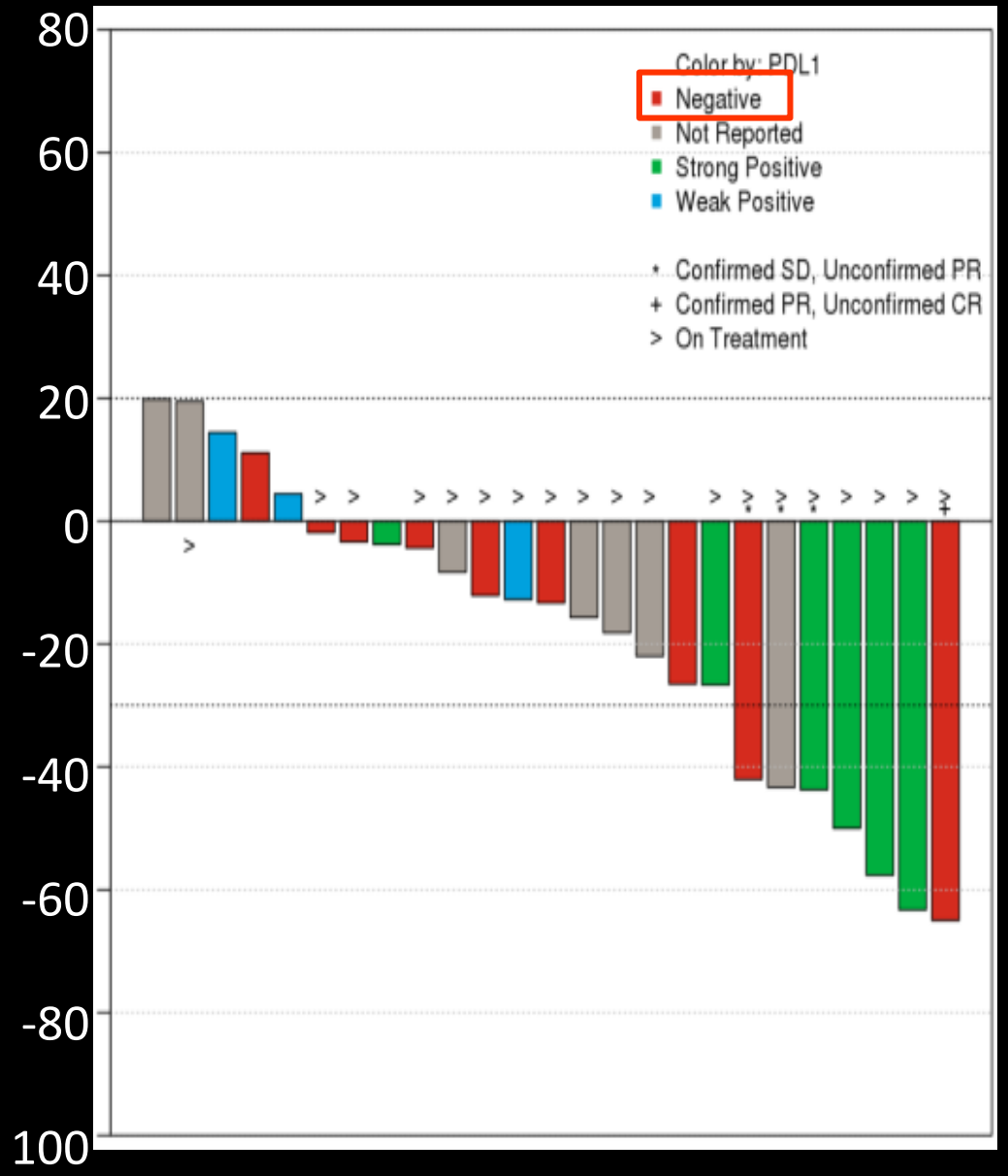
No. at Risk														
Atezo+CP	53	51	50	48	46	41	37	24	22	20	16	13	8	6	4
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

Phase 1 ramucirumab plus pembrolizumab in patients with NSCLC: KEYNOTE-021 cohorts A-CA phase 1 study

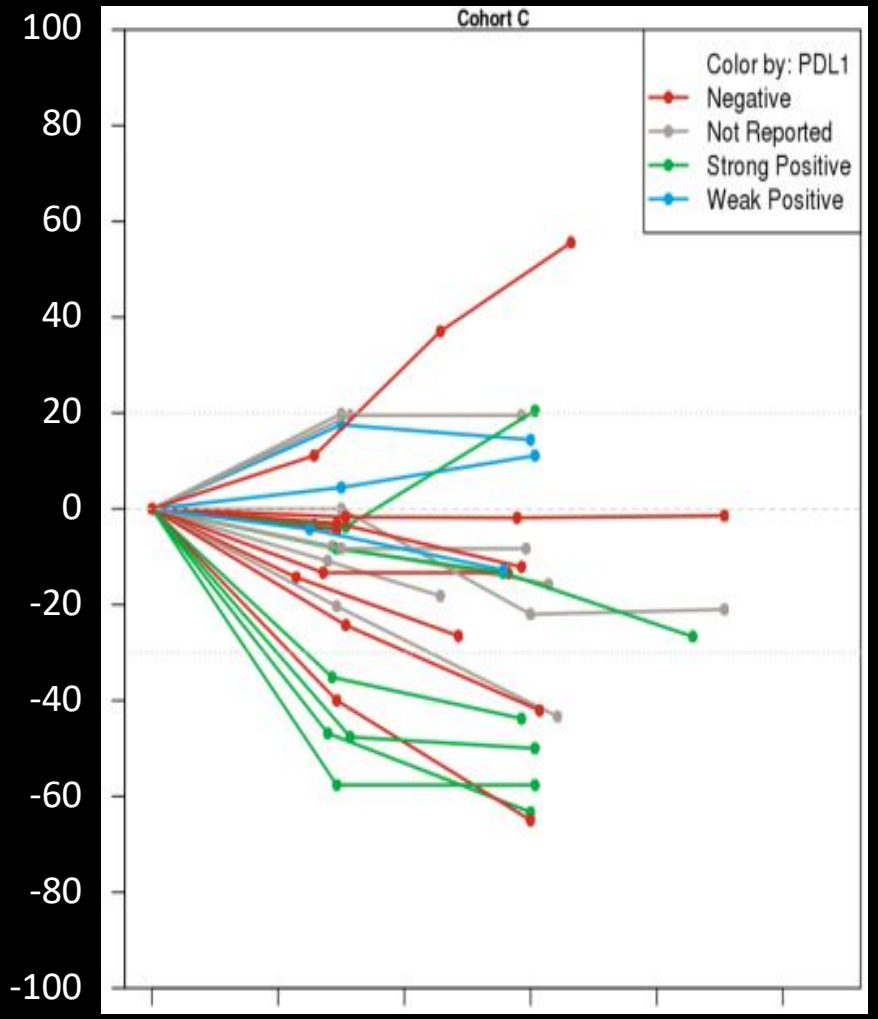
Herbst et al, # 378 ASCO 2016

Decreased Tumor Burden NSCLC (RECIST 1.1)



