

SITC R&D Day

November 12, 2022

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding Agenus', MiNK's, and SaponiQx's clinical development and regulatory plans (including the scope of any regulatory approval and the ability to obtain priority review) and timelines for product candidates including balstilimab, zalifrelimab, botensilimab, AGEN1327, AGEN1777, AGEN2373, AGEN1571, and AGENT-797; our commercialization plans and pipeline's potential to meet multiple blockbuster opportunities; anticipated safety, efficacy, potency, activity, superior responses, and durability; our goals, milestones and value drivers; anticipated commercial market opportunities (including partnering and licensing opportunities); our ability to collect milestone and royalty payments; our ability to continue to self-finance Agenus; our ability to develop first and best in class drug candidates, adjuvants, antigens and formulations; and our ability to meet manufacturing demands. Statements containing the words "may," "believes," "expects," "anticipates," "hopes," "intends," "plans," "will," "designed," "potential," "best in class," "value," and similar expressions are intended to identify forward-looking statements. These forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially. These risks and uncertainties include, among others, the factors described under the Risk Factors section of our most recent Quarterly Report on Form 10-Q or Annual Report on Form 10-K filed with the Securities and Exchange Commission and made available on our website at www.agenusbio.com and www.minktherapeutics.com. Agenus and MiNK caution investors not to place considerable reliance on the forward-looking statements contained in this presentation. These statements speak only as of the date of this presentation, and Agenus and MiNK undertake no obligation to update or revise the statements, other than to the extent required by law. All forward-looking statements are expressly qualified in their entirety by this cautionary statement

INNOVATION AND SPEED FOR CANCER CURES

- Drug Development for Global Access. Next-Gen products - unprecedented data - ***Dr. Todd Yancey***
- The Path to Get to Curative Therapies for Patients with Advanced Cancers - ***Dr. Mike Atkins***
- Cancers' Pathway; How to Block it - ***Dr. Larry Norton***

THE ROAD TAKEN

- Novel Medicines, Accessible Combinations, with integrated Platforms - ***Dr. Jennifer Buell***

THE DATA

- Agenus Portfolio for Curative Therapies - ***Dr. Steven O'Day***
- Treating the most difficult cancers – Botensilimab - ***Dr. Bree Wilky***
- Botensilimab – a Transformative Treatment for CRC - ***Dr. Joseph Grossman***
- The Path to Botensilimab Approval – Dr. ***Patricia Carlos***
- The Future of Cancer Immunotherapy - ***Dr. Alexander M.M. Eggermont***

REFLECTIONS – MODERATION LED BY ALEXANDER M.M. EGGERMONT

- Agenus Next - ***Dr. Todd Yancey***


The ROADTAKEN
agenus
INNOVATION AND SPEED
FOR CANCER CURES

AGENUS PORTFOLIO DESIGNED TO REACH UNTAPPED I-O MARKET

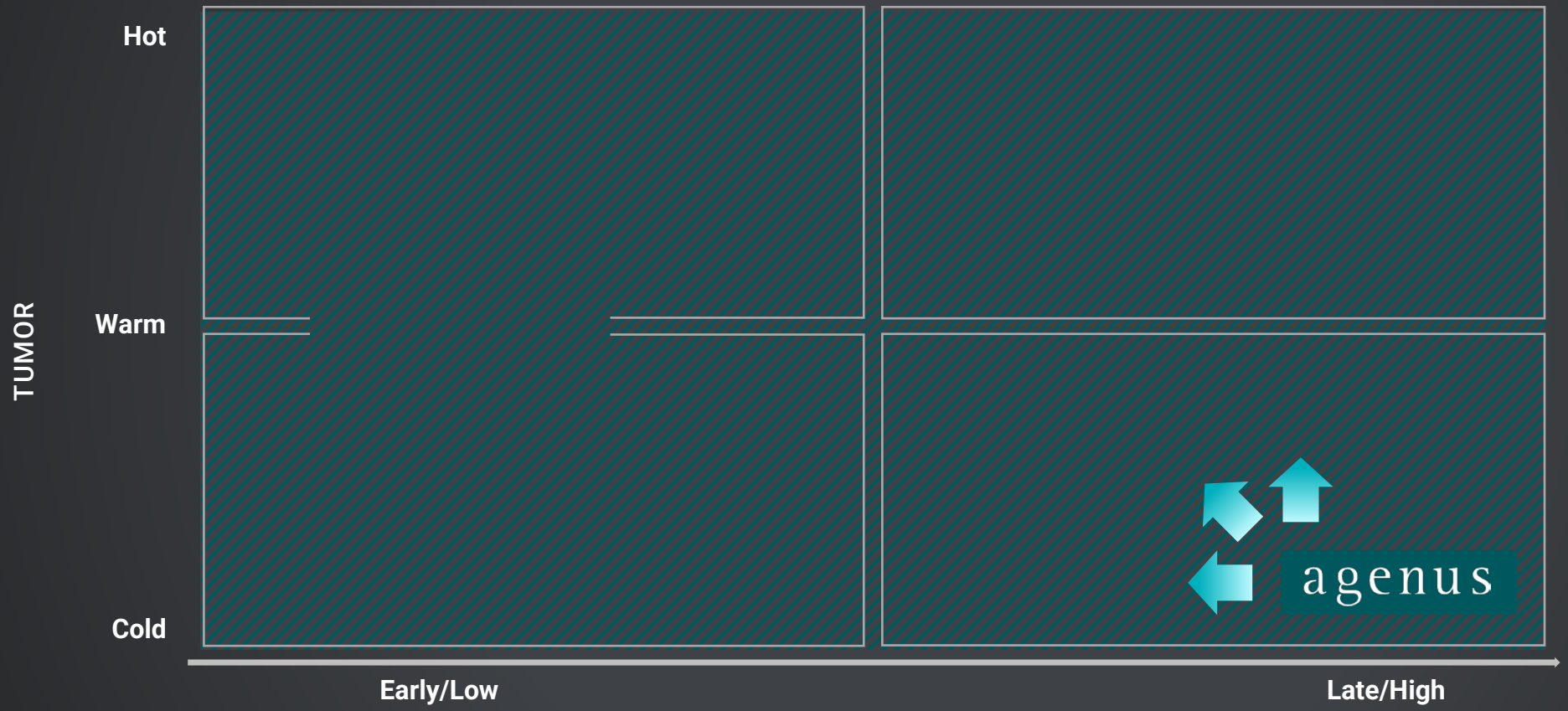


Current I-O market

$47B

Source: Evaluate Pharma 2022 global revenue estimates, Agenus analysis

AGENUS PORTFOLIO DESIGNED TO REACH UNTAPPED I-O MARKET



Source: Evaluate Pharma 2022 global revenue estimates, Agenus analysis

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DRUG DEVELOPMENT FOR GLOBAL ACCESS, NEXT-GEN PRODUCTS, UNPRECEDENTED DATA

Todd Yancey, MD

Senior Global Clinical Development,
Medical Affairs and Commercial Advisor

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THE PATH TO GET TO CURATIVE THERAPIES FOR PATIENTS WITH ADVANCED CANCERS

Michael B. Atkins, M.D.
Deputy Director Lombardi Comprehensive Cancer Center
Georgetown-Lombardi Comprehensive Cancer Center
William M. Scholl Professor and Vice-Chair
Department of Oncology
Georgetown University Medical Center

November 12, 2022

Cancer Immunotherapy – a journey from the Wilderness toward the Promised Land

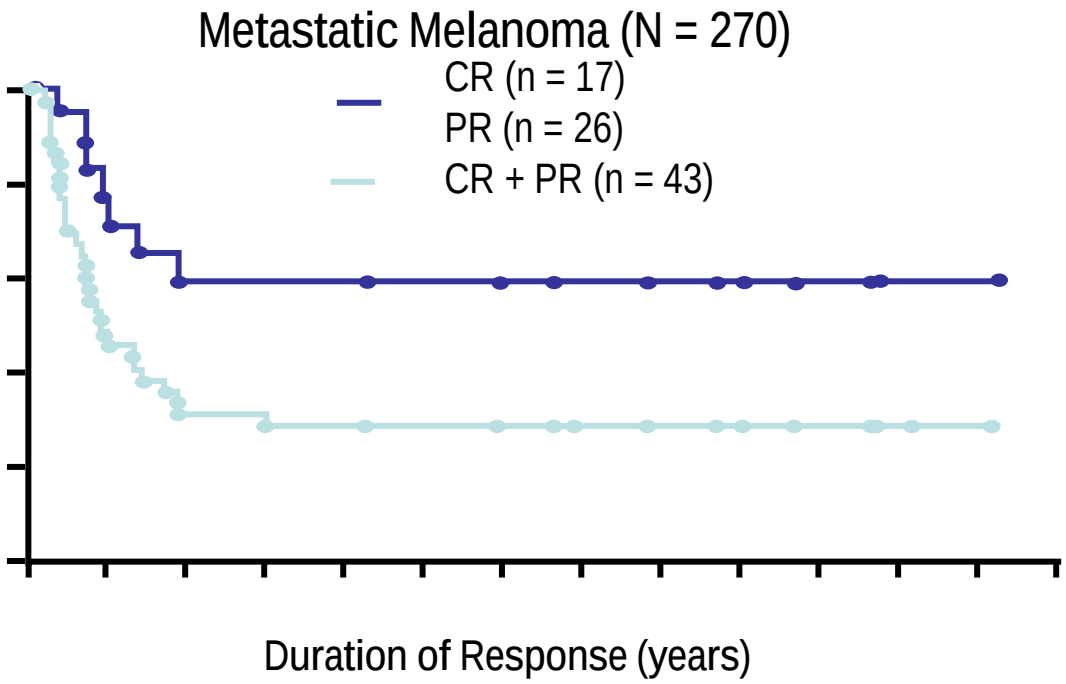
Michael B. Atkins, M.D.
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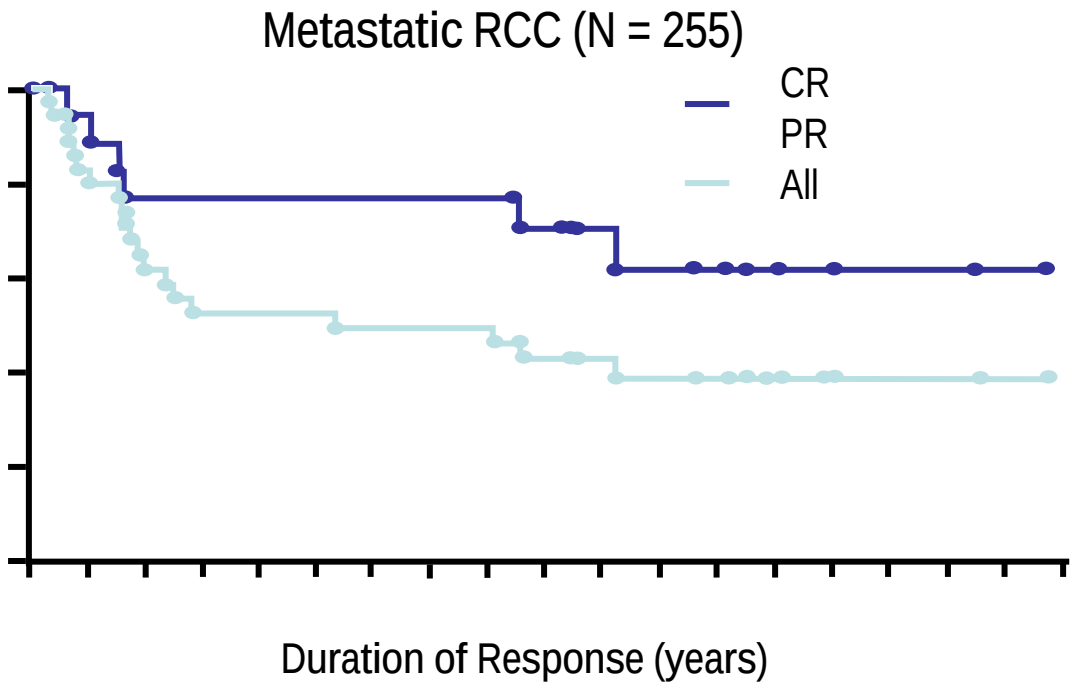
Cancer Immunotherapy Principles

- All “successful” cancers must solve the challenges of overcoming defenses erected by host immune systems
- “Treating the immune system so that it can treat the cancer”
  Jedd Wolchok
- Because the activated immune system can target many tumor antigens simultaneously, and deepen and broaden over time, IT can cure patients with metastatic cancer
- The hallmark of effective immunotherapy is a tail on the KM-curve

HD IL-2 Therapy: Durable Responses/Cures

- HD IL-2 produces durable responses in ~10% of patients with advanced melanoma or RCC
  - Few relapses in patients responding for over 2.5 years (likely cured)
  - FDA approval in 1992 (RCC) and 1997 (melanoma)





Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116. McDermott DF, et al. Expert Opin Biol Ther. 2004;4:455-468.

High Dose IL-2 Therapy

1985



High Dose IL-2 Therapy

1985



2000+

A case study for what is wrong with cancer clinical development

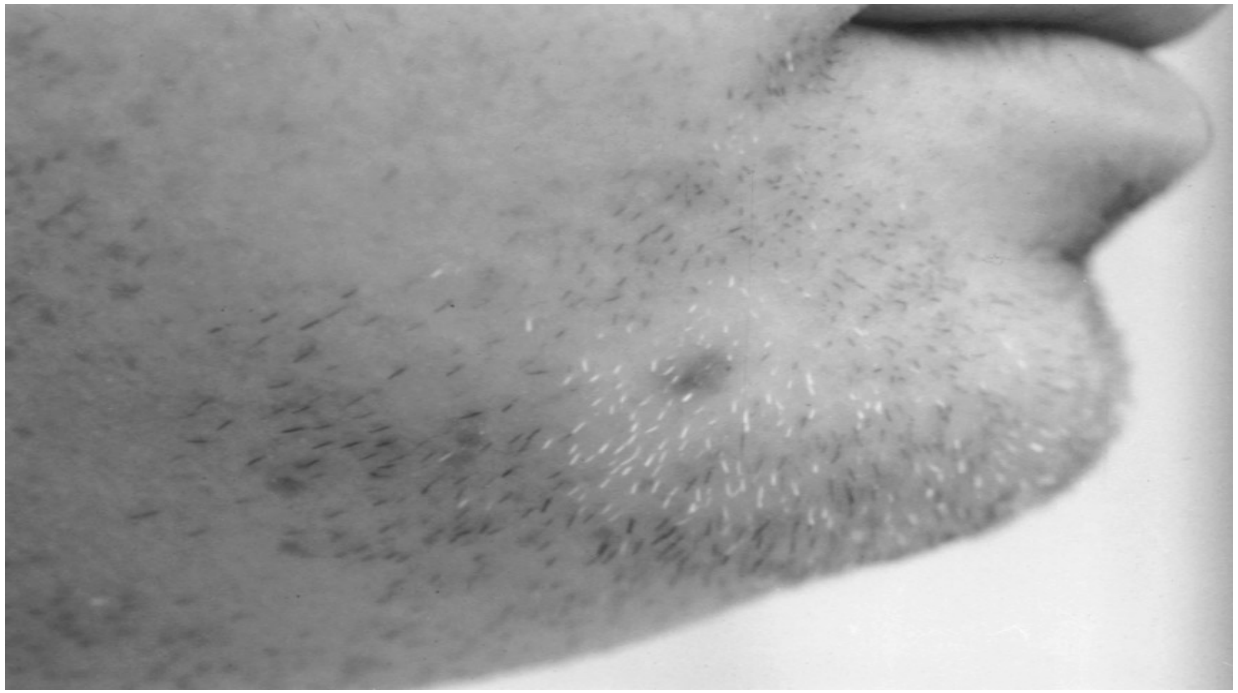
- Uncontrolled
- No target
- No target population
- Toxic
- Inpatient
- No correlates

Proof of Principle

Efforts to Improve IL-2 Therapy: Lessons Learned

- Lower dose IL-2
  - CRs only seen with HD IL-2 (McDermott et al JCO 2005)
- Dissociation of toxicity from Efficacy
  - Toxicity and efficacy elimination with steroid (Mier et al 1990)
  - Efficacy, but no toxicity reduction with sTNFR or sIL-1R (Du Bois JCO 1997, McDermott CCR 1998)
- Treatment selection
  - Inflamed TME
  - iRAEs associated with increased efficacy
- IL-2 combinations (Biochemotherapy, TILs, vaccines)
  - Immune effect lost with concurrent administration
  - Tumor-reactive TILs exist; no need to vaccinate

Vitiligo and hypothyroidism following HD IL-2 Rx

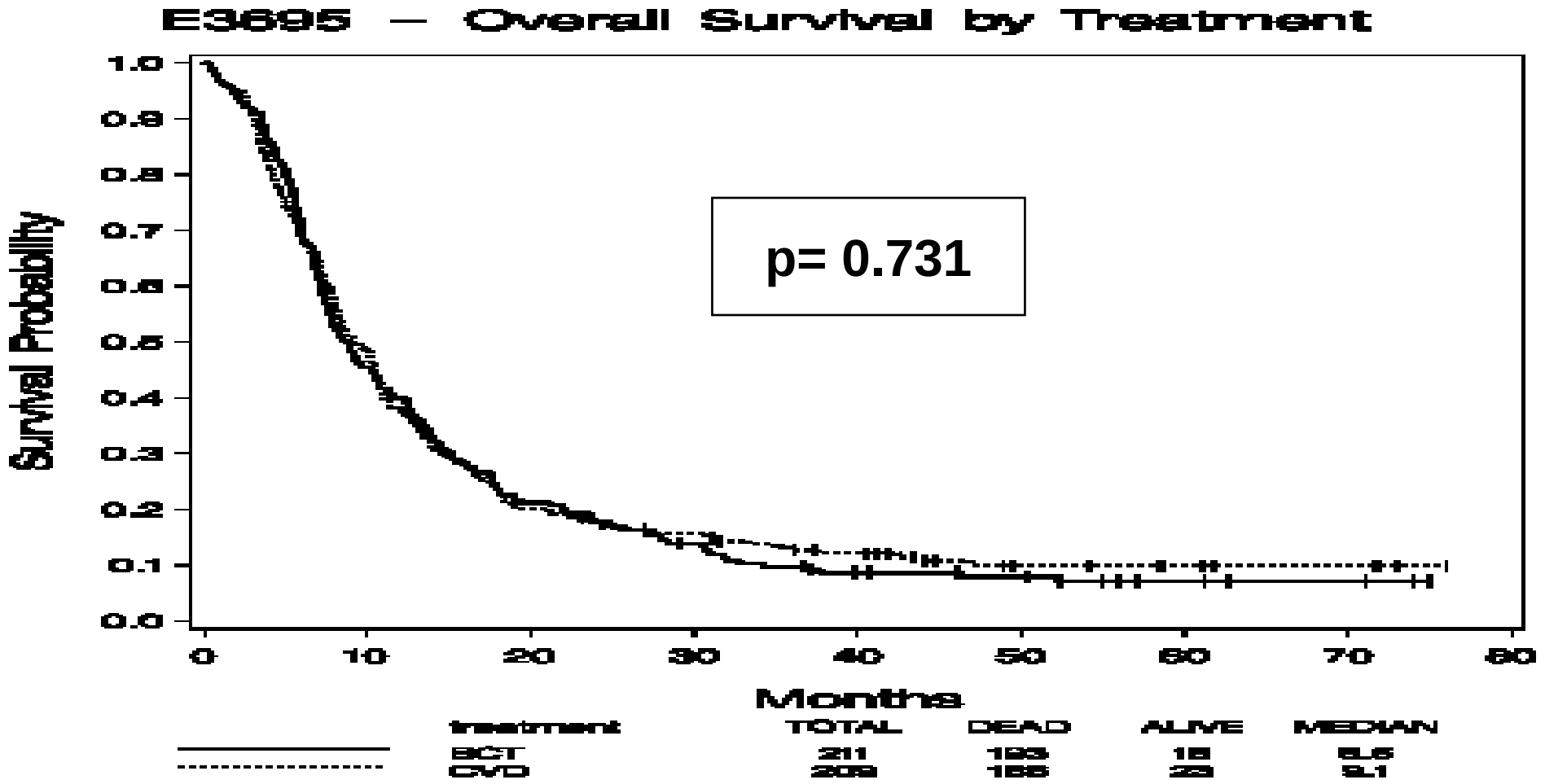




Treated May 1986 – Alive today without disease

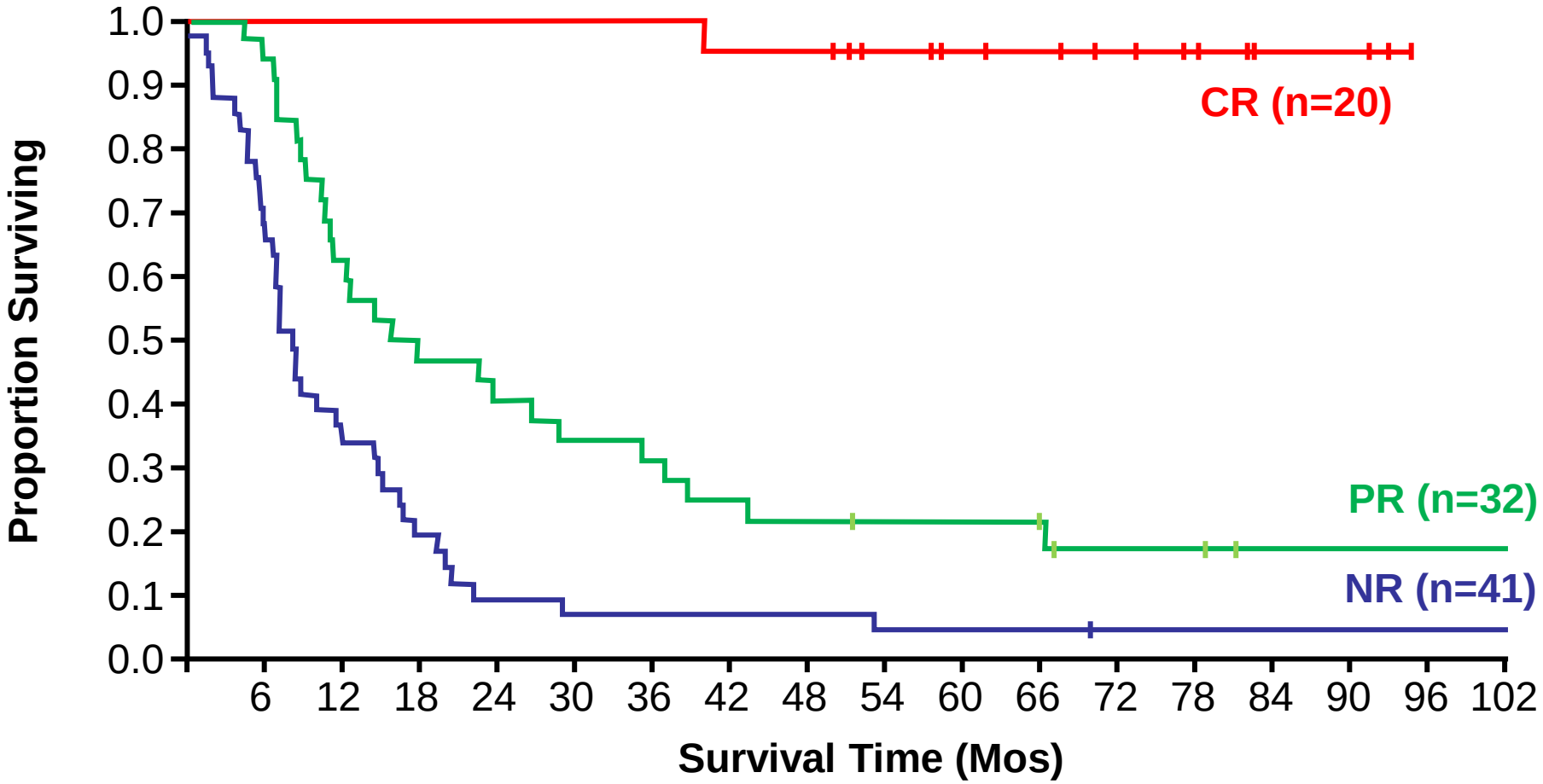
Atkins et al NEJM 318:1557 62,1988.

