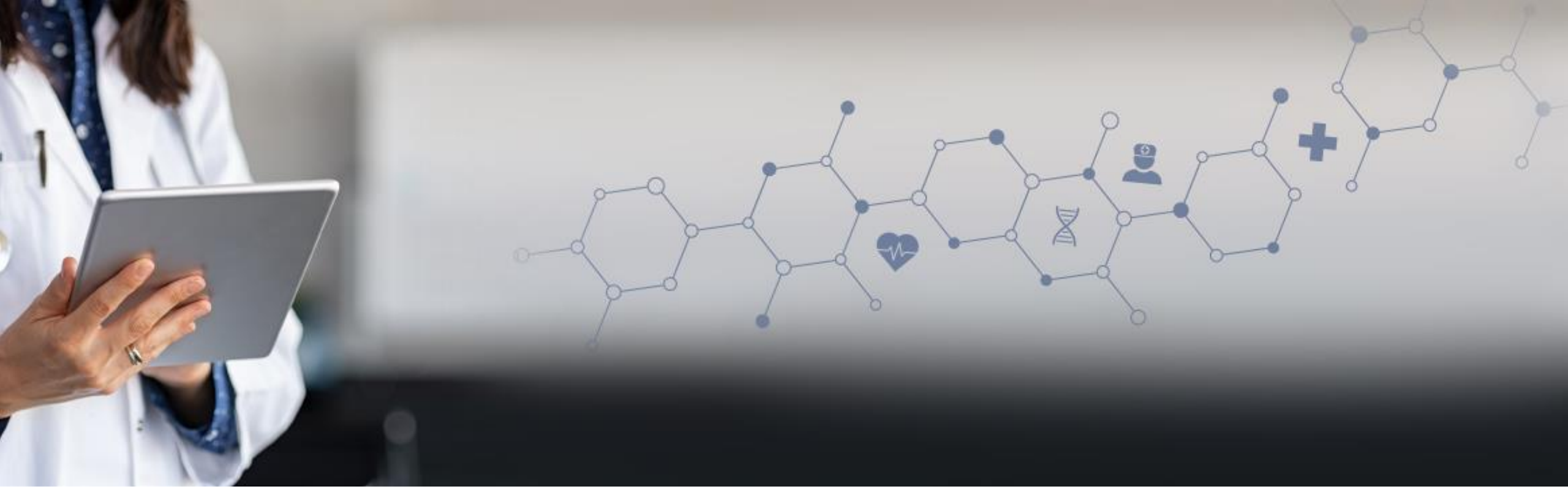

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Single Agent Activity of Anti-LAG3 Antibody

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NASEM-National Cancer Policy Forum Workshop, Nov 14th, 2022

Conflict of Interest Disclosure

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- Bristol Myers-Squibb
- Novartis
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- GlaxoSmithKline
- EMD Serono
- Eisai
- Dragonfly Therapeutics
- RAPT Therapeutics

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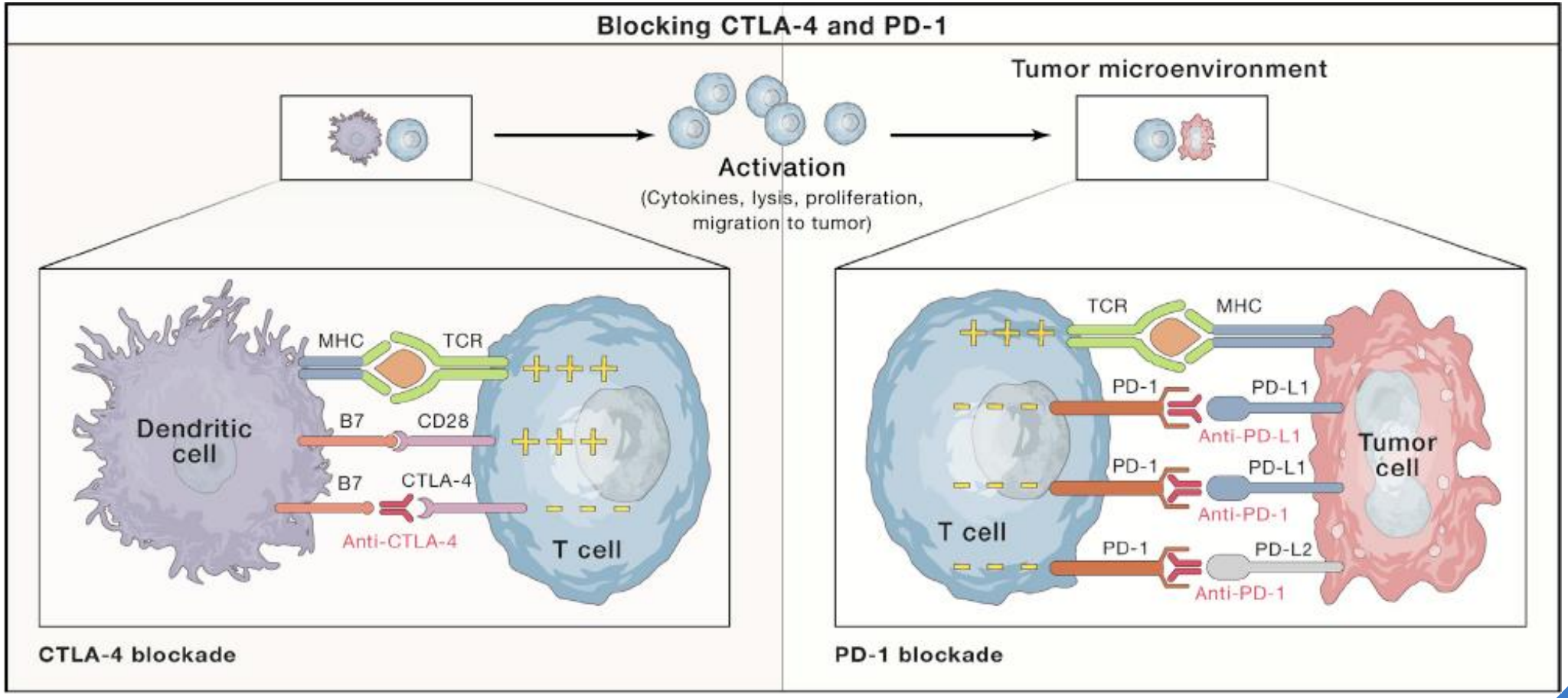
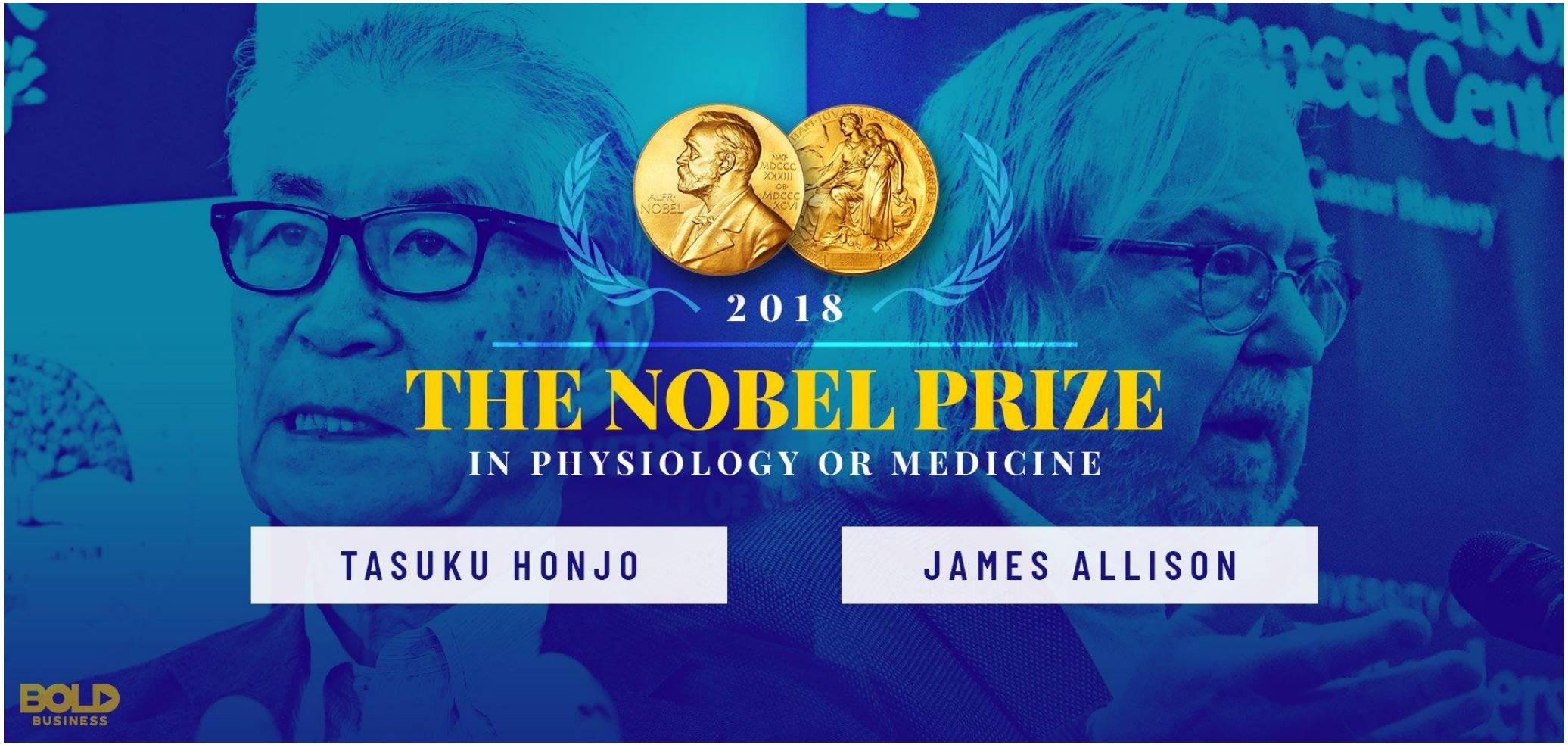
- Bristol Myers-Squibb
- Genentech
- Novartis
- Merck
- Boxer Capital
- Karyopharm
- Iovance
- Eisai
- Jazz Pharmaceuticals
- Medicenna