Herbst et al, # 378 ASCO 2016

Tumor Response Over Time in Patients with NSCLC



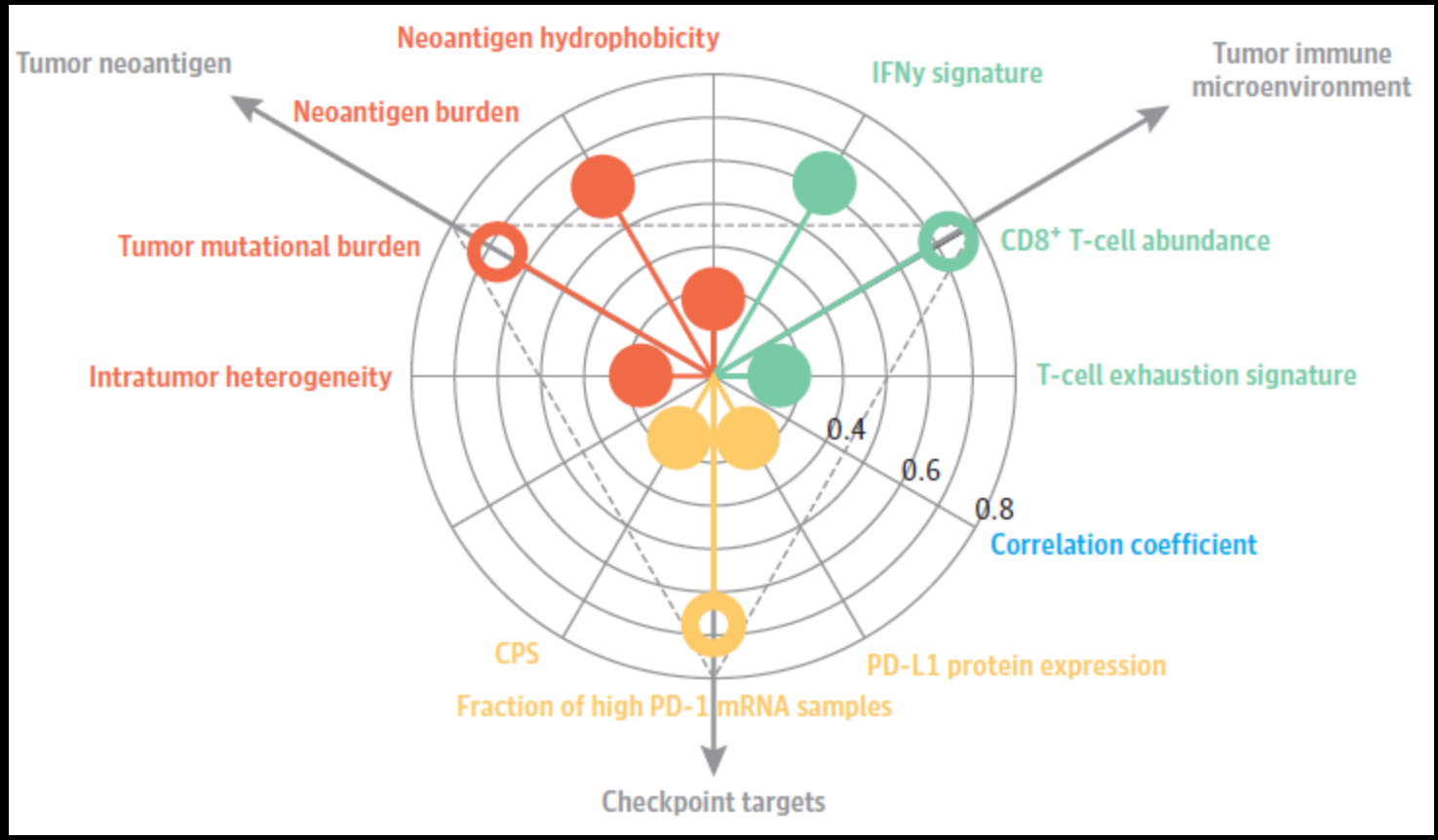
Herbst et al, # 378 ASCO 2016

Anti-angiogenesis + IO: Ongoing clinical trial

- APPLE (atezo + chemo +/- beva): phase III
- Atezo + Carbo + Paclitaxel + Beva in EGRF Mutation or ALK Translocation NSCLC: phase III
- Nivo + paclitaxel + carboplatin + bevacizumab: phase III
- Atezolizumab Plus Bevacizumab in First Line NSCLC Patients (TELMA): phase II
- Atezolizumab Versus Atezolizumab Plus Bevacizumab as First Line in NSCLC Patients (BEAT): phase II
- Carboplatin + Pemetrexed + Atezolizumab + Bevacizumab in Chemotherapy and Immunotherapy-naïve Patients With Stage IV Non-squamous NSCLC: phase II
- Atezolizumab and Bevacizumab in Epidermal Growth Factor Receptor (EGFR) Mutant Non-Small Cell Lung Cancer in Patients With Progressive Disease After Receiving Osimertinib phase II
- Pembrolizumab Plus Bevacizumab for Treatment of Brain Metastases in Metastatic Melanoma or Non-small Cell Lung Cancer phase II
- Platinum-Pemetrexed-Atezolizumab (+/-Bevacizumab) for Patients With Stage IIIB/IV Non-squamous NSCLC With EGFR Mutations, ALK Rearrangement or ROS1 Fusion Progressing After Targeted Therapies (GFPC 06-2018) phase II

Anti-angiogenesis immune-modulatory effects

No effect in tumor neoantigen



Immunosupportive TME

No effect in T cell function

Modified from JAMA Oncol. 2019;5(11):1614-1618

Immune-modulatory effects

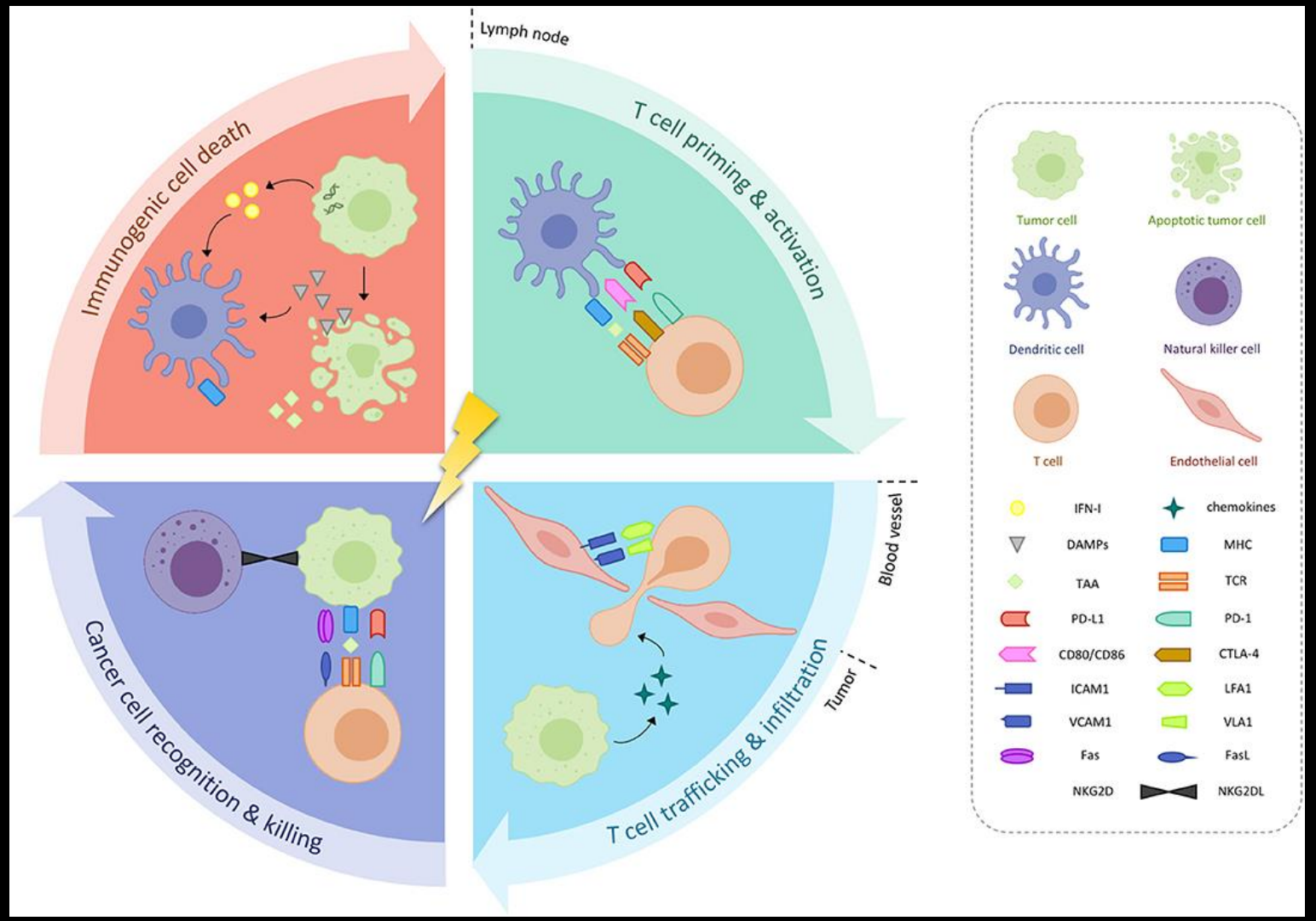
Chemotherapy

Targeted therapy

Anti-angiogenesis

Radiotherapy

Immunologic Effects of Radiotherapy



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Radiotherapy as immunostimulant

- **RT Dose**: low dose may have immunosuppressive responses, but the enhanced immunogenicity does not seem to extend beyond a certain dose range
- **RT Timing and Sequencing:** MHC-I-associated peptide pool increase between 8h and 11 D (in vitro), T-cells initial decline in week 1, but quickly recovered and even increased in weeks 3–5, sequencing RT ICI is proved by PACIFIC trial, concurrent studies ongoing
- **RT Target Volume and Organs:** avoid RT induced lymphopenia and decrease heart lung exposure. RT to tumor-associated draining lymph nodes (DLN) affects adaptive immune responses and combinatorial efficacy (in vitro)

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IO RT combinations in locally advanced NSCLC