E3695: Concurrent Biochemotherapy (BCT) vs CVD – Final Result



Atkins et al JCO 2008

Tumor-Infiltrating Lymphocytes + IL-2 in Metastatic Melanoma: OS



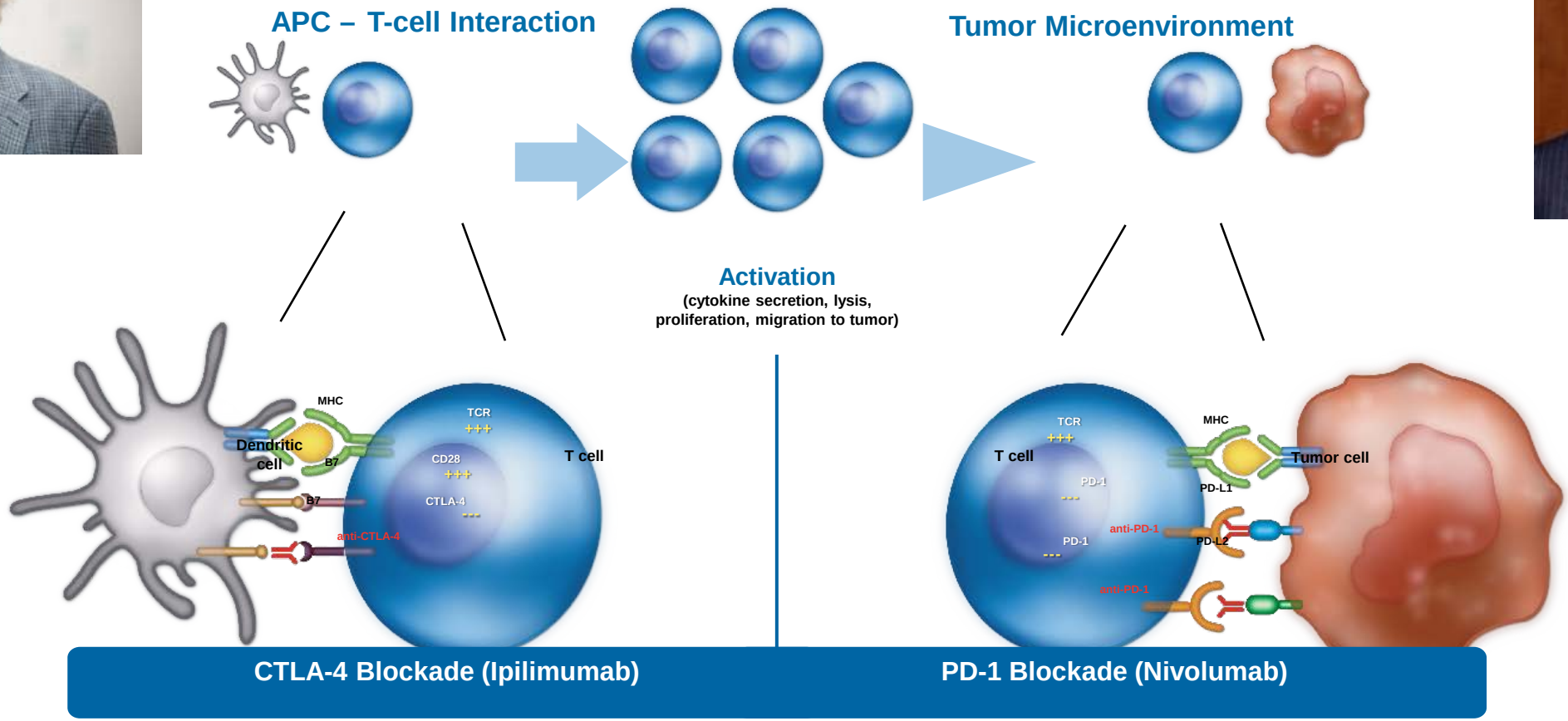
What is keeping these cells from killing the tumor *in vivo*?

Robbins PF, Rosenberg et al. Nat Med. 2013;19:747-752.

Biologic Rationale for Combined PD-1 and CTLA-4 Blockade

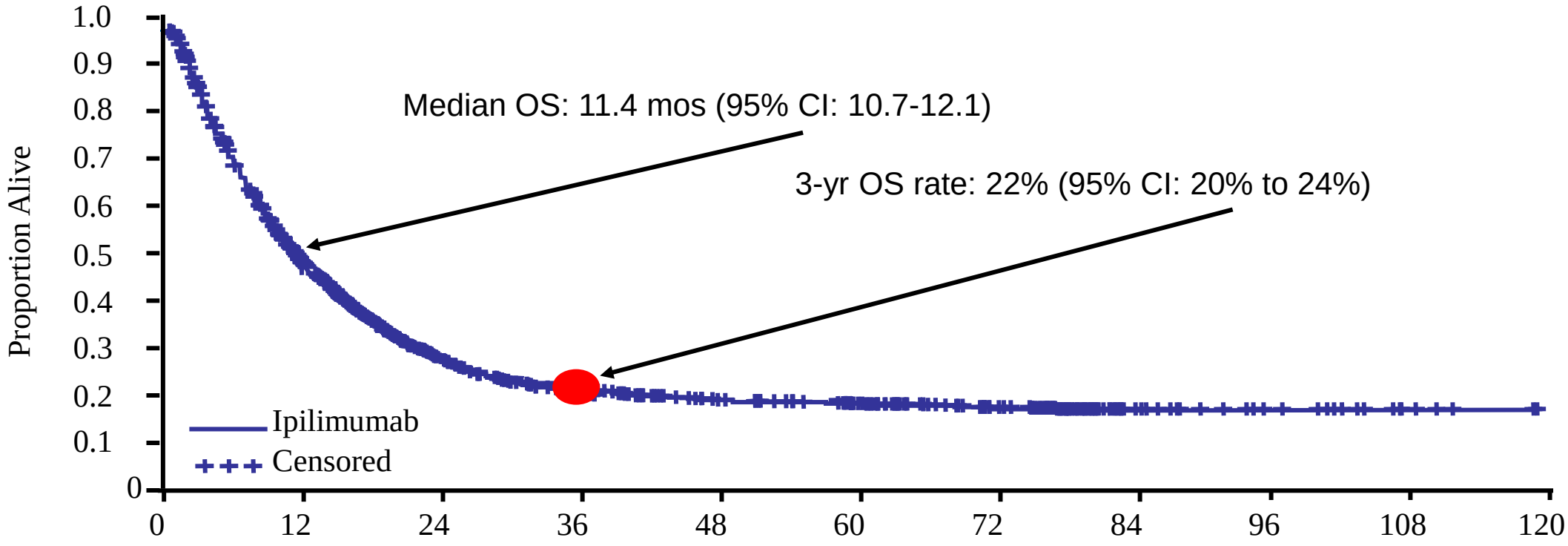






Analysis From Phase II and Phase III Trials of Ipilimumab Show OS Plateau at 3 Years

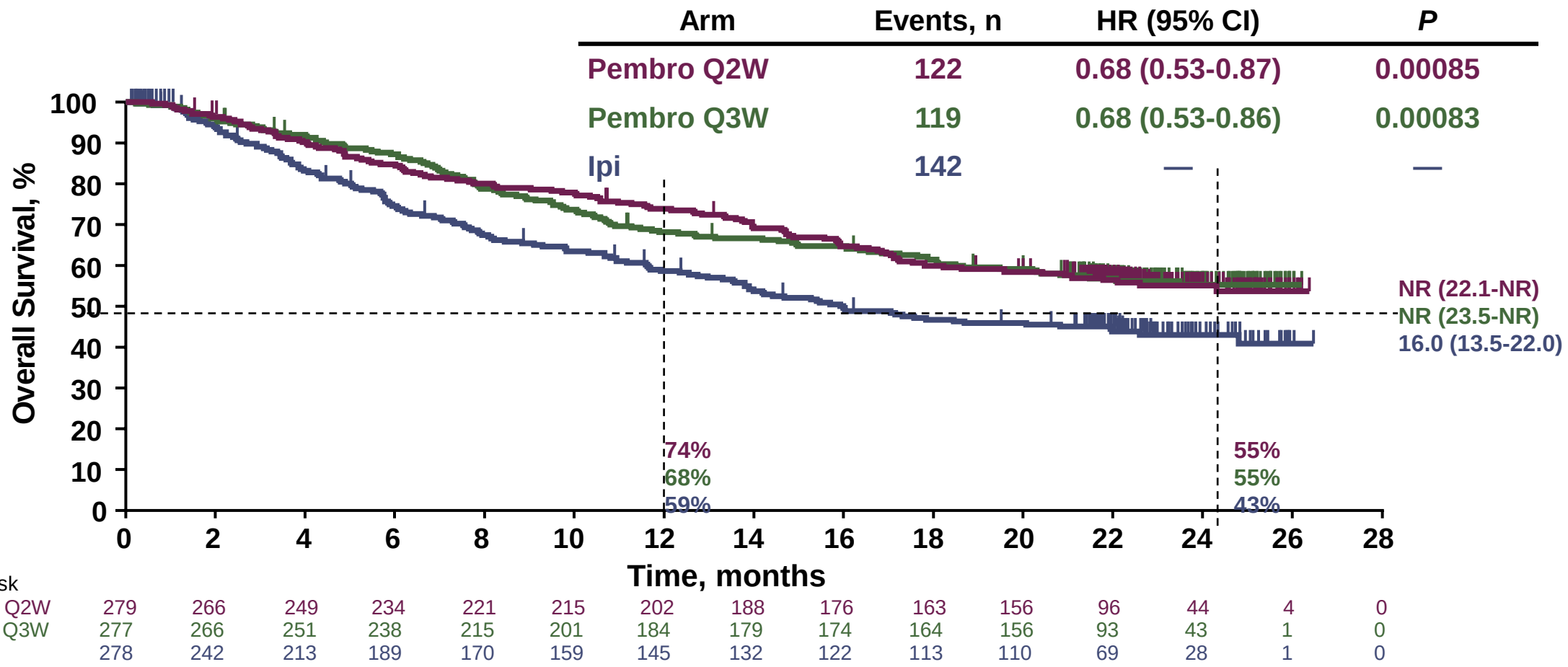
Schadendorf D, et al. J Clin Oncol. 2015 [Epub ahead of print].



Pts at Risk, n										
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

KEYNOTE-006 Results: Final Analysis

- ORR, PFS, and OS superiority of pembrolizumab over ipilimumab

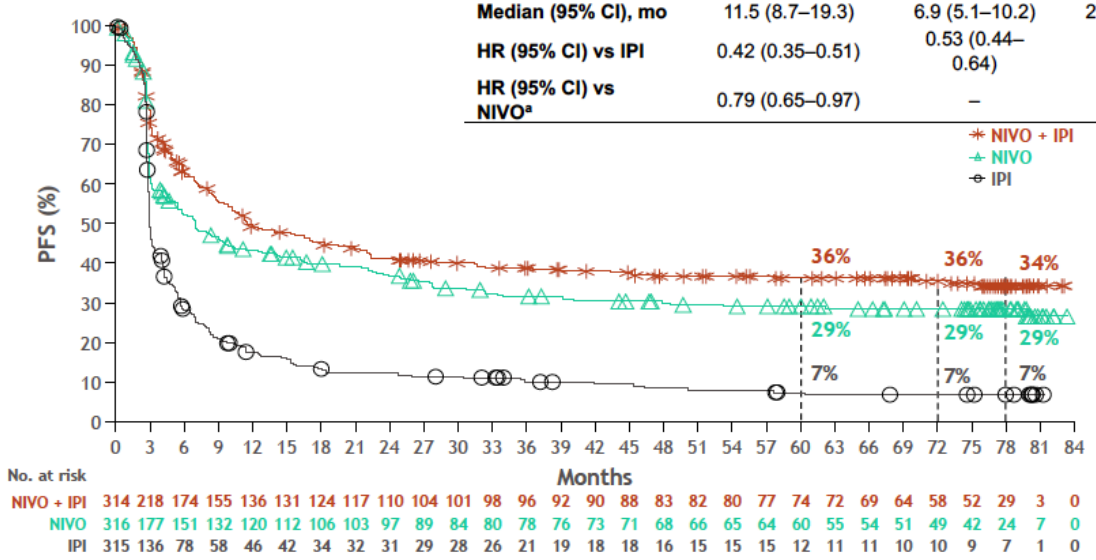


Schachter J et al. Presented at ASCO 2016; Jun 2-7, 2016; Chicago, IL. Abstr. 9504.

CheckMate-067: Melanoma 6.5-year follow-up Data

Progression-free Survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.65–0.97)	–	–

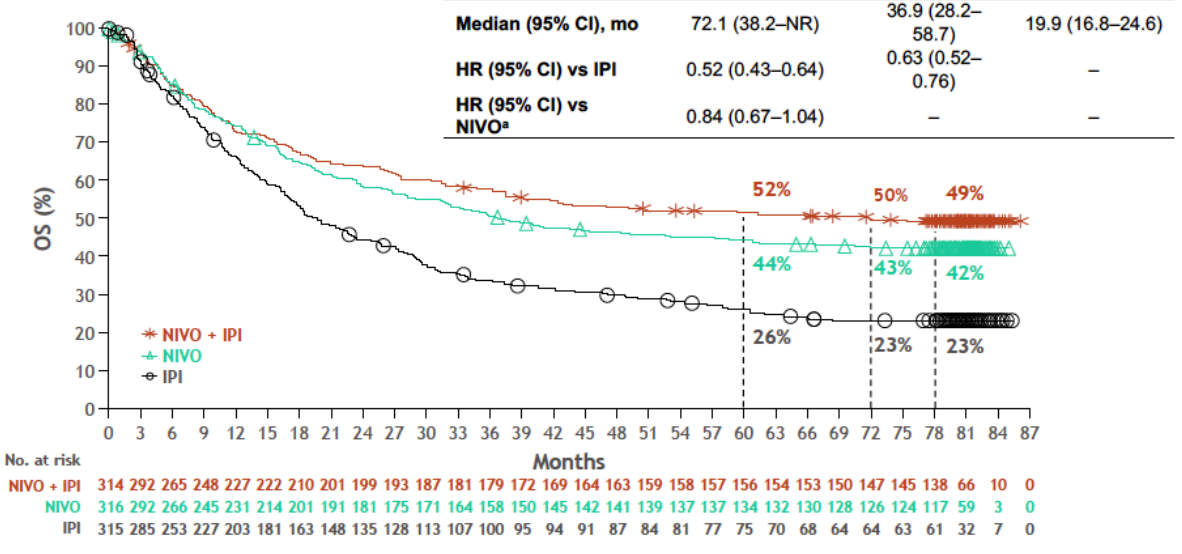


No. at risk

NIVO + IPI	314	218	174	155	136	131	124	117	110	104	101	98	96	92	90	88	83	82	80	77	74	72	69	64	58	52	29	3	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	68	66	65	64	60	55	54	51	49	42	24	7	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	7	1	0