CTLA-4 and PD-1



Wolchok, J. *Cell, 2018*


2018
THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE
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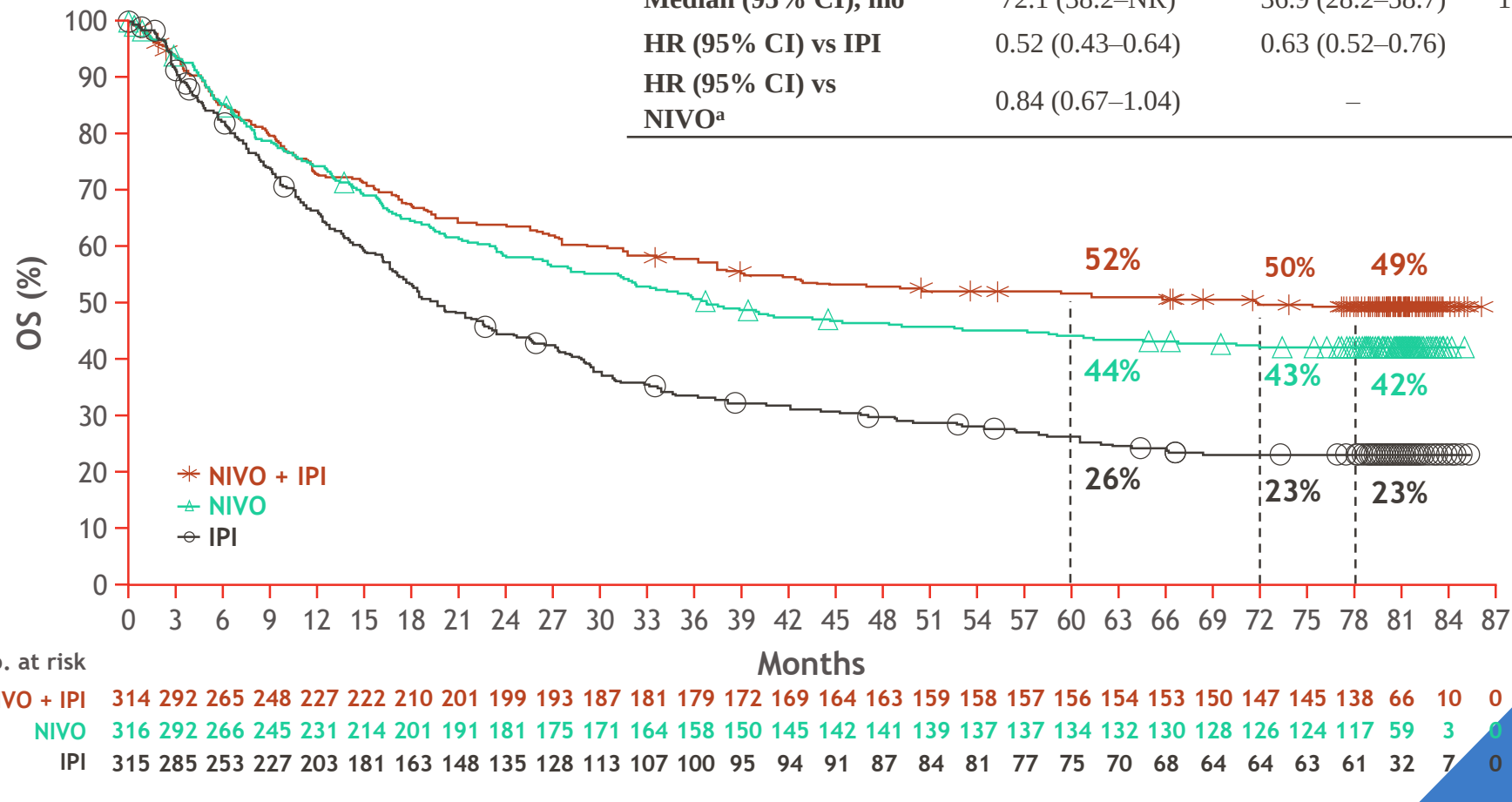
BOLD
BUSINESS

Single Agent or Combination Checkpoint Blockade

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.43–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.84 (0.67–1.04)	–	–



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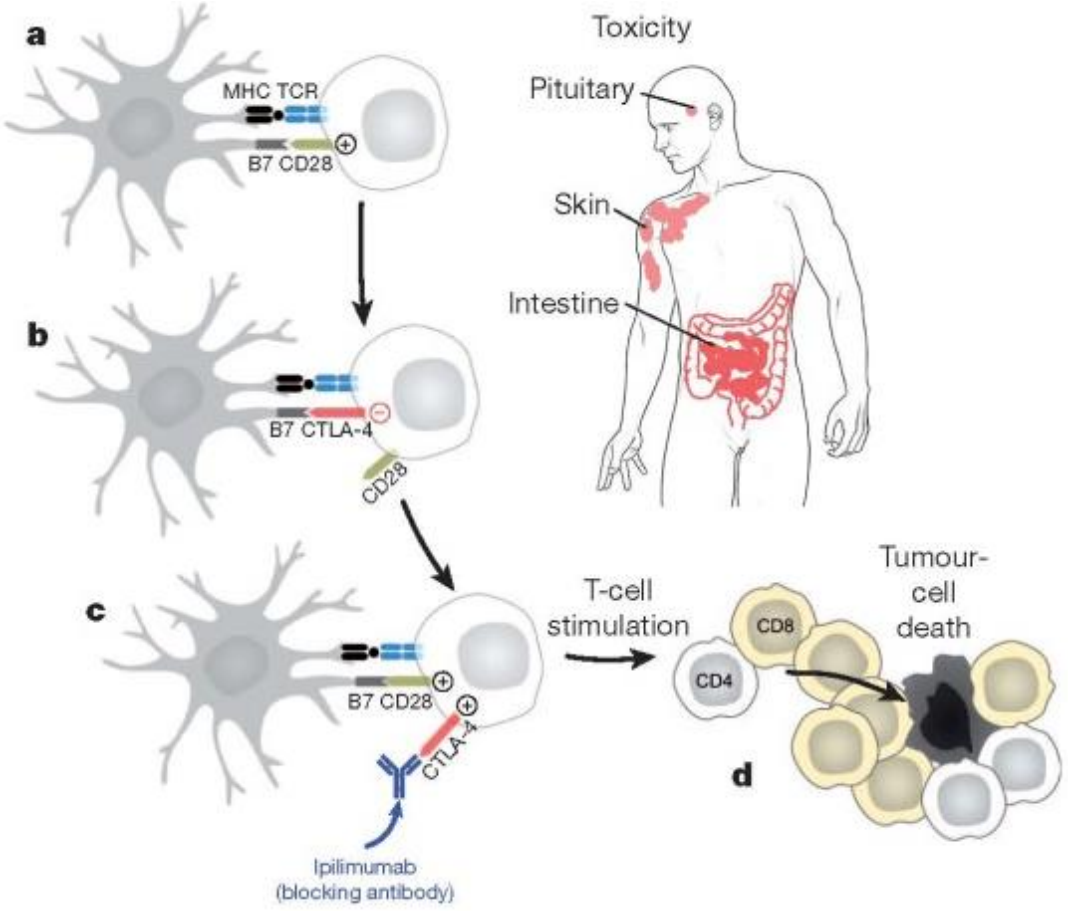
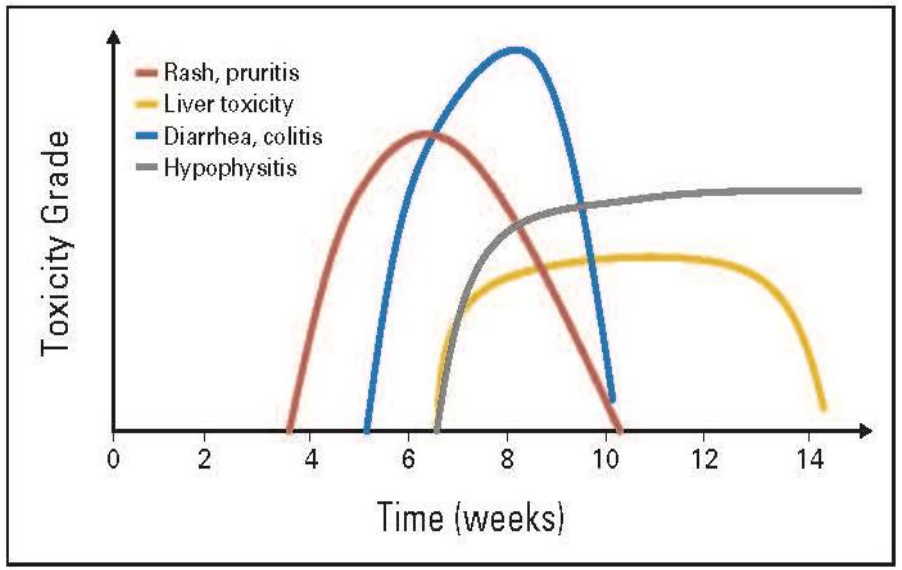
[a]Descriptive analysis.