References	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Primary outcome
ANTIGEN-SPECIFIC IMMUNOTHERAPY						
Ohyanagi et al. (48)	I	Stage III, unresectable, CR/PR/SD after CRT ($N = 6$)	Tecemotide	≥50 Gy, sequentially or concurrently with CT	CRT > tecemotide[b]	≥1 AE in 83.3% of pts, all G1
Butts et al. (49)	IIB	Stage IIIB, CR/PR/SD after CRT ($N = 65$)[c]	Tecemotide	Dose NS, sequentially or concurrently with	CRT > BSC	Median OS 30.6 vs. 13.3 m (HR 0.548, 95% CI 0.301–0.999)[c]
Mitchell et al. (50) (START)	III	Stage III, unresectable, CR/PR/SD after CRT ($N = 1,239$)	Tecemotide	with CT	• CRT > tecemotide[b] • CRT > placebo	Median OS 58.7 vs. 57.3 m (HR 0.89; $p = 0.111$)
Patel et al. (51)	II	Stage III, unresectable, non-squamous (N		66 Gy/33 fx, concurrently with CT	CRT > CT > tecemotide + bevacizumab	≥G3 toxicity in 11 pts, G3 hypertension ($n = 6$)
Brunsvig et al. (52)	II	Stage	GV1001 + GM-CSF	60 Gy/30 fx, concurrently with CT	CRT > GV1001 + GM-CSF	No treatment-related SAE
Pujol et al. (53)	I/II	resectable, MAGE A3-positive ($N = 12$)[c]	MAGE-A3 immunotherapeutic	NS	CT > RT > MAGE-A3	Treatment-related AE in 7/12 pts; all <G3. Induced CD4+ and CD8+ T-cell response in 5/6 and 2/6 pts resp.[c]
IMMUNE CHECKPOINT BLOCKADE						
Antonia et al. (31) (PACIFIC)	III	Stage III, unresectable ($N = 713$)	Durva	54–66 Gy, concurrently with CT	• CRT > durva • CRT > placebo	Median OS NR vs. 28.7 m (HR 0.68; $p = 0.0025$); median PFS 17.2 vs. 5.6 m (HR 0.51)
Durm et al. (54)	II	Stage III, unresectable, CR/PR/SD after CRT (N=92)	Pembro		CRT > pembro	Median TMDD 22.4 m (95% CI 17.9-NR)
Lin et al. (55) (DETERRED)	II	Stage III, unresectable ($N = 40$)		66 Gy/30–33 fx, concurrently with CT	• CRT > CT + atezo • CRT + atezo > CT + atezo	≥G3 atezo-related toxicity in 6 pts; G5 TE fistula ($n = 1$). G3 radiation pneumonitis ($n = 1$)
Peters et al. (56, 57) (NICOLAS)	IA/II	Stage III, unrese	Nivo	• 66 Gy/33 fx, concurrently with CT • 66 Gy/24 fx, sequentially after CT	CRT + nivo > nivo	No ≥G3 post-RT pneumonitis, 1-year PFS 50%

No clinical benefit in antigen-specific immunotherapy

Prolong OS in ICI combination

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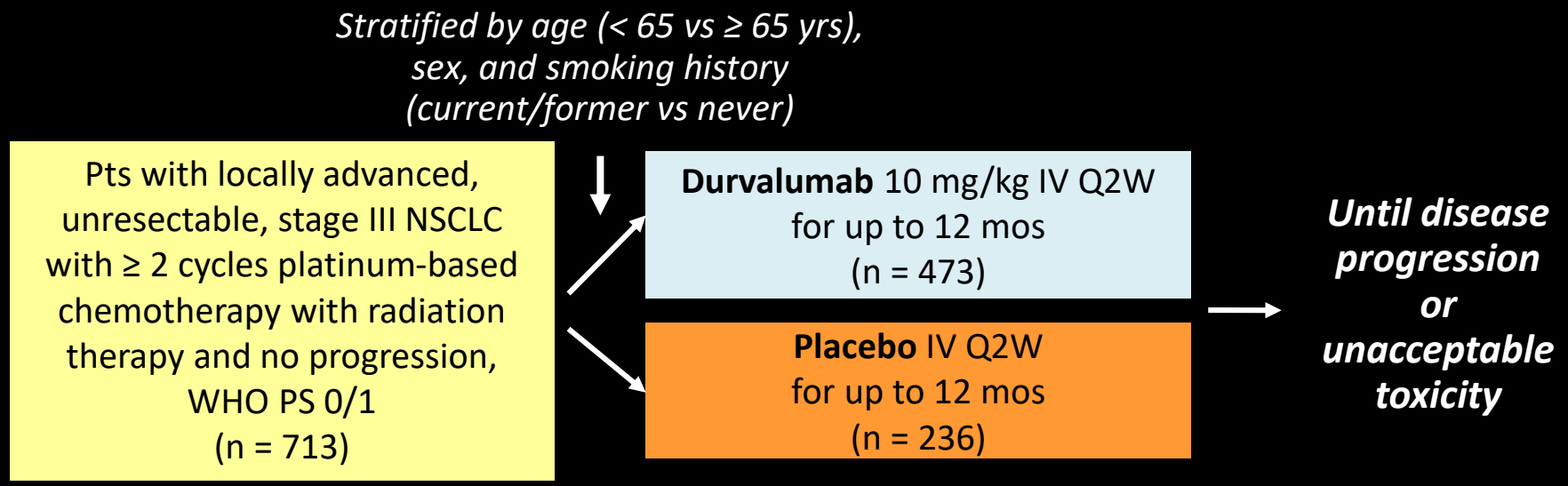
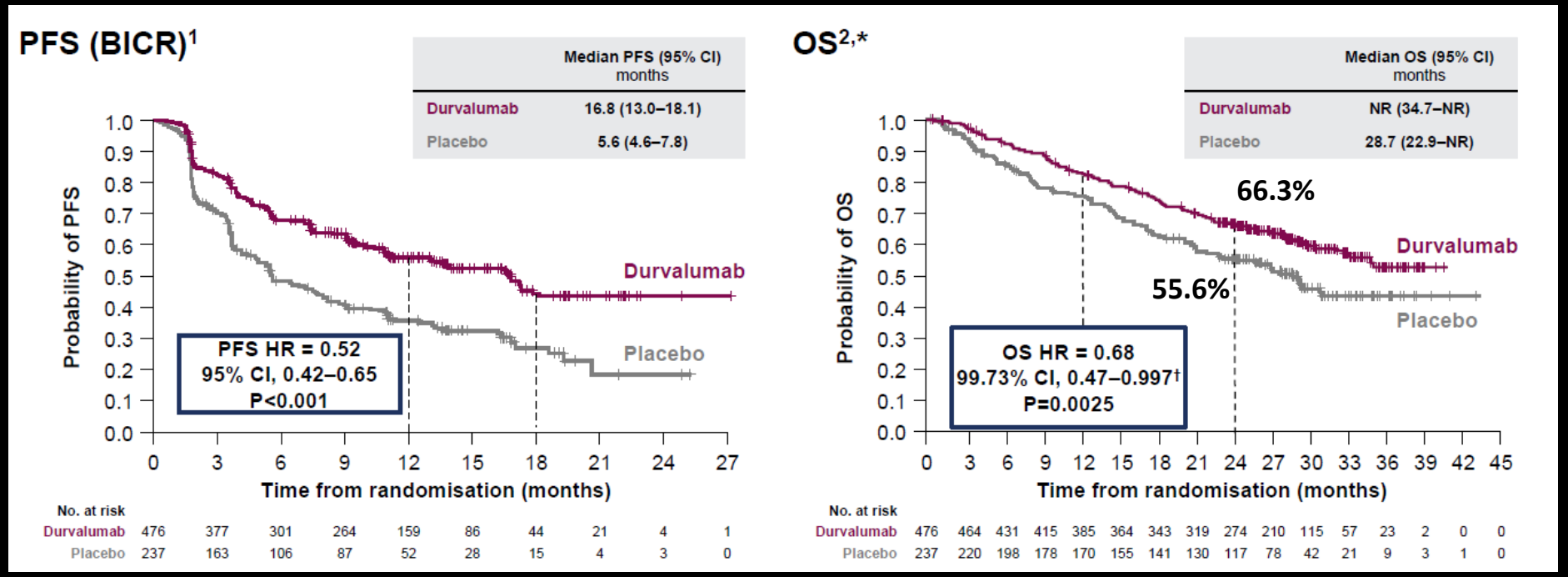
Durvalumab vs Placebo After Concurrent CRT in Unresectable Stage III NSCLC (PACIFIC)



- Primary endpoints: PFS, OS
- Secondary endpoints including: 12, 18 mos PFS, ORR, DoR, the time to death or distant metastasis, the time to second progression, safety