Overall Survival

	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)	–	–

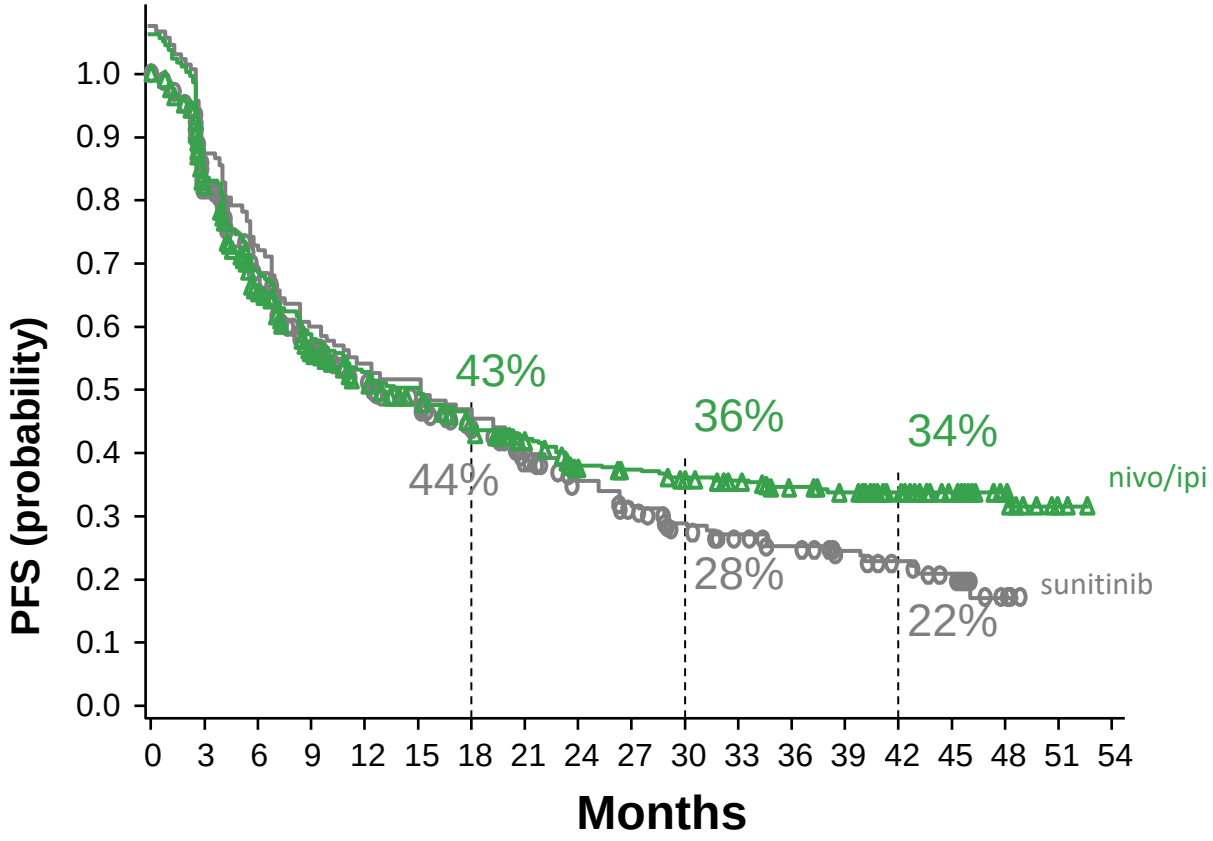


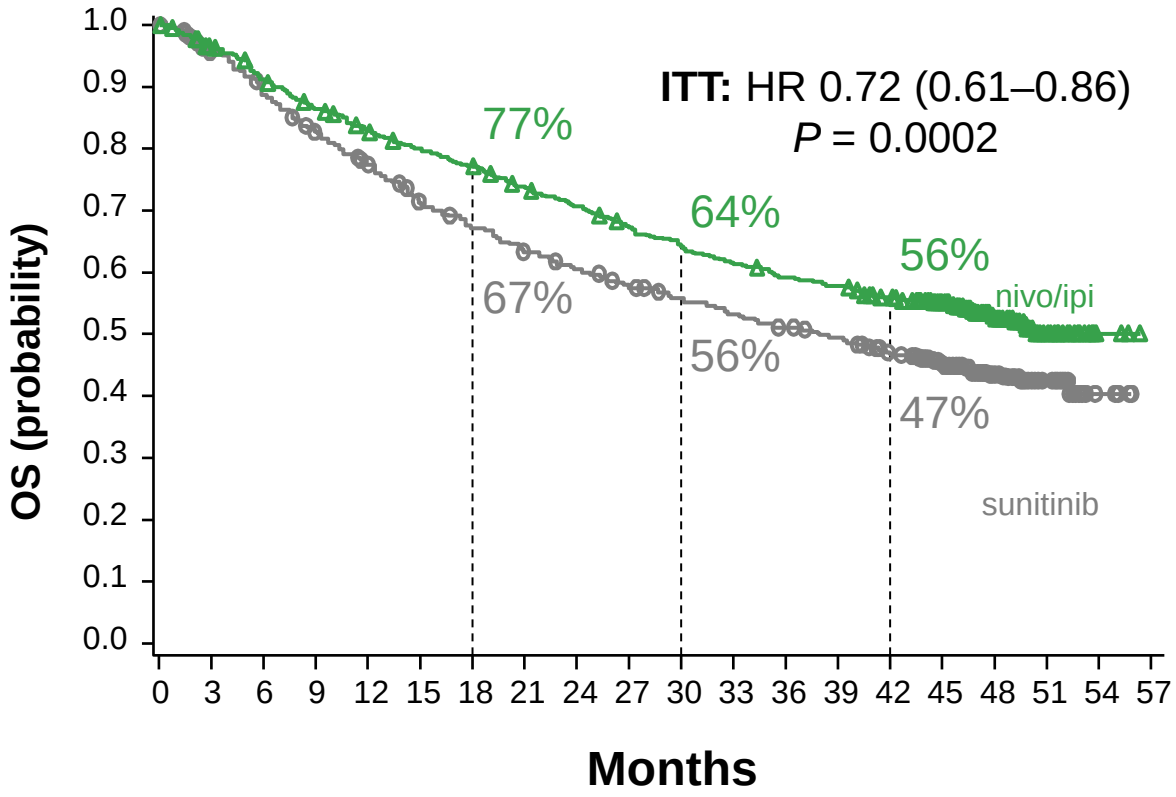
No. at risk

NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

Wolchok et al JCO 2021

CM 214:Nivo/Ipi in RCC



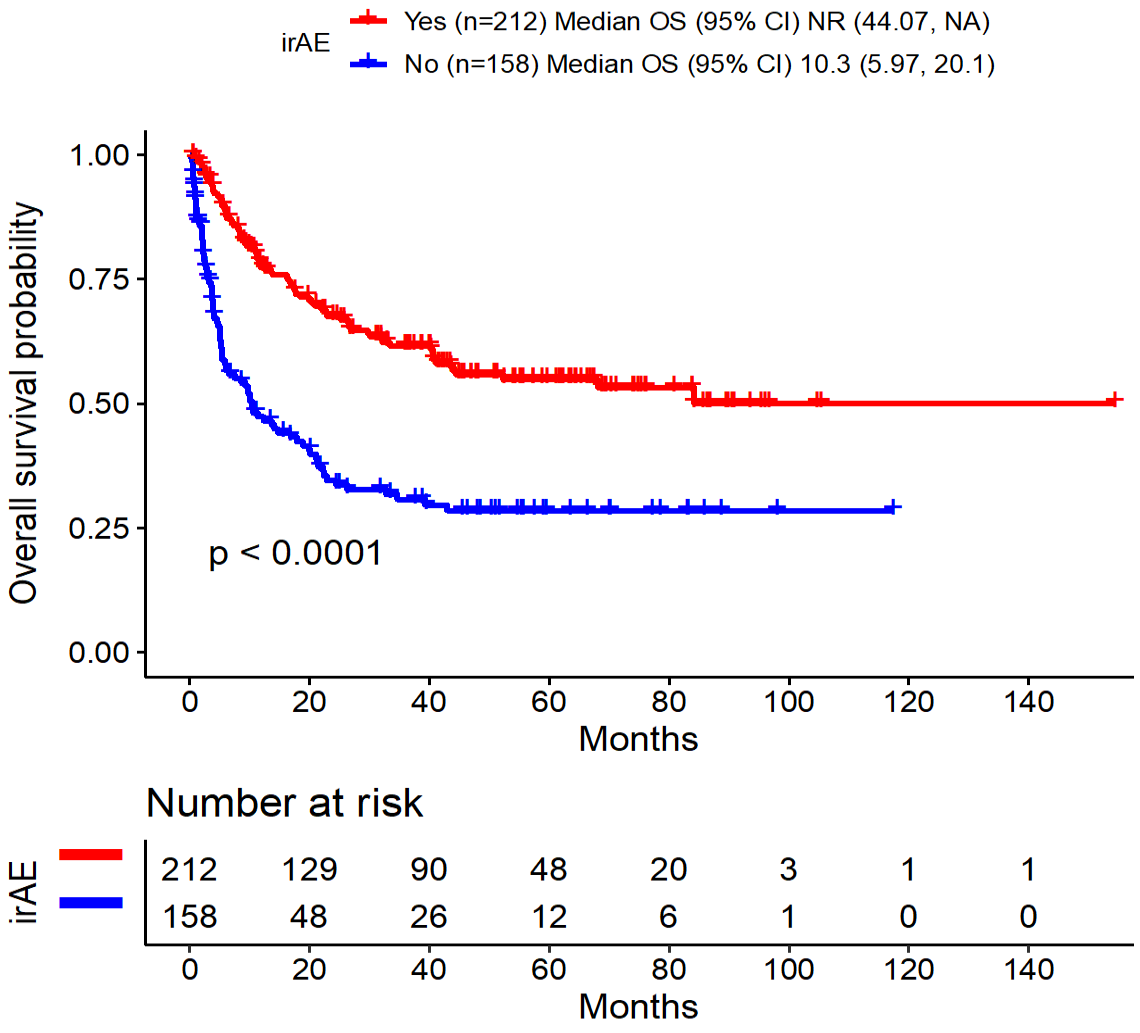


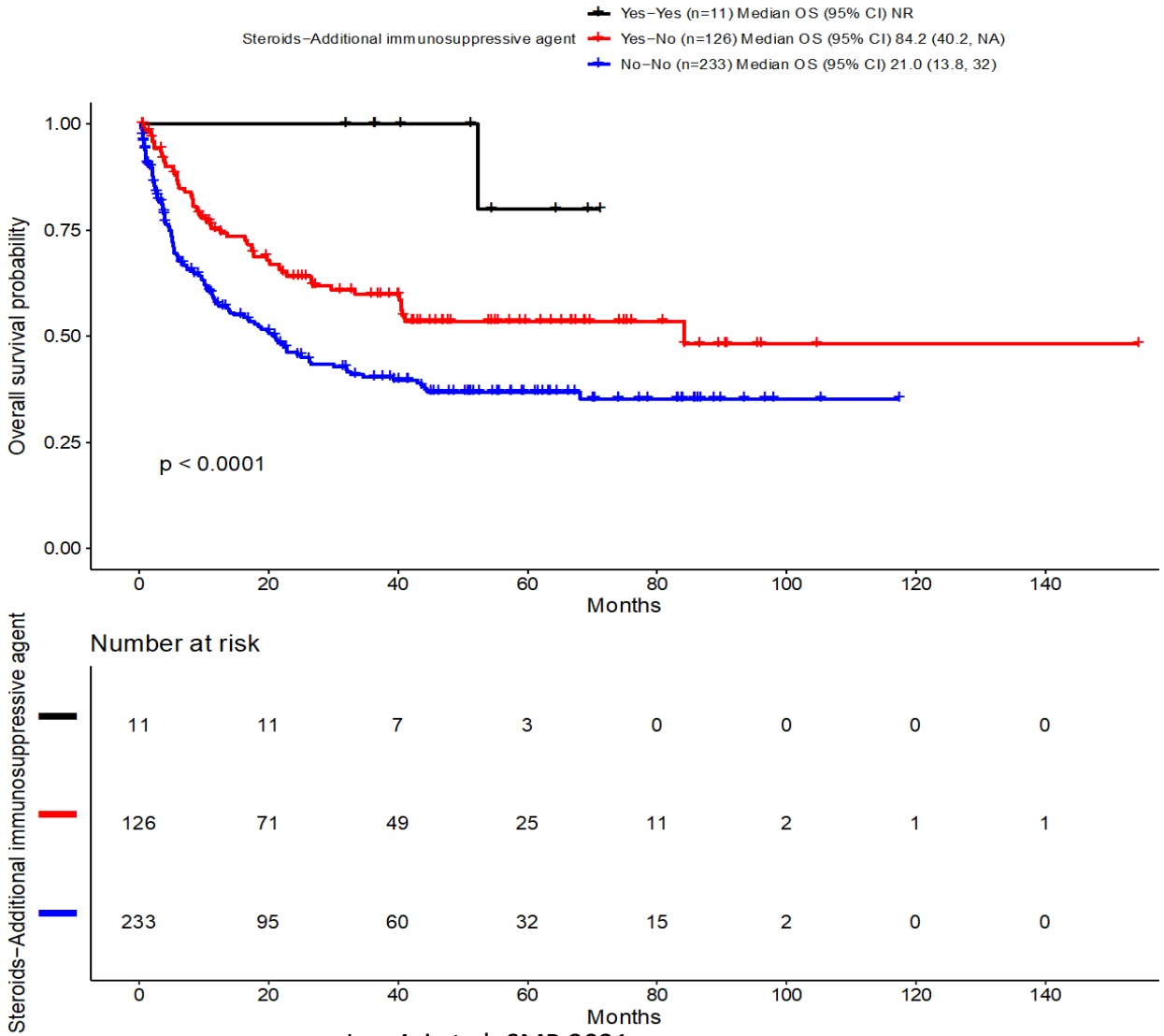
Tannir N et al. Presented at: ASCO GU 2020; February 13-15, 2020; San Francisco, CA. Abstract 609

Checkpoint Inhibitor Lessens

- Relation of irAEs and benefit
- Stopping therapy-creating TFS
- Activity in patients with brain metastases
- Sequencing with standard therapies
- Mixed Combination Issues

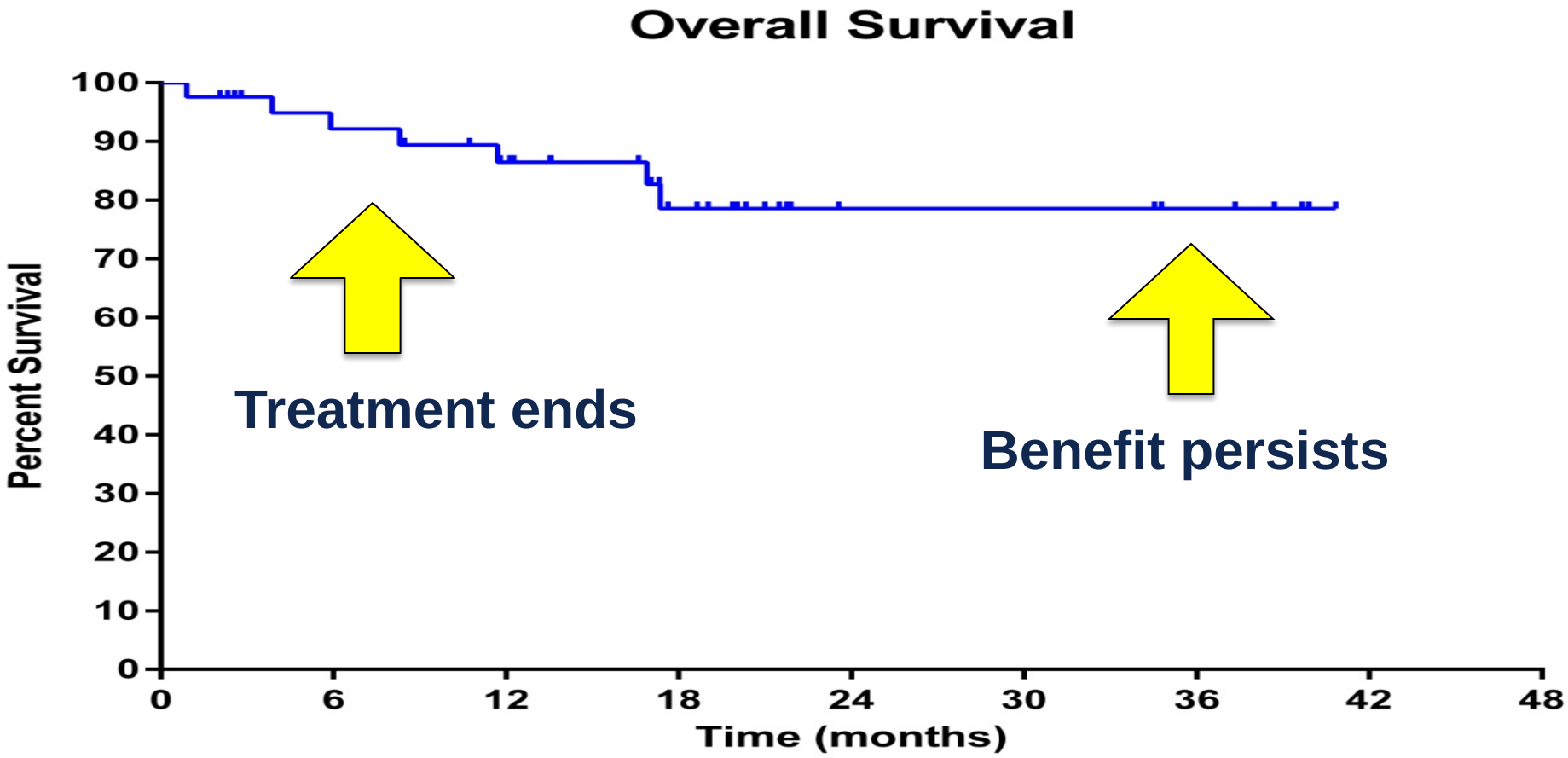
Advanced Melanoma Patients Treated with ICIs
Georgetown-Lombardi IO Database





Lev-Ari et al- SMR 2021

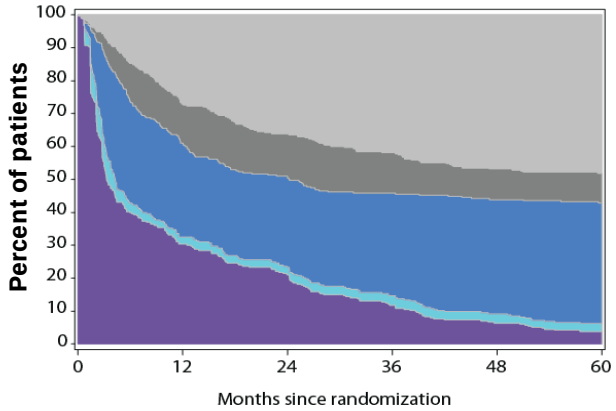
Combination I/0 Achieves “Many” Patients’ Preferred Outcome- Treatment Free Survival or “TFS”



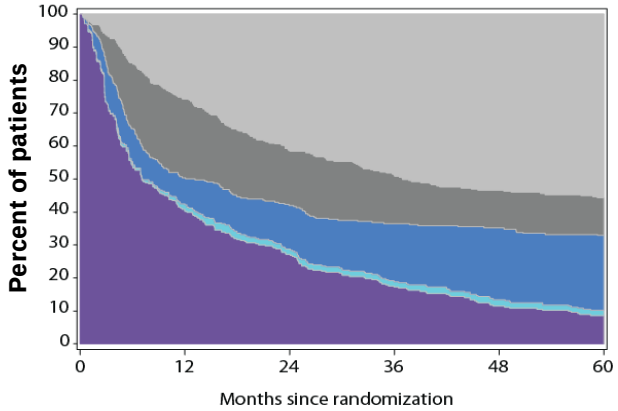
Gibney et al JITC 2021
EA-6192 (PET-Stop)

TFS and Survival States Over 60-Month Follow-Up Period

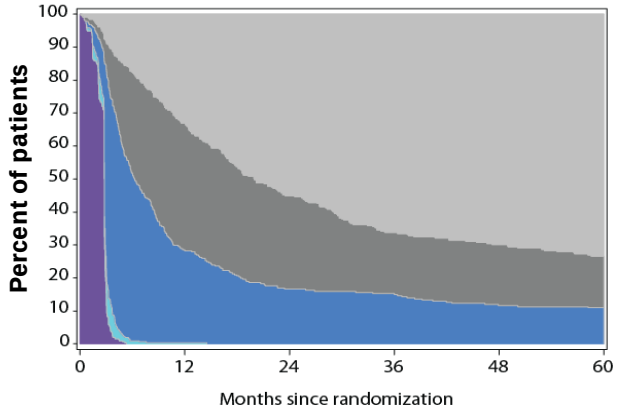
A) NIVO + IPI



B) NIVO



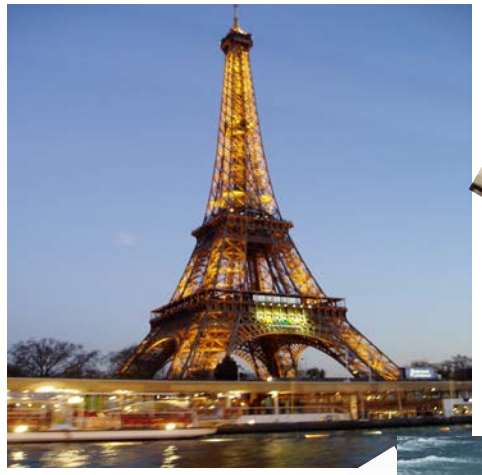
C) IPI



Survival State	NIVO + IPI		NIVO		Difference (95% CI): NIVO + IPI vs NIVO (mo)	IPI		Difference (95% CI): NIVO + IPI vs IPI (mo)
	60-mo mean time (mo)	Percent of 60-mo period	60-mo mean time (mo)	Percent of 60-mo period		60-mo mean time (mo)	Percent of 60-mo period	
OS	38.6	(64)	36.1	(60)	2.5 (−1.1, 6.2)	28.4	(47)	10.2 (6.6, 13.9)
Survival after subsequent therapy initiation	6.6	(11)	9.3	(15)	−2.7 (−4.9, −0.4)	13.9	(23)	−7.3 (−9.8, −4.8)
TFS	19.7	(33)	9.9	(17)	9.8 (6.7, 12.8)	11.9	(20)	7.8 (4.6, 11.0)
Without grade ≥ 3 TRAE	18.1	(30)	9.0	(15)	9.0 (6.1, 12.0)	11.7	(19)	6.4 (3.3, 9.5)
With grade ≥ 3 TRAE	1.6	(3)	0.9	(2)	0.7 (−0.4, 1.8)	0.2	(< 1)	1.4 (0.5, 2.3)
Time on protocol therapy	12.3	(21)	16.9	(28)	−4.6 (−7.3, −1.8)	2.6	(4)	9.8 (7.9, 11.6)
With grade ≥ 3 TRAE	*0.5*	*(1)*	*0.7*	*(1)*	*-0.2 (-0.8, 0.5)*	*0.1*	*(< 1)*	*0.4 (0.2, 0.6)*
Without grade ≥ 3 TRAE	*11.8*	*(20)*	*16.2*	*(27)*	*-4.4 (-7.1, -1.7)*	*2.5*	*(4)*	*9.3 (7.5, 11.1)*

- TFS, treatment-free survival; TRAE, treatment-related adverse event.
- Regan MM, et al. J Immunother Cancer. 2021;9:e003743.