Wolchok, J. *ASCO Annual Meeting, 2021*

Toxicity: organs, incidence, patterns



Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	95.8	**59.1**	86.3	**22.4**	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	**30.4**	12.5	**8.0**	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	



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Weber, et al., *The Oncologist*, *2016*.

Combination checkpoint blockade

- ✓ **No improved overall survival over single agent anti-PD1**
- ✓ **Improved activity in several settings: brain metastases, neo-adjuvant, rate melanoma subtypes (mucosal, acral, uveal).**
- ✓ **Role in other malignancies:**
  - ➢ NSCLC,
  - ➢ RCC,
  - ➢ MSI-H CRC
  - ➢ druvalumab+tremelimumab in HCC, etc..

- ✓ **At the cost of <u>increased toxicity</u>**

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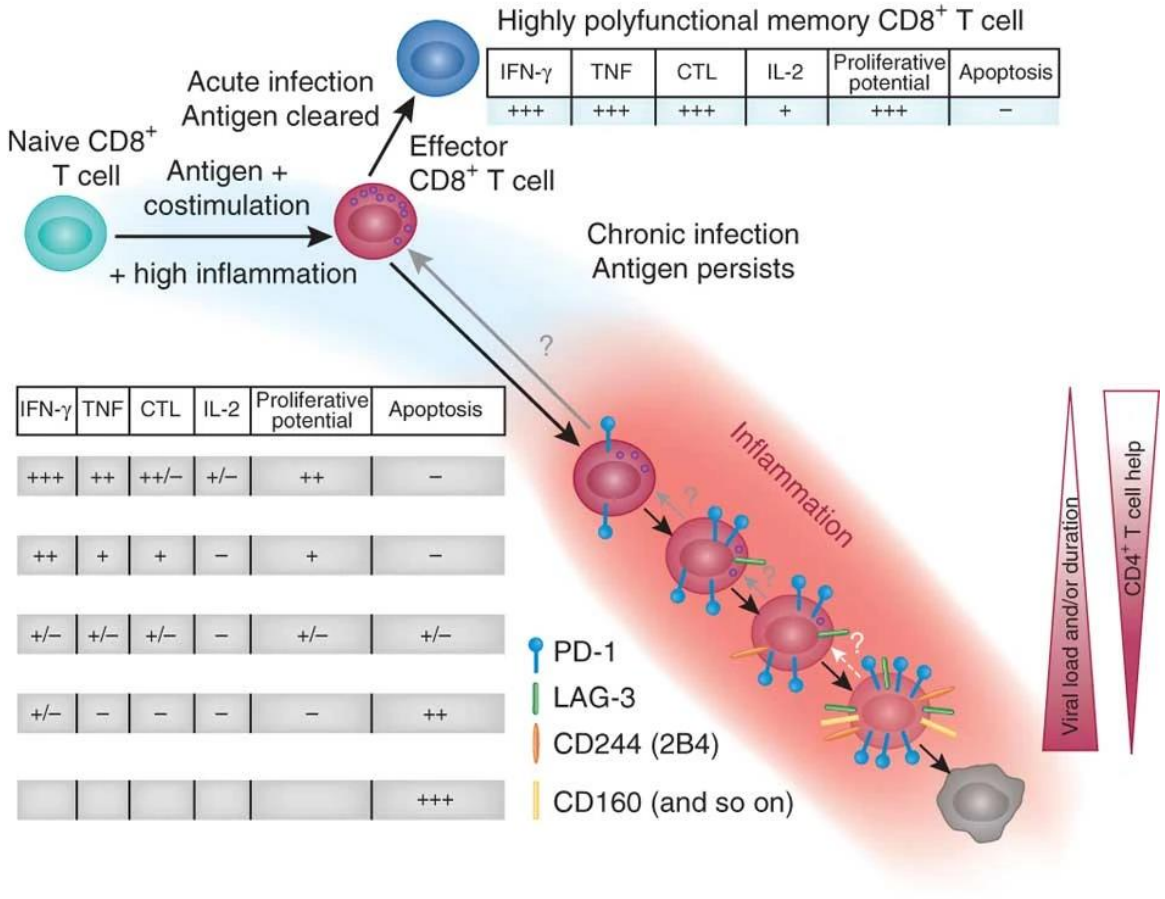
LAG3 a marker of T cell exhaustion



- ✓ **With chronic antigen stimulation, T cells progressively co-express inhibitory checkpoints**
- ✓ **Expressed on CD4+ and CD8+ T cells**
- ✓ **Also expressed on B cells, NK cells, T_{regs} and pDCs**