Antonia SJ, et al. N Engl J Med. 2017

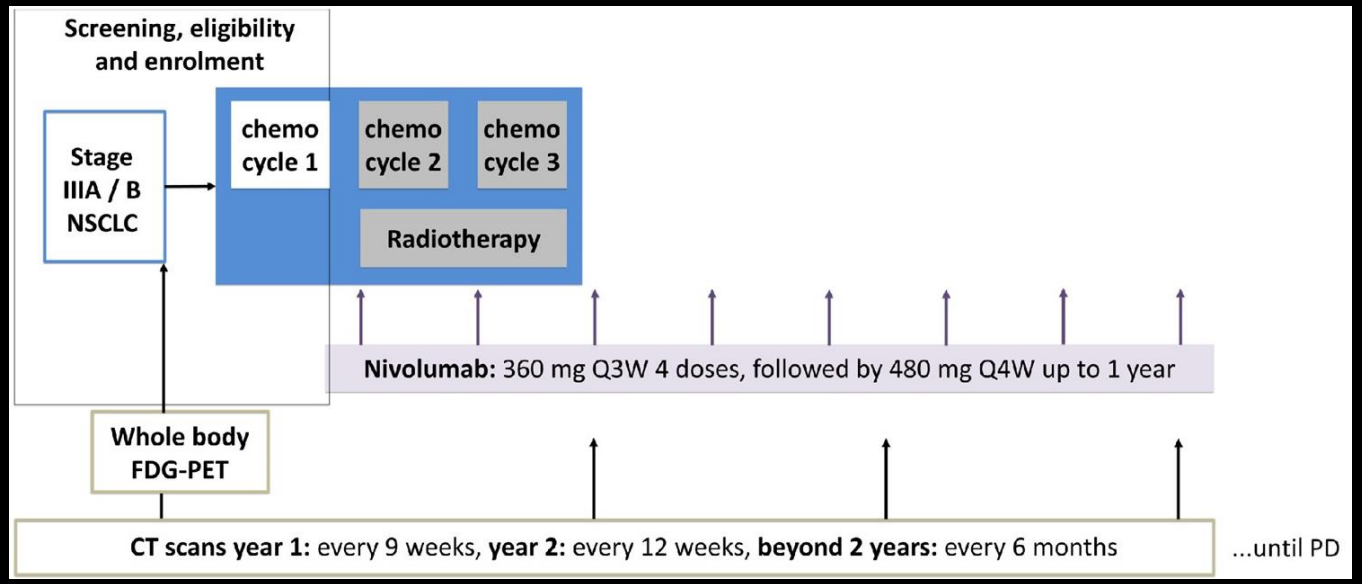
Durvalumab vs Placebo After Concurrent CRT in Unresectable Stage III NSCLC (PACIFIC Trial)

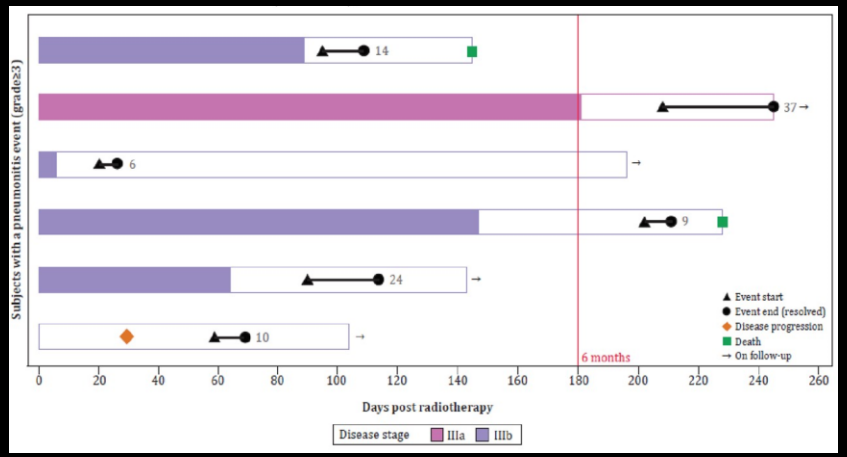


Updated **PFS 17.6 m vs. 5.6 m**
Gr 3-4 adverse events 30.5 % vs. 26.1%
Discontinued 15.4% vs. 9.8%

Antonia SJ, et al. N Engl J Med 2017;377:1919-29
Antonia SJ, et al. N Engl J Med 2018; 379:2342-2350

ETOP NICOLAS Trial





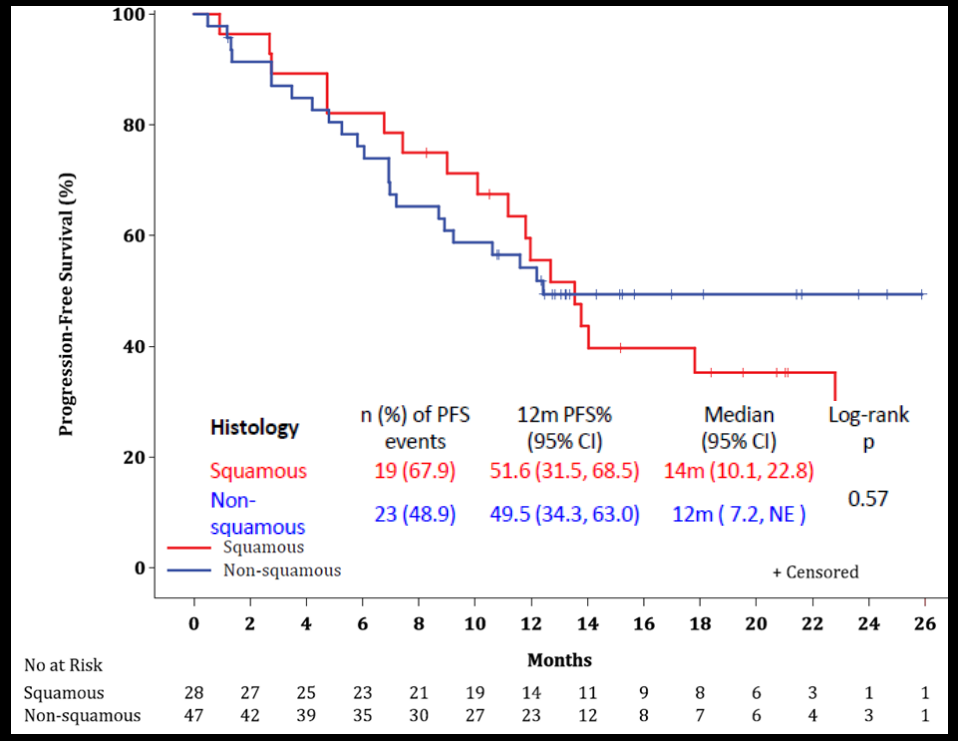
Pneumonitis
G2 2 patients
G3 6 patients

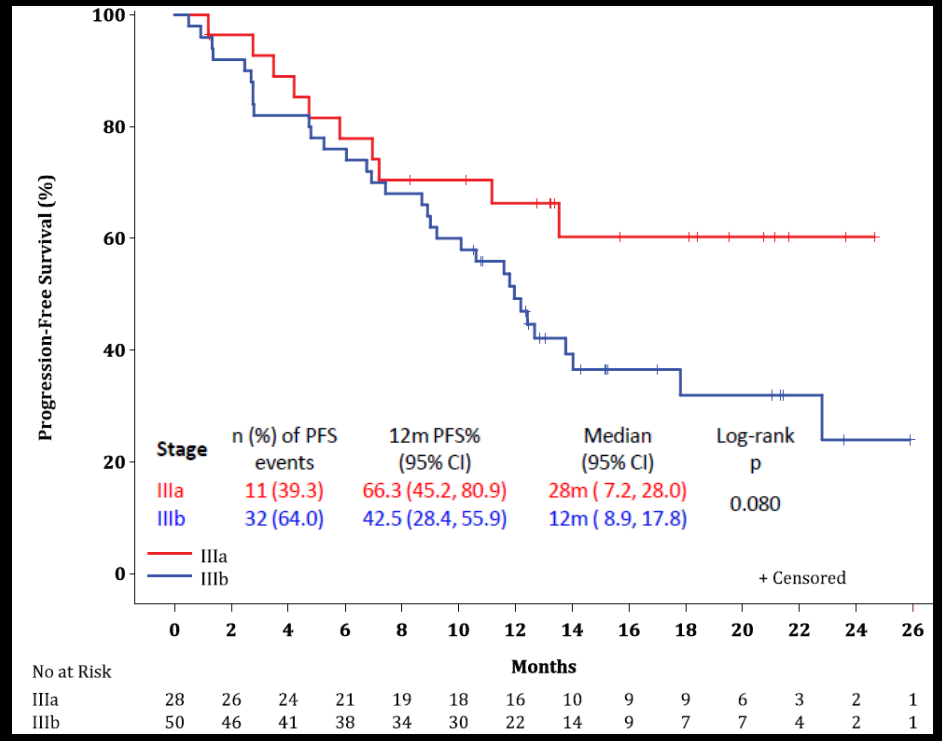
Primary endpoints:
•Pneumonitis-free rate of grade ≥ 3 (CTCAEV4.0) anytime during 6 months postradiotherapy.
•Hierarchically tested: 1-year progression-free survival (PFS) (from chemotherapy start)

Hierarchical design: IF safety proven→Efficacy evaluation:
•**1-year PFS, sample size n=74**
•H_0: $PFS_0 \leq 45\%$ vs H_1: $PFS_1 > 60\%$ (1-sided alpha=5%, power=83%)
•*Success rule: at least 41 patients reach 1-year without PFS event (i.e., maximum 33 PFS events)*

ASCO 2018 -ETOP NICOLAS trial *Peters S et al, ASCO 2018*

Results: Progression-free survival





Conclusion

- Based on the formal hierarchical efficacy analysis, we cannot reject the null hypothesis of 1-year PFS rate ≤45% versus 60% (p=0.23).
- Overall (N = 79patients), the estimate of 1-year survival rates 50.1% (95% CI: 38.3, 60.7%).
- NICOLAS PFS with a median of 12.7 months, compares favorably to studies in the same population, all reporting less than 12 months median.

