IMMUNOTHERAPY IN LUNG CANCER

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What Do We Already Know and It's Old…..

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Immunotherapy→ Non-Squamous NSCLC [latest NCCN recommendations]

- What therapies have been approved until today?:
  - PD-L1 ≥ 50%→ Pembro alone or Plat/Pem/Pem or Carbo/Pac/Bev/Atezo (KN-24, KN-189, IMp-150) **CAT 1**
  - PD-L1 ≥1-49%→ Plat/Pem/Pem (KN-189) **CAT 1**
  - PD-L1 >1-49%→ Carbo/Pac/Bev/Atezo (IMpower-150) **CAT 1**
  - PD-L1 ≥1-49% → Carbo/nab-Pac/Atezo (IMp-130) **CAT 2A**
  - PD-L1 ≥1-49%→ Pembro alone (KN-042) **CAT 2B**
  - PD-L1 ≥1-49%→ Nivo + Ipi (CM227) **CAT 2A**

New indications; NCCN v2.2020

Prior NCCN v7.2019

- PD-L1 <1%→ Plat/Pem/Pem (KN-189) [NCCN does not comment on PD-L1 <1%]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)
No contraindications to PD-1 or PD-L1 inhibitors[c]
Preferred
- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]**

Other Recommended
- **Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]**
- **Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]**
- **Nivolumab + ipilimumab[5,d]**

NCCN. Version 2.2020

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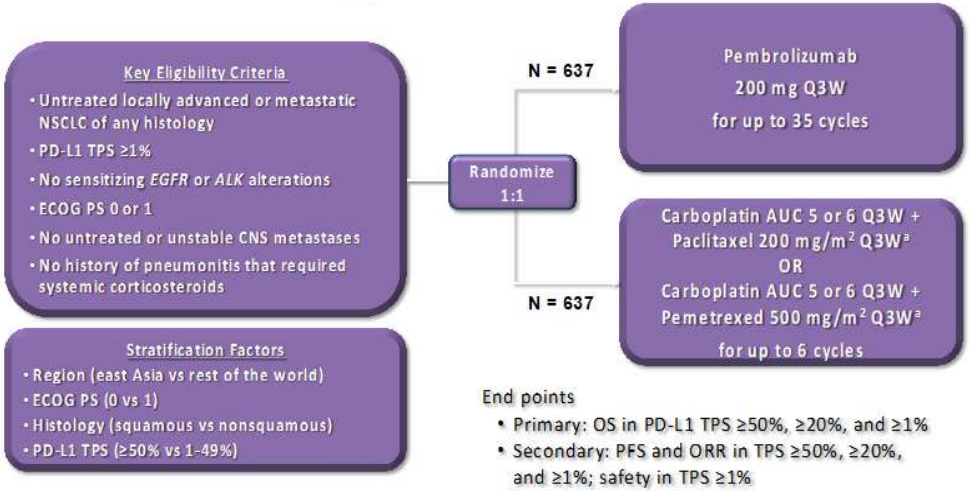
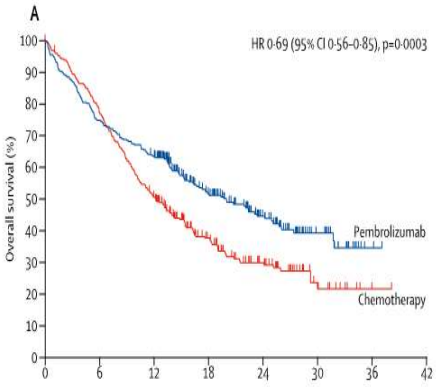
So many options for nSq-NSCLC, PD-L1 ≥ 1-49%

Randomized Trial of Pembrolizumab and Platinum-based Chemotherapy in Patients with PD-L1 ≥1%

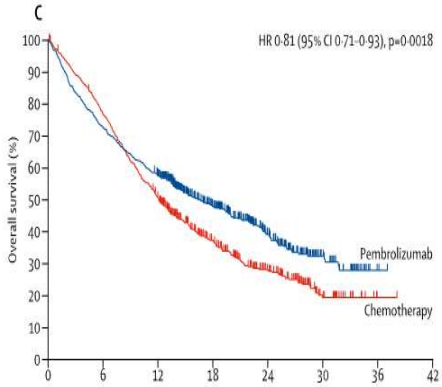


KEYNOTE-042

PDL1 ≥ 50%



PDL1 ≥ 1%



Hence, what is better on this population? Pembro alone (KN-042) or Pembro/Chemo (KN-189)?

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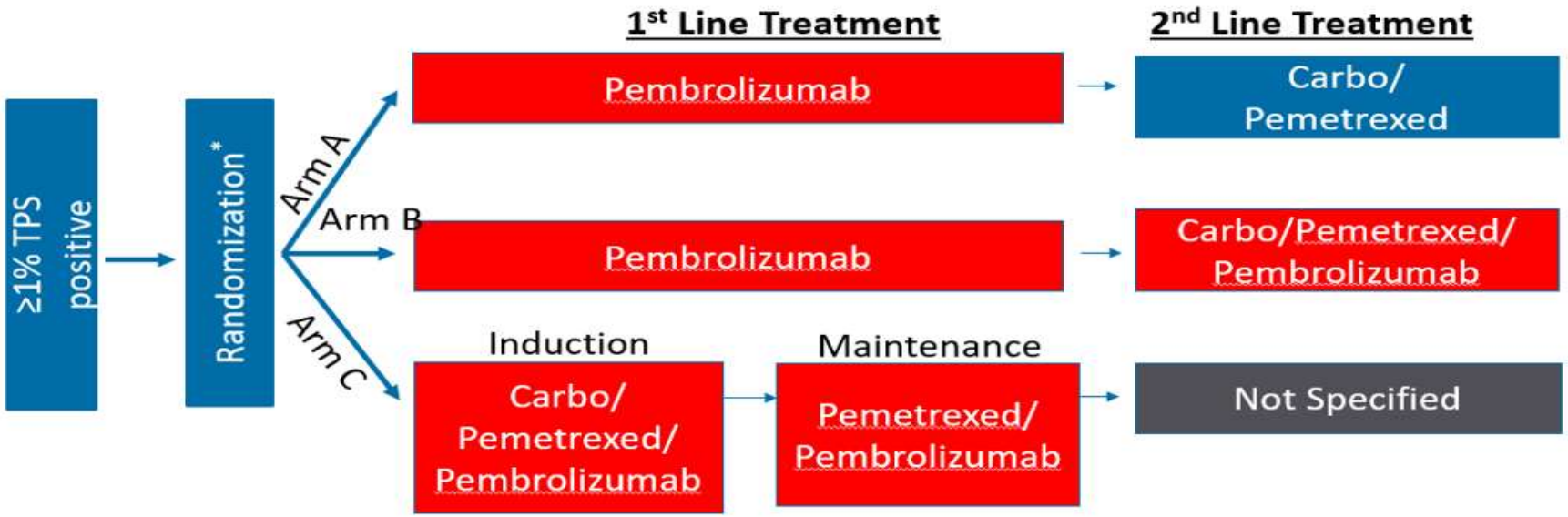
The answer maybe here…

ECOG 5163/SWOG1709



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Background….. Squamous cell histology

- What therapies have been approved until today?:
  - PD-L1 ≥ 50%→ Pembro alone or Carbo/Pac or nab-Pac/Pem (KN-24, KN-407) **CAT 1**
  - PD-L1 ≥ 50%→ Ipi + Nivo (CM-227) **CAT 2A**
  - PD-L1 ≥1-49%→ Carbo/Pac or nab-Pac/Pem (KN-407) **CAT 1**
  - PD-L1 >1-49%→ Ipi + Nivo (CM-227) **CAT 2A**
  - PD-L1 >1-49%→ Pembro alone (KN-042) **CAT 2B**

New indications; NCCN v2.2020

Prior NCCN v7.2019

- [NCCN does not comment on PD-L1 <1%]

SQUAMOUS CELL CARCINOMA (PS 0–1)
No contraindications to PD-1 or PD-L1 inhibitors[c]
Preferred
- **Pembrolizumab/carboplatin/paclitaxel[33,d] (category 1)**
- **Pembrolizumab/carboplatin/albumin-bound paclitaxel[33,d] (category 1)**

Other recommended
- **Nivolumab + ipilimumab[5,d]**

NCCN. Version 2.2020

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Where Are The New Changes Coming From?

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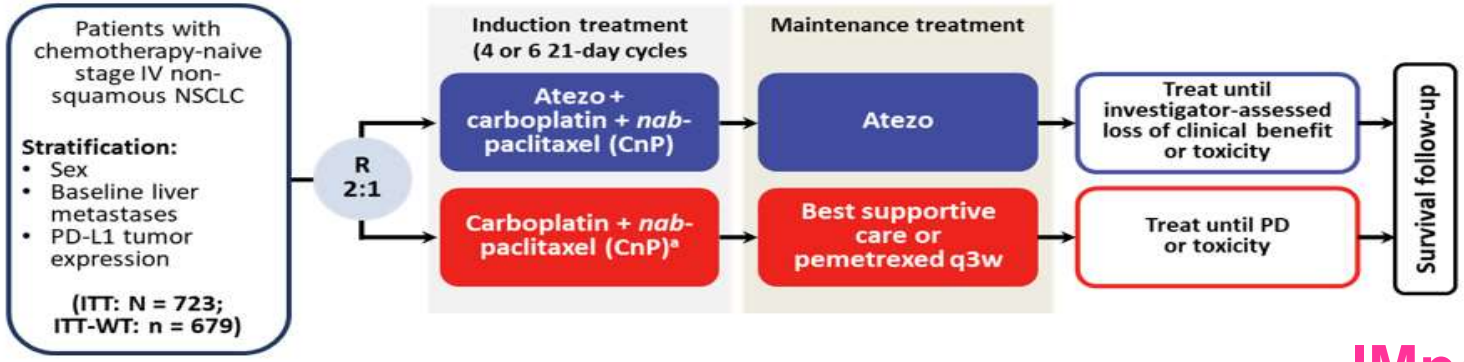
Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130)



IMpower130

- Co-primary endpoints: investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with *EGFR* or *ALK* genomic alterations
- Key secondary endpoints: OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

Atezo 1200 mg IV q3w; carboplatin area under the curve 6 mg/mL/min q3w; *nab*-paclitaxel 100 mg/m^2 IV q3w. PD-L1 status tested with VENTANA SP142 IHC assay. Data cutoff: 15 March 2018. [a] Crossover to receive atezo at PD was permitted only for patients enrolled to protocol versions 1 - 4.

Cappuzzo F, et al. IMpower130. ESMO 2018 [Abstract LBA53].