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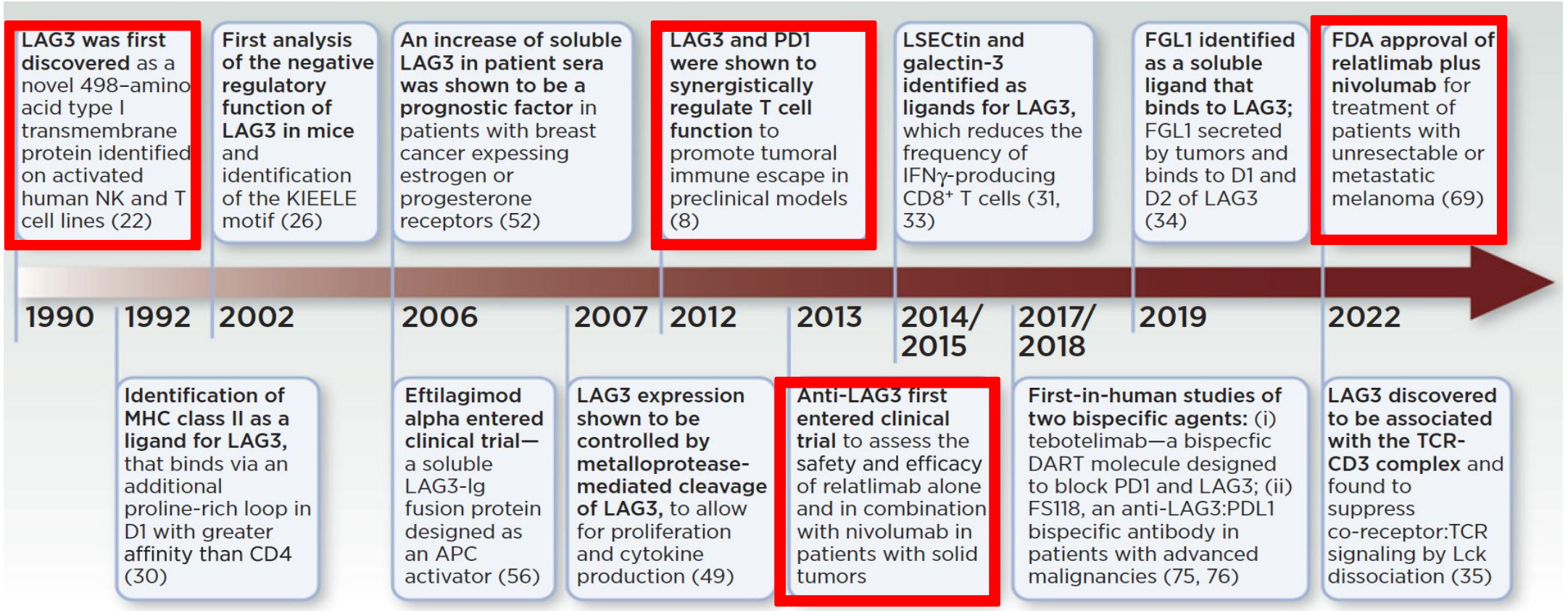
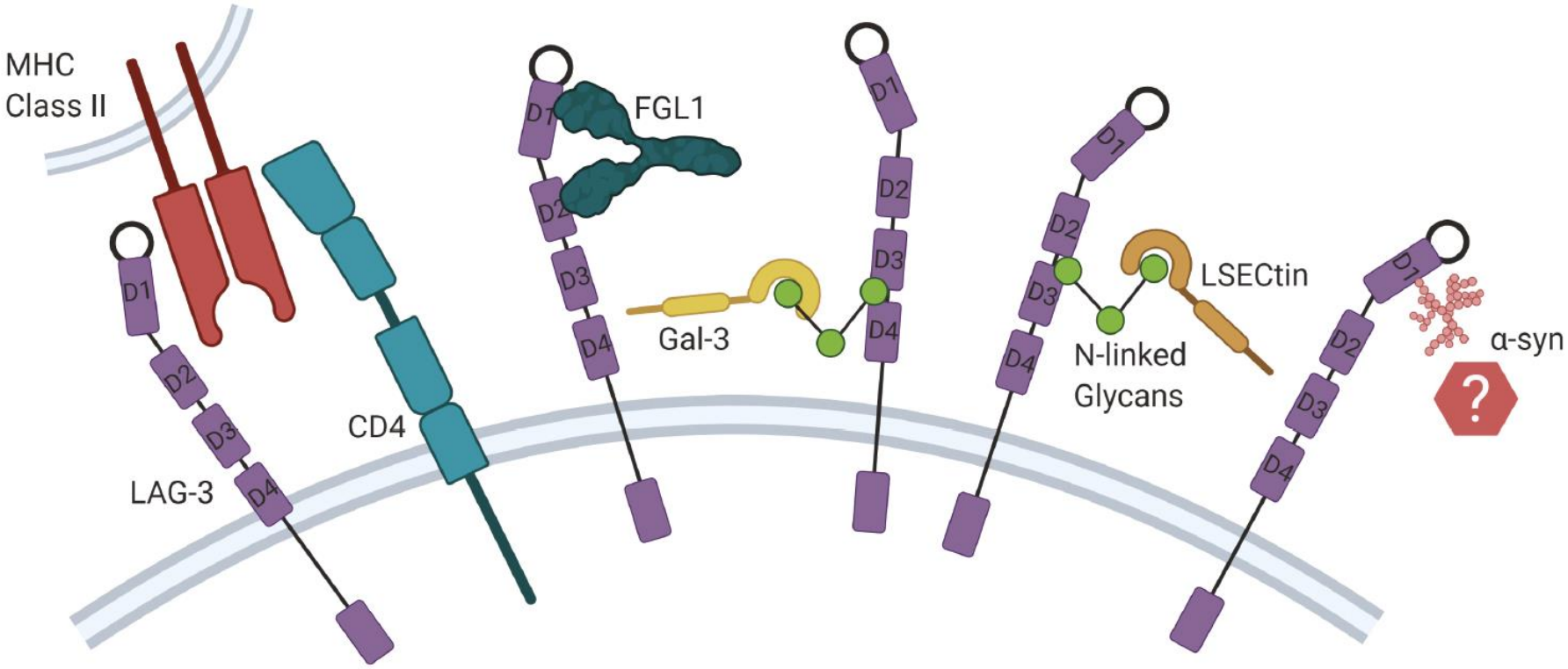
Wherry, EJ. *Nat Immunol. 2011*

Milestones in LAG3 Blockade



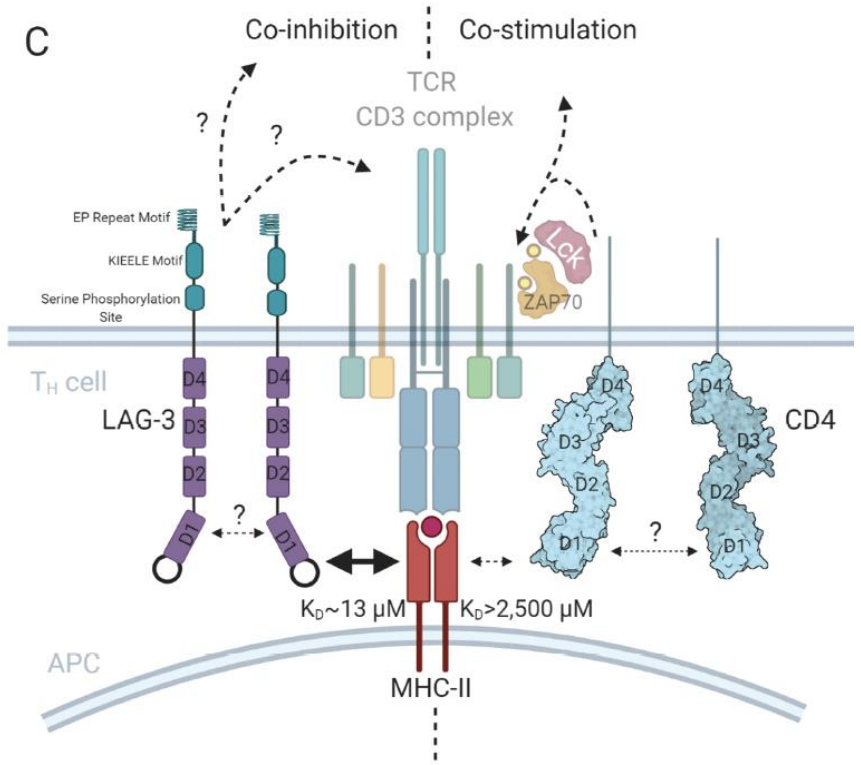
Andrews, et al. CCR 2022

LAG3 ligand, MHC Class II?



Burnell, et al. *Immunother Adv 2022.*
Wang, et al. *Cell 2019.*

LAG3 intracellular signaling



- ✓ **LAG3 dimerization required for optimal MHCII binding**
- ✓ **No ITIM & unique intracellular KIEELE motif**
- ✓ **Role of EP Repeat & Serine phosphorylation site FxxL more relevant**
- ✓ **Co-localization with TCR/CD3 complex**
- ✓ **LAG-3 activation leads to decreased ZAP70 phosphorylation**
- ✓ **<u>LAG-3 modulates TCR signaling</u>**

Workman, et al., *J Immunol 2003*.
Workman, et al., *J Immunol 2005*.
Burnell, et al., *Immunother Adv 2022*.

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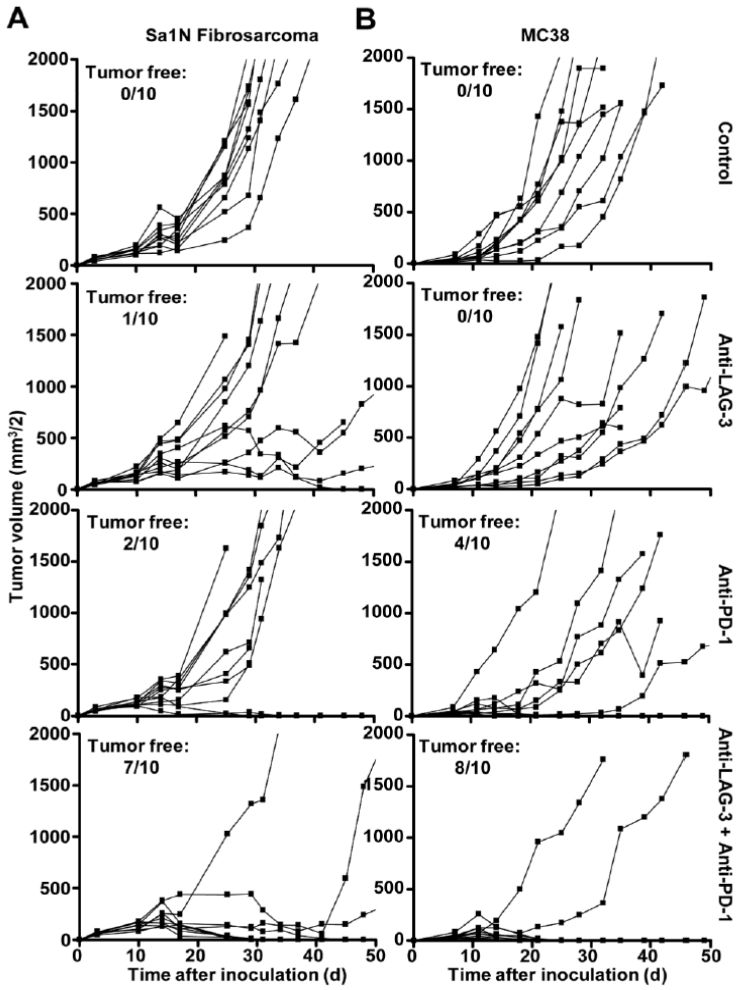
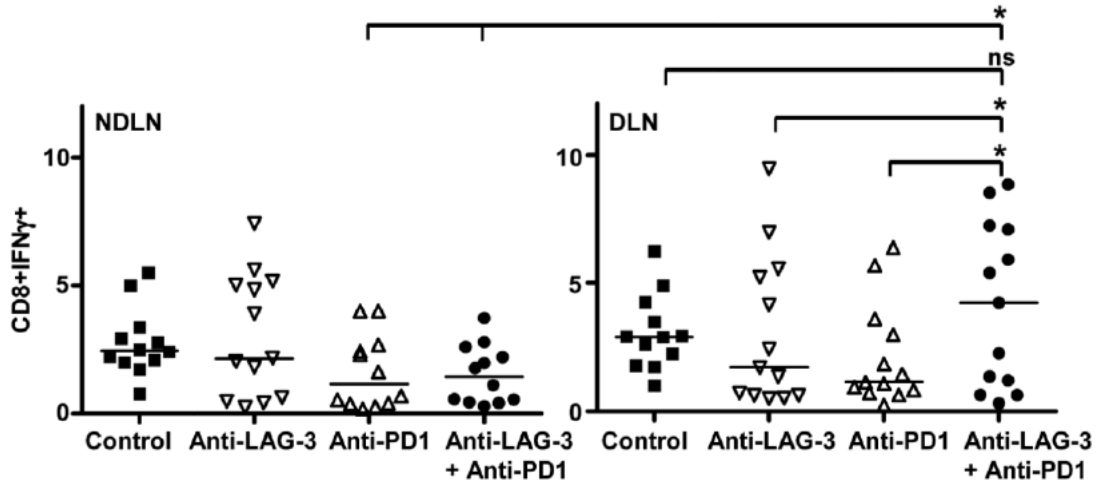
Anti-PD1/LAG3 Combo in MC38, B16 models