Solange Peters et al. ESMO 2019 1457 PD

IO RT combinations in metastatic NSCLC

References	Phase	NSCLC setting (accrual)	Immunotherapy	Radiotherapy	Design	Primary outcome
NON-SPECIFIC IMMUNOTHERAPY						
van den Heuvel et al. (84)	IB	Stage IV, CR/PR/SD after 1st line CT (N=13)	NHS-IL2	20 Gy/5 fx, single pulmonary nodule	RT > NHS-IL2	
Golden et al. (85)	NS	Stage IV, ≥3 sites of measurable disease, SD/PD on CT (*N* = 18)[a]	GM-CSF	35 Gy/[illegible]	[illegible] + GM-CSF	[illegible]ponse in 4/18 pts
Ohri et al. (86)	II	[illegible]	[illegible]	[illegible]y/1–5 fx, single intrathoracic site of disease	SBRT + CDX-301	5/9 pts with PFS at 4 m
AN[illegible]						
Pa[illegible]		Stage IV, PR/SD after 1st line CT or TKI, ≥2 sites of disease (*N* = 26)	CV9202	20 Gy/4 fx, single lesion	• RT + CT + CV9202 • RT + CV9202 • RT + TKI + CV9202	≥G3 treatment-related AE in 4/26 pts
IMMUNE CHECKPOINT BLOCKADE						
Formenti et al. (88)	I/II	Stage IV, ≥2 measurable metastatic sites (*N* = 39)	Ipi	• 30 Gy/5 fx • 27 Gy/3 fx Single lesion	RT + ipi	CR, PR and SD in 2, 5 and 5/21 evaluable pts resp.
Tang et al. (89)	I	Stage IV, ≥2 sites of disease (*N* = 21)	Pembro	• 50 Gy/4 fx, single liver or lung lesion • 45 Gy/15 fx, SIB allowed up to 60 Gy larger field	RT + pembro	G2 and G3 treatment-related AE in 8 and 3/21 pts resp.
Kumar et al. (90) (PEAR)	I	Stage IV, requiring palliative thoracic RT (*N* = 14)	Pembro	• 20 Gy/5 fx		
Decker et al. (91)	I/II	Stage IV, ≥2 measurable disease sites (*N* = 8)	[illegible]	[illegible]	[illegible]bro until irPD > SBRT + pembro	No ≥G2 treatment-related AE during and post-SBRT
Moreno et al. (92)	I	[illegible]	[illegible]	27 Gy/3 fx	• RT + cemi • Cemi	G5 treatment-related pneumonitis (*n* = 1). ORR 18.2 vs. 40.0%; DCR 72.7 vs. 60/0%
Alameddine et al. (93)	I	[illegible]tage IV, ≤10 cc untreated brain metastases (*N* = 7)[a]	Nivo	15–20 Gy/1 fx, brain metastasis	SRS + nivo	Treatment-related AE in 3/5 evaluable pts
Miyamoto et al. (94)	NS	Stage IV, ≥1 lesion amenable to SBRT outside brain/bone (*N* = 6)	Nivo	25.5–48 Gy/3–4 fx, single lesion	SBRT > nivo	G3 pneumonitis in 1/6 pts
Theelen et al. (95) (PEMBRO-RT)	II	Stage IV, ≥2 separate lesions, after ≥1st line treatment (*N* = 76)	Pembro	24 Gy/3 fx, single tumor site	• SBRT > pembro • Pembro	ORR at 12 w 36 vs. 18% ($p = 0.07$)
Luke et al. (96)	I	Stage IV, ≥2 metastases, after ≥1st line treatment (*N* = 7)[a]	Pembro	30–50 Gy/3–5 fx, 2–4 metastases, partial for metastases >65 mL	SBRT > pembro	≥G3 treatment-related toxicity in 6/73 pts
Bauml et al. (97)	II	Stage IV, ≤4 metastases (*N* = 45)	Pembro	Stereotactic or standard fraction, dose NS	LAT > pembro	PFS after LAT 19.1 m vs. historical 6.6 m ($p = 0.005$)

No clinical benefit in antigen-specific or nonspecific immunotherapy

No Phase III trial available in ICI combination

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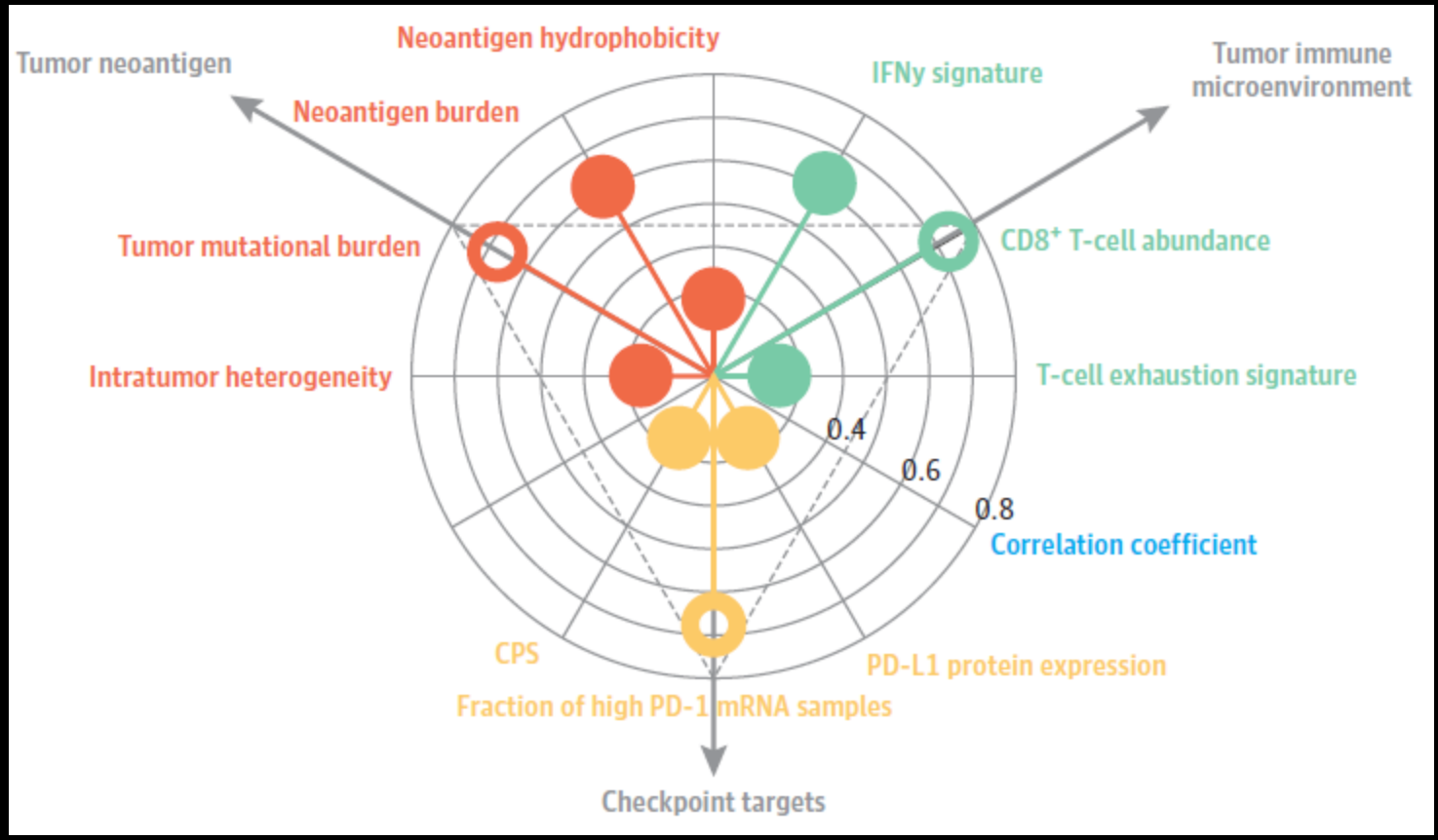
Radiotherapy immune-modulatory effects