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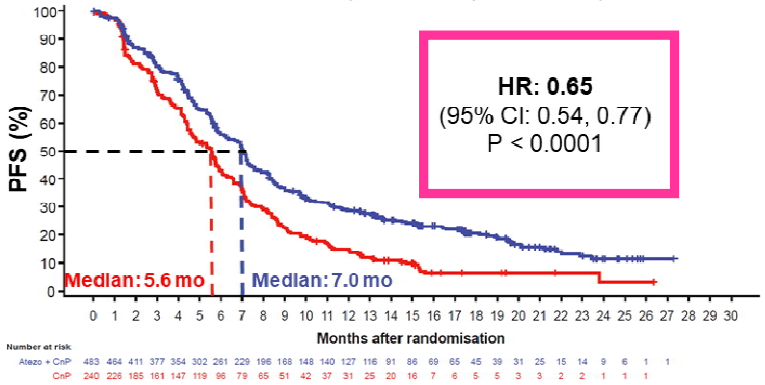
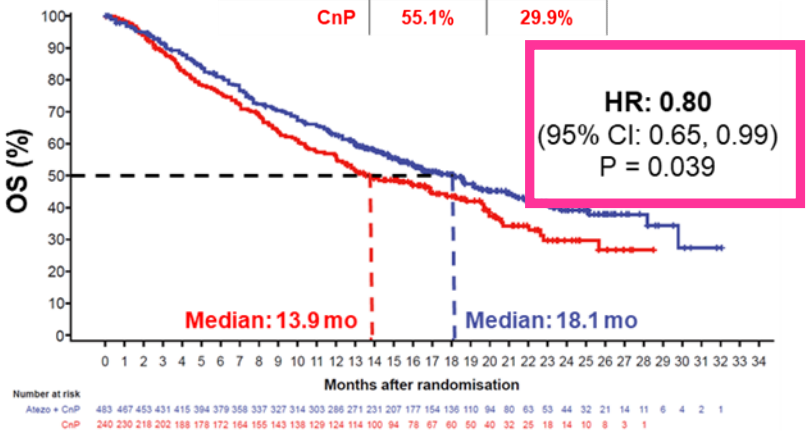
PFS (%)	6 months	12 months
Atezo + CnP	56.4%	28.9%
CnP	42.9%	14.2%



Investigator-assessed PFS and OS (ITT)

OS (%)	1 year	2 years
Atezo + CnP	62.7%	39.3%
CnP	55.1%	29.9%



Cappuzzo F, et al. IMpower130. ESMO 2018 [Abstract LBA53].

- IMpower130 met its co-primary PFS and OS endpoints and demonstrated a statistically significant and clinically meaningful benefit of 4.7 months' OS (and 1.5 months' PFS) for atezo plus chemotherapy in the ITT-WT population, compared with chemotherapy alone
  - OS and PFS benefits were observed across all PD-L1 subgroups

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BARCELONA 2019 ESMO congress

Nivolumab + Low-Dose Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis

Solange Peters,[1] Suresh Ramalingam,[2] Luis Paz-Ares,[3] Reyes Bernabe Caro,[4] Bogdan Zurawski,[5] Sang-We Kim,[6] Aurelia Alexandru,[7] Lorena Lupinacci,[8] Emmanuel de la Mora Jimenez,[9] Hiroshi Sakai,[10] István Albert,[11] Alain Vergnenegre,[12] Martin Reck,[13] Hossein Borghaei,[14] Julie R. Brahmer,[15] Kenneth O'Byrne,[16] William J. Geese,[17] Prabhu Bhagavatheeswaran,[17] Faith E. Nathan,[17] Matthew D. Hellmann[18]

[1]Centre hospitalier universitaire Vaudois (CHUV), Lausanne University, Lausanne, Switzerland; [2]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Hospital Universitario Doce de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Hospital Universitario Virgen Del Rocio, Seville, Spain; [5]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [6]Asan Medical Center, Seoul, Republic of Korea; [7]Institute Of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucha, Bucharest, Romania; [8]Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; [9]Instituto Jalisciense De Cancerología, Guadalajara, Jalisco, Mexico; [10]Saitama Cancer Center, Saitama, Japan; [11]Matrai Gyogyintezet, Matrahaza, Hungary; [12]Limoges University Hospital, Limoges, France; [13]Lung Clinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; [14]Fox Chase Cancer Center, Philadelphia, PA, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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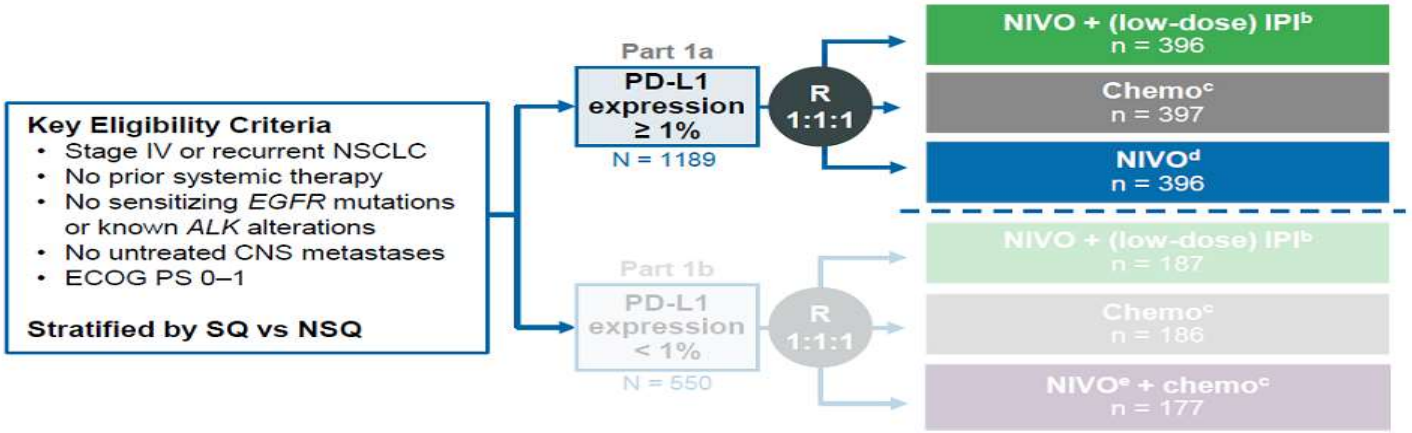
CheckMate 227 Part 1 Study Design[a]



Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

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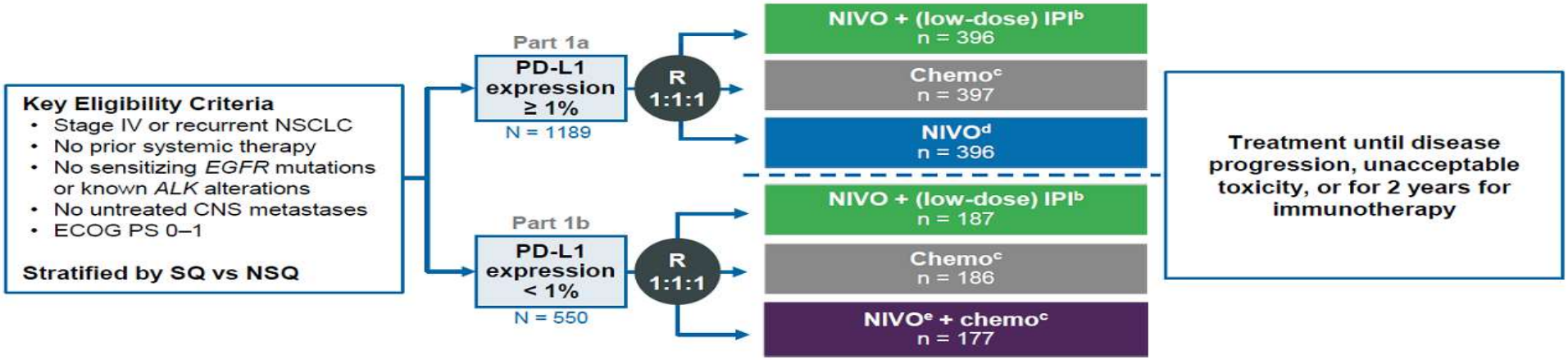
CheckMate 227 Part 1 Study Design[a]



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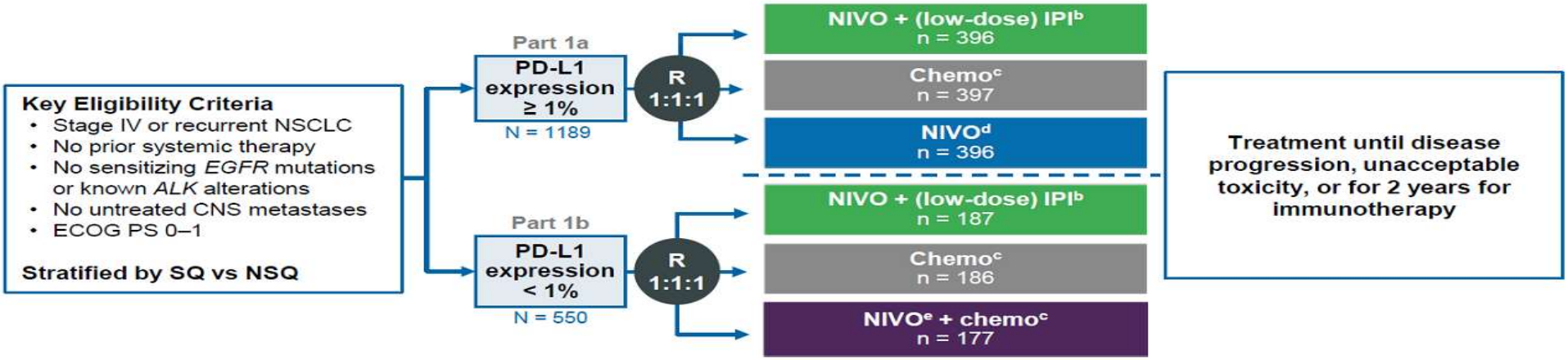
CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

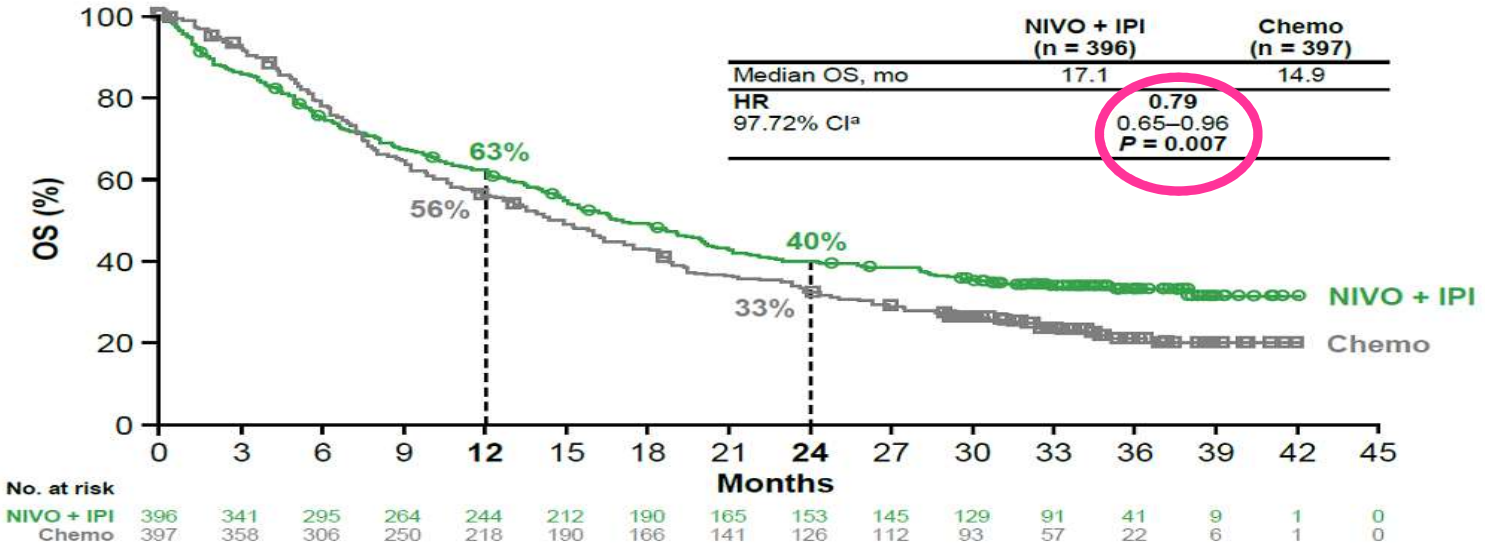
Evolving Treatments in Immunotherapy and Targeted Therapies

CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

Study!!