TFS = Travel Full Survival







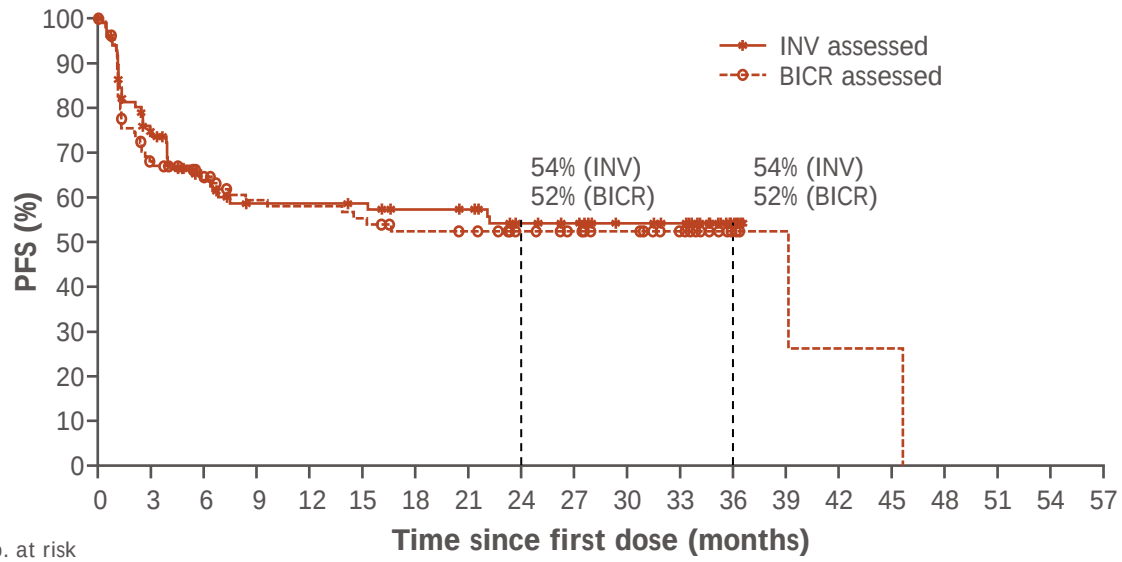






Survival in Pts with asymptomatic CNS Disease

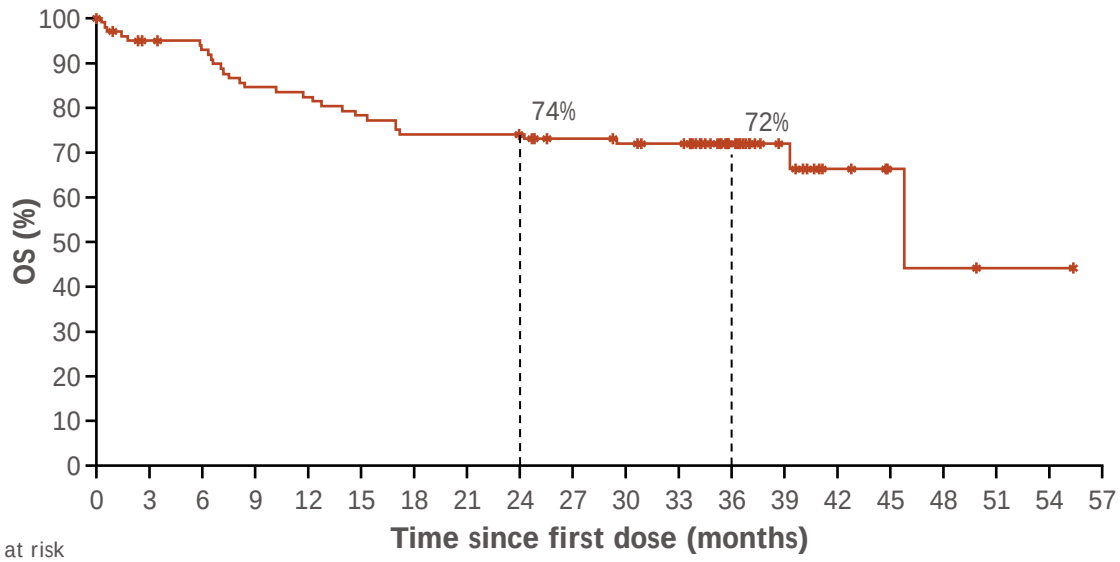
Intracranial PFS



No. at risk

Investigator assessed: 101	66	50	43	43	42	39	38	32	30	24	22	6	0	0	0	0	0	0	0
BICR-assessed: 101	63	52	44	43	41	37	36	32	29	26	22	8	2	1	1	0			

OS



No. at risk

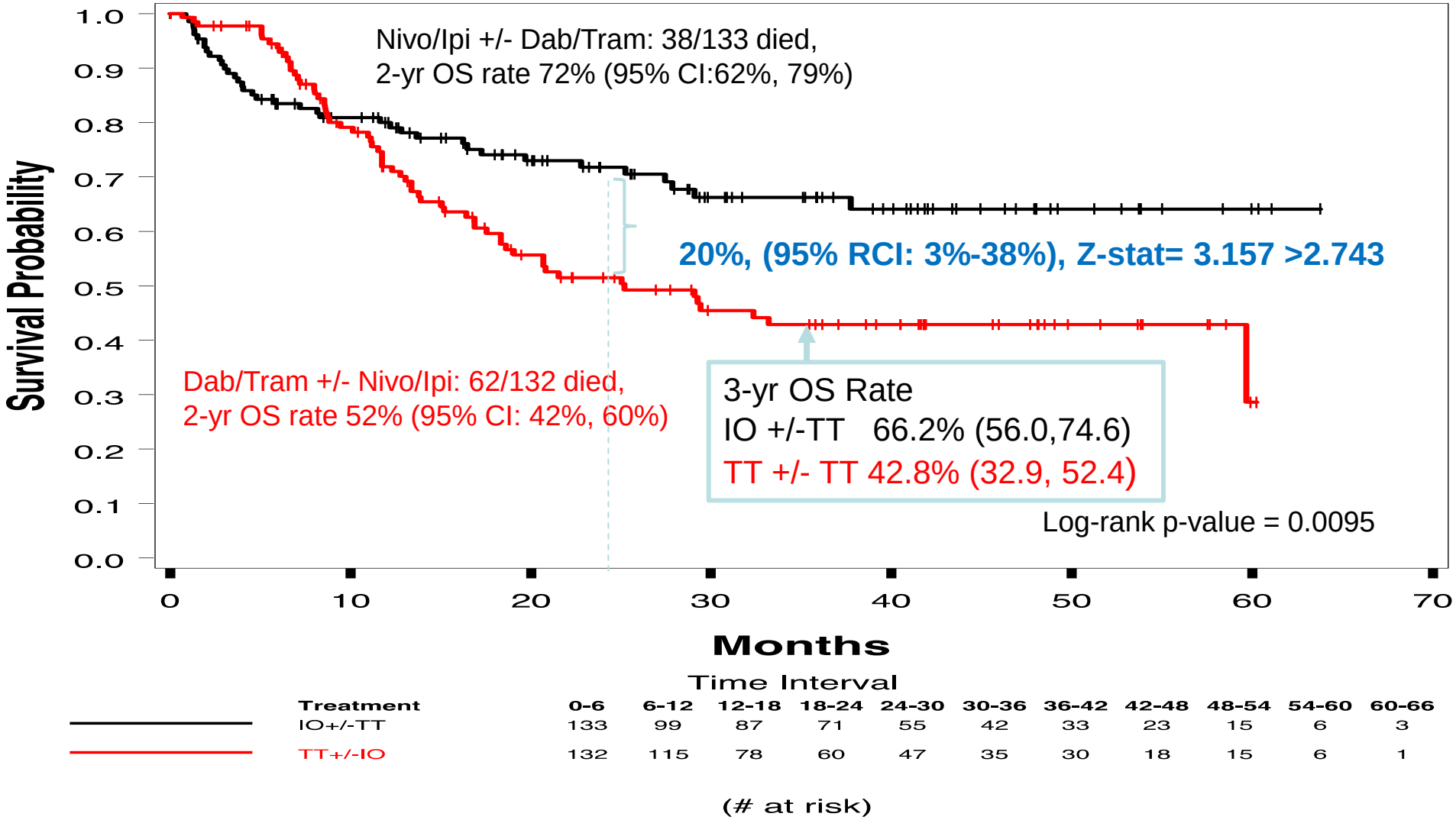
Asymptomatic: 101	92	89	81	79	75	71	71	70	66	64	62	30	13	6	3	2	1	1	0

IO Therapy appears to overcome the blood brain barrier

Checkmate 204

Tawbi, H. et al, *Lancet Oncology, Nov 10, 2021.*

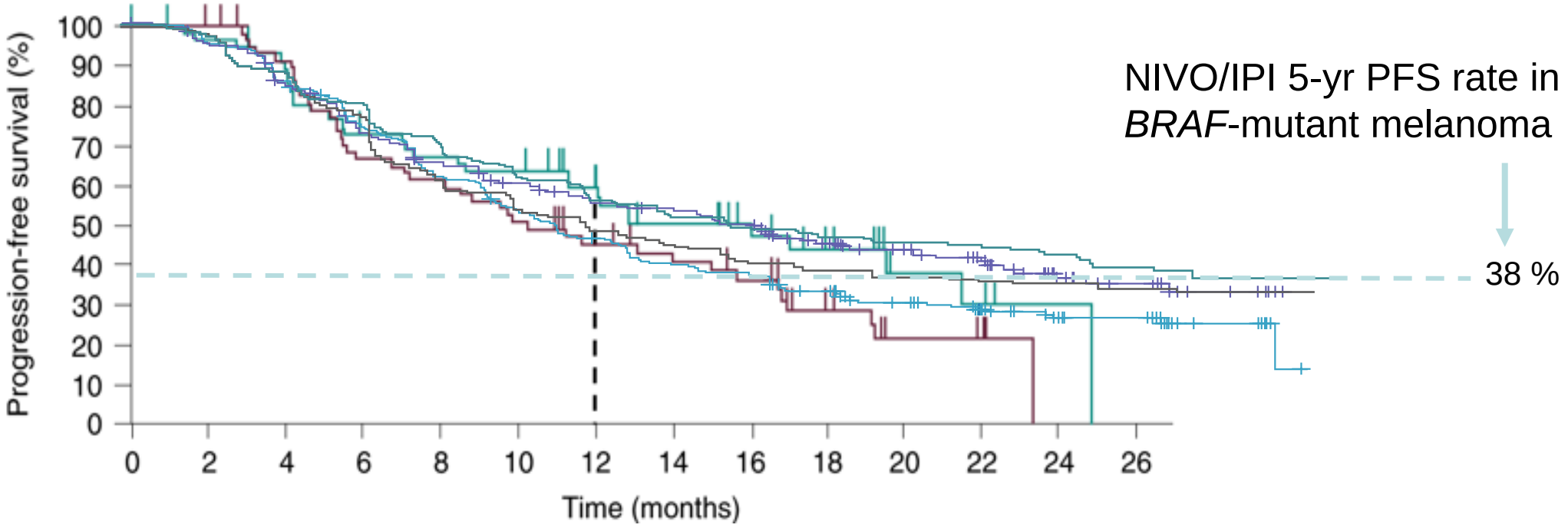
Overall Survival (OS): Step 1 +/- Step 2



- Atkins MB, et al. J Clin Oncol. 2022; Sep 27:101200JCO2201763. Online ahead of print; Atkins M. Poster presented at: ASCO Plenary Series; November 16, 2021. Abstract 356154.

Triplet Therapy: BRAF/MEK+anti-PD-(L)1

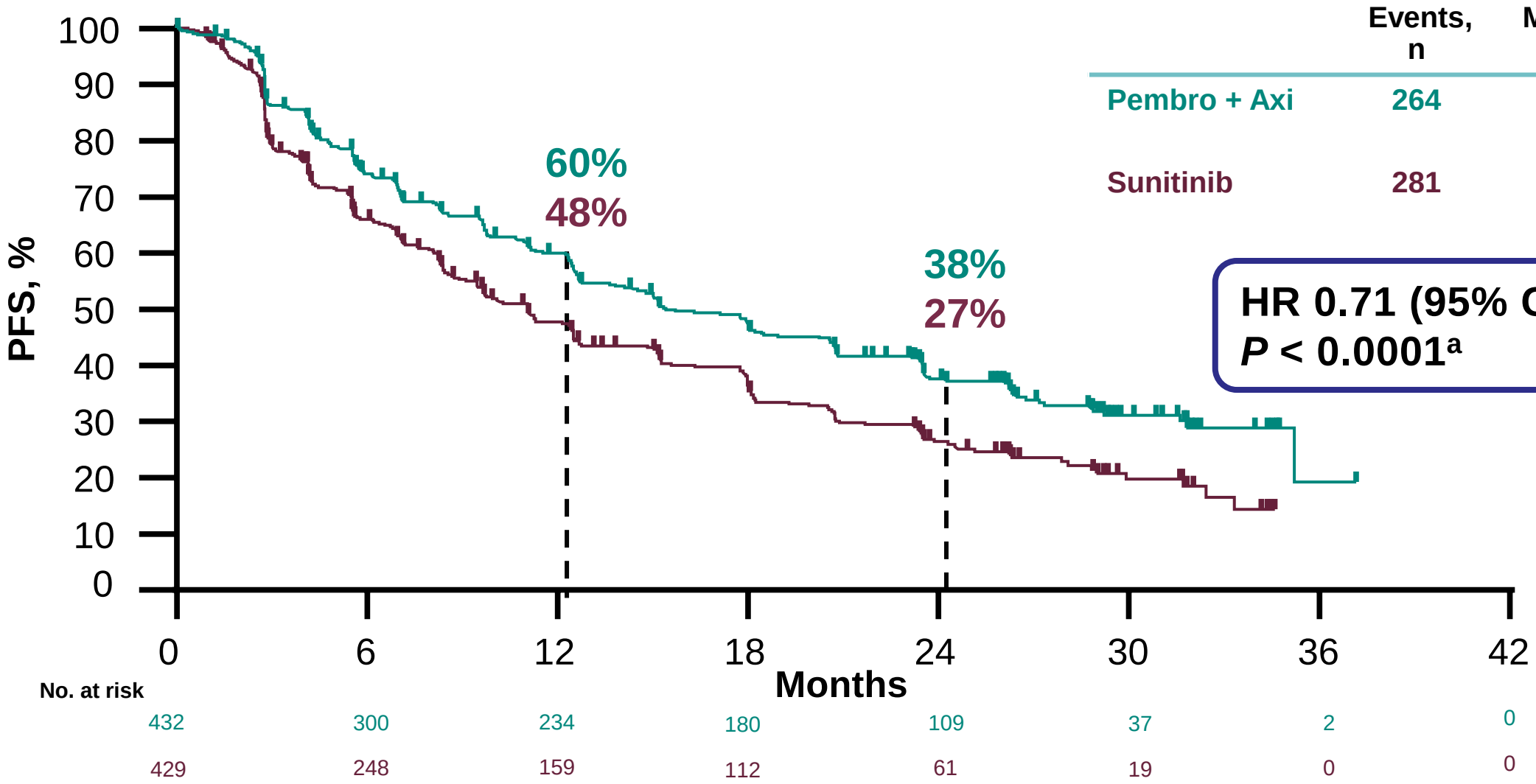
- **KEYNOTE-022, IMspire150, COMBI-i**



No tail on PFS Curve !!!

Chmielowski B. Poster presented at: ESMO; September 19-21, 2020. Presentation 4816.

KN-426: IO+VEGFR-TKI in RCC



	Events, n	Median (95% CI), mo
Pembro + Axi	264	15.4 (12.7-18.9)
Sunitinib	281	11.1 (9.1-12.5)

HR 0.71 (95% CI 0.60-0.84)
***P* < 0.0001[a]**

Plimack E et al. Presented at: ASCO 2020; May 29-31, 2020; Virtual Meeting. Abstract 5001.

IO-Non IO Combinations: Cautions

- IO is different than tumor-directed therapy, because of its ability to produce Treatment-free survival (TFS)/”Cure”
- Combinations that improve median PFS or median OS without producing TFS, may sacrifice the potential of IO while contributing toxicity, inconvenience and tremendous extra cost
- Not only must A+B be > than A to B (or B to A), but TFS/”Cure” must be maintained in order for such combos to be fully embraced
- Clinical trials with IO agents need to use IO endpoints

Principal IO Endpoints

- Landmark PFS/OS
- Complete (near complete) Response Rate
- Response Duration
- Time to initiation of subsequent therapy
- Treatment Free Survival/ “Cure”
- Overall Quality of Life/Overall Value

Our goal should not be simply to turn cancer into a chronic disease…

We should strive to make cancer a curable disease

Using agents/combinations that maximize the anti-tumor immune response (raise the plateau and enable TFS) is critical to achieving that goal

Acknowledgements

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  - David McDermott
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  - Arlene Sharpe

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- Brent Harris
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Other

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- Ben Izar
- Bartozc Chmielowski
- HCRN GU Team
- Brian Rini
- Mario Sznol

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- DFHCC Kidney Cancer SPORE
- DOD Translational Science Team Award
- NCI Provocative Question R01
- NCI CCSG Program
- William M Scholl Foundation
- Stan and Linda Sher Immunotherapy Grant
- Gieseman Foundation

Special Acknowledgements







CANCERS PATHWAY; HOW TO BLOCK IT

Larry Norton, MD

Memorial Sloan Kettering Cancer Center

Senior Vice President, Office of the President,
Medical Director, Evelyn H. Lauder Breast Center

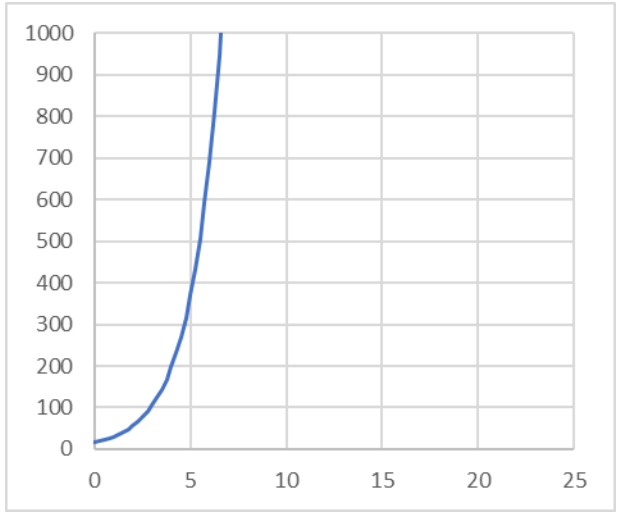
Why is it so hard to cure cancer in the clinic?

Why is it so hard to cure cancer in the clinic?

What can we do about this?

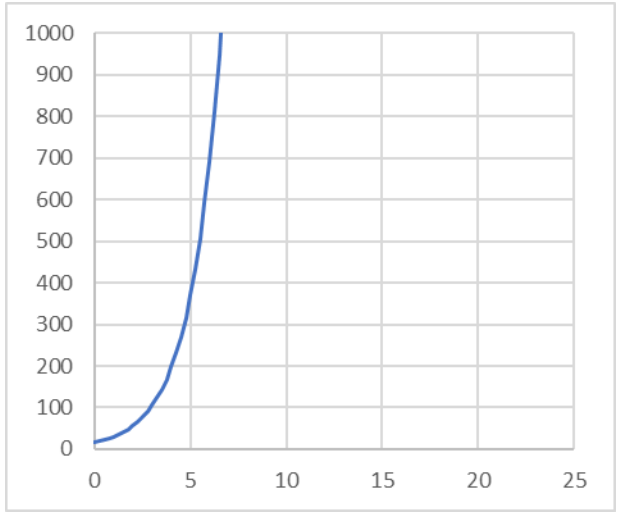
It is rather easy to cure cancer in the laboratory

Exponential Growth

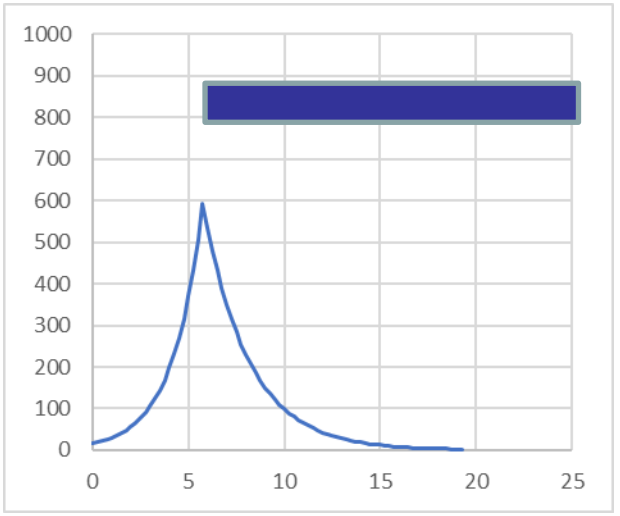


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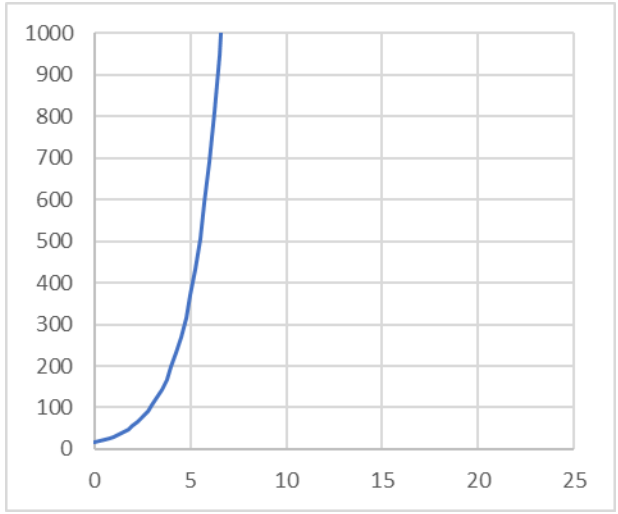
Anti-Mitotic Therapy



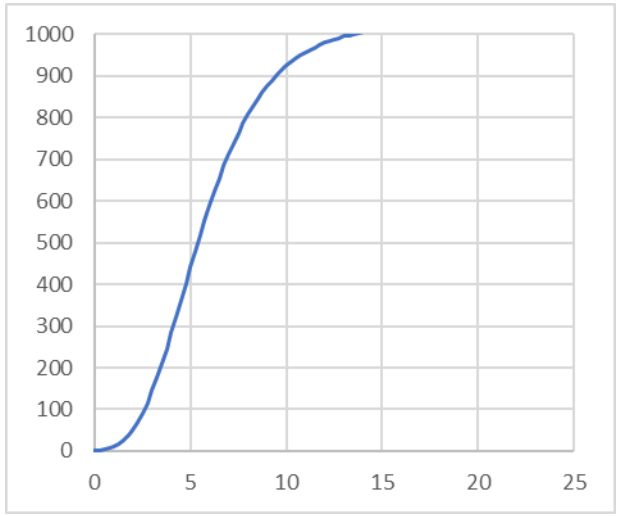
But clinical cancers do not grow exponentially!