Increase Tumor neoantigen



Low dose immunosuppression
Higher dose immunosupportive with limitation

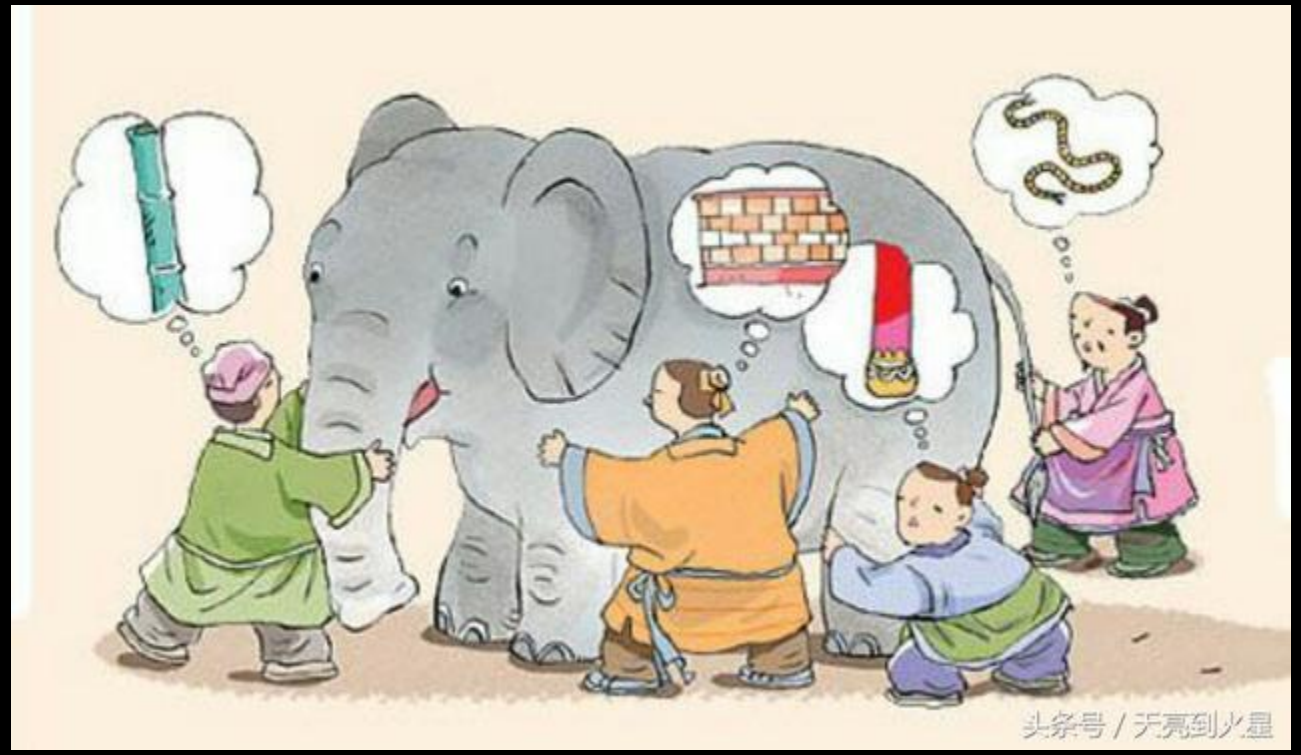
No effect in T cell function (avoid RT induced lymphopenia)

Modified from JAMA Oncol. 2019;5(11):1614-1618

Conclusions

- Anticancer agents have both immunosuppressive and immune supportive effects.
- Chemotherapy has promising immune-modulatory effects, also proven by phase III clinical trials
- TKIs (for driver mutation) immune-modulatory effects is not clear. IO + TKI: no clinical benefit but higher toxicity. Sequential or intermittent combination?
- Anti-angiogenesis has a modest survival benefit with promising immune-modulatory effects, clinical trials ongoing
- Radiotherapy modify TME and enhance IO effect in locally advanced NSCLC. In metastatic disease, combination trials are ongoing

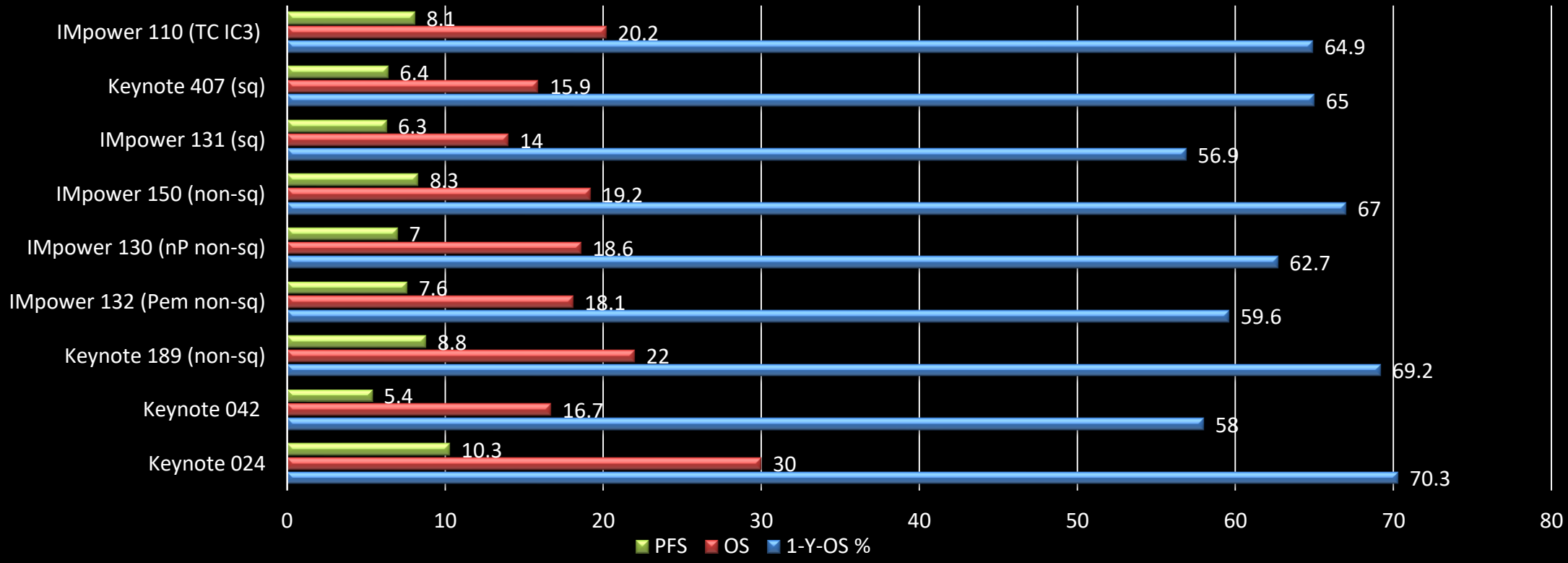
Thanks for your attention !



host effects generated by cancer therapies based on preclinical and clinical evidence

Host effect	In animal models	In humans
Cytotoxic and cytotoxic-like agents		
Endothelial-precursor-cell mobilization	+	+
MDSC colonization of treated tumors	+	+
Macrophage colonization of treated tumors	+	+
Macrophage residence at perivascular sites	+	+
Astrocyte contributions to drug resistance	+	NA
MSC contributions to drug resistance	+	NA
BMDC contributions to metastasis	+	NA
VEGFR1-positive pulmonary endothelial cell contributions to metastasis	+	NA
Cathepsin release from macrophages	+	+
Induction of proinflammatory factors	IL-6, IL-1β	IL-6
Induction of cytokines and growth factors	GM-CSF, G-CSF, VEGF-A, SDF-1	GM-CSF, G-CSF, VEGF-A
Upregulation of prostaglandins and growth-promoting factors	+	NA
Molecularly targeted drugs		
MDSC colonization of tumors following antiangiogenic therapy	+	NA
Induction of cytokines and growth factors following antiangiogenic drug therapy	SDF-1, osteopontin, SCF-1, G-CSF, VEGF-A, Bv8 (Prokineticin-2)	VEGF-A, PlGF
Reduction in soluble factors following antiangiogenic therapy	sVEGFR2	sVEGFR2
Induction of factors following EGFR inhibition	TGF-α, amphiregulin, epiregulin	TGF-α, amphiregulin
Radiation		
Circulating endothelial-cell mobilization	NA	+
Myeloid cell colonization of irradiated tumors	+	NA
Macrophage colonization of irradiated tumors	+	NA
Induction of circulating factors	VEGF-A, SDF-1, SCF-1, Arg1 (Arginase-1), Fizz (Resistin), IL-1β, IL-10, MMP-9, CD206 (mannose receptor), TGF-β	IL-6, SCF-1
Surgery		
Endothelial-progenitor-cell mobilization	NA	+
Reduced NK-cell activity	+	+
Increased number of circulating tumor cells	NA	+