- ✓ **Single agent Anti-LAG3 relatlimab has little anti-tumor activity or T cell potentiation**
- ✓ **Combination Anti-LAG3 + Anti-PD1 synergistic with impressive tumor control correlative with increased CD8+ T cell activity**

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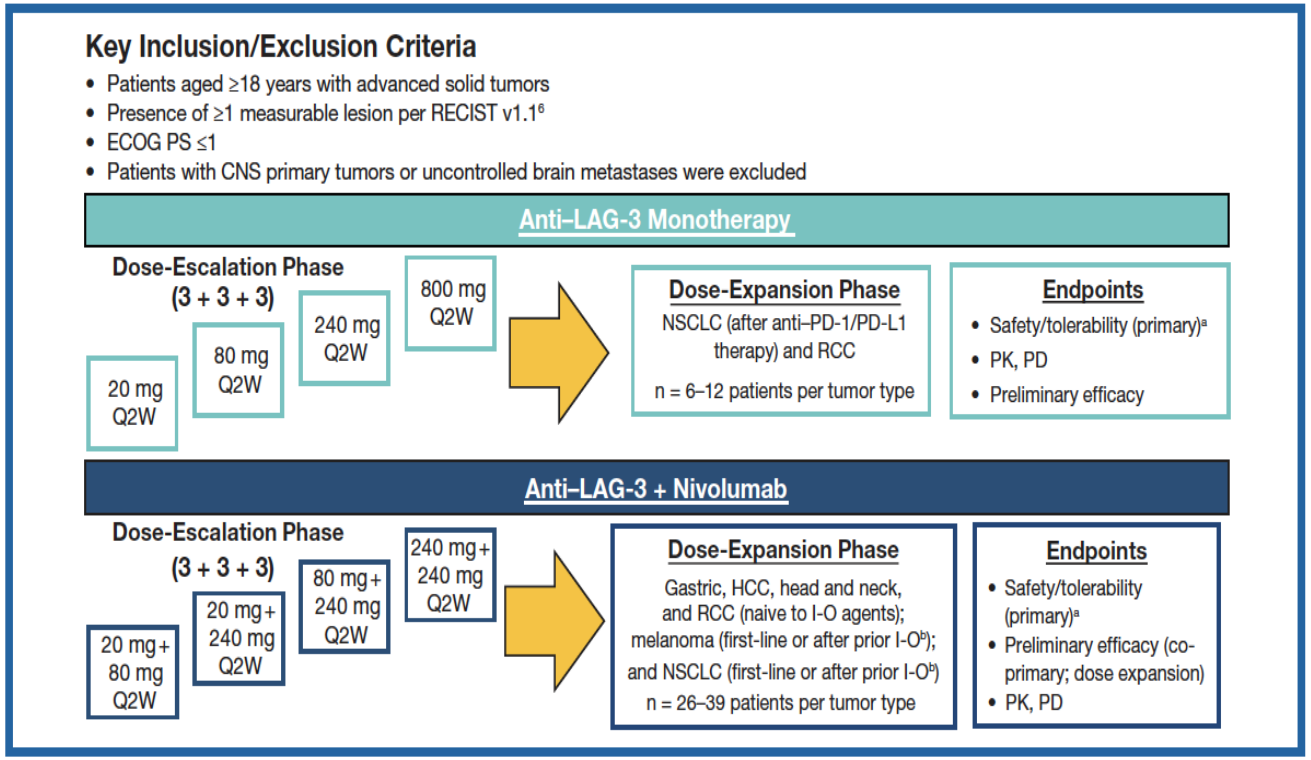
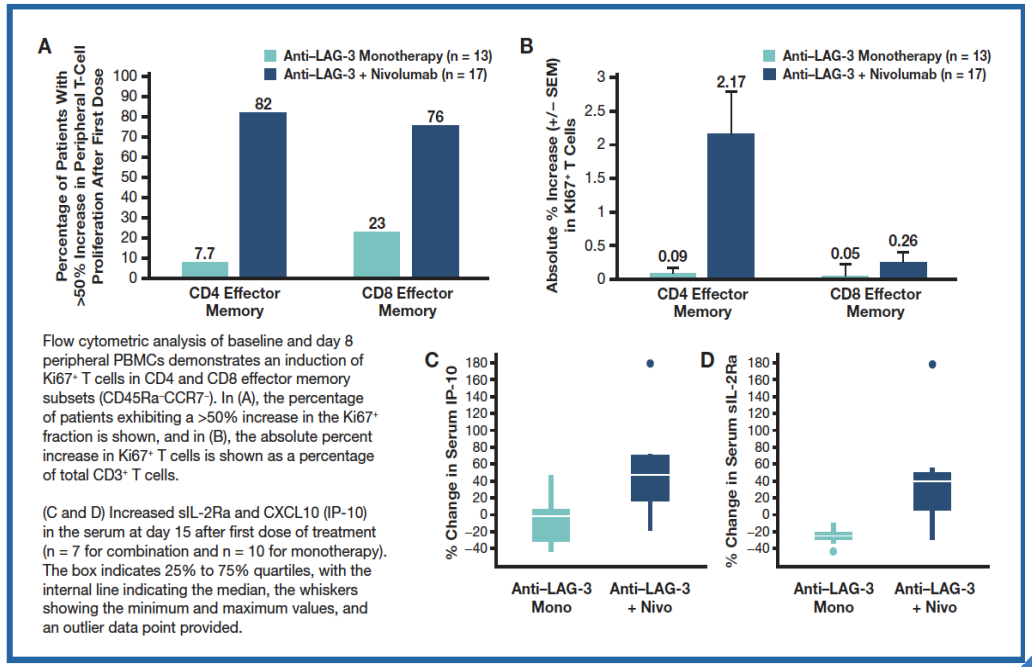
Woo, SR et al, *Cancer Research 2012*.