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Exponential Growth

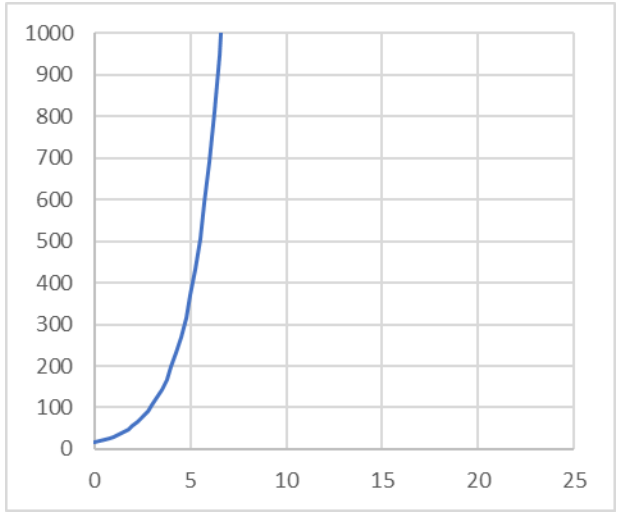


Gompertzian Growth

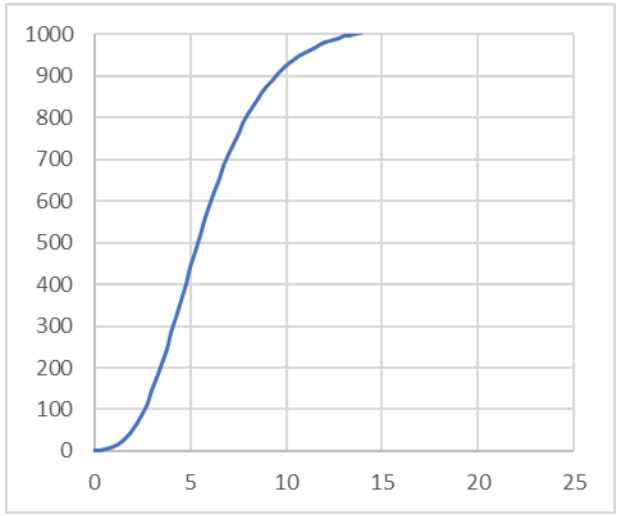


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Gompertzian Growth

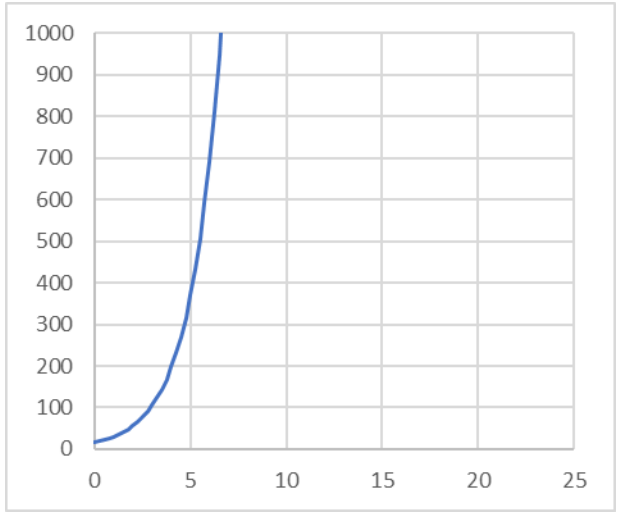




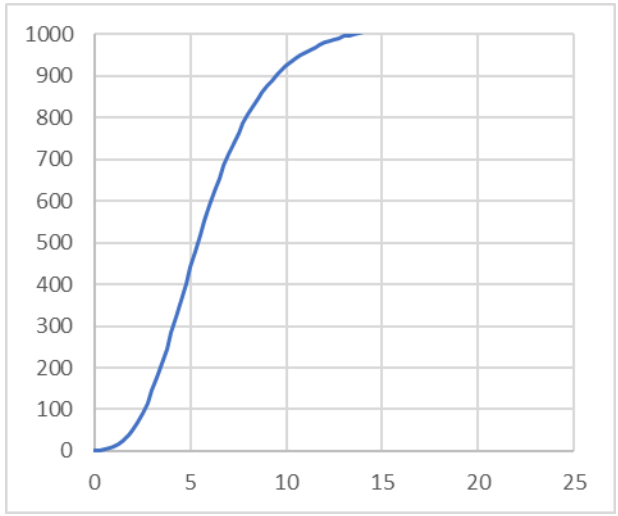
Benjamin Gompertz 1779-1865

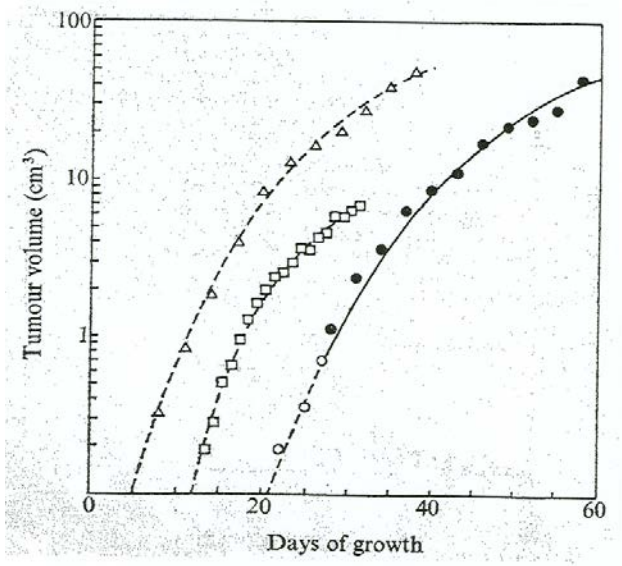
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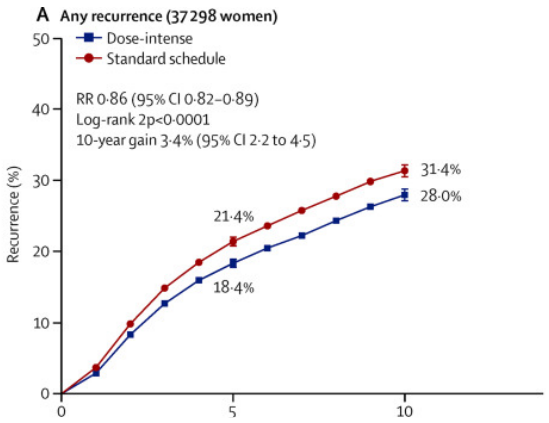




Norton L *et al.*, Nature, 1976

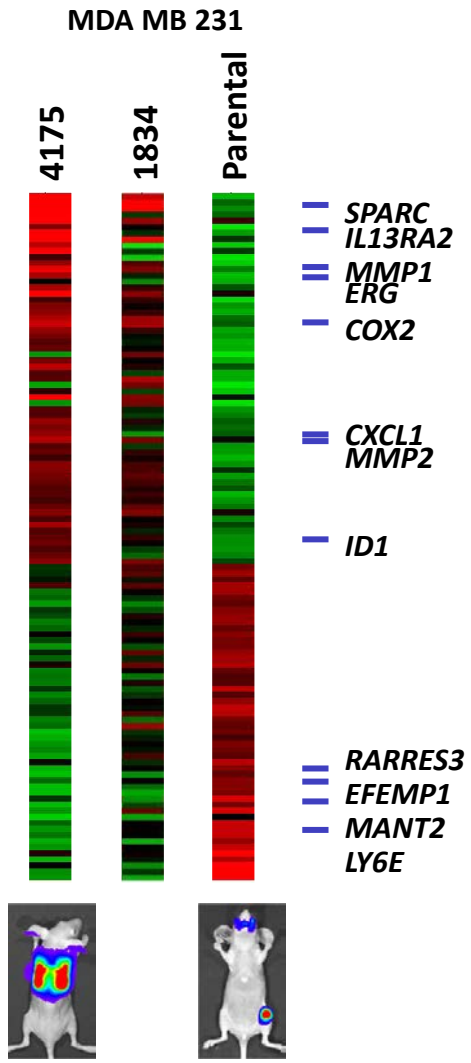
Chemotherapy based on Gompertzian kinetics improves cure rates

Recurrence Reduced

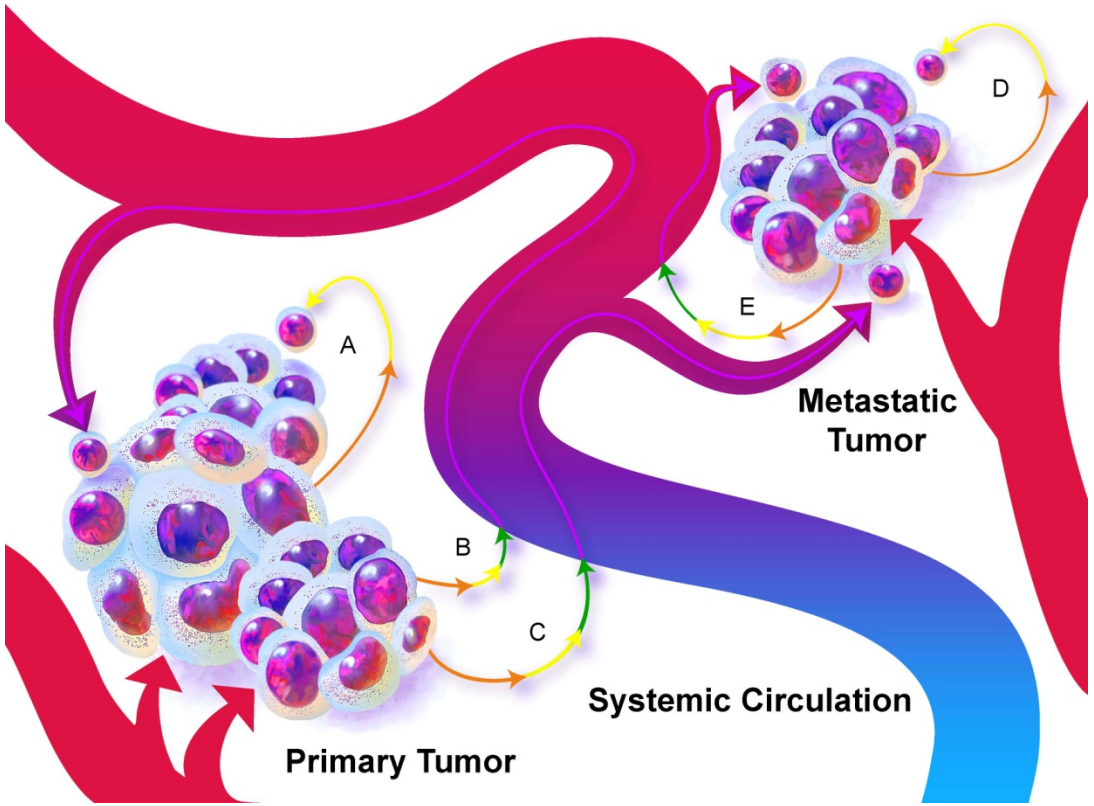


26 Randomized Trials, 37,298 Patients: EBCTCG, Lancet, 2019

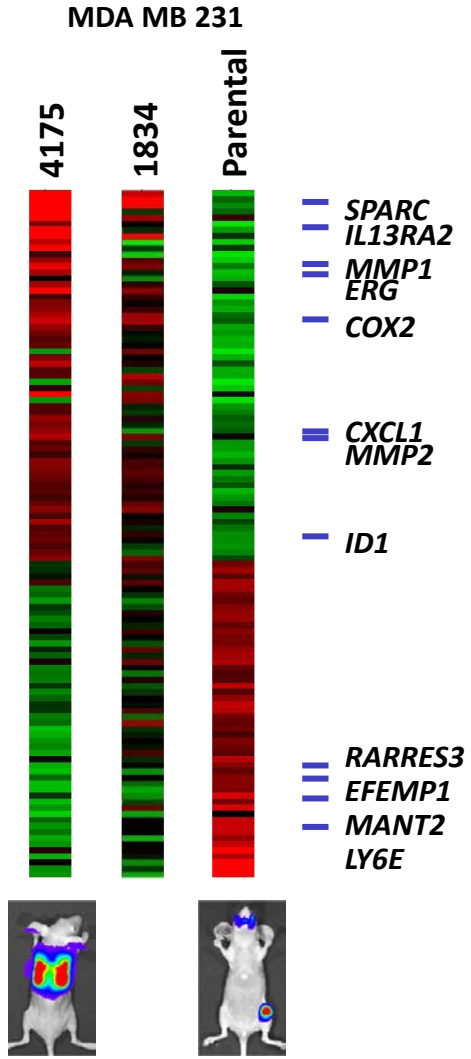
Tumor growth and cancer cell metastases are linked



Tumor growth and cancer cell metastases are linked



Norton and Massague, Nature Med, 2006

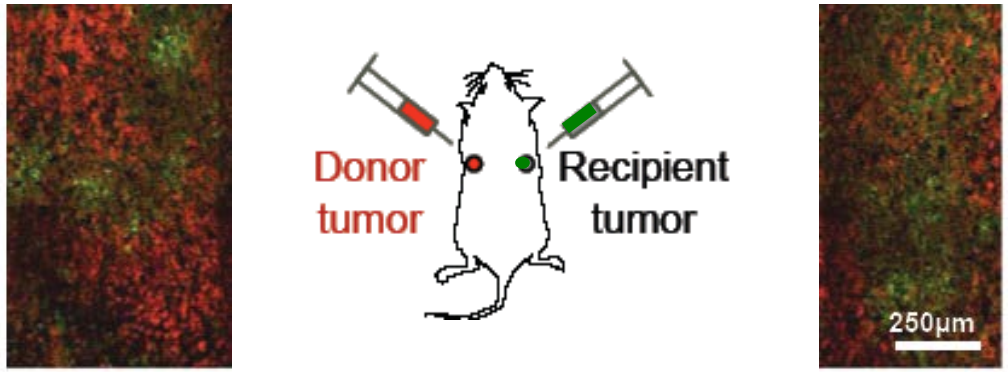


Tumor growth and cancer cell mobility (seeding) are linked



Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J. Cell, 2009

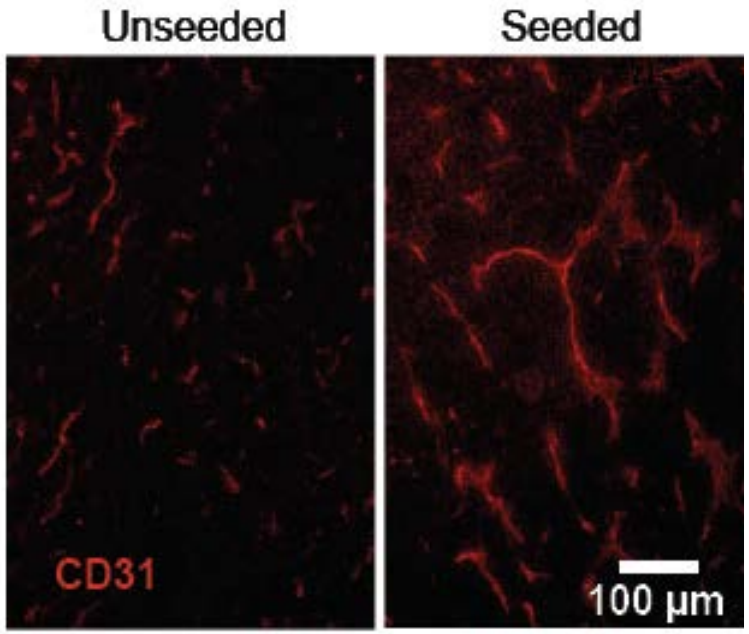
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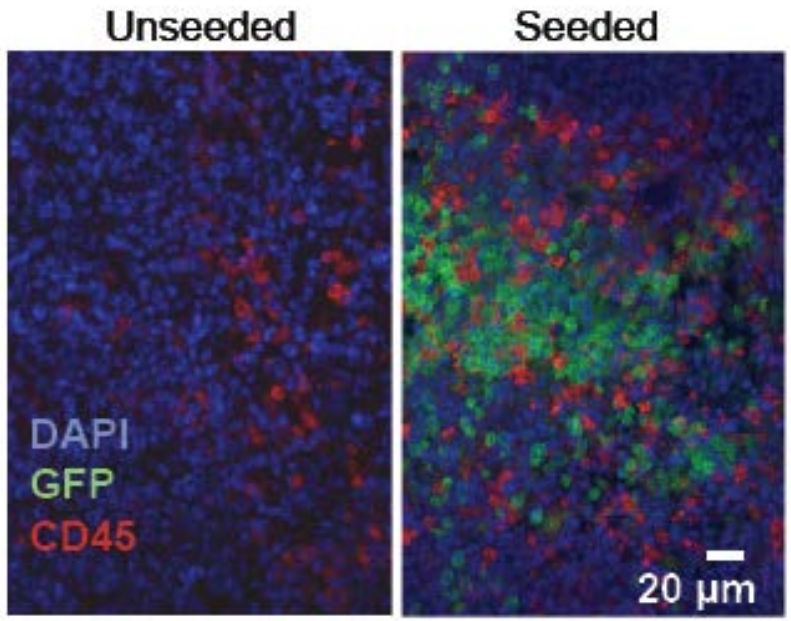
Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J. Cell, 2009

Breast cancer seeds create their own microenvironment by recruitment

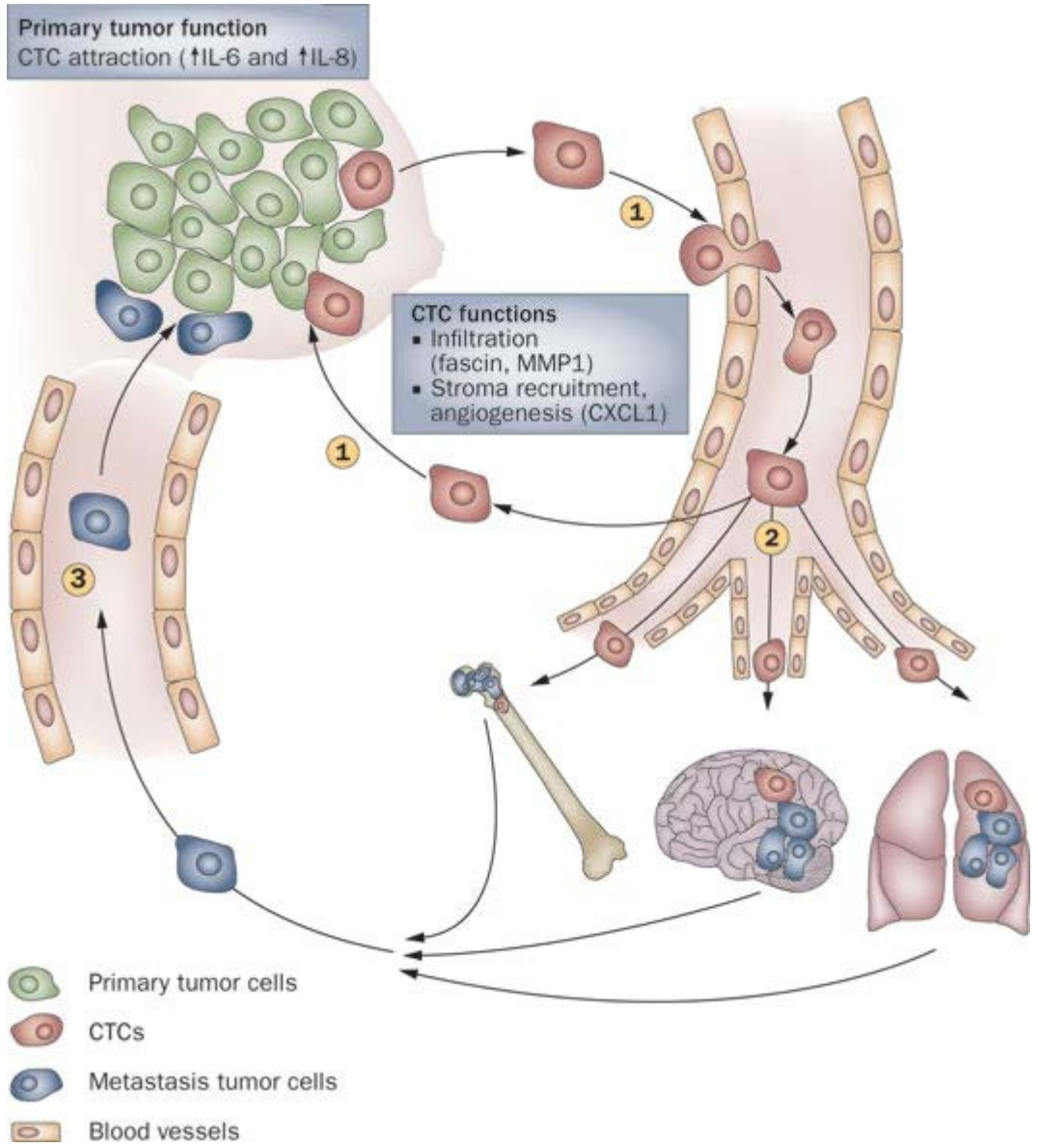
Angiogenesis



Leukocytes



Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J. Cell, 2009



Comen E, Norton L, Massagué. Nature Rev Clin Oncol, 2011

So, the growth of human cancers has two components:

So, the growth of human cancers has two components:

Mitosis (the division of the cancer cells)