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR 97.72% CI[a]	0.79 0.65–0.96 *P* = 0.007	

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 43%, respectively.
[a]95% CI, 0.67–0.94.

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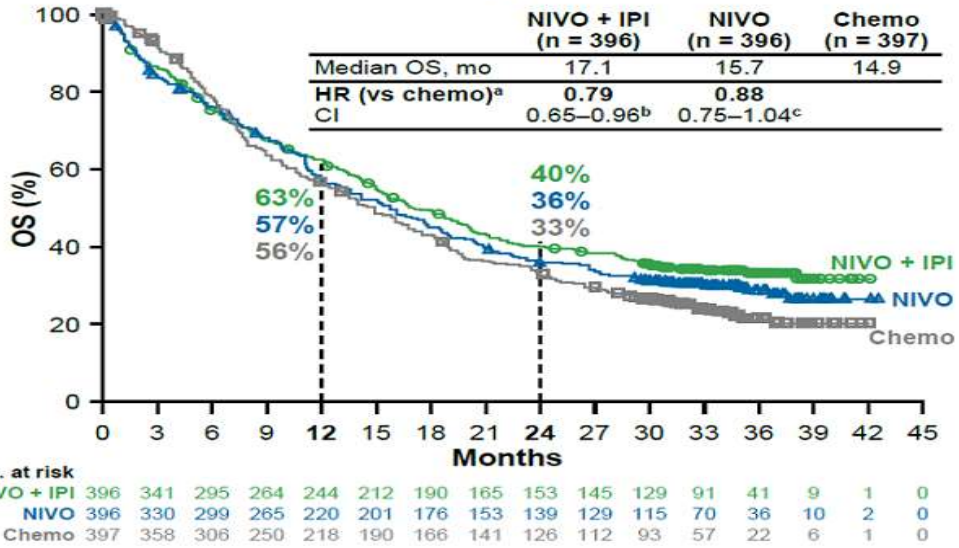
Evolving Treatments in Immunotherapy and Targeted Therapies

CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

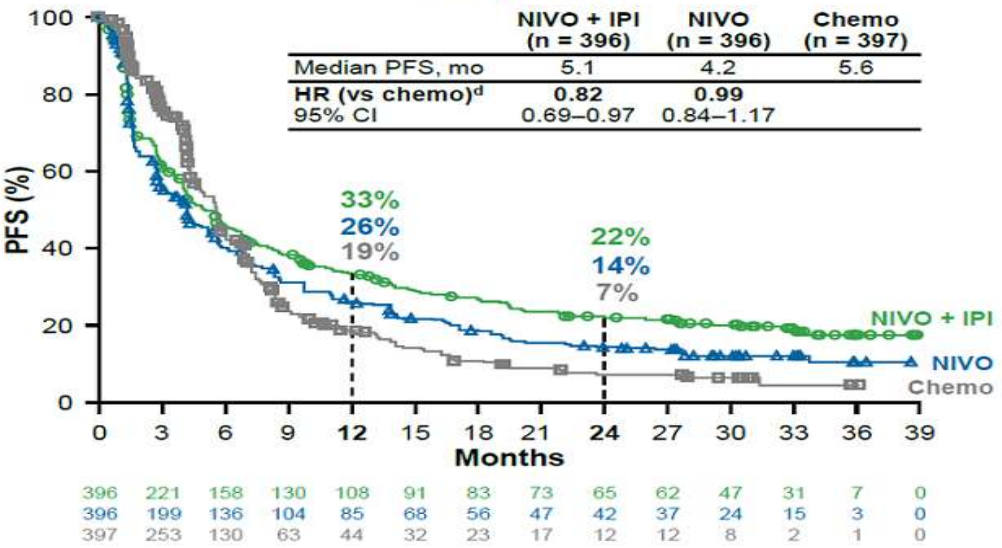
OS



	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	0.79	0.88	
CI	0.65–0.96[b]	0.75–1.04[c]	

No. at risk																
NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR



	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[d]	0.82	0.99	
95% CI	0.69–0.97	0.84–1.17	

NIVO + IPI	396	221	158	130	108	91	83	73	65	62	47	31	7	0		
NIVO	396	199	136	104	85	68	56	47	42	37	24	15	3	0		
Chemo	397	253	130	63	44	32	23	17	12	12	8	2	1	0		

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% of patients in the NIVO arm, and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6%, 8%, and 43%, respectively.
[a]HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); [b]97.72% CI; [c]95% CI; [d]HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).

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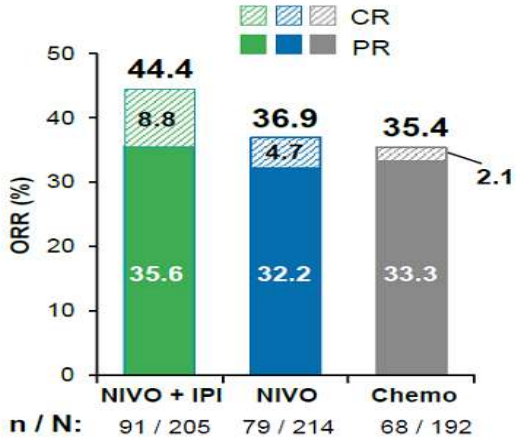
CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

Efficacy With NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 50%

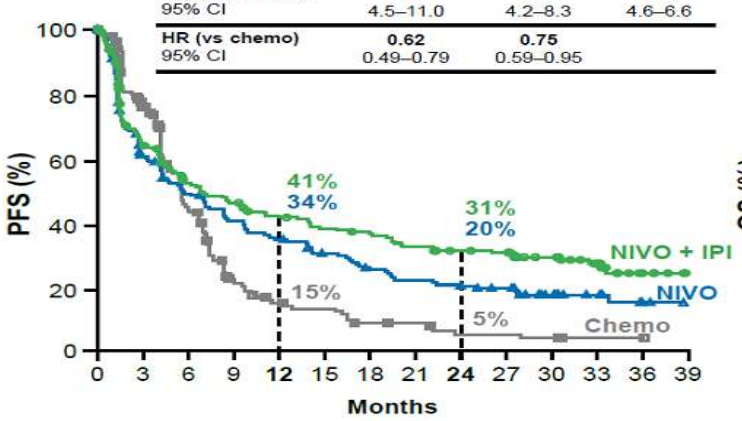
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



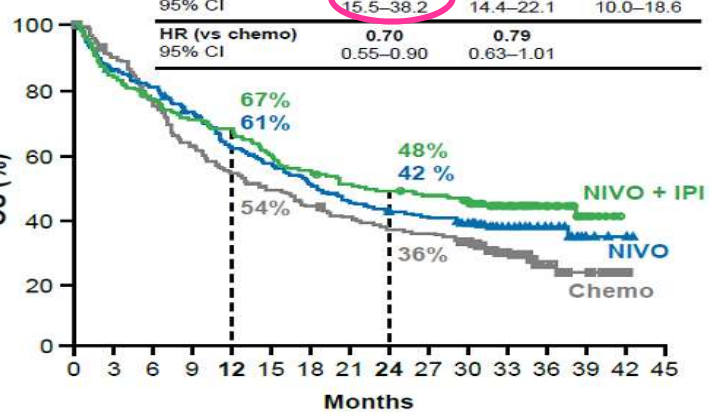
PFS by BICR

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median PFS, mo 95% CI	6.7 4.5–11.0	5.6 4.2–8.3	5.6 4.6–6.6
HR (vs chemo) 95% CI	0.62 0.49–0.79	0.75 0.59–0.95	



OS

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	0.70 0.55–0.90	0.79 0.63–1.01	



- Median DOR with NIVO + IPI, NIVO and chemo was 31.8, 17.5 and 5.8 months, respectively

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.

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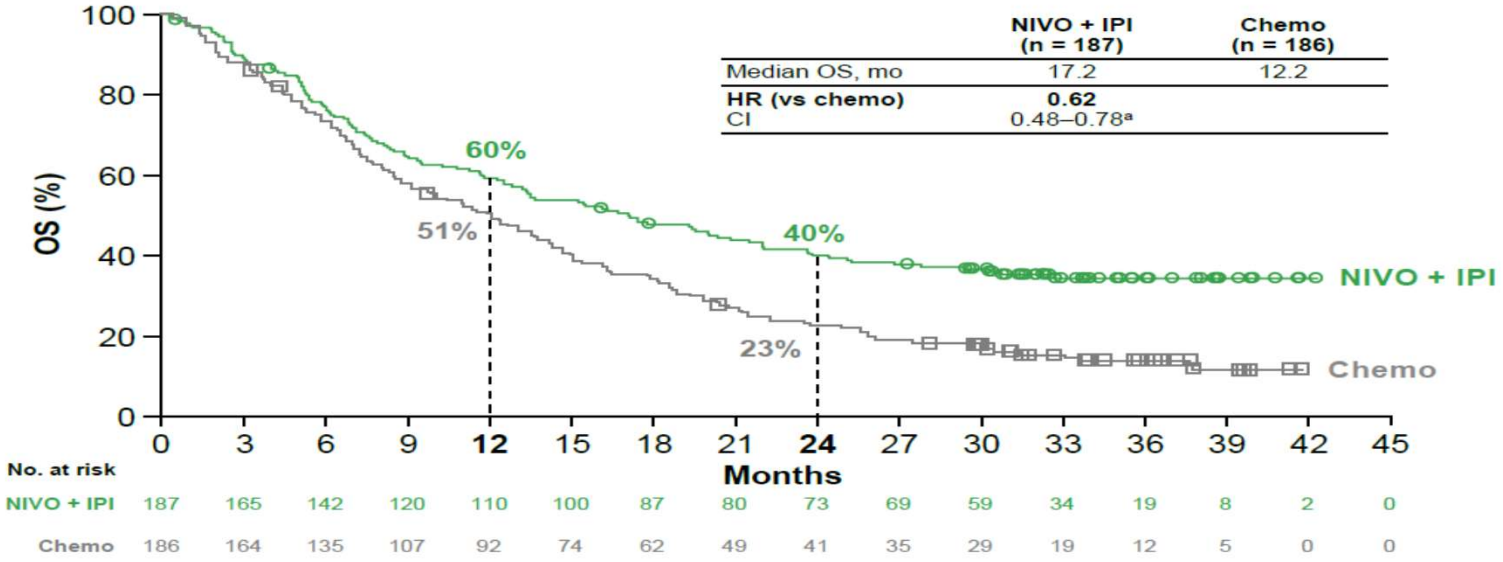
CheckMate 227 Part 1: NIVO + IPI in 1L NSCLC

OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo



	NIVO + IPI (n = 187)	Chemo (n = 186)
Median OS, mo	17.2	12.2
HR (vs chemo)	**0.62**	
CI	0.48–0.78[a]	

No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI.