RELATIVITY-020: Monotherapy vs combo

Figure 2. Study Design for CA224020 (solid tumors)





- ✓ **No activity for Single agent Relatlimab in PD-1 refractory pts**
- ✓ **Pharmacodynamic effects also indicating combo carries the impact**

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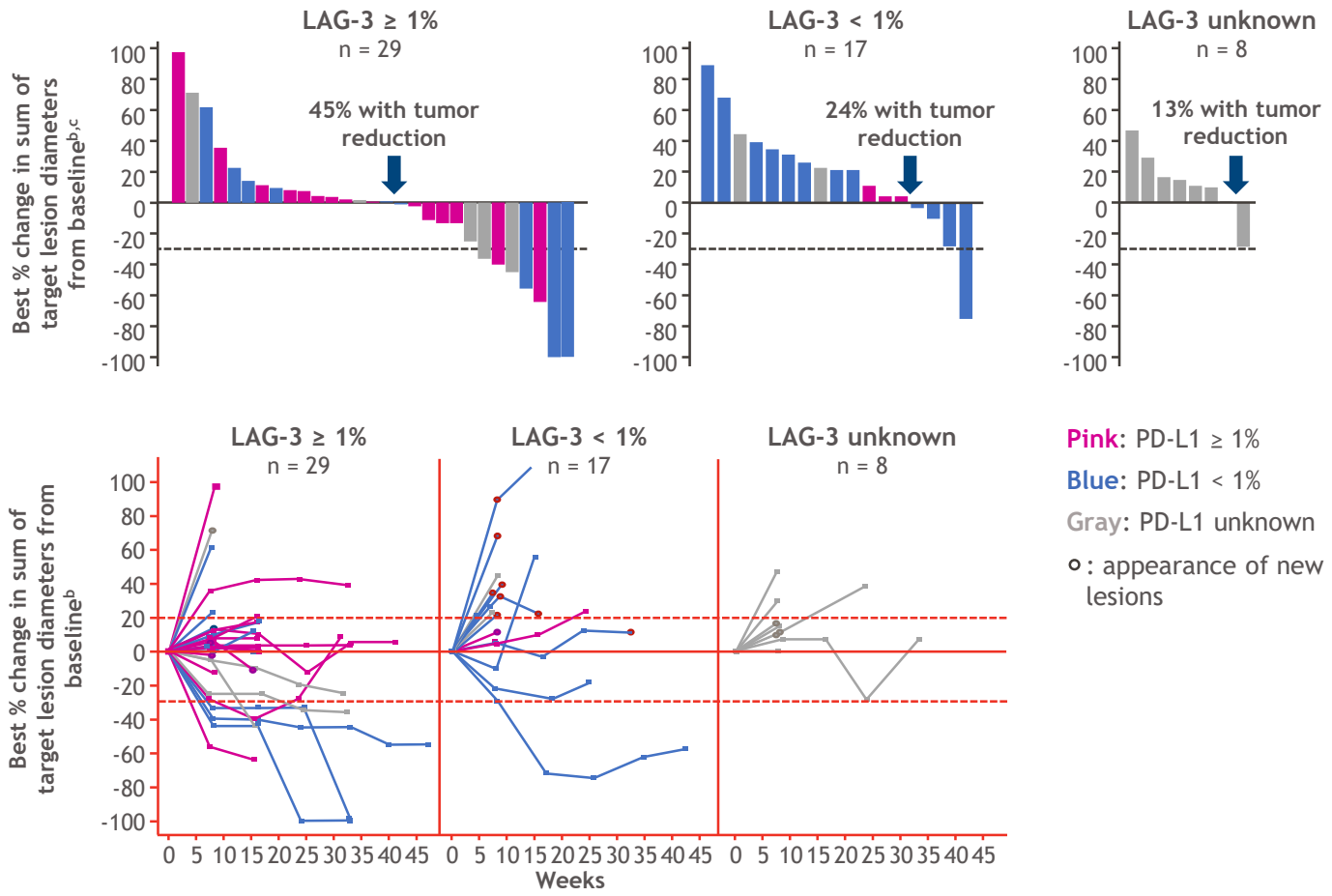
Lipson, E et al, *SITC 2016.*

RELATIVITY-020: efficacy in PD-1 refractory



- ✓ **Responses were more likely in patients with LAG-3 expression ≥ 1%**
- ✓ **PD-L1 expression did not appear to enrich for response**
- ✓ **Among the overall study population,[a] any-grade and grade 3-4 TRAEs were reported in 51% and 10% of patients, respectively**
- ✓ **The safety profile of the melanoma prior PD-1 / PD-L1 cohort was similar to that of the overall population**

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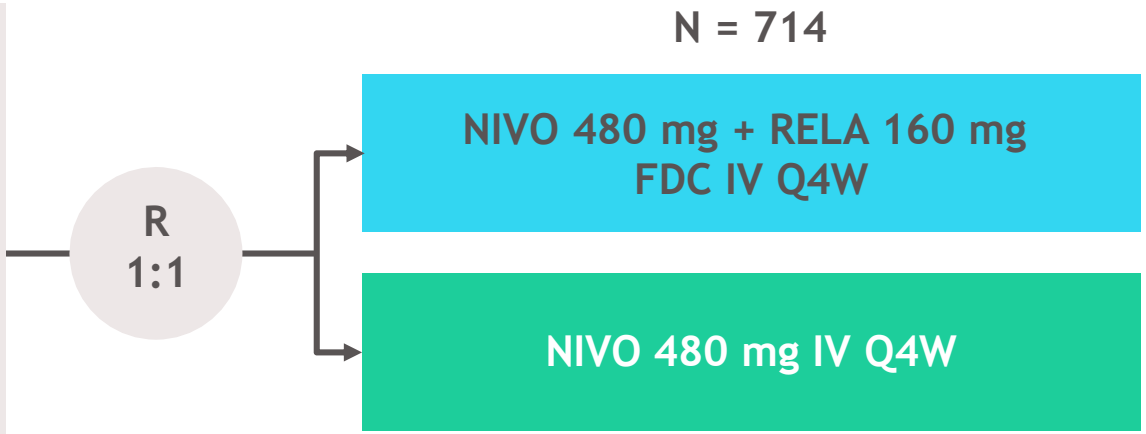
Ascierto PA., ASCO 2017

Combination anti-LAG3 + anti-PD1 in First Line Met. Melanoma

- RELATIVITY-047 is a global, randomized, double-blind, gated, phase 2/3 study

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0–1

Stratification factors
- LAG-3[a]
- PD-L1[b]
- *BRAF*
- AJCC v8 M stage



	Primary disclosure	Updated disclosure
Database lock date Median follow-up, mo Minimum follow-up, mo[d]	March 9, 2021 13.2 1.3	October 28, 2021 19.3 8.7
Data disclosed	Primary endpoint • PFS	Primary endpoint • Updated PFS
		Secondary endpoints • OS[e] • ORR

Primary endpoint
- PFS by BICR[c]

Secondary endpoints
- OS
- ORR by BICR[c]

Endpoints were tested in hierarchy
- PFS → OS → ORR

Tawbi, et al. *NEJM*, *Jan 2022*.

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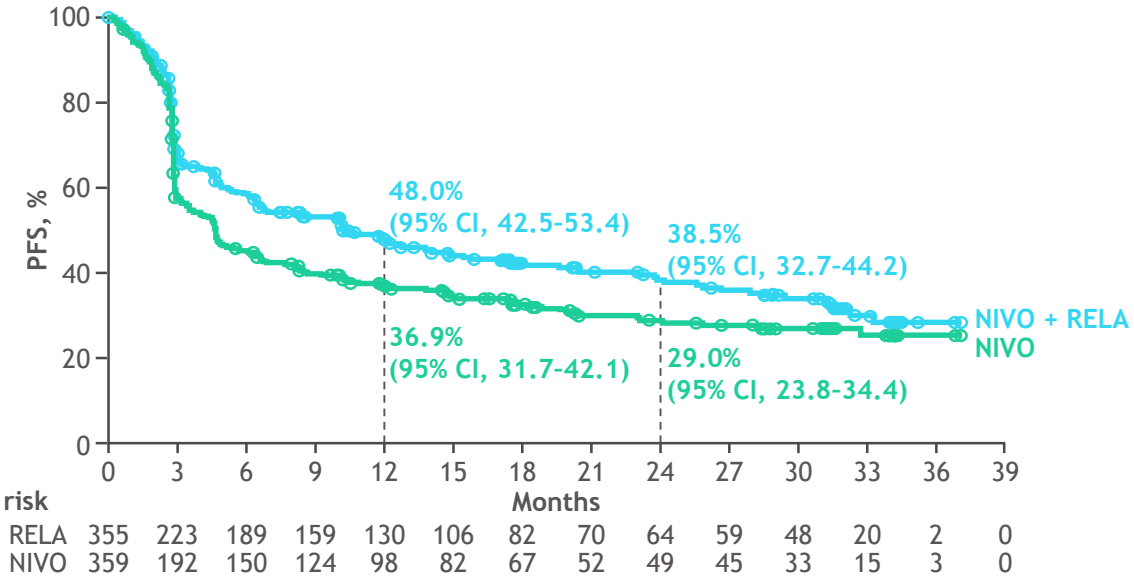
[a]LAG-3 expression on immune cells (1%) determined by analytically validated IHC assay (Labcorp, Burlington, NC, USA); [b]PD-L1 expression on tumor cells (1%) determined by validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA); [c]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks; [d]Minimum potential follow-up (time from last patient randomized to last patient, last visit); [e]OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75.
NCT03470922; Tawbi HA, et al. *N Engl J Med* 2022;386:24–34.