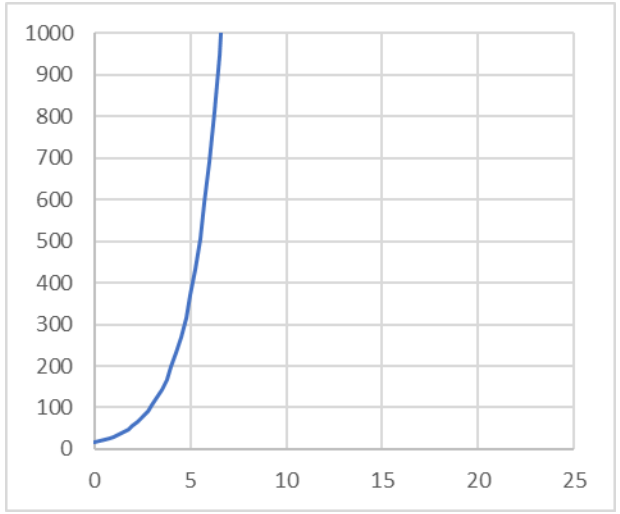
Geometry (the relationship of the cancer to its microenvironment)

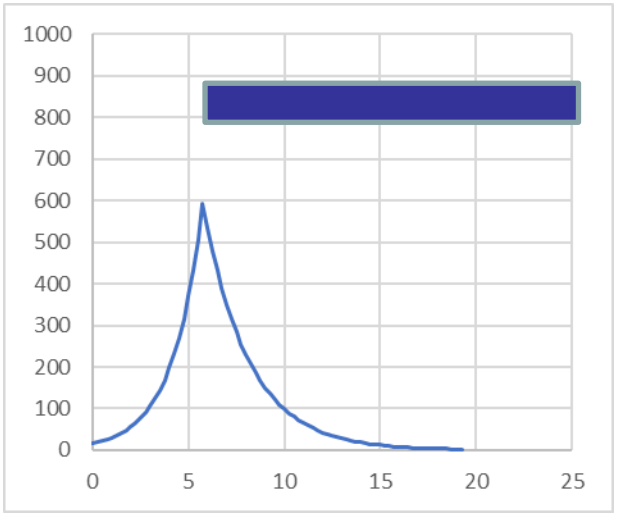
Gompertzian cancers are not cured by the same anti-mitotic therapy that cures exponential cancers in the laboratory

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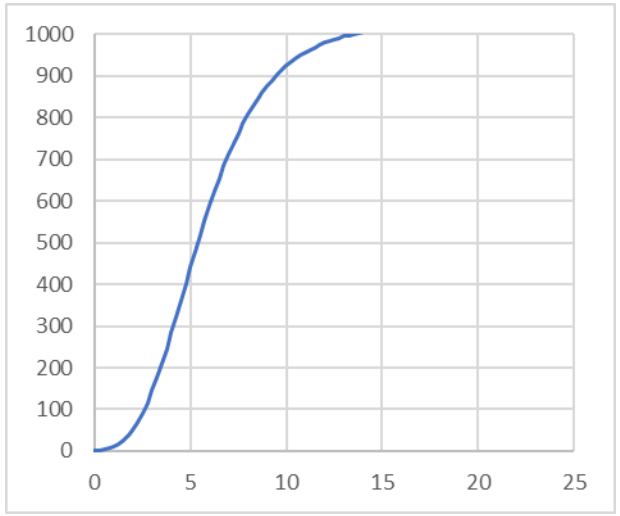
Anti-Mitotic Therapy

Exponential Growth





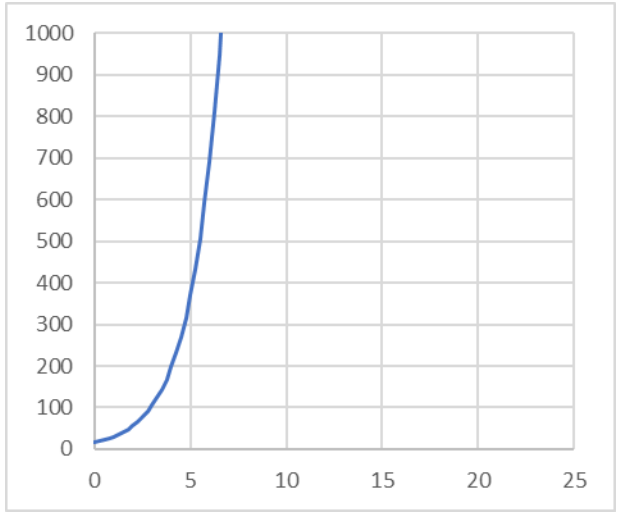
Gompertzian Growth

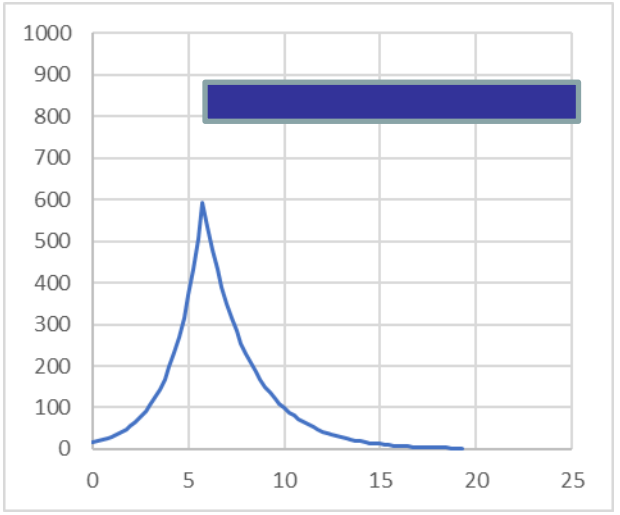


Gompertzian cancers are not cured by the same anti-mitotic therapy that cures exponential cancers in the laboratory

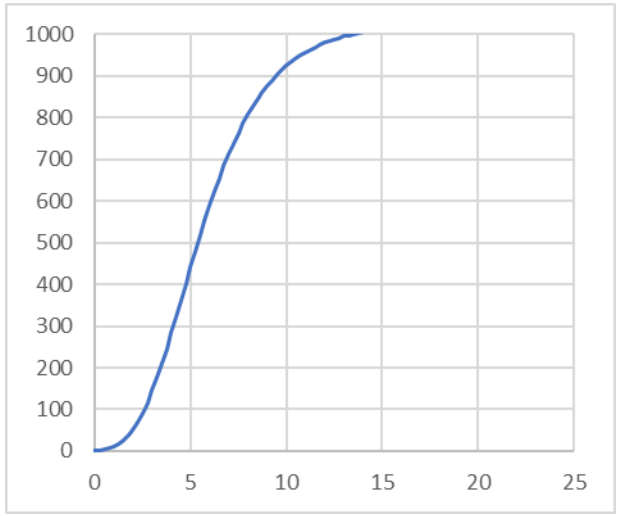
Anti-Mitotic Therapy

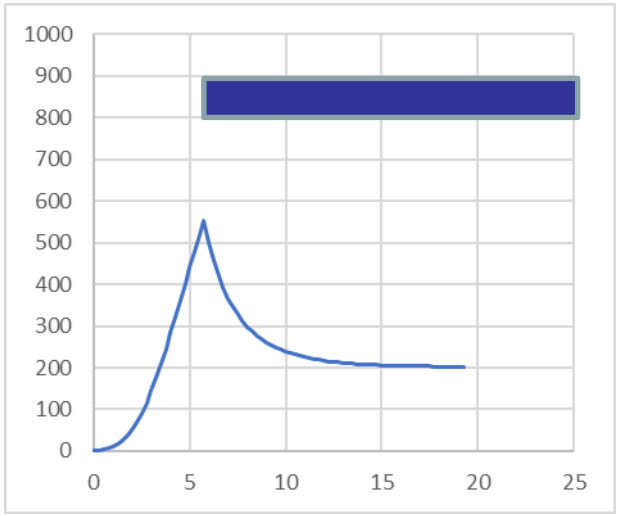
Exponential Growth





Gompertzian Growth

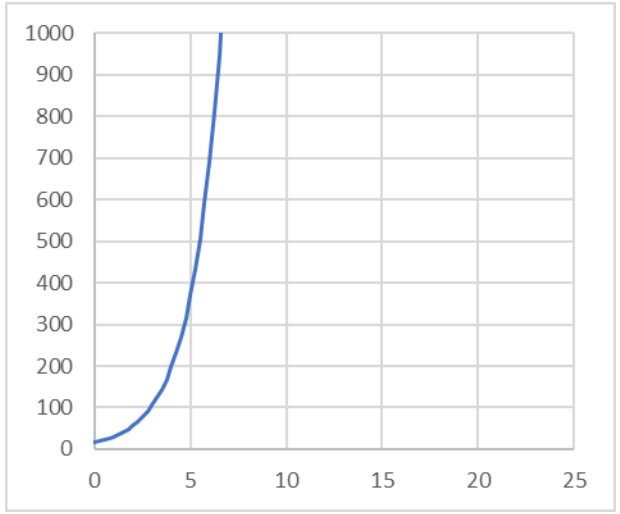


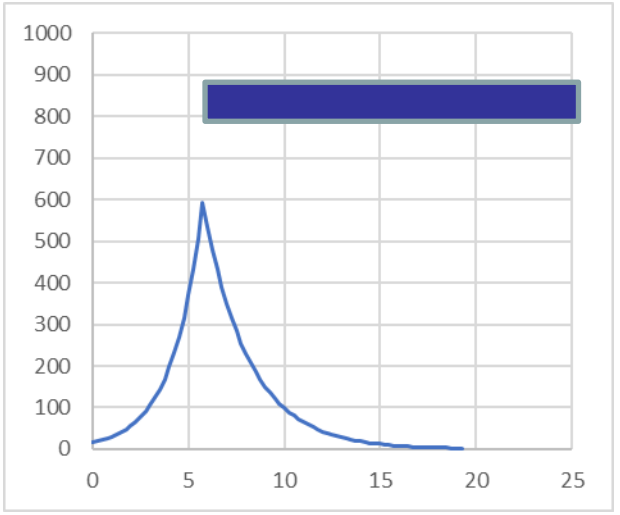


…but immunotherapy added to antimitotic therapy can cure!

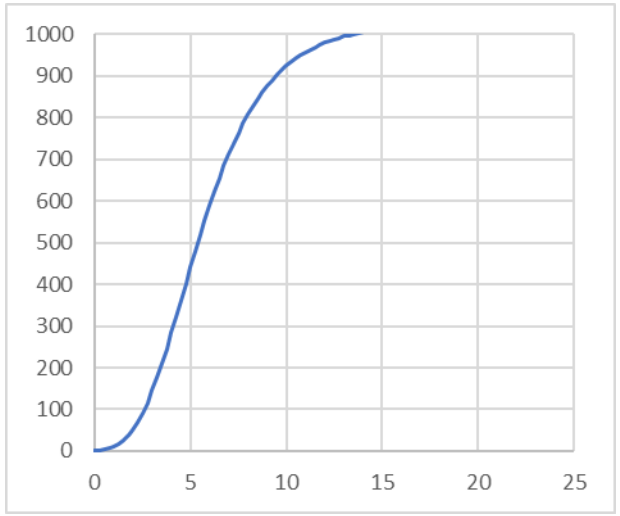
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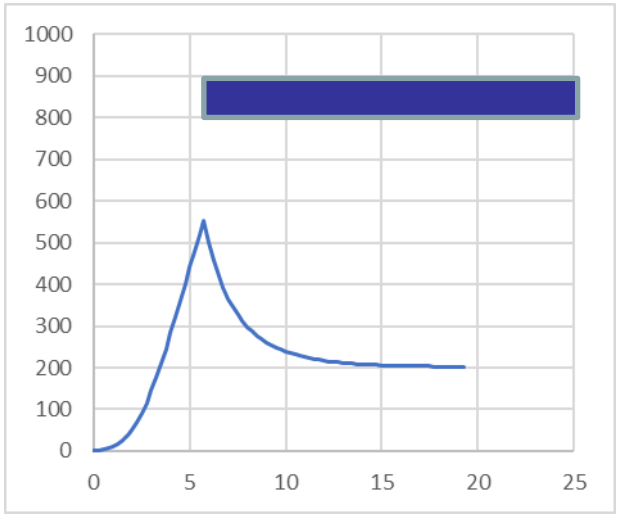
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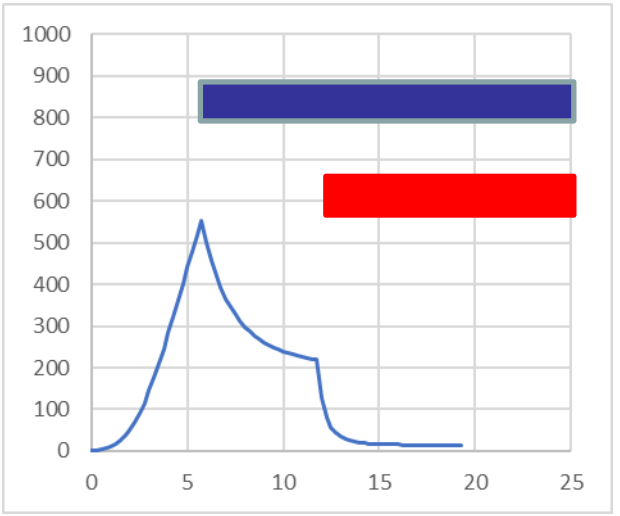


Gompertzian Growth

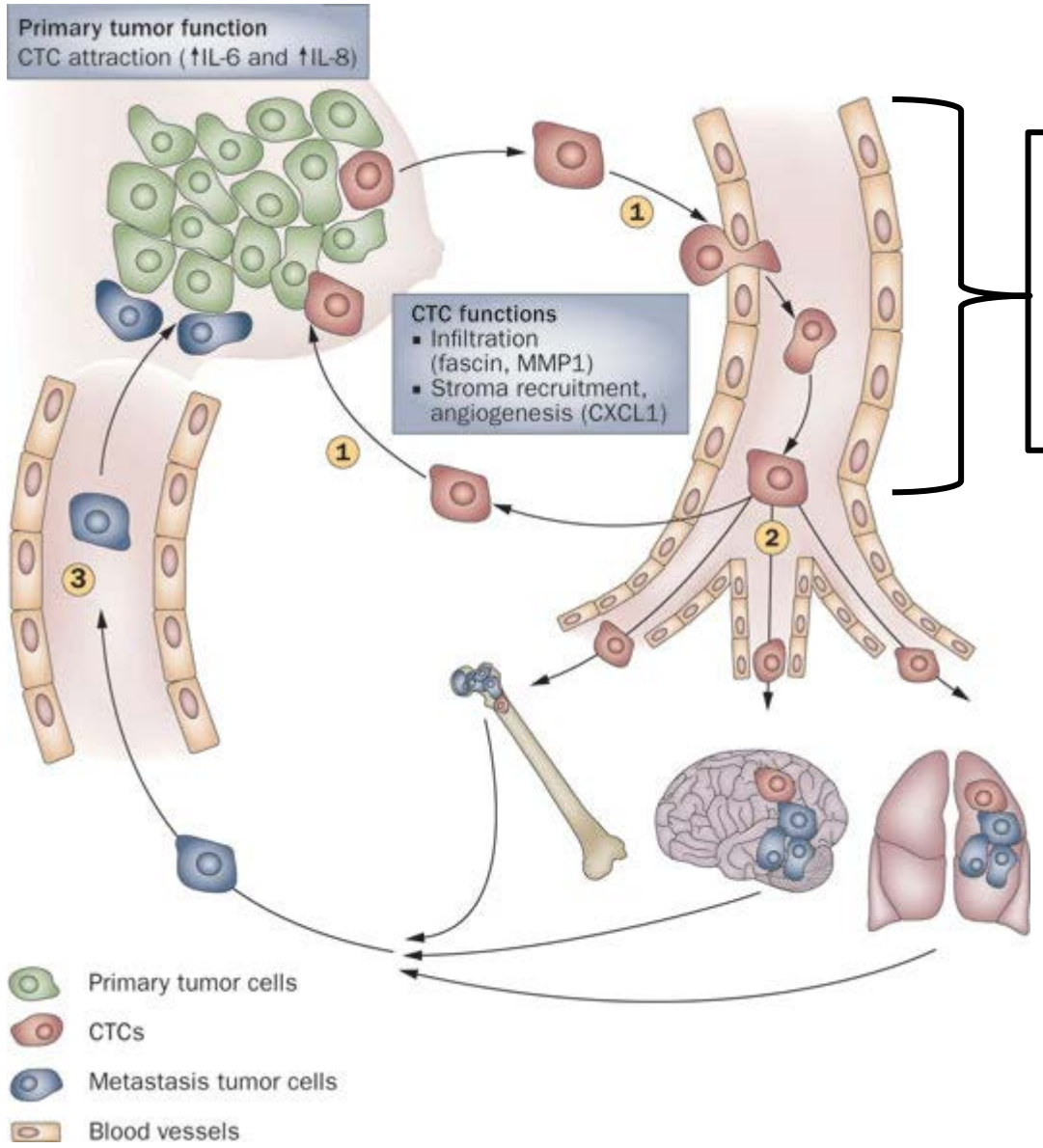




Anti-Mitotic Therapy plus Immunotherapy



Anti-Mitotic Therapy



Therapy that Addresses the Tumor Microenvironment (Immunotherapy)

Comen E, Norton L, Massagué. Nature Rev Clin Oncol, 2011

Why is it so hard to cure cancer in the clinic?

What can we do about this?

Why is it so hard to cure cancer in the clinic?

Human cancers are Gompertzian.

What can we do about this?

Why is it so hard to cure cancer in the clinic?

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What can we do about this?

Expand the activity of highly effective immunotherapy to currently “cold” cancers.

Why is it so hard to cure cancer in the clinic?

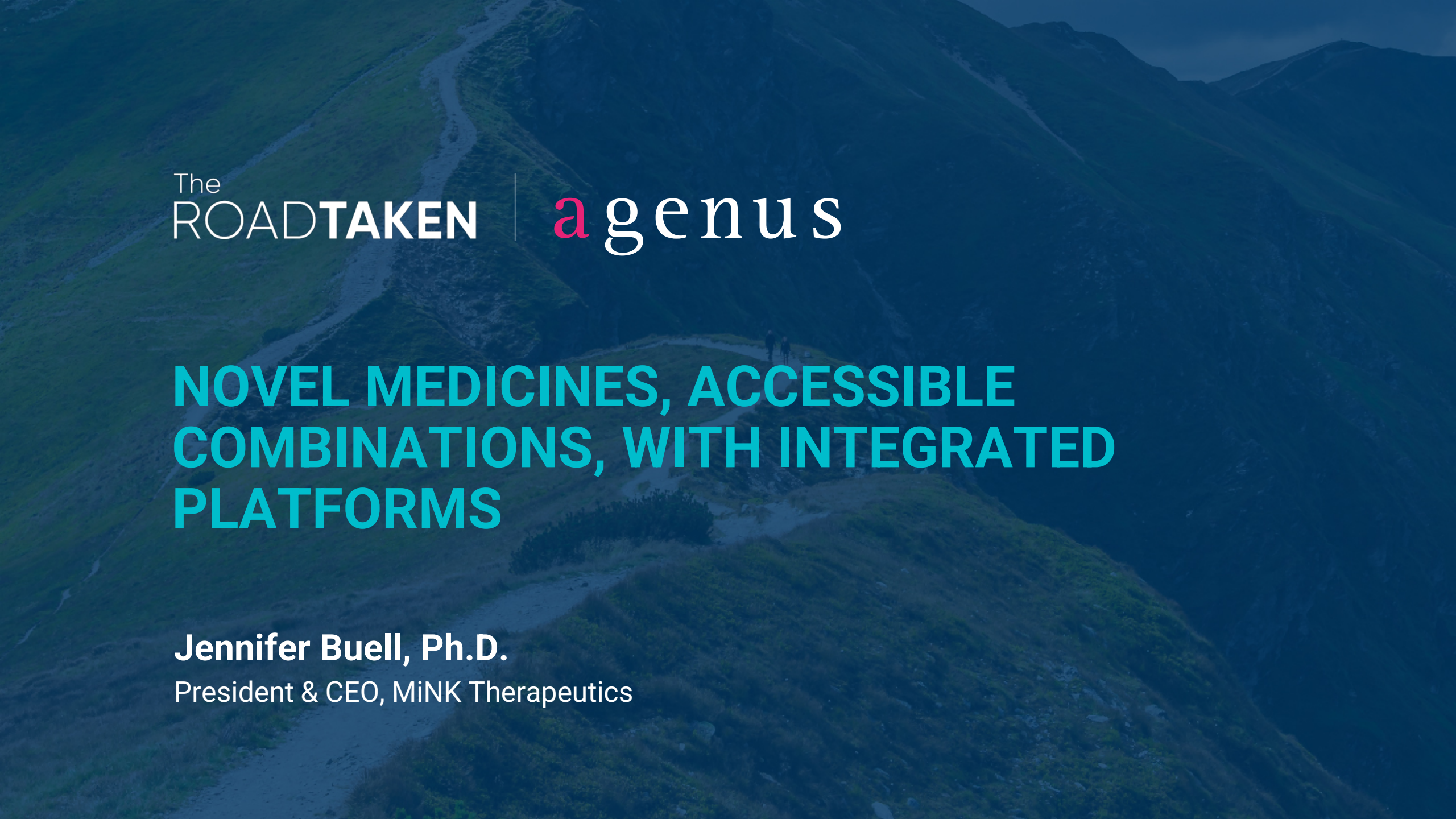
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What can we do about this?

Expand the activity of highly effective immunotherapy to currently “cold” cancers.

Thank You!