Yuval Shaked *Nat. Rev. Clin. Oncol*. 13, 611–626 (2016).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IMpower 131 (sq)
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IMpower 150 (non-sq)
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IMpower 130 (nP non-sq)
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IMpower 132 (Pem non-sq)
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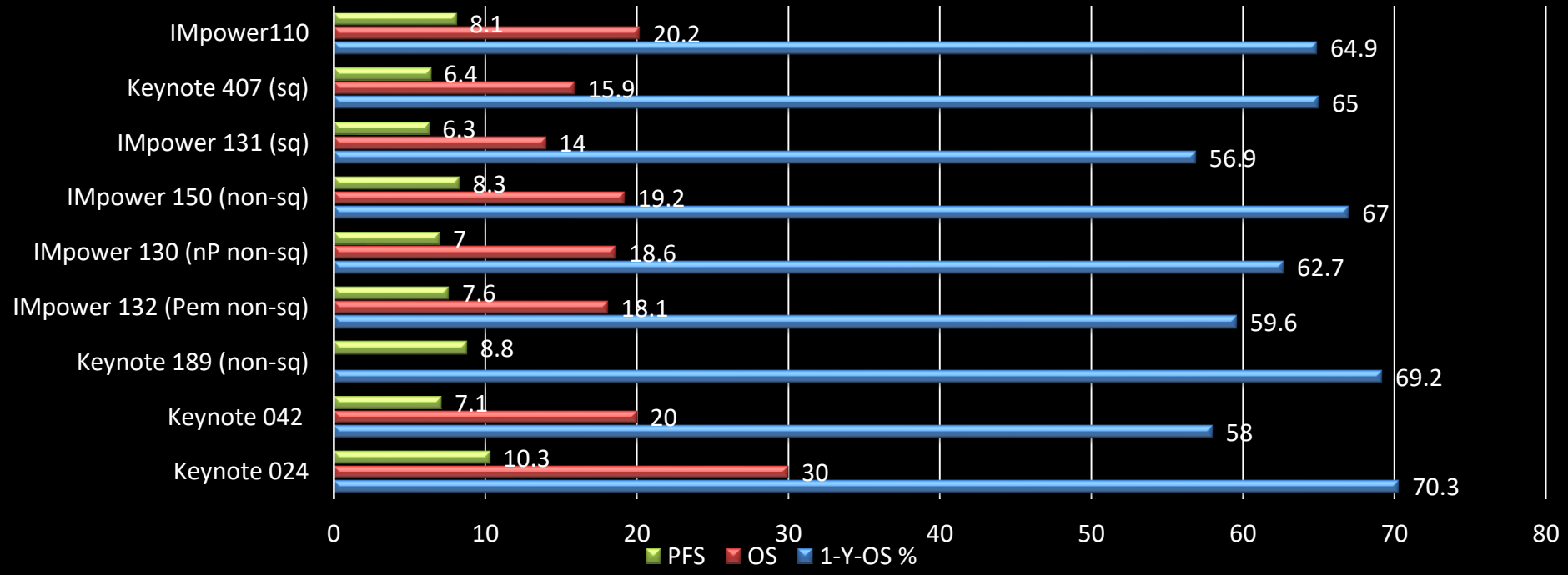
40
50
60
70
80
PFS
OS
1-Y-OS %

PD-L1>50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Keynote 189 (non-sq)
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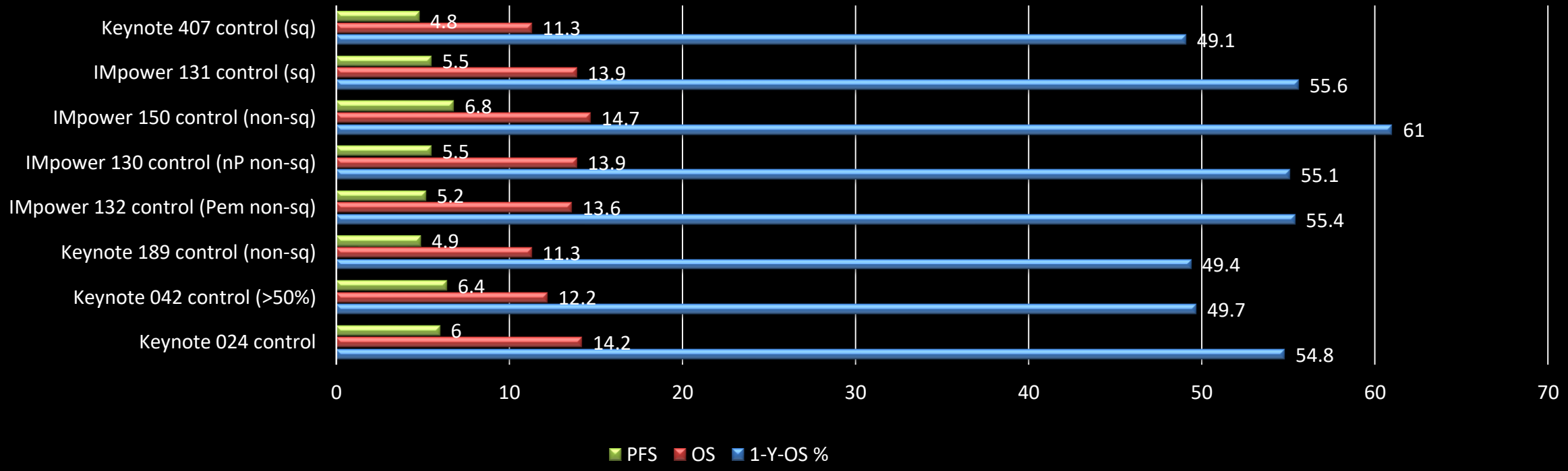
Keynote 407 control (sq)
IMpower 131 control (sq)
IMpower 150 control (non-sq)
IMpower 130 control (nP non-sq)
IMpower 132 control (Pem non-sq)
Keynote 189 control (non-sq)
Keynote 042 control (>50%)
Keynote 024 control
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13.6
55.4
4.9
11.3
49.4
6.4
12.2
49.7
6
14.2
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20
30
40
50
60
70
PFS
OS
1-Y-OS %

Selected Randomized Trials of Combination IO + CT vs. CT

Trial reference	Drug	Phase no. pts	Histology	PD-L1	FU time median mo.	HR OS (95% CI) *P*-value	HR PFS (95% CI) *P*-value
KN-189 (1)	Pembrolizumab ± Platinum-Pem	III 616	NonSq	any	10.5	0.49 (0.38–0.64) <0.001	0.52 (0.43–0.64) <0.001
KN-021 (2, 3)	Pembrolizumab ± Carbo-Pem	II 123	NonSq	any	10.6	0.90 (0.42–1.91) 0.39	0.53 (0.31–0.91) 0.010
KN-407[a] (4)	Pembrolizumab ± Carbo-(nab)Pac	III 559	Sq	any	7.7	0.64 (0.49–0.85) 0.0008	0.56 (0.45–0.70) <0.0001
IMPower131 (5)[a]	Atezolizumab ± Carbo-nabPac	III 683	Sq	any	9.8[b]	0.96 (0.78–1.18) 0.69	0.71 (0.60–0.85) 0.0001
IMPower150 (6)	Atezolizumab ± Carbo-Pac-Beva	III 696	NonSq	any	15.5	0.78[a] (0.64–0.96) $P = 0.02$	0.62 (0.52–0.74) $P < 0.001$
IMPower150bis (7)	Atezolizumab + Carbo-Pac vs. Carbo-Pac-Beva	III 686[c]	NonSq	any	20.0	NR	0.88 [a] (0.72-1.08) 0.20
IMPower132 (8)[a]	Atezolizumab ± Platinum-Pem	III 578	NonSq	any	NR	0.81 (0.64–1.03) $p = 0.08$	0.60 (0.49–0.72) $P < 0.0001$
IMPower130 (9)	Atezolizumab ± Carbo-nabPac	III 679	NonSq	any	13.0[b]	0.79 (0.64–0.98) 0.03	0.64 (0.54–0.77) <0.0001
CM-227 (10)	Nivolumab ± Platinum-Pem in NonSq Platinum-Gem in Sq	III 363	NonSq (273) Sq (90)	<1%	11.2[b]	NR	0.74 (0.58–0.94) $P = NR$