PFS, OS, and ORR in all randomized patients

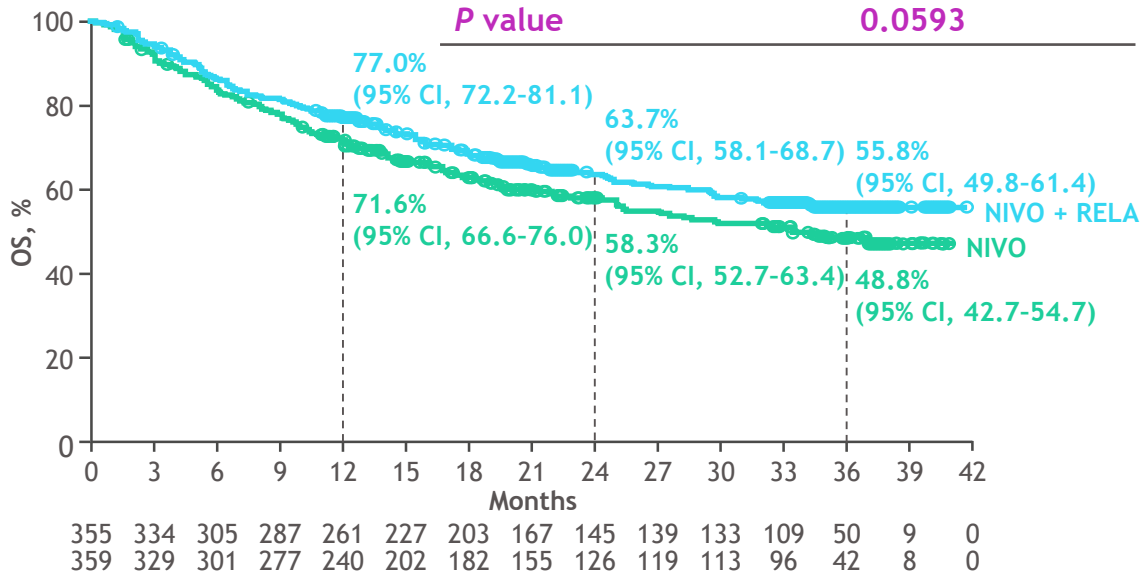
Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	NR (34.20-NR)	34.10 (25.23-NR)
HR (95% CI)	0.80 (0.64-1.01)	
P value	0.0593	



Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

DBL date: October 28, 2021. Median follow-up: 19.3 mo

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Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients; OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; ORR could not be formally tested and was descriptively analyzed. Minimum potential follow-up (time from last patient randomized to last patient last visit) was 8.7 mo.

Long GV, et al. Oral presentation at the American Society of Clinical Oncology (ASCO) 2022 March Plenary Series; March 15, 2022; Virtual. Abstract 360385.

Tawbi, et al. *NEJM*, *Jan 2022*.

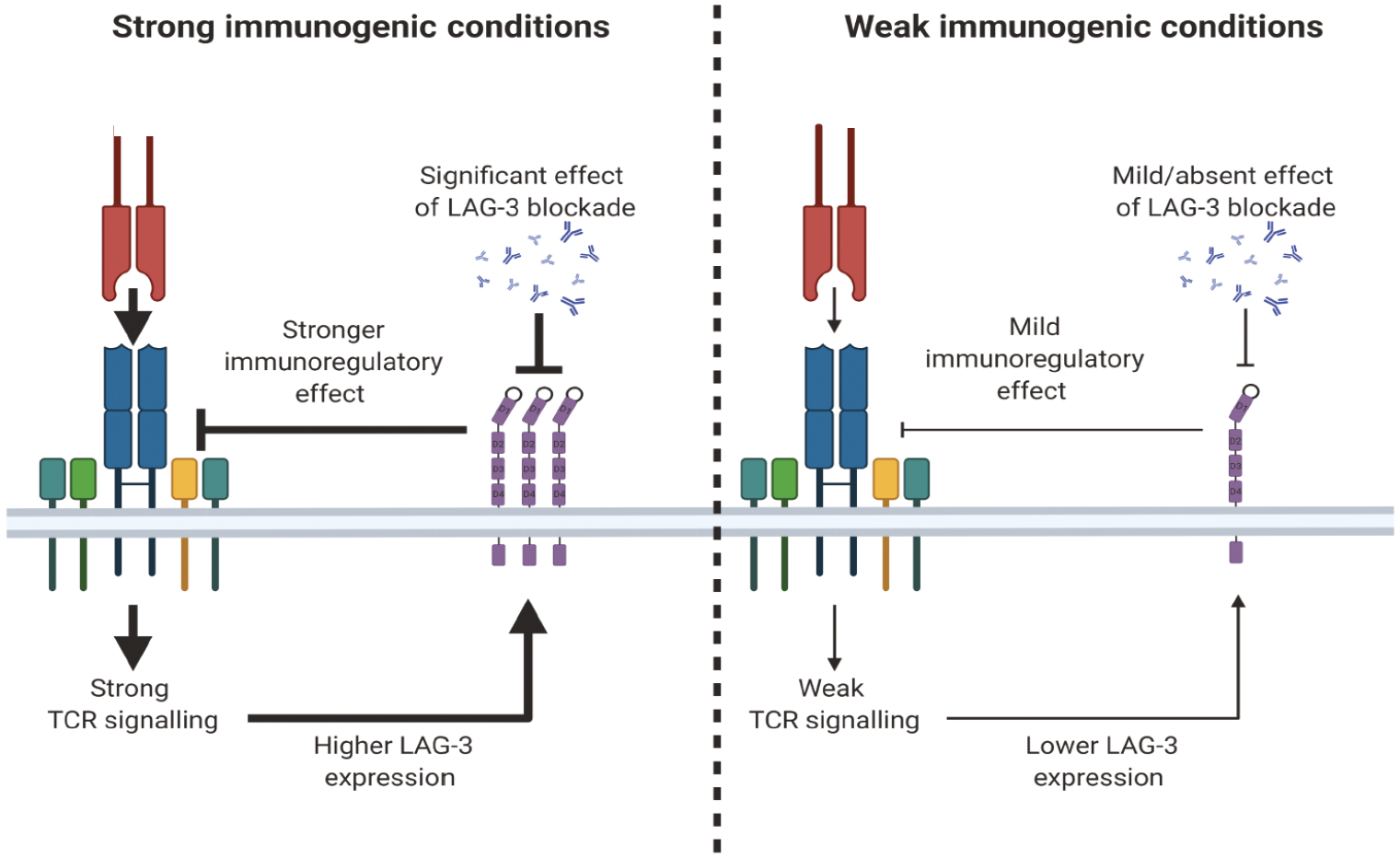
Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
Leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths[a]	4 (1.1)	0	2 (0.6)	0

DBL date: October 28, 2021. Median follow-up: 19.3 mo. Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3–4 TRAEs that were associated with any-grade TRAEs occurring in < 10% of patients not shown.

[a]Treatment-related deaths: NIVO + RELA (n = 4) – hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis, and multiorgan failure; NIVO (n = 2) – sepsis and myocarditis, and worsening pneumonia.

Why more activity in first line?



- ✓ **Given its impact on modulating TCR signaling, effect is amplified in conditions of strong immunogenic signaling**
- ✓ **Earlier stage of disease has less T cell exhaustion, more TCR signaling**

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Burnell, et al. *Immunother Adv 2022.*