The ROADTAKEN
agenus
THE ROAD TAKEN



NOVEL MEDICINES, ACCESSIBLE COMBINATIONS, WITH INTEGRATED PLATFORMS

Jennifer Buell, Ph.D.
President & CEO, MiNK Therapeutics

CLINICAL STAGE PIPELINE

Diverse portfolio targeting multiple aspects of the cancer immunity cycle

	Mechanism/target	Product Candidate	Partner	Phase 1	Phase 2
Majority / fully owned pipeline	PD-1 +/- CTLA-4	Balstilimab +/- Zalifrelimab	Greater China	Cervical (2nd line)	
	Fc-enhanced CTLA-4 + PD-1	Botensilimab +/- Balstilimab		MSS colorectal cancer	
	Fc-enhanced CTLA-4	Botensilimab		PD-1 r/r melanoma, pancreatic (w/chemo)	
	CD137 + Fc-enhanced CTLA-4	AGEN2373 + Botensilimab		PD-1 r/r melanoma	
	CD137	AGEN2373	GILEAD Option program	Solid tumors	
	CD73 / TGFβ trap + PD-1 + chemo	AGEN1423 + Balstilimab		Pancreatic cancer (w/chemo)	
	ILT2	AGEN1571		Solid tumors	
	OX40	AGEN1949		Solid tumors	
Partner directed pipeline	ILT4	MK-4830	MERCK	NSCLC, ES-SCLC, EC, melanoma, CRC, RCC	
	TIM-3	INCAGN2390	Incyte	PD-1 r/r melanoma, SCCHN	
	LAG-3	INCAGN2385	Incyte	PD-1 r/r melanoma, SCCHN	
	GITR	INCAGN1876	Incyte	SCCHN	
	TIGIT (bispecific)	BMS-986442	Bristol Myers Squibb	NSCLC and solid tumors	
	RTGel™ + CTLA-4	UGN-301	UroGen Pharma	NMIBC	
Clinical collaborations	EP4 + PD-1	CR6086 + Balstilimab	ROTTAPHARM BIOTECH	MSS-colorectal cancer	
	Hedgehog + CTLA-4	NLM001 + Zalifrelimab	Nelum	Pancreatic cancer	

AGENUS HIGHLIGHTS

Agenus is a clinical-stage immuno-oncology (I-O) company advancing a deep pipeline of checkpoint inhibitors, immune activators, and tumor microenvironment conditioning agents, including a novel innate and adaptive immune activator (botensilimab)

Botensilimab

Fc-enhanced anti-CTLA-4 antibody with broad franchise potential

Unprecedented clinical responses in 9 cold and treatment-resistant cancers, including expansion cohorts in MSS-CRC, NSCLC, ovarian, and sarcomas

Robust Portfolio

Deep clinical pipeline addressing complementary mechanisms, with broad indication potential

12 clinical-stage antibody programs advancing in 10 unique combinations, by Agenus and through partnerships

Track Record

Proven R&D engine with track record of value creation through strategic partnerships

Generated $825M in cash through partnerships ($220M in 2021), with potential $2.7B milestones

INTEGRATED CAPABILITIES FOR DIFFERENTIATION & SPEED

Commercial and cGMP Manufacturing

Reduces timelines & costs, improves flexibility

- **Berkeley, CA**
  - 25,000 sq. ft clinical cGMP facility
  - Team of 70 scientists, engineers, and technologists who have developed >20 antibody candidates
- **Emeryville, CA**
  - ~83,000 sq. ft commercial facility under construction
  - Fully integrated biologics cGMP and commercial production
- **Vacaville, CA**
  - 80-acre greenfield site with plans to house a ~500,000 sq. ft facility

Clinical Operations

Enables rapid, high quality clinical enrollment

- 2 in-house CROs with suite of capabilities – medical writing, stats/data management, pharmacovigilance, regulatory, clinical monitoring
- Expertise in Phase I – IV clinical trials in over 15 therapeutic areas
- > 200 personnel
- KOL and site relationships across >40 countries

ATLANT CLINICAL an agenus company

CTC North an agenus company

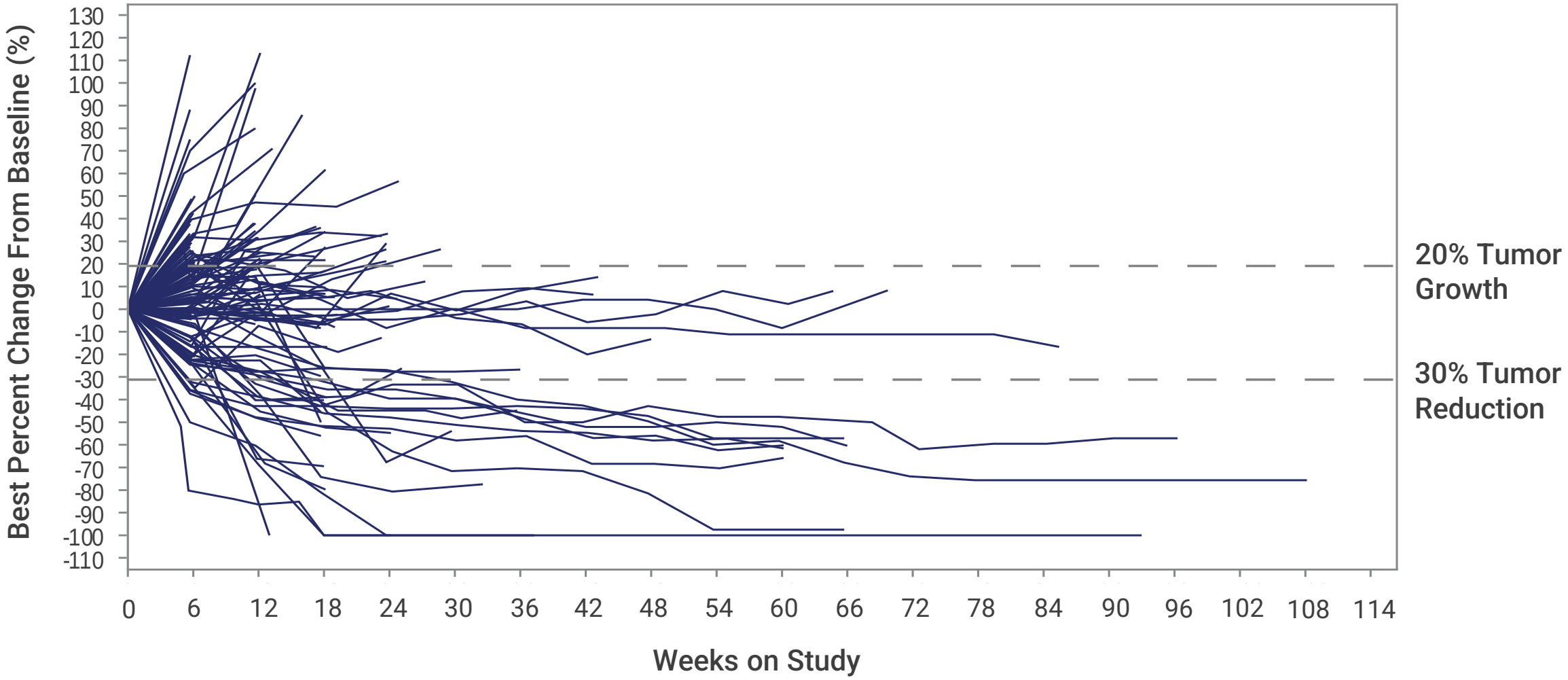

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agenus
THE DATA



AGENUS PORTFOLIO FOR CURATIVE THERAPIES

Steven O'Day, MD
Chief Medical Officer

BOTENSILIMAB/BALSTILIMAB EFFICACY IN COMBINATION PATIENTS (N=125)



The ROADTAKEN | agenus

TREATING THE MOST DIFFICULT CANCERS - BOTENSILIMAB

Breelyn Wilky, MD

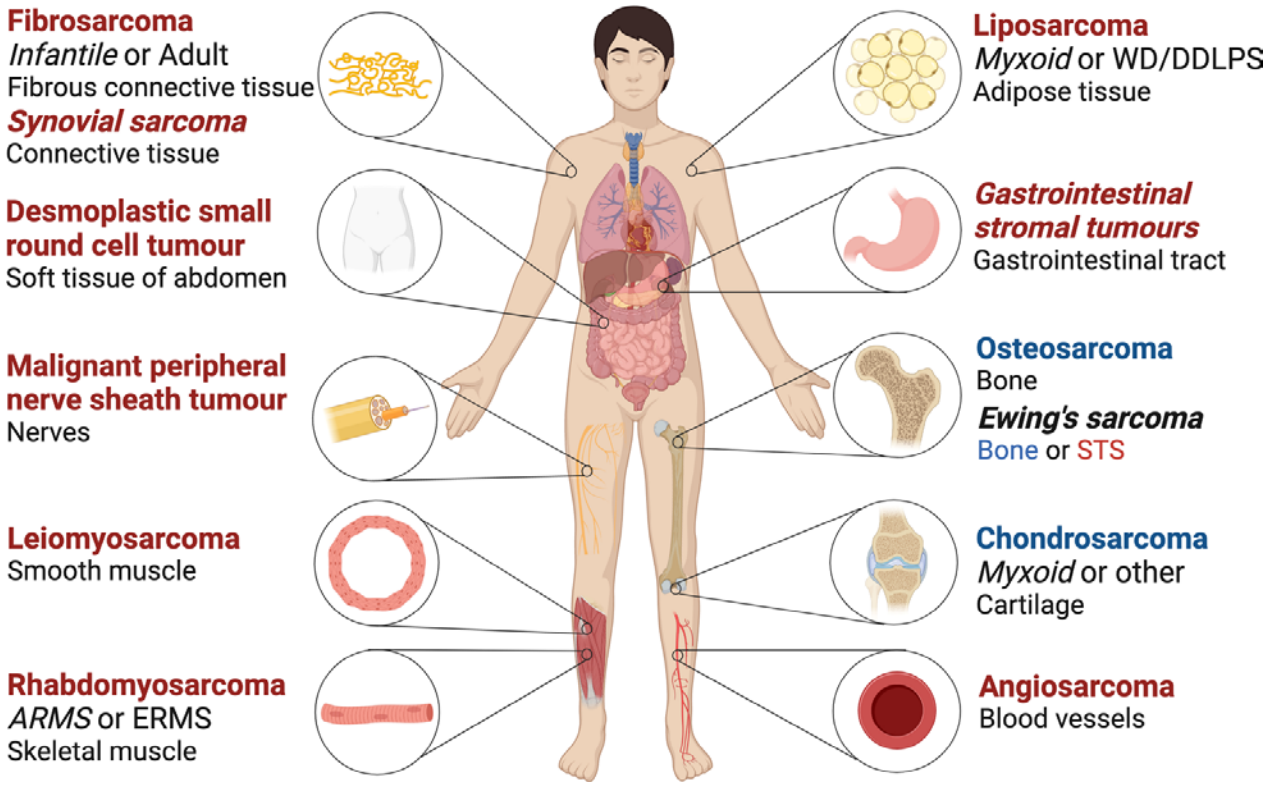
University of Colorado Cancer Center
Director of Sarcoma Medical Oncology
Deputy Associate Director for Clinical Research

A Look Back…

Perspectives on immunotherapy in sarcoma

University of Colorado
Anschutz Medical Campus

Sarcomas: Over 100 different cancers!

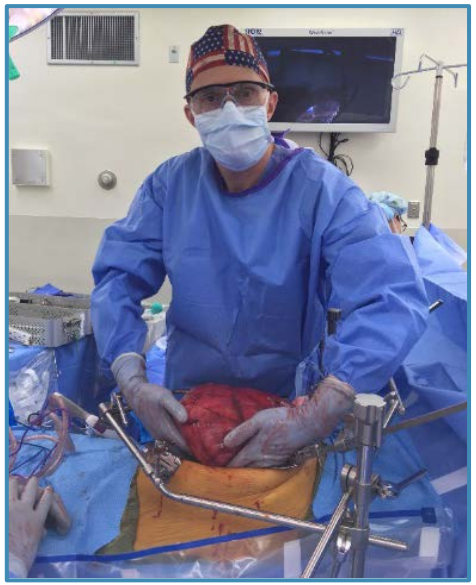


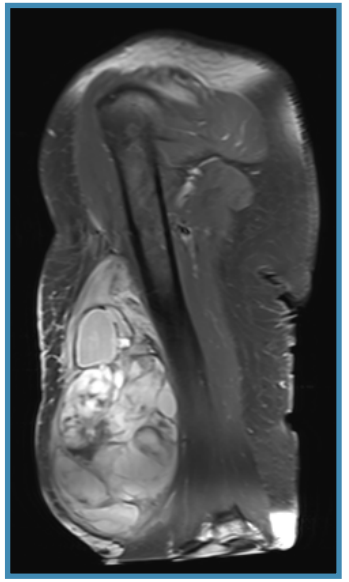


Head to toe…

Young to old…

Benign to aggressive…





High-grade undifferentiated sarcomas – mesenchymal stem cells

University of Colorado
Anschutz Medical Campus

Damerell et al, Signal Transduct Target Ther, 2021

Sarcomas: Customizing treatment approaches by subtype and genetic drivers

The "Others"

Limited activity of cytotoxics and targeted therapies

Common "adult" subtypes

- High grade pleomorphic sarcomas (UPS, MFH)
- Liposarcomas
- Angiosarcomas
- Leiomyosarcomas
- MPNST
- Epithelioid sarcomas

Drug	RR (%)	PFS (median, months)	OS (median, months)
Doxorubicin	18.3	6.8	19.7
Liposomal doxorubicin	10	2.1	10.6
Doxorubicin/ Ifosfamide	26	7.4	14.3
Gemcitabine/ Docetaxel	17	6.2	17.9
Trabectedin	9.9	4.2	12.4
Eribulin	4	2.6	13.5
Pazopanib	6	4.6	12.5
Aldoxorubicin	8.3	4.11	12.9

Other targeted therapies – tazemetostat, CDK4 inhibitors

Adapted from Alavi…Wilky et al, Discov Med 2018

Sarcomas and immune surveillance?



Surgical Section.

July 13, 1909.

Mr. J. Warrington Haward, President of the Section, in the Chair.

The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).

By William B. Coley, M.D. (New York.)[1]

The subject upon which I have been asked to address you is one upon which I have been working constantly the last seventeen years, and one which has grown more interesting to me with each succeeding year. While the results have not been as satisfactory as one who is seeking perfection could wish, they have been sufficiently real and tangible, I think, to be entitled to more careful consideration than they have yet received. Furthermore, they may have an important bearing upon the whole cancer problem, since, if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumour cells of one variety of cancer—sarcoma—it is not unreasonable to suppose that by the use of some other forms of bacterial toxins we may succeed in destroying or inhibiting the growth of the other and more common variety—carcinoma.

At the outset I wish, at the risk of tiring the few of you who may have read and remember some of my former papers upon this subject, to give in the briefest possible words an outline of the early history of the method of treatment, and the several stages of its development, for the benefit of the many who have never heard of the mixed toxins of

[1] Professor of Clinical Surgery at Cornell University.

N—22

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

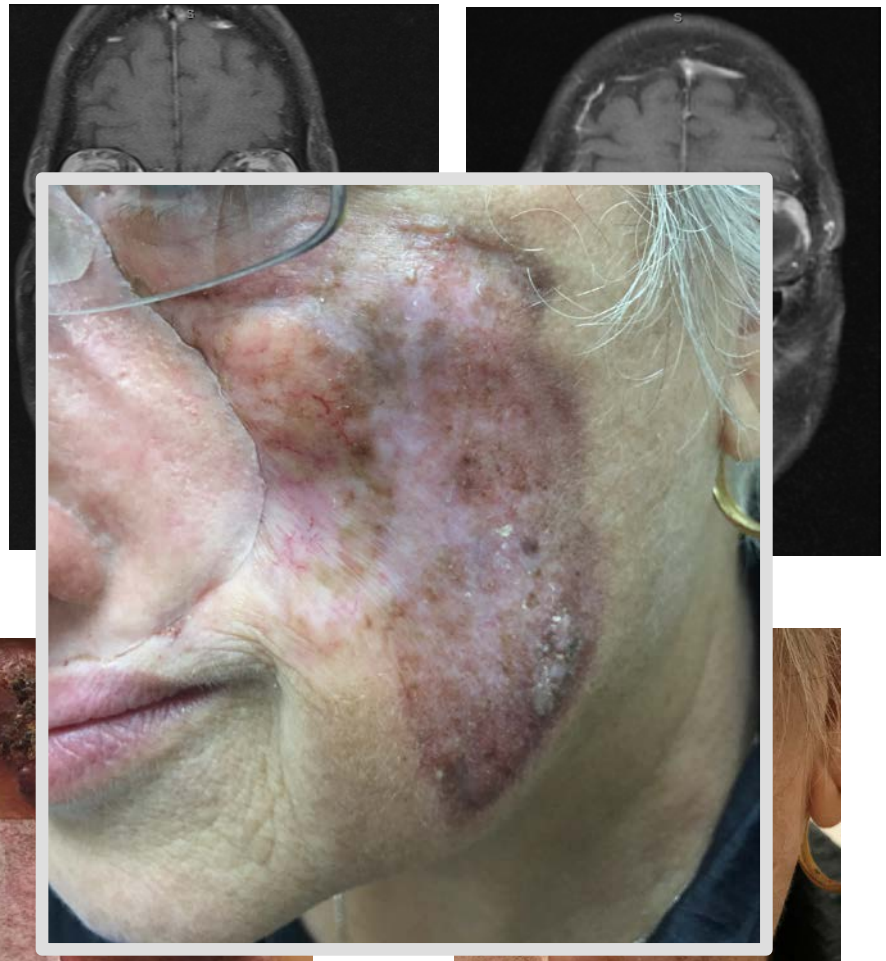
Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yesterday that nearly 100 cases of that supposely incurable disease have been cured in this city during the last few years, all through the use of the fluid discovered by Dr. Coley.

- Coley's Toxins
- Occasional cures of oligometastatic sarcomas by resection
- Variability in progression of disease

Angiosarcoma - my first immunotherapy super-responder

- Treated with AGEN1884 (anti-CTLA4) on Phase 1 trial at dose level 1 – **0.1 mg/kg** every 3 weeks x 18 months
- Radiographic complete response since March 2017, path CR confirmed February 2018 – remains cured!
- Remarkable responses in cutaneous angiosarcoma with checkpoint inhibitors in retrospective case series