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Summary: NIVO + IPI in First-Line NSCLC

- CheckMate 227 met its primary endpoint of OS in patients with PD-L1 ≥ 1%
  - First phase 3 study to show PD-1 and CTLA-4 inhibition is effective in NSCLC
- Clinically meaningful OS improvement vs chemo was observed regardless of PD-L1 expression, with deep and durable responses
- Addition of IPI to NIVO improved outcomes
  - vs NIVO monotherapy in PD-L1 ≥ 1%
  - vs NIVO + chemo in PD-L1 < 1%
- No new safety signals were observed for NIVO + low-dose IPI
- This dual immunotherapy represents a potential new first-line treatment option for patients with advanced NSCLC

What's The Future?

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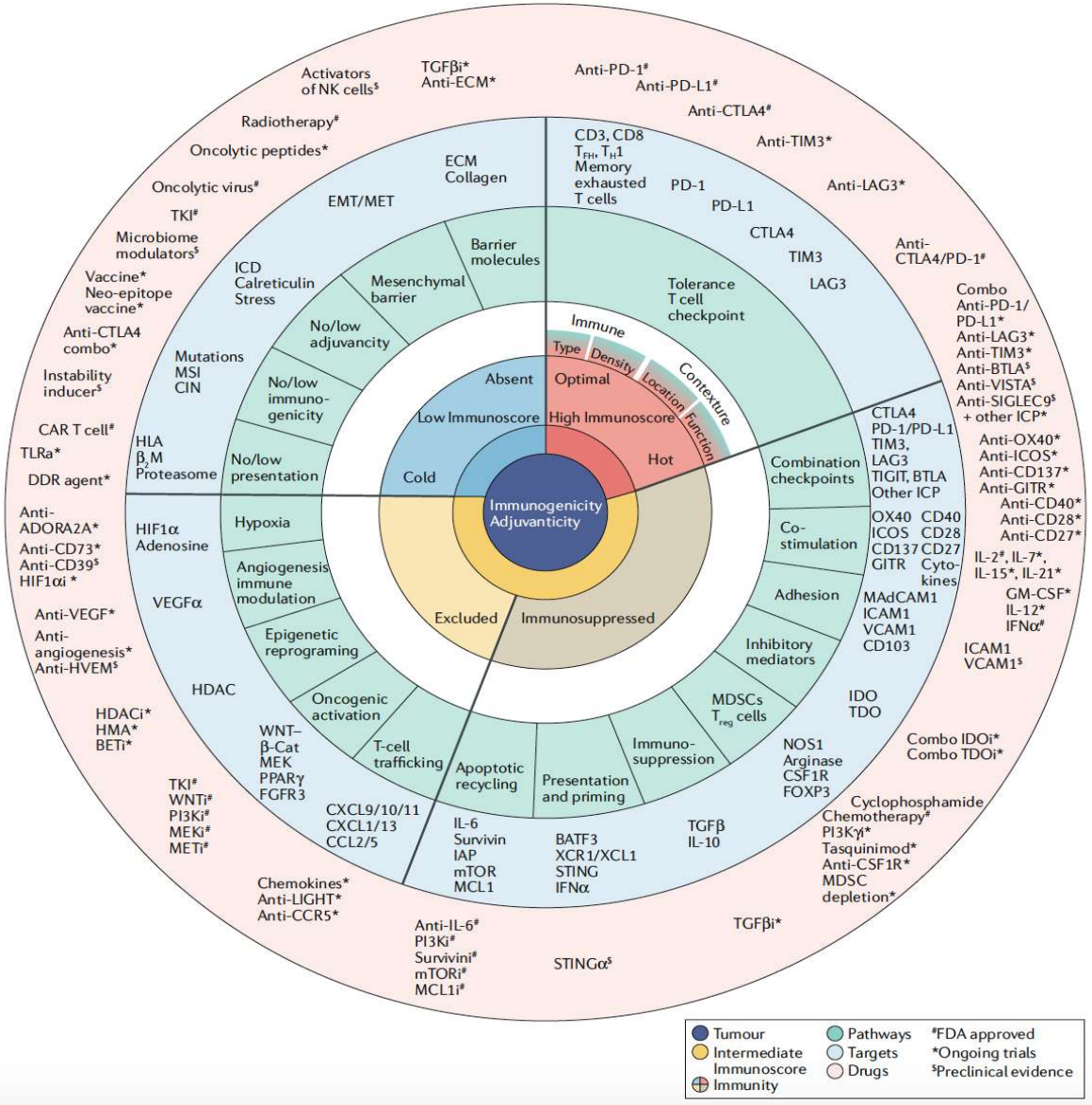
All the best is yet to come!!



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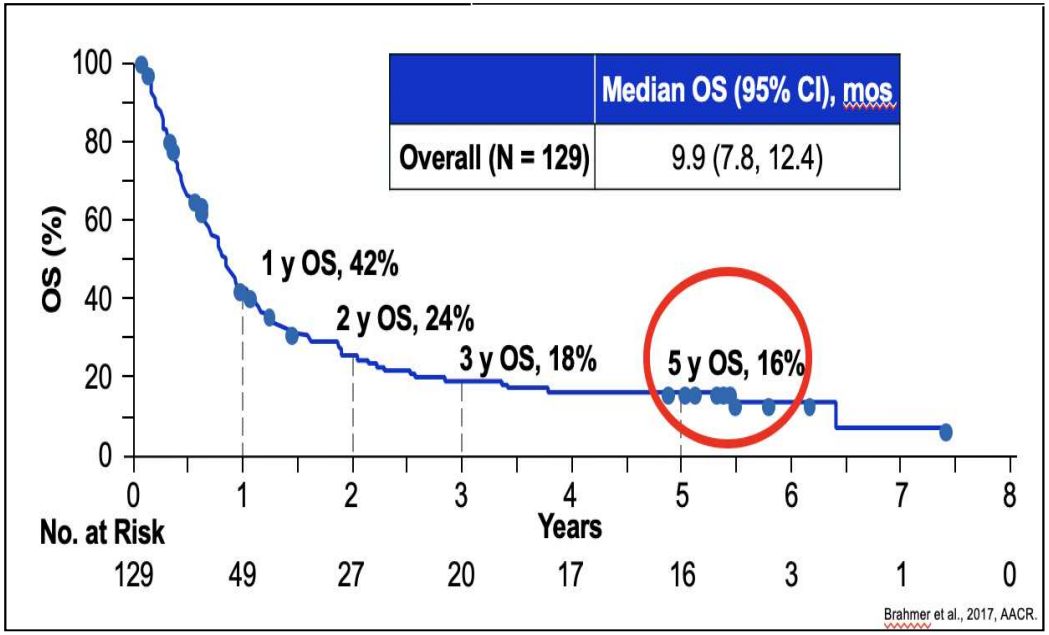
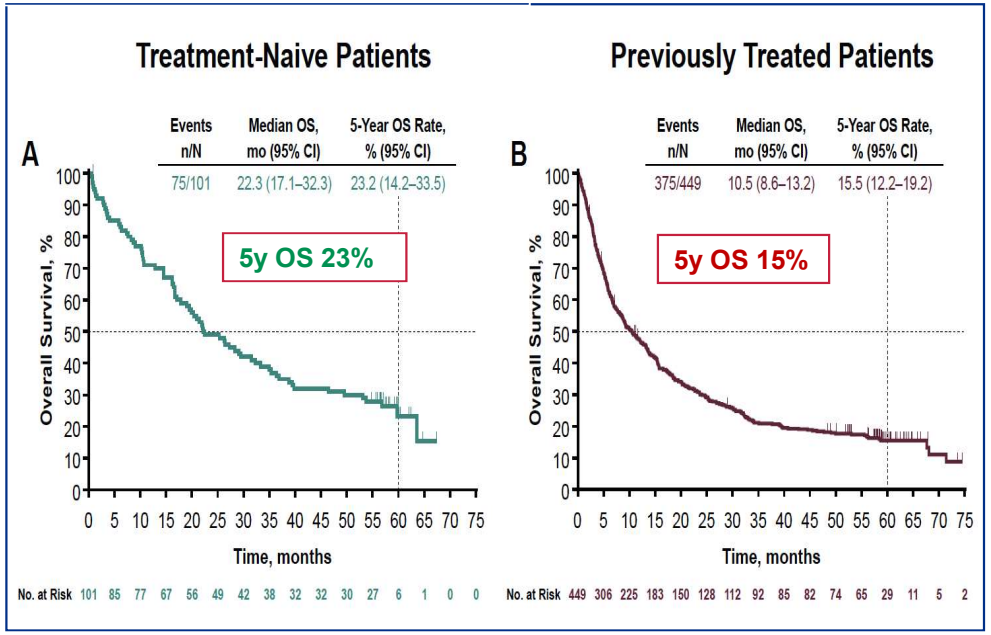
Immunotherapy and long-term survivors