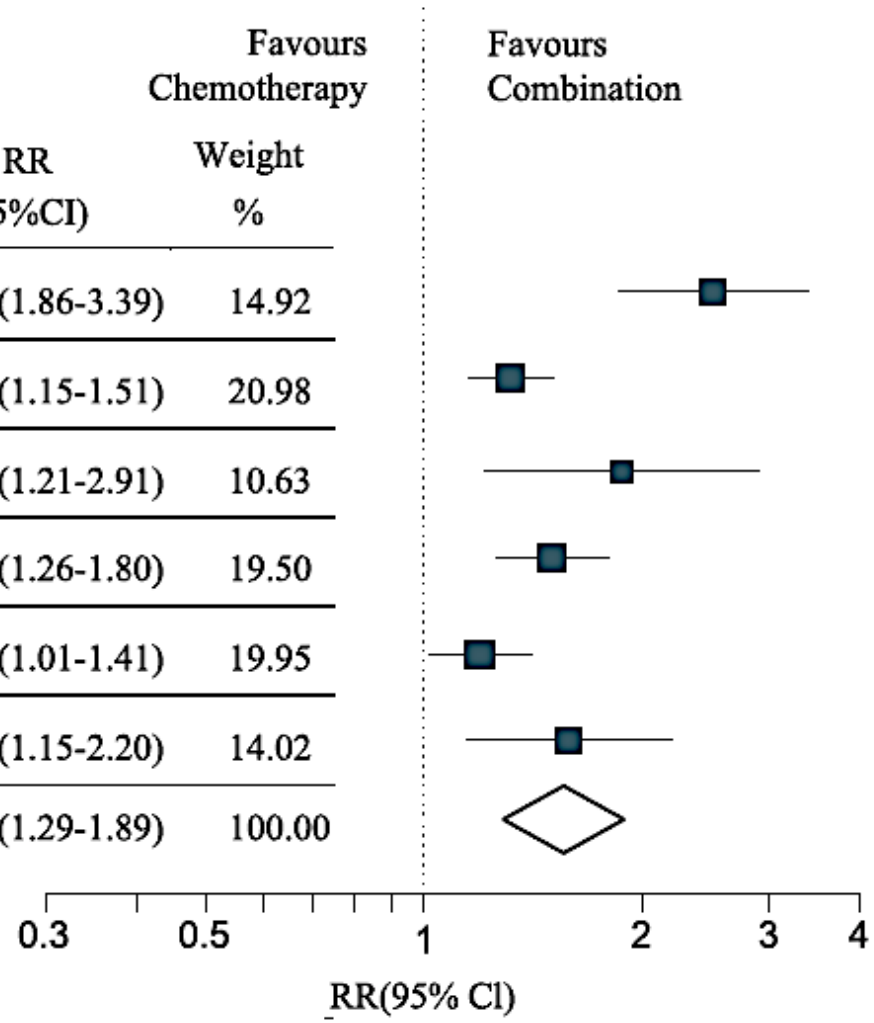
Addeo A, et al. Front Onclo April, 2019. https://doi.org/10.3389/fonc.2019.00264

Objective Response Rate

Source	No. of patients: Combination Events	Combination Total	Chemotherapy Events	Chemotherapy Total	RR (95%CI)	Weight %
KEYNOTE-189, 2018	195	410	39	206	2.51 (1.86-3.39)	14.92
IMpower150, 2018	226	356	161	336	1.32 (1.15-1.51)	20.98
KEYNOTE- 021, 2016 and 2018	34	60	19	63	1.88 (1.21-2.91)	10.63
KEYNOTE-407, 2018	161	278	108	281	1.51 (1.26-1.80)	19.50
IMpower131, 2018	169	343	140	340	1.20 (1.01-1.41)	19.95
CheckMate 227, 2018	65	177	43	186	1.59 (1.15-2.20)	14.02
Overall	850	1668	1476	1668	1.56 (1.29-1.89)	100.00

Heterogeneity: $\chi^2 = 22.36$, $P < .001$; $I^2 = 77.6\%$

Test for overall effect: z = 4.52 (P <.001)



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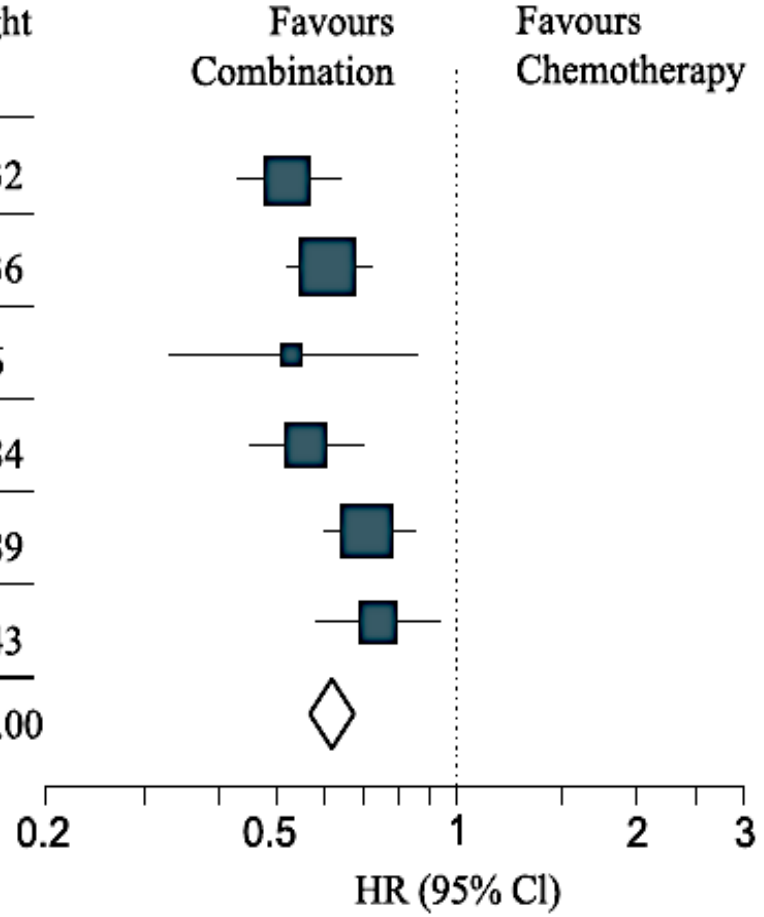
Progression Free Survival

Source	No. of patients: Combination	No. of patients: Chemotherapy	HR (95%CI)	Weight %
KEYNOTE-189, 2018	410	206	0.52 (0.43-0.64)	18.32
IMpower150, 2018	400	400	0.61 (0.52-0.72)	27.36
KEYNOTE- 021, 2016 and 2018	60	63	0.53 (0.33-0.86)	3.16
KEYNOTE-407, 2018	278	281	0.56 (0.45-0.70)	14.84
IMpower131, 2018	343	340	0.71 (0.60-0.85)	23.89
CheckMate 227, 2018	177	186	0.74 (0.58-0.94)	12.43
Overall	1668	1476	0.62 (0.57-0.67)	100.00

Heterogeneity: $\chi^2 = 8.66$, $P = .123$; $I^2 = 42.3\%$

Test for overall effect: z = 11.06 (P <.001)



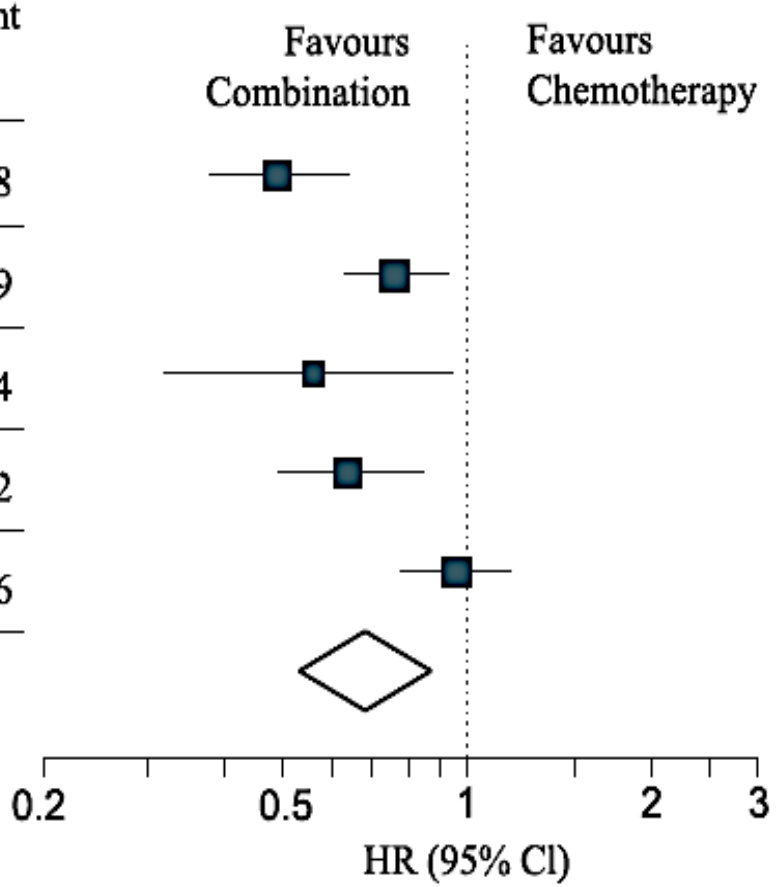
Zhou Y, et al. Journal for ImmunoTherapy of Cancer (2018) 6:155

Overall Survival

Source	No. of patients: Combination	No. of patients: Chemotherapy	HR (95%CI)	Weight %
KEYNOTE-189, 2018	410	206	0.49 (0.38-0.64)	21.08
IMpower150, 2018	400	400	0.76 (0.63-0.93)	23.49
KEYNOTE-021, 2016 and 2018	60	63	0.56 (0.32-0.95)	11.84
KEYNOTE-407, 2018	278	281	0.64 (0.49-0.85)	20.52
IMpower131, 2018	343	340	0.96 (0.78-1.18)	23.06
Overall	1491	1290	0.68 (0.53-0.87)	100

Heterogeneity: $\chi^2 = 17.61$, $P = .001$; $I^2 = 77.3\%$

Test for overall effect: z = 3.04 (P =.002)



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