Article

Neoadjuvant relatlimab and nivolumab in resectable melanoma

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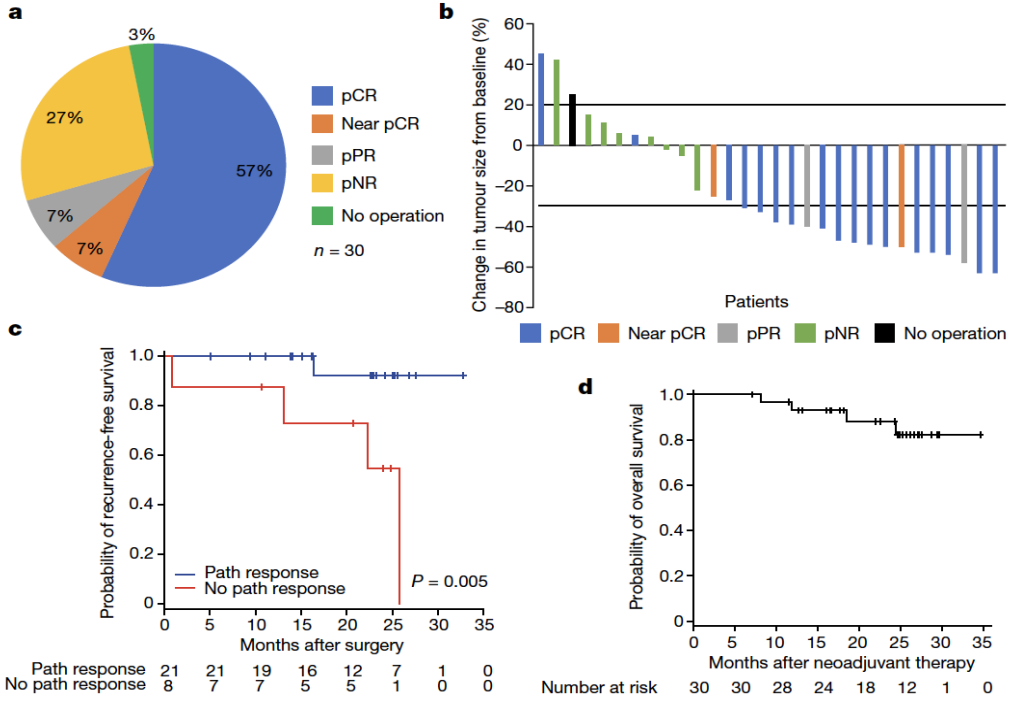
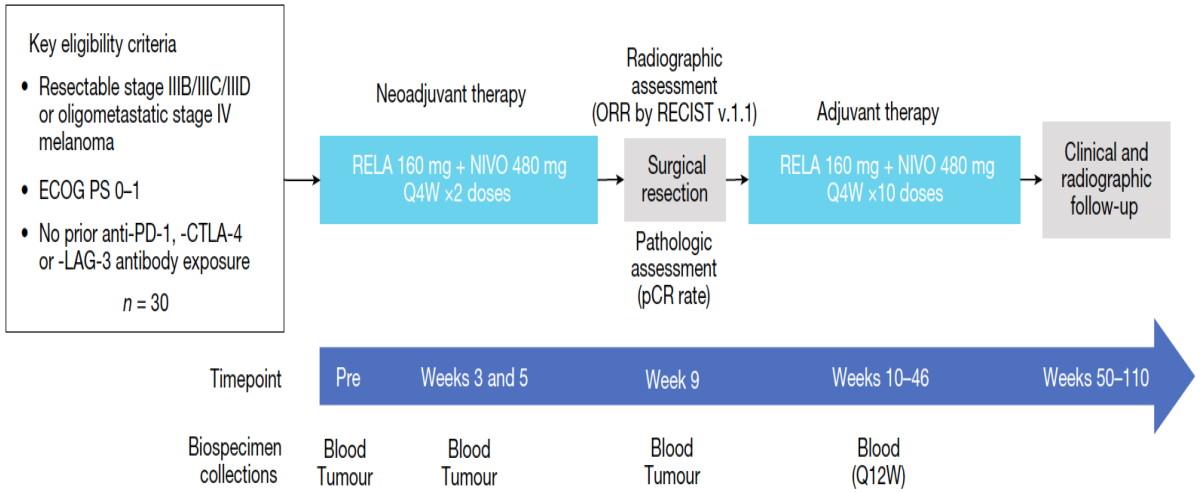
Rodabe N. Amaria[1,12], Michael Postow[2,12], Elizabeth M. Burton[1,12], Michael T. Tezlaff[3], Merrick I. Ross[4], Carlos Torres-Cabala[5], Isabella C. Glitza[1], Fei Duan[6], Denái R. Milton[7], Klaus Busam[8], Lauren Simpson[1], Jennifer L. McQuade[1], Michael K. Wong[1], Jeffrey E. Gershenwald[4], Jeffrey E. Lee[4], Ryan P. Goepfert[9], Emily Z. Keung[4], Sarah B. Fisher[4], Allison Betof-Warner[2], Alexander N. Shoushtari[2], Margaret Callahan[2], Daniel Coit[10], Edmund K. Bartlett[10], Danielle Bello[10], Parisa Momtaz[2], Courtney Nicholas[6], Aidi Gu[6], Xuejun Zhang[6], Brinda Rao Korivi[11], Madhavi Patnana[11], Sapna P. Patel[1], Adi Diab[1], Anthony Lucci[4], Victor G. Prieto[5], Michael A. Davies[1], James P. Allison[6], Padmanee Sharma[6,13], Jennifer A. Wargo[4,13], Charlotte Ariyan[10,13] & Hussein A. Tawbi[1,13]





- ✓ **pCR of 57%**
- ✓ **No grade 3-4 toxicity in Neoadjuvant phase**
- ✓ **pCR leads to excellent RFS**

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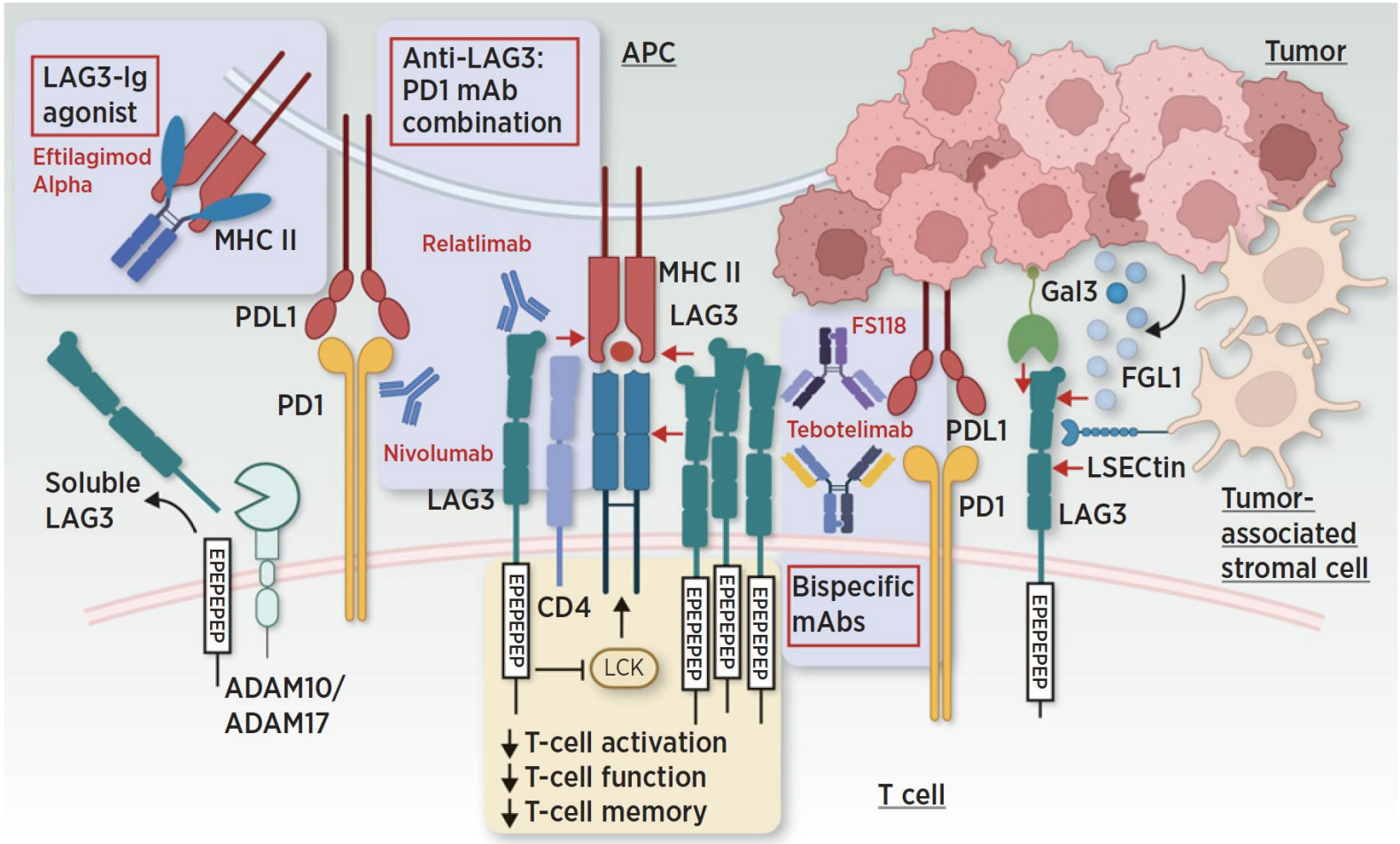
Amaria, RN…., Tawbi, H., *Nature 2022.*

Agents in development targeting LAG3



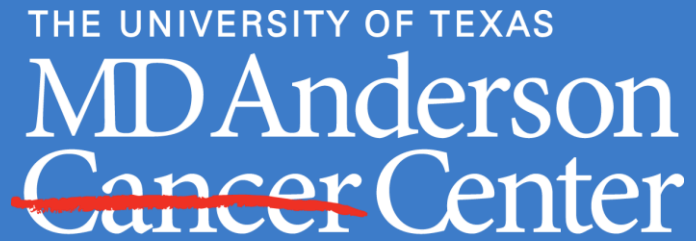
Andrews, et al. CCR 2022

Summary and Conclusions

- ✓ **LAG3 is a novel checkpoint with unique mechanisms**
- ✓ **LAG3 blockade is now validated as a therapeutic target in combination**
- ✓ **FDA approval in melanoma starts a new era of investigation**
- ✓ **Many unanswered questions**
  - ➢ structure and function
  - ➢ role in other settings like brain metastases
  - ➢ Role in other cancers
  - ➢ Combo with other checkpoints or other immune modulators
  - ➢ Biomarkers of response/resistance critical to drive future breakthroughs

- ✓ **<u>Mechanism-driven evaluation for contribution of novel agent</u>**

THANK YOU!



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