8th TNM IASLC Classification, 5-y OS M1c: ~1%





Brahmer JR et al. Oral presentation at AACR 2017 Garon E– ASCO 2019

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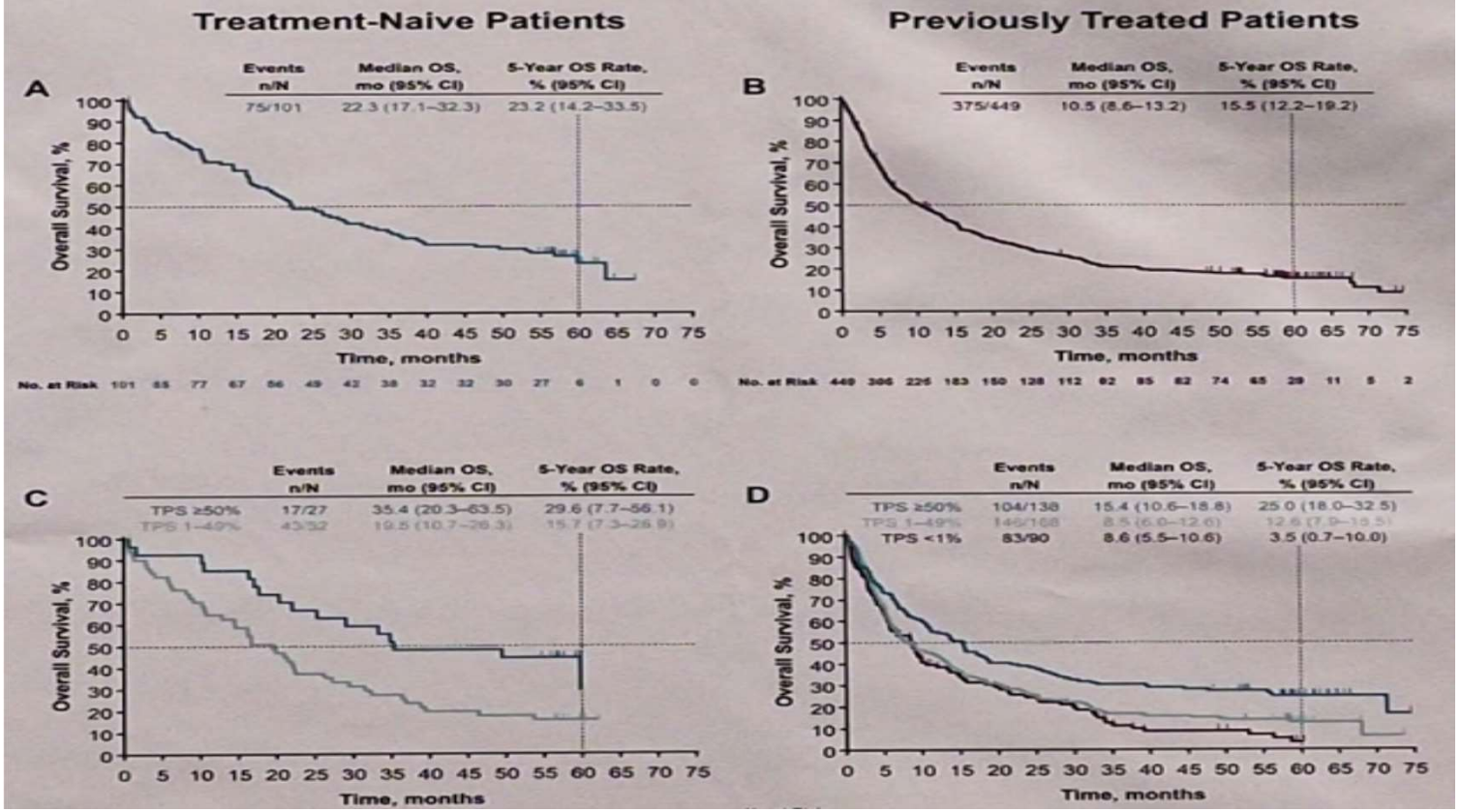
Figure 1. Kaplan-Meier Estimates of OS. (A) Treatment-Naive Patients. (B) Previously Treated Patients. (C) Treatment Naive Patients by PD-L1 TPS ≥50% and 1%–49%.[a] (D) Previously Treated Patients by PD-L1 TPS ≥50%, 1%–49%, and <1%.



Type of Immuno Resistance

Primary: Lack of initial response or clinical benefit to therapy

Secondary: Disease progression after an initial period of clinical benefit.

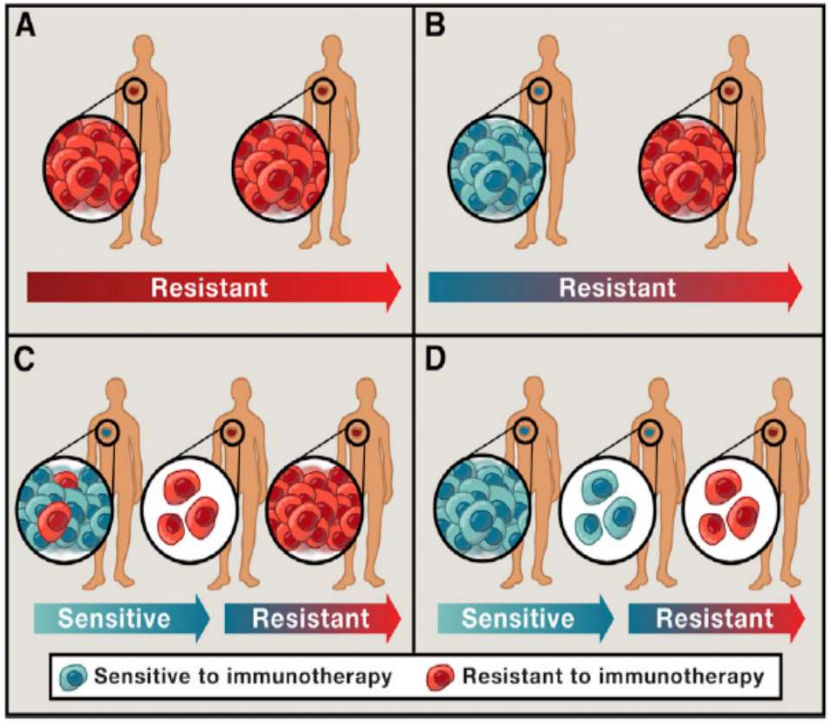


Table 2. Mechanisms of Primary and Adaptive Resistance to Immunotherapy

	Mechanism	Examples
tumor cell intrinsic	absence of antigenic proteins	low mutational burden lack of viral antigens lack of cancer-testis antigens overlapping surface proteins
	absence of antigen presentation	deletion in TAP deletion in B2M silenced HLA
	genetic T cell exclusion	MAPK oncogenic signaling stabilized b-catenin mesenchymal transcriptome oncogenic PD-L1 expression
	insensibility to T cells	mutations in interferon gamma pathway signaling
tumor cell extrinsic	absence of T cells	lack of T cells with tumor antigen-specific TCRs
	inhibitory immune checkpoints	VISTA, LAG-3, TIM-3
	immunosuppressive cells	TAMs, Tregs

Sharma P, et al. *Cell*, 2016

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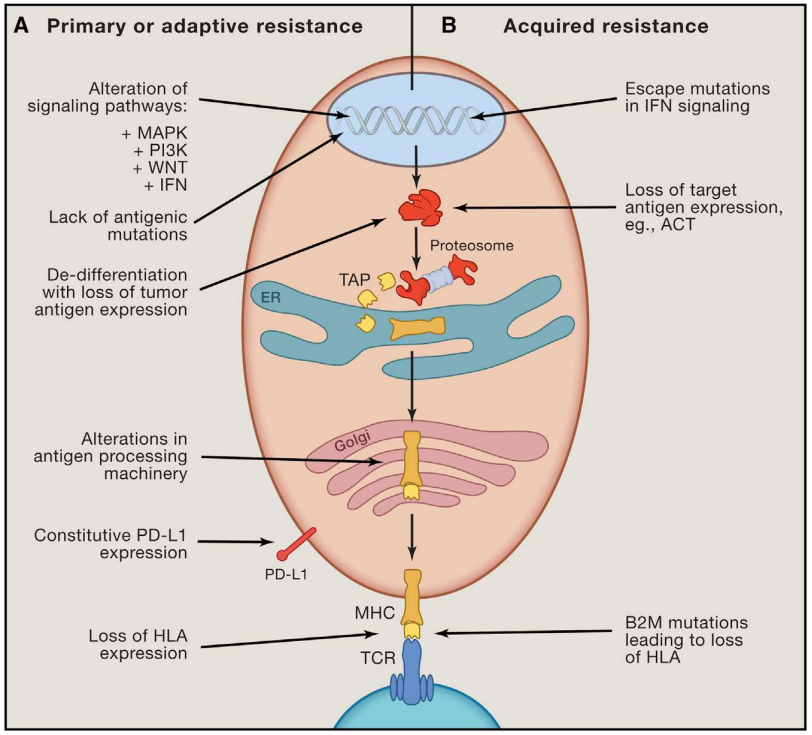
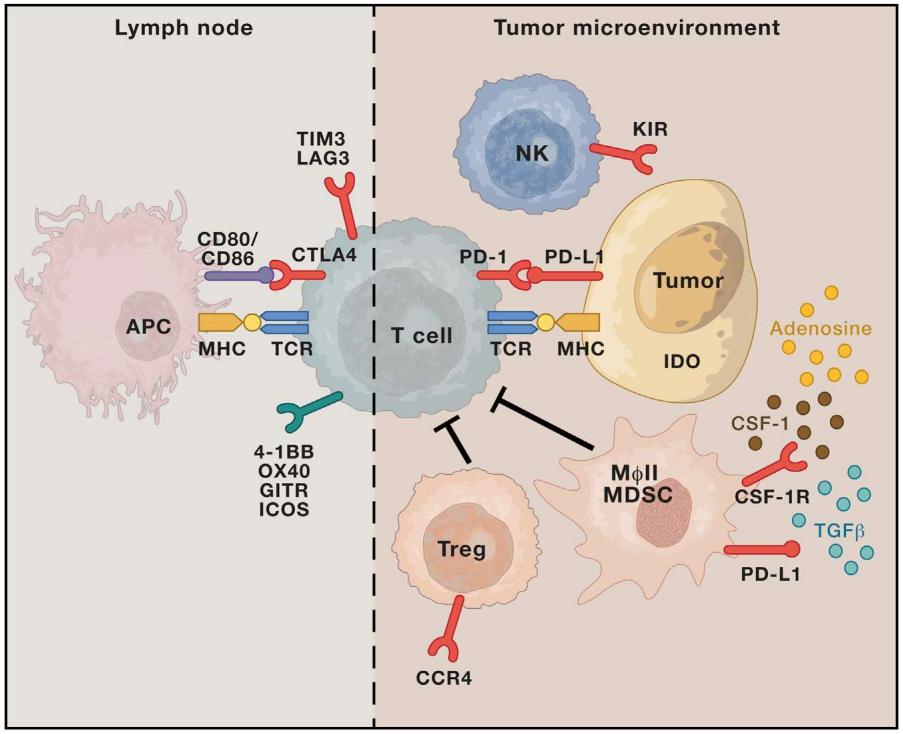
Mechanisms of Primary and Adaptive Resistance to Immunotherapy

Tumor Intrinsic Mechanisms



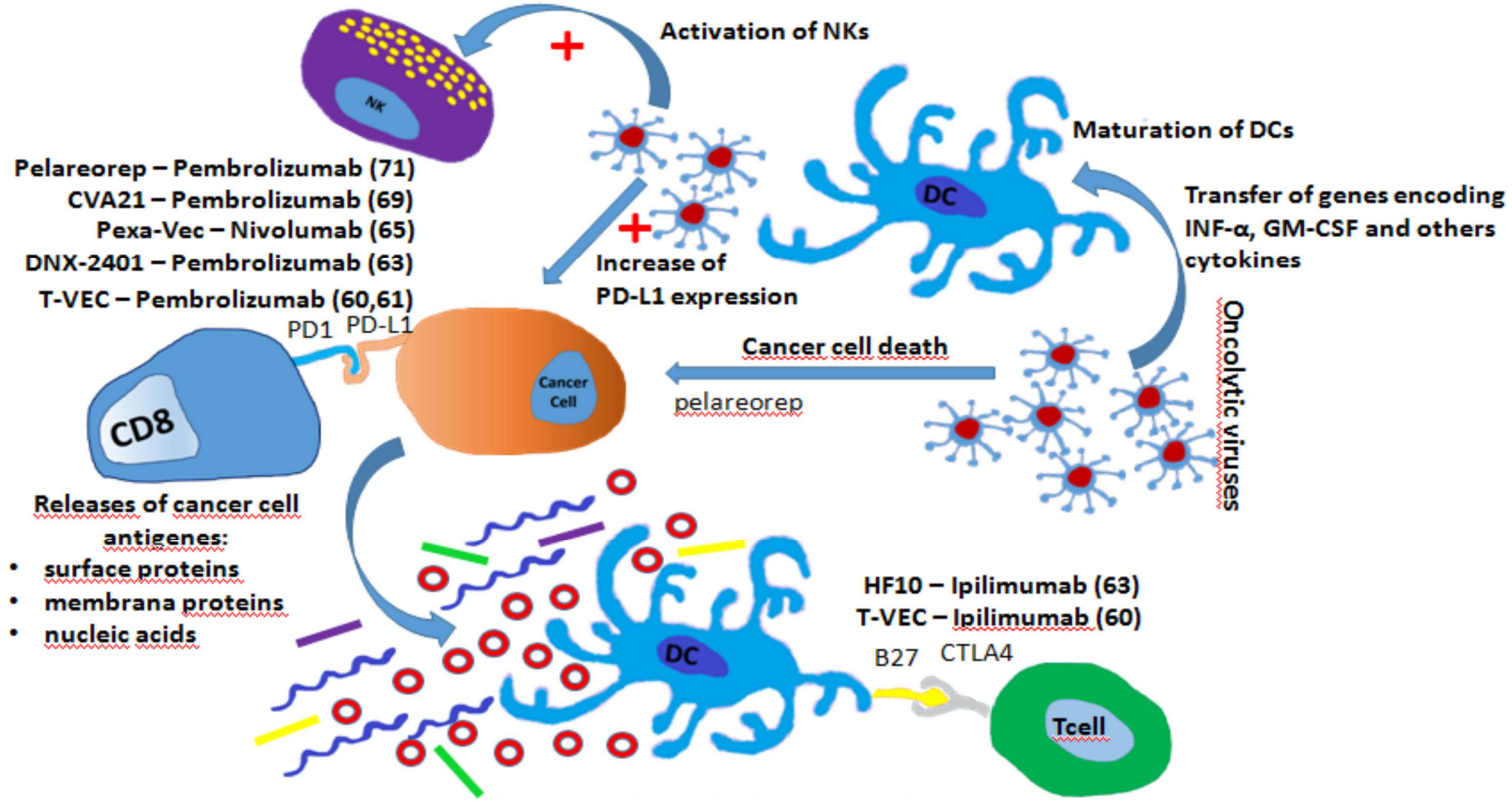
Tumor Extrinsic Mechanisms



Sharma P, et al. Cell 2017

Oncolytic viruses

Release of cancer cell antigens



Cancers (Basel). 2019 Apr 15;11(4)

New strategies specifically exploited in NSCLC
Cytokines

Infiltration of T cells into tumors

- M7824 (PD-L1 / TGFb trap)
- ALT-803 (Nivolumab / IL-15)
- NKT214 (Nivolumab or Pembro / IL-2)
- Pegilodecakin (PD-1 / IL-10)
- CEA-IL2

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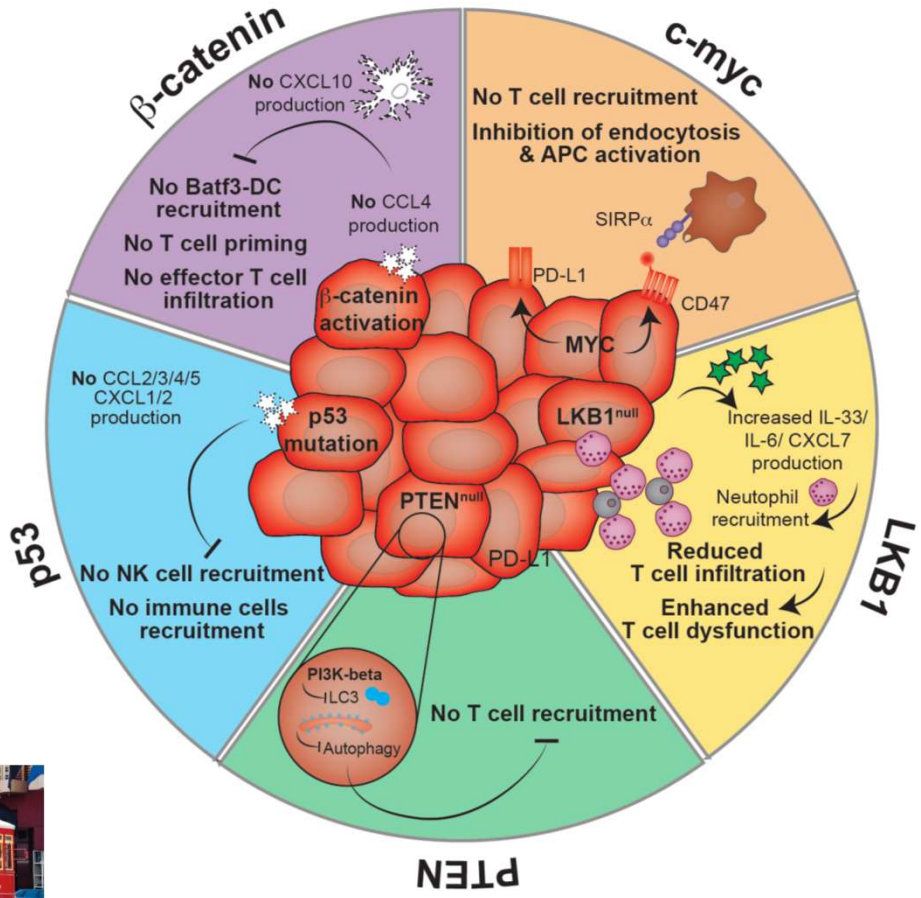
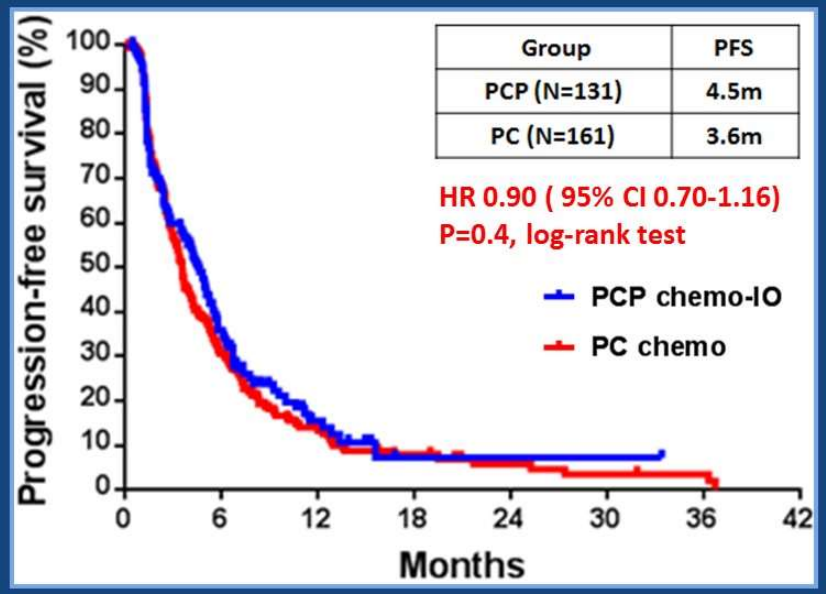
Others oncogenic pathways shown to be immune-evasive in mouse models



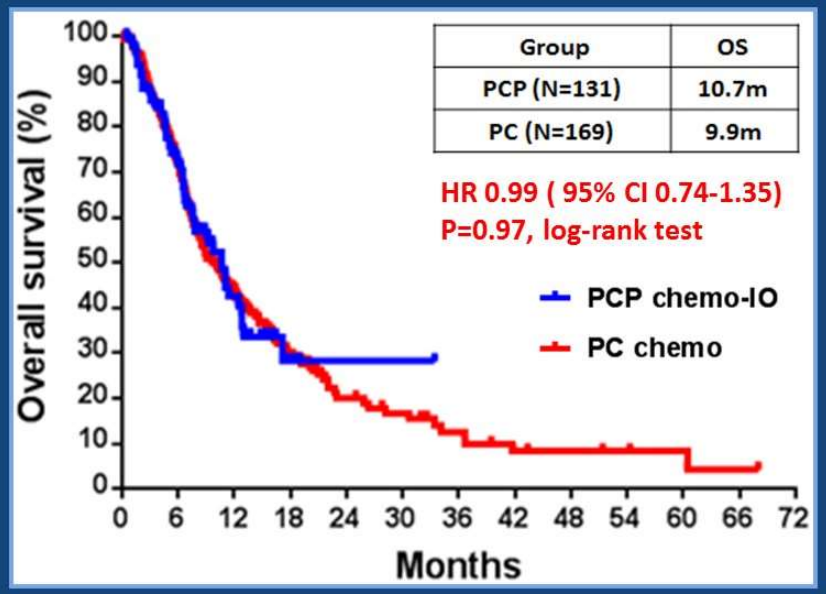
Nat Rev Cancer. 2018

Lack of benefit from addition of pembrolizumab to CP chemotherapy in *STK11* and/or *KEAP1*-mutant non-squamous NSCLC

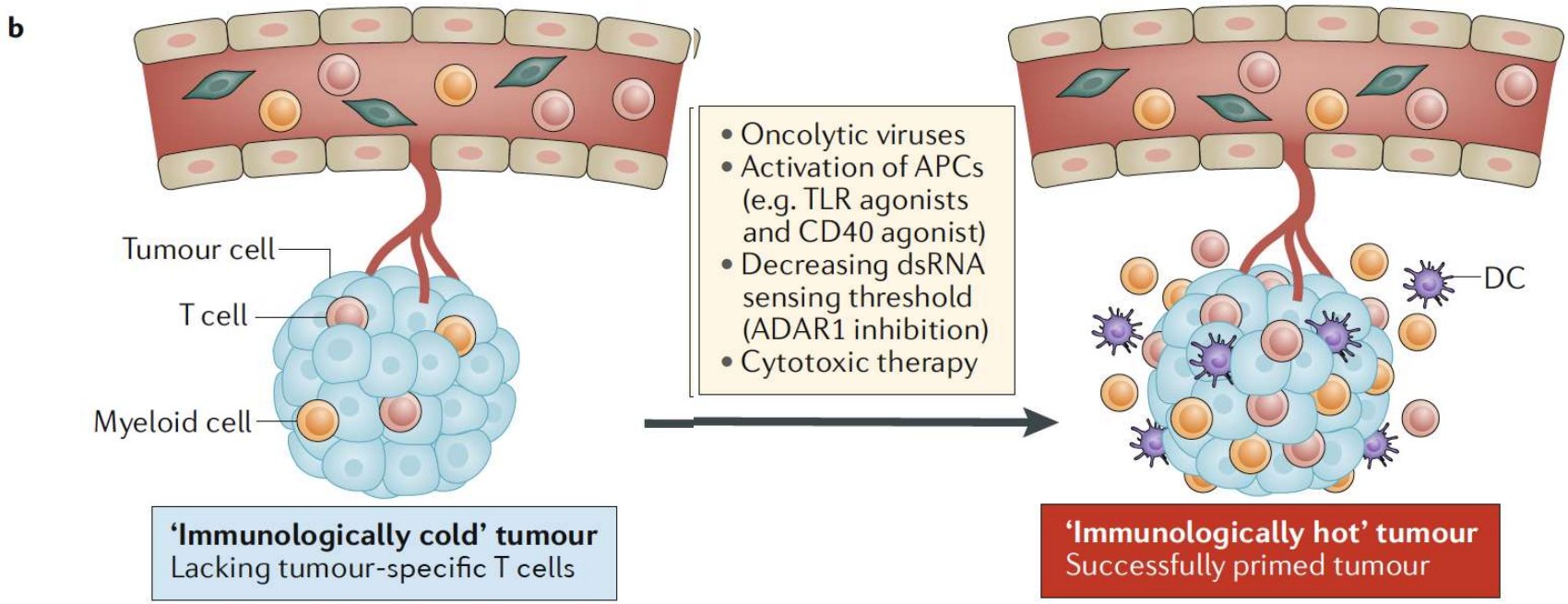
***STK11*^{MUT} and/or *KEAP1*^{MUT}**



***STK11*^{MUT} and/or *KEAP1*^{MUT}**



Immunologically cold tumour types lack pre- existing antitumour T- cell responses, rendering immune checkpoint blockade ineffective



Anusha Kalbasi & Antoni Ribas. Nature Reviews Immunology (2019)

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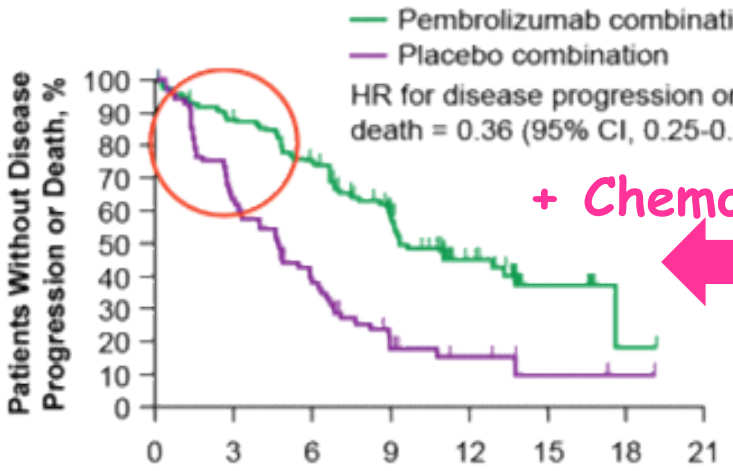
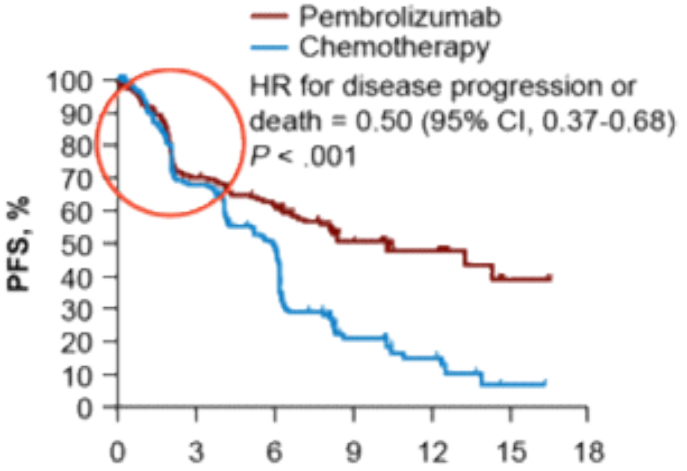
Chemotherapy enhance immunotherapy efficacy in PD-L1 strong positive



+ Chemotherapy



No. at Risk								
Pembrolizumab combination	132	112	95	60	23	7	1	0
Placebo combination	70	43	26	11	5	2	1	0

No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

Gandhi NEJM 208; Reck NEJM 2018

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Evolving Treatments in Immunotherapy and Targeted Therapies

The addition of chemotherapy improves ORR and the % of PD as best response is reduced

Study	PD-L1 status	ORR	PD as best response
KN024	50%+	45%	22%
KN042	1%+	27%	21%
CM026	1%	26%	27%
KN189	ITT	48%	9%
KN407	ITT	58%	7%
IMpower130	ITT	49%	11%
IMpower131	ITT	49%	7%

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Immune checkpoints | **Co-stimulatory targets**

Priming and Activation

Target	Molecule	Antibody isotype	Company	Stage
CD27	Varlilumab (CDX-1127)	IgG1	Celldex	Phase I/II
CD40	CDX-1140	IgG2	Celldex	Phase I
	SEA-CD40	Non-fucosylated IgG1	Seattle Genetics	Phase I
	RO7009789	IgG2	Roche	Phase I/II
	JNJ-64457107 (ADC1013)	IgG1	Janssen	Phase I
	APX-005M	IgG1	Apexigen	Phase I
	Chi Lob 7/4	Mouse/human chimaera IgG1	BioNTech RNA Pharmaceuticals GmbH, University of Southampton	Phase I
GITR	TRX-518	Aglycosyl IgG1	Leap Therapeutics	Phase I
	MK-4166	IgG1	Merck & Co.	Phase I
	MK-1248	IgG4	Merck & Co.	Phase I
	GWN-323	IgG1	Novartis	Phase I
	INCAGN01876	IgG1	Incyte	Phase I/II
	BMS-986156	IgG1	Bristol-Myers Squibb	Phase I/II
	AMG-228	IgG1	Amgen	Phase I
OX40	Tavolimab (MEDI0562)	IgG1	AstraZeneca	Phase I
	PF-04518600	IgG2	Pfizer	Phase II
	BMS-986178	IgG1	Bristol-Myers Squibb	Phase II
	MOXR-0916	IgG1	Roche	Discontinued; phase at termination: phase II clinical
	GSK-3174998	IgG1	GlaxoSmithKline	Phase I
	INCAGN01949	IgG1	Incyte	Phase II
4-1BB	Utomilumab (PF-05082566)	IgG2	Pfizer	Phase II
	Urelumab (BMS-663513)	IgG4	Bristol-Myers Squibb	Phase II
ICOS	GSK-3359609	IgG4	GlaxoSmithKline	Phase I
	JTX-2011	IgG1	Jounce Therapeutics	Phase I
CD28	Theralizumab (TAB-08)	IgG4	TheraMAB	Phase I/II

GITR, glucocorticoid-induced tumour necrosis factor receptor-related protein; ICOS, inducible T cell co-stimulator; IgG, immunoglobulin G.

Mayes, Nat Rev Drug Discovery 2018

Evolving Treatments in Immunotherapy and Targeted Therapies

Overcoming resistance in IO naïve: combination of novel agent to immunotherapy in 1st line NSCLC

Study phase	Therapy	Target or pathway	Population	Primary endpoint	NCT number
III	Pembro +/- Lenvatinib	VEGFR	PD-L1 1%+	PFS, OS	NCT03829332
rII	Pembro +/- Pegilodecakin	IL-10	PD-L1 50%+	ORR	NCT03382899
II	Pembro + Itacitinib	JAK1	PD-L1 50%+	Response rate at 12w, toxicity	NCT03425006
rII	Pembro +/- Epacadostat	IDO	PD-L1 50%+	ORR	NCT03322540
I/ II	Pembro + Decitabine + THU	DNMT	NSCLC	MTD, ORR	NCT03233724
III	Pembro + Ipilimumab	CTLA-4	NSCLC	PFS, OS	NCT03302234
I	Pembro or Atezo + NKTR-214	IL-2R	NSCLC	TEAE, RP2D	NCT04009681
I/II	NKTR-214 + Nivo NKTR-214 + Nivo + Ipi	IL-2	NSCLC	Safety, ORR	NCT02983045
II	LN-145 +/- durva	TILs	NSCLC	ORR, safety	NCT03419559

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Evolving Treatments in Immunotherapy and Targeted Therapies

Overcoming resistance in IO naïve: combination of novel agent and chemoimmunotherapy in 1st line NSCLC

Study phase	Therapy	Target or pathway	Population	Primary endpoint	NCT number
III	Pemetrexed + Platinum + Pembrolizumab +/- Lenvatinib	VEGFR	non-Sq	toxicity, PFS, OS	NCT03829319
III	Platinum doublet + Pembrolizumab +/- canakinumab	IL-1b	NSCLC	toxicity, PFS, OS	NCT03631199
III	Pemetrexed + Platinum + Pembrolizumab +/- maint olaparib	PARP	non Sq	PFS, OS	NCT03976323
rII	pembrolizumab + platinum-based chemotherapy +/- Epacadostat	IDO	NSCLC	ORR	NCT03322566
I/II	IO102 + pembro +/- chemo	IDO	NSCLC	Toxicity, ORR	NCT03562871
I	Pembro+ Carbo+ pemetrexed+ NEO-PV-01	Vaccine	NSCLC	Toxicity	NCT03380871

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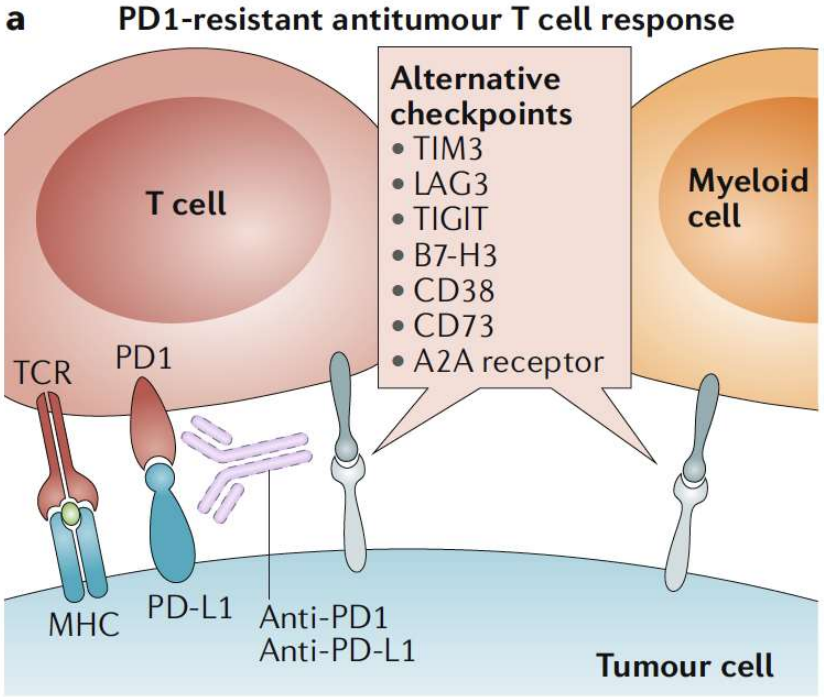
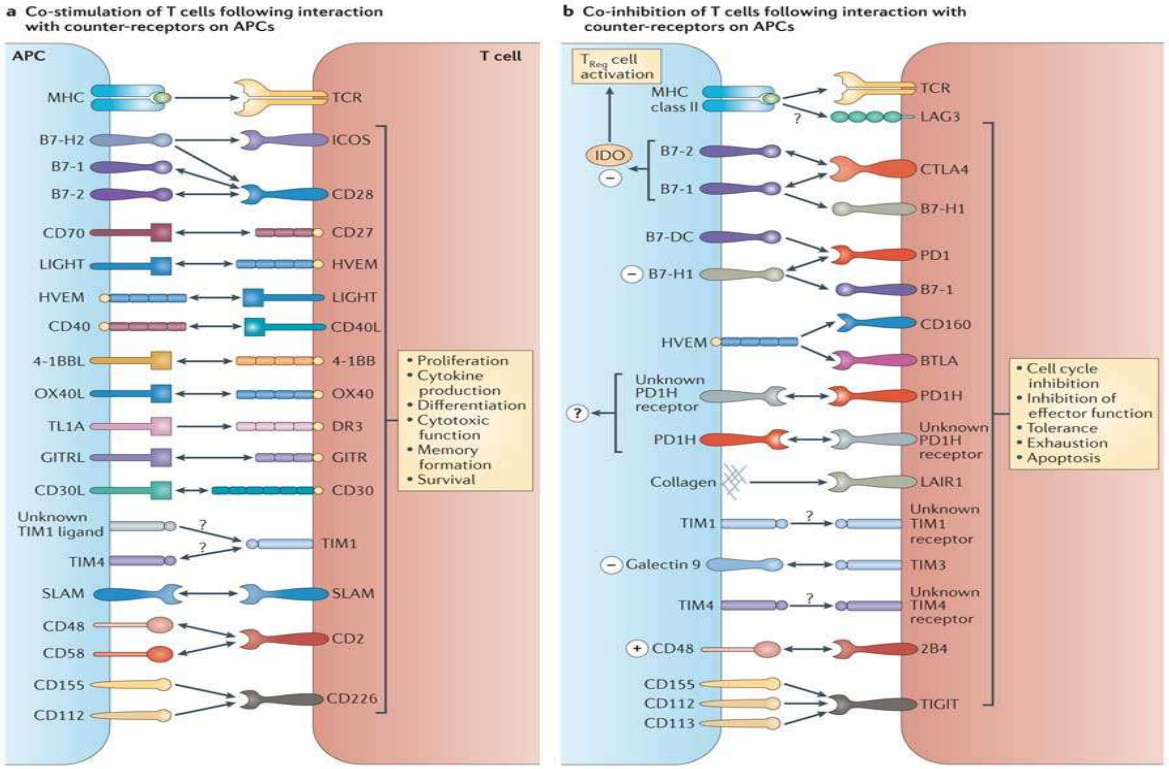
Alternative immune checkpoint molecules expressed on tumour cells or myeloid cells in the tumour microenvironment, prevent effective antitumour immunity





Anusha Kalbasi & Antoni Ribas. Nature Reviews Immunology (2019)

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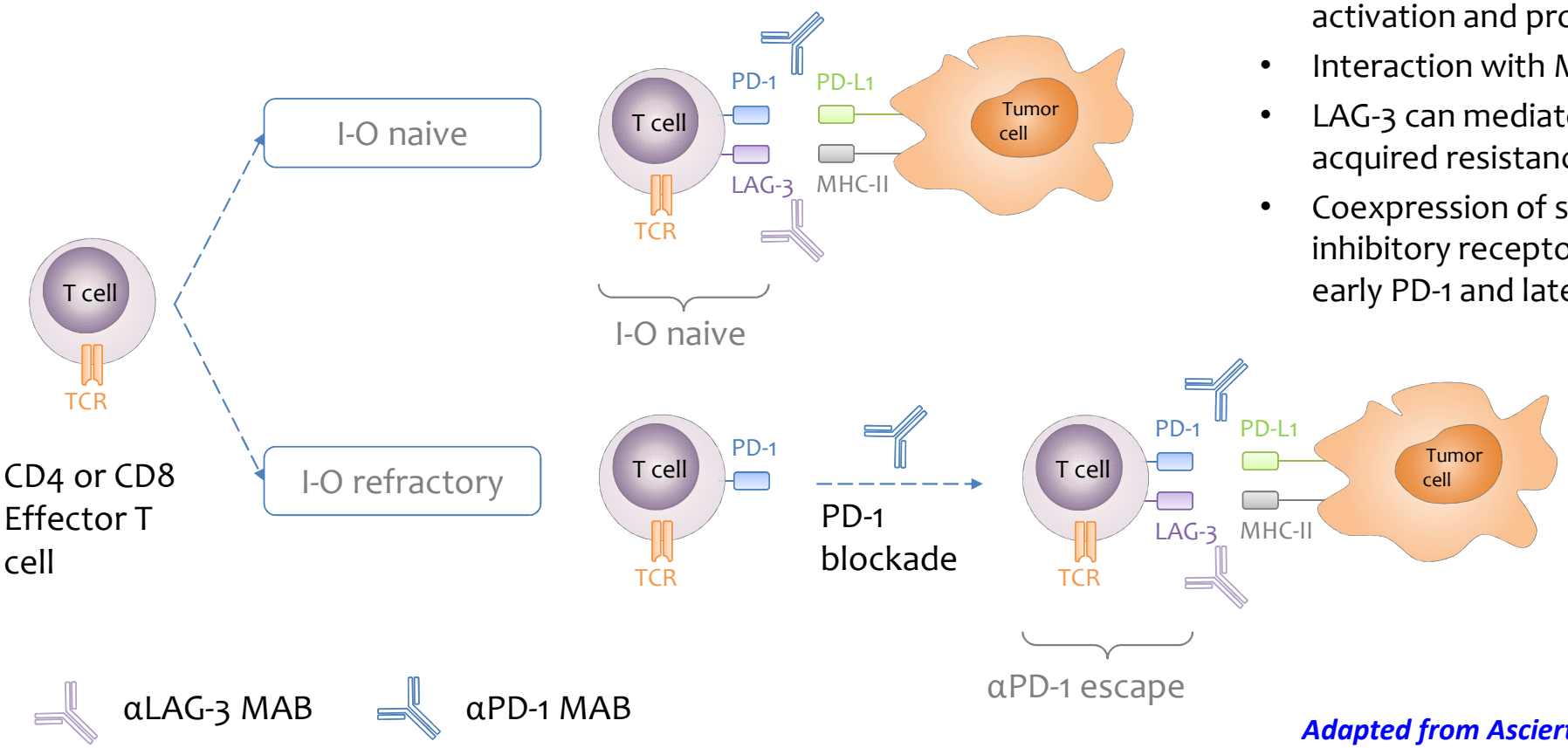
Checkpoints
LAG-3 and T cell exhaustion: clinical scenario



- Negatively regulates T-cell activation and proliferation
- Interaction with MHC class II
- LAG-3 can mediate primary or acquired resistance
- Coexpression of several inhibitory receptors with early PD-1 and late LAG-3

Adapted from Ascierto, ESMO 2017

Ongoing Trials with Anti-LAG3 Antibodies

Company	Drug	Study phase	Cancer type	Combination
BMS	relatlimab	Phase 1,2, and 3 Phase 1/2 NSCLC NCT01968109; NCT02750514	Solid tumors Haematological malignancies	Nivolumab Phade 1/2 CA224-048 ipi+nivo+relatlimab 1L NCT03459222
Novartis	LAG525	Phase 1, 2	Solid tumors Haematological malignancies	spartalizumab
MSD	MK4280	Phase 1	Solid tumors	pembrolizumab
Regeneron/Sanofi	REGN3767	Phase 1	Solid tumors	cemiplimab (anti-PD-1)
Macrogenics	MGD013	Phase 1	Solid tumors Haematological malignancies	-
Tesaro	TSR-033	Phase 1	Solid tumors	Anti-PD-1
Boehringer/ Ingelheim - Sarah Cannon Research Institute	BI754111	preclinical	-	BI754091 (anti-PD-1)
Agenus/Incyte	Not available	preclinical	-	-
PRIMA	IMP321	Phase 1,2	Solid tumors	pembrolizumab, chemotherapy

Ongoing trials of inhibitors of the adenosine pathway

Target	Drug	Company	Cinical trial number	Study phase	Cancer type	Combination partner
CD73	oleclumab	MedImmune	NCT02503774	I	Solid tumors	Anti-PDL1 (MEDI4736; durvalumab
	BMS-986179	BMS	NCT02754141	I and IIa	Solid tumors	Nivolumab
A2AR	CPI-444	Corvus Pharmaceuticals	NCT02655822	I and Ib	• NSCLC • Malignant melanoma • Renal cell carcinoma • TNBC • Colorectactal cancer • Bladder cancer	Anti-PDL1 (MPDL3280A; atezolizumab)
	PBF-509	Palobiofarma	NCT02403193	I and Ib	NSCLC	Anti-PD1 (PDR001)
	AZD4635	AstraZeneca	NCT02740985	I	Advanced cancers	Anti-PDL1 (MEDI4736; durvalumab)
combo	oleclumab	MedImmune	NCT03381274	I/II	NSCLC EGFR M+	Osimertinib Or AZD 4635

Evolving Treatments in Immunotherapy and Targeted Therapies

Conclusions

- Although no perfect, in the absence of a driver mutation, PD-L1 is the best predictor biomarker for IO.
- Based on the PD-L1 expression, patient may receive IO alone or combo chemo/IO.
- Nivo + Ipi also improves OS in patients with PD-L1 $\geq$ 1%. (CM-227 met its primary endpoint).
- Nab-paclitaxel is another alternative for non-Squamous histology based on ImPower-130 (+ PFS and OS regardless of PD-L1 expression).
- Although not presented here, atezolizumab as a single agent showed OS advantage over chemotherapy for TC3/IC3 WT (ImPower-110).
- We need more trials to rescue patients from refractory IO or IO resistance; it is crucial to understand primary vs secondary mechanisms of resistance.

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