Baseline



Day 12



Day 22

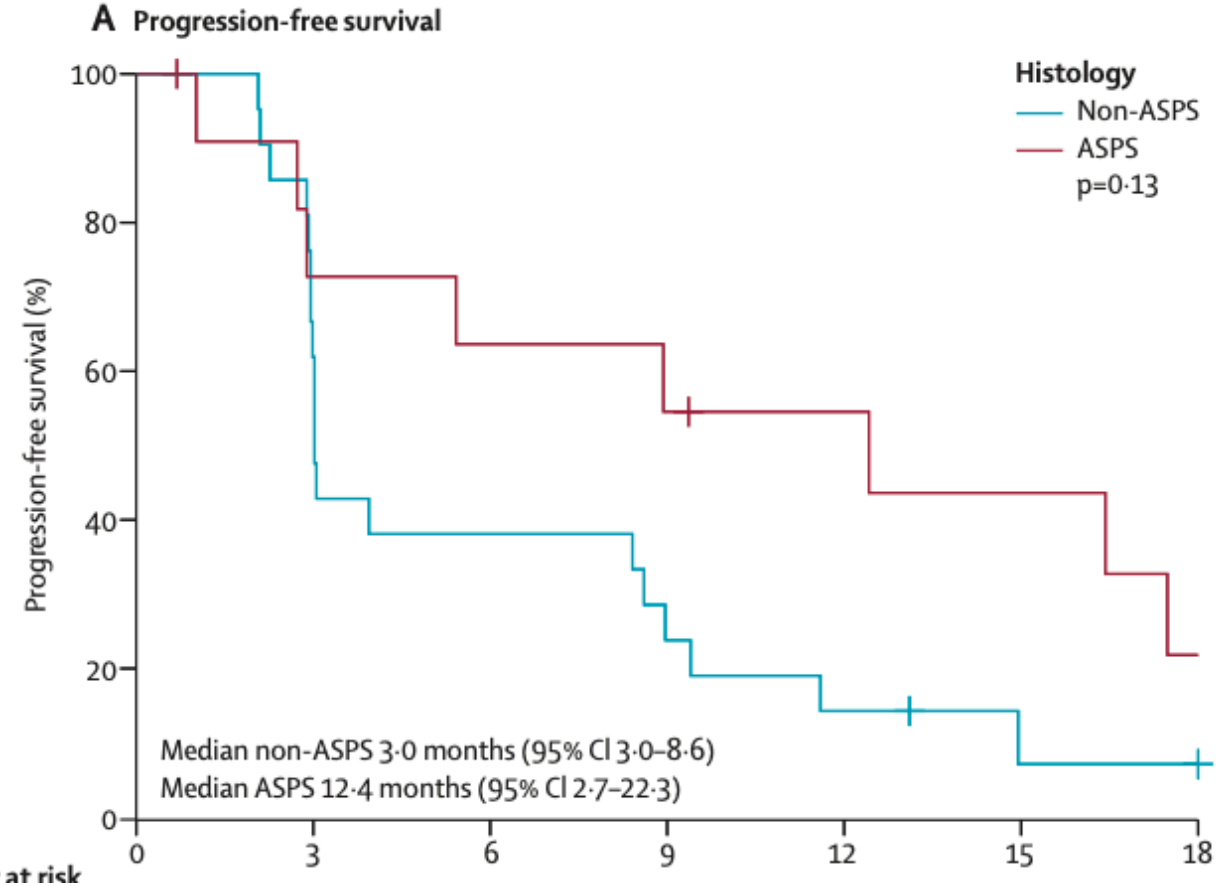
Week 43

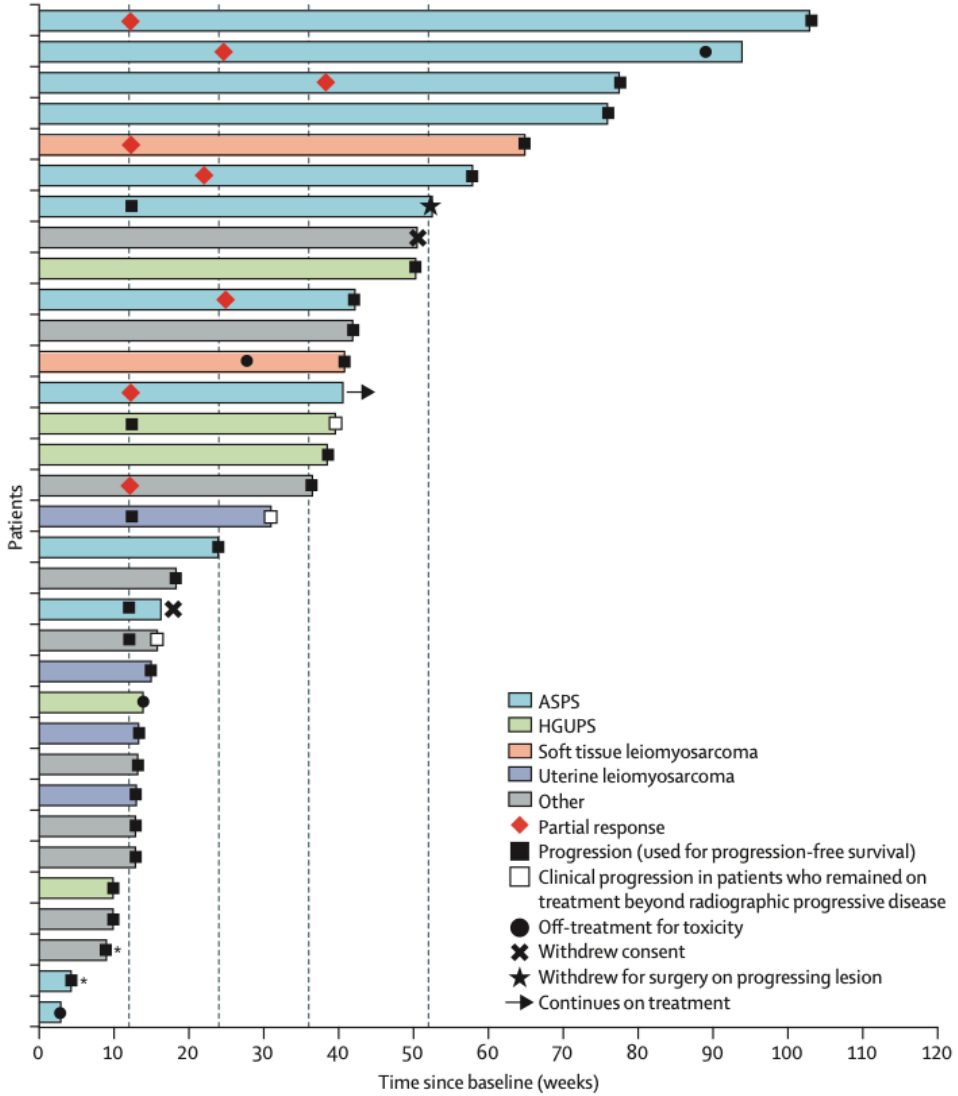
University of Colorado
Anschutz Medical Campus

Florou…Wilky et al, JITC 2019

Alveolar soft part sarcoma – the real success story!

Axitinib plus pembrolizumab





University of Colorado
Anschutz Medical Campus

Wilky et al, Lancet Oncol 2019

Alveolar soft part sarcoma – the real success story!

Therapy	N	RR (95% CI)	mPFS (months, 95% CI)	Reference
OSCAR, Nivolumab (ASPS only)	14	**7.1%** (0.2-33.9)	**6.0** (3.7-9.3)	Kawai et al, CTOS 2020
Hindi et al (retrospective)	21	**47.6%** (Not reported)	**10.9** (9.9-11.9)	Hindi et al, CTOS 2020
Durvalumab/Tremelimumab (ASPS subset)	10	**40%** (Not reported)	**34.23** (1.84-NR)	Somaiah et al, Lancet Oncol 2022
Atezolizumab (anti-PD-L1)	31	**37.2%** (Not reported)	Not reported	Naqash et al, ASCO 2021
Axitinib/Pembrolizumab (ASPS subset)	11	**54.5%** (24.6-81.9)	**12.4** (2.7-22.3)	Wilky et al, Lancet Oncol, 2019
Geptanolimab (GB226, anti-PD1)	37	**37.8%** (22.5-55.2)	**6.9** (5.0-NR)	Shi et al, Clin Cancer Res, 2020
Toripalimab (anti-PD1), ASPS subset	12	**25.0%** (Not reported)	**11.1** (Not Reported)	Yang et al, Eur J Cancer, 2020

Selected PD1/PD-L1 combination trials in sarcomas

CTLA-4
Macrophages
Microenvironment
Chemo

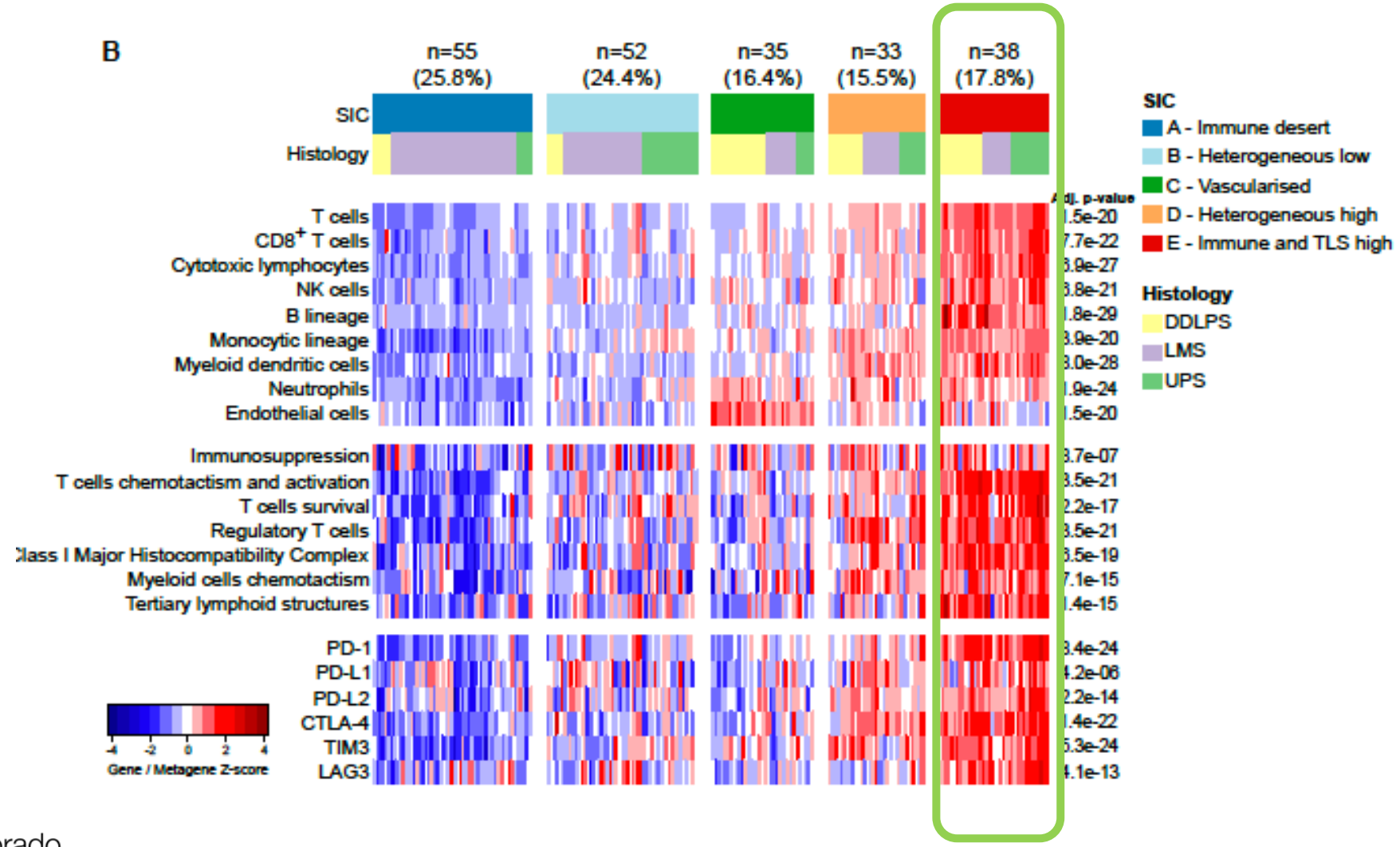
Study Agents	ORR	mPFS	Subtypes (RR)
Pembrolizumab[1]	18%	4.5 mo	UPS 23%[2], LPS 10%
Ipilimumab/Nivolumab[3,4]	16%	4.1 mo	UPS 28.6%[4], LPS 14.3%
Cyclophosphamide/Pembro[5]	2%	1.4 mo	1 PR mSFT
Axitinib/Pembro[6]	25%	4.7 mo	Non-ASPS 9.5%, ASPS 54.5%
Doxorubicin/Pembro[7,8]	22 – 36.7%	5.7-7.8 mo	LMS 30%, UPS 66%, LPS 40%
Sunitinib/Nivolumab[9]	9.3%	5.9 mo	PRs in AS, ESMC, SS, ASPS
Atezolizumab[10]	37.2%	Not reported	ASPS
Trabectedin/**Ipi**/Nivo[11] (Ph II)	22%	6.7 mo	UPS, SS, LPS, LMS
Durvalumab/**Tremelimumab**[12]	12%	2.8 mo	ASPS 40%, chordoma 20%, AS and UPS (20% ea)
Ipilimumab/Nivolumab[13]	25%	PFS_{6mo} 38%	AS only
Gemcitabine/Docetaxel/Retifanlimab[14]	17-50%	PFS_{6mo} 44-60%	LMS, UPS, LPS, AS, MFS

SS: synovial sarcoma, UPS: undifferentiated pleomorphic sarcoma, LPS: liposarcoma, uLMS: uterine leiomyosarcoma, mSFT: malignant solitary fibrous tumor, ASPS: alveolar soft part sarcoma, AS: angiosarcoma, ESMC: extraskeletal myxoid chondrosarcoma

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1. Tawbi et al, Lancet Oncol 2017. 2. Burgess et al ASCO 2019. 3. D'Angelo et al, Lancet Oncol 2018. 4. Chen et al, ASCO 2020. 5. Toulmonde et al, JAMA Oncol, 2018. 6. Wilky et al, Lancet Oncol 2019. 7. Pollack et al, JAMA Oncol 2020. 8. Livingston et al, CCR, 2021. 9. Martin-Broto et al, ESMO 2019 10. Naqash et al, ASCO 2021 11. Chawla et al, ASCO 2019 12. Somaiah et al, Lancet Oncol 2022 13. Wagner et al, JITC 2021 14. Rosenbaum et al, ASCO 2022.

Only ~20% of common soft tissue sarcomas have robust immune expression



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Petitprez et al, Nature 2020

Fundamental questions for immunotherapy in sarcomas…

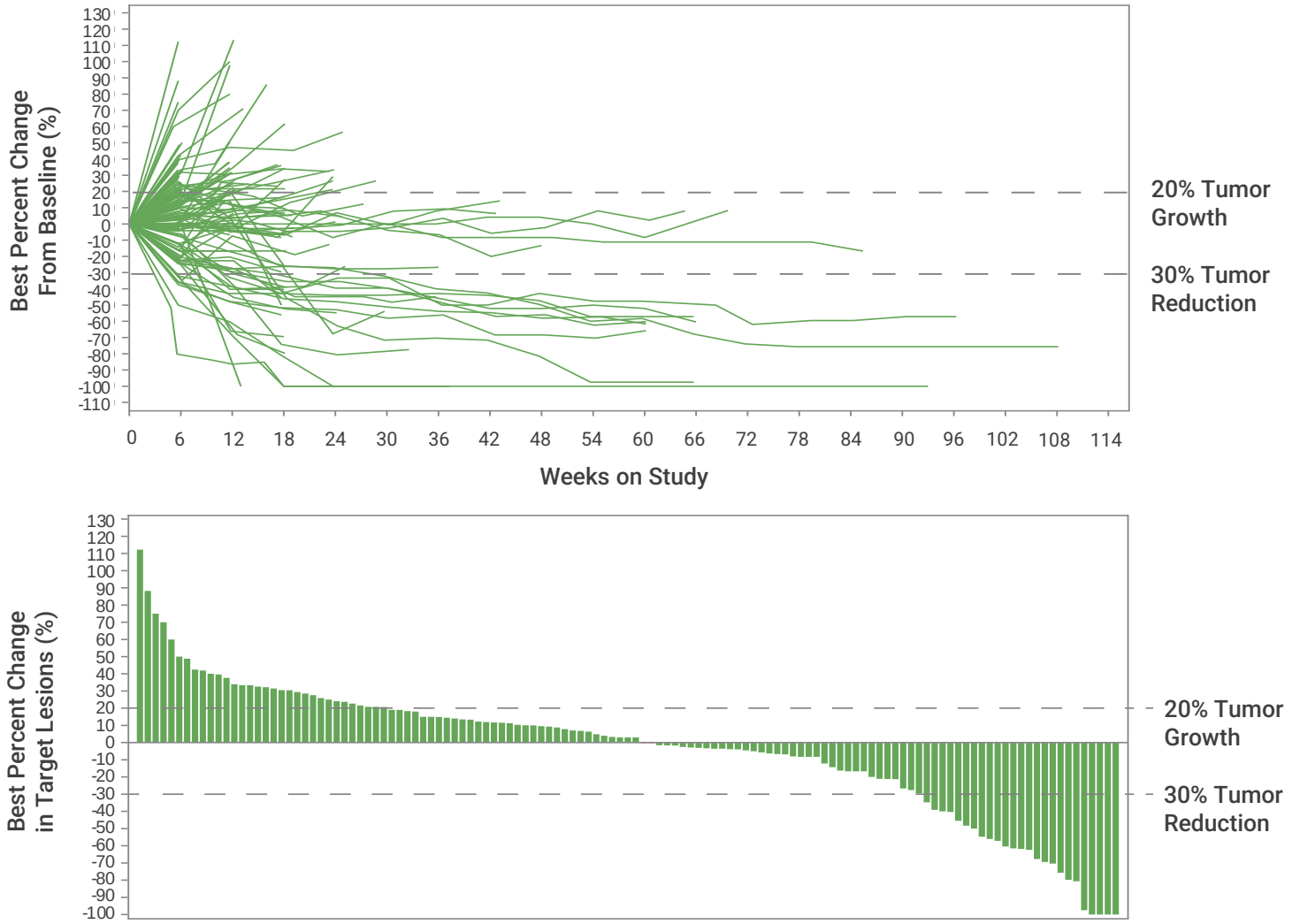
1. **Why are we stuck at 20% ceiling despite trying numerous combinations to target evasion mechanisms?**
2. **Who benefits and how should we enrich future studies for responders?**
   - Subtypes?
   - Presence of tertiary lymphoid structures?
   - Other emerging biomarkers?
3. **How do we induce immune responses in the other 80% - immune cold sarcomas?**
   - Combinations with chemotherapy and radiation?
   - Novel strategies…

SITC Data Recap

Botensilimab/balstilimab in “cold” and I-O refractory metastatic solid tumors

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All combination patients (N=125)

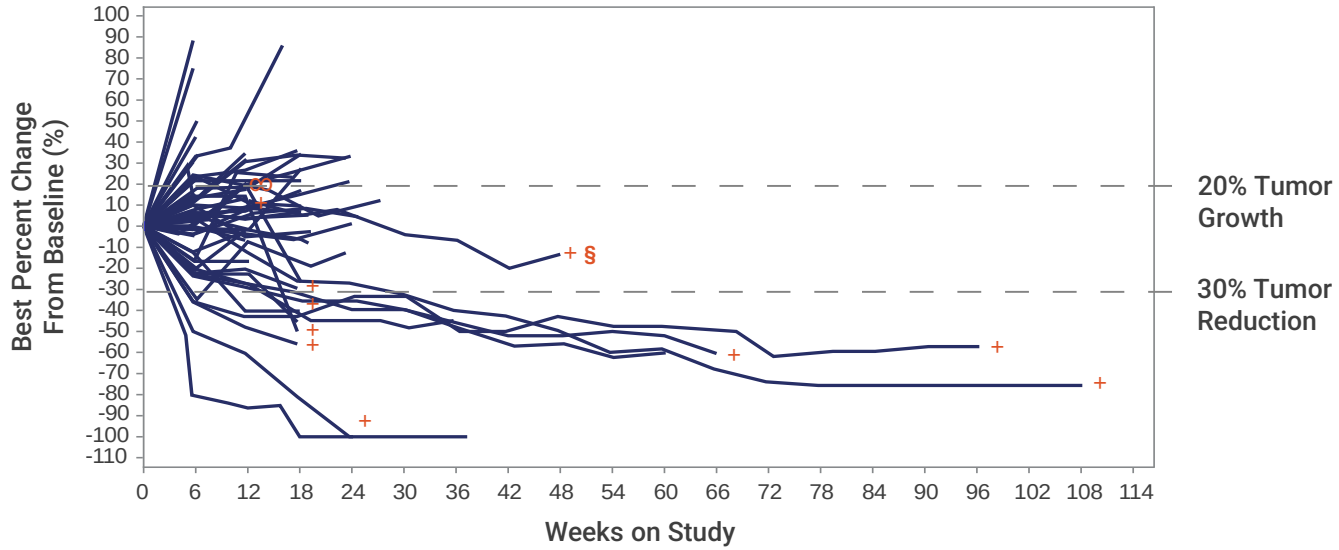


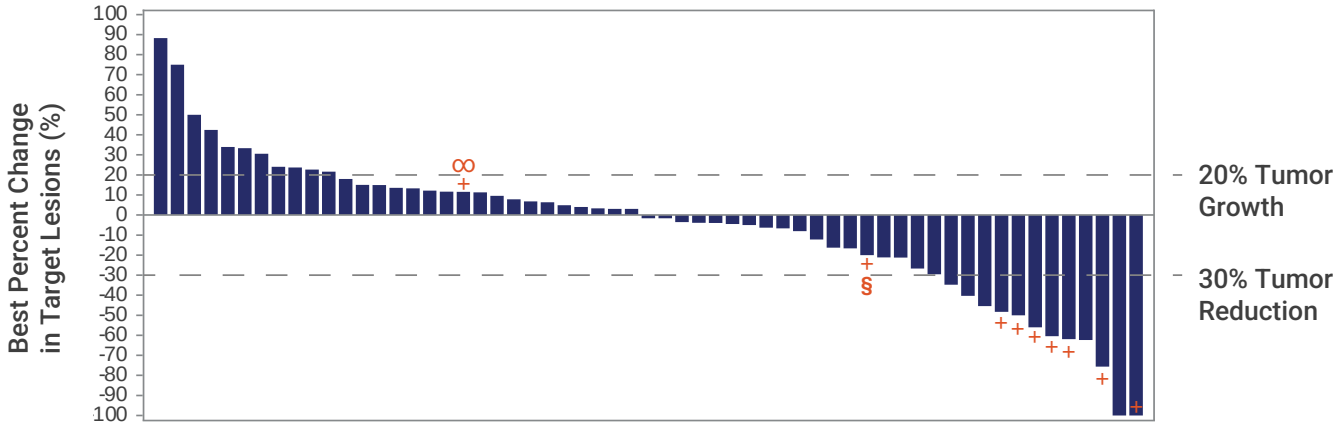
EFFICACY	
ORR, %*	**20%** (95% CI, 13-28%)
BOR, n (%)	
CR	3 (2)
PR	22 (18)
SD	58 (46)
PD	42 (34)
DCR (CR + PR + SD), %	**66%** (95% CI, 57-74%)
Median DOR, months	NR (95% CI, 4.5-NR)
Median PFS, months	2.8 (95% CI, 2.7-4.2)
Median OS, months	NR (95% CI, 12.9-NR)
12-month OS, months	66% (95% CI, 54-76%)
Median F/U, months	6.2 (Range, 1.1-29.3)

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*Includes unconfirmed responses.

MSS CRC (n=59)





EFFICACY	
ORR, %*	**22%** (95% CI, 12-35%)
BOR, n (%)	
CR	1 (2)
PR	12 (20)
SD	30 (51)
PD	16 (27)
DCR (CR + PR + SD), %	**73%** (95% CI, 60-84%)
Median DOR, months	NR (95% CI, 2.8-NR)
Median PFS, months	4.1 (95% CI, 2.7-4.4)
Median OS, months	NR (95% CI, 9.4-NR)
12-month OS, months	60% (95% CI, 42-75%)
Median F/U, months	6.2 (Range, 1.6-29.3)

Responder Characteristics (n=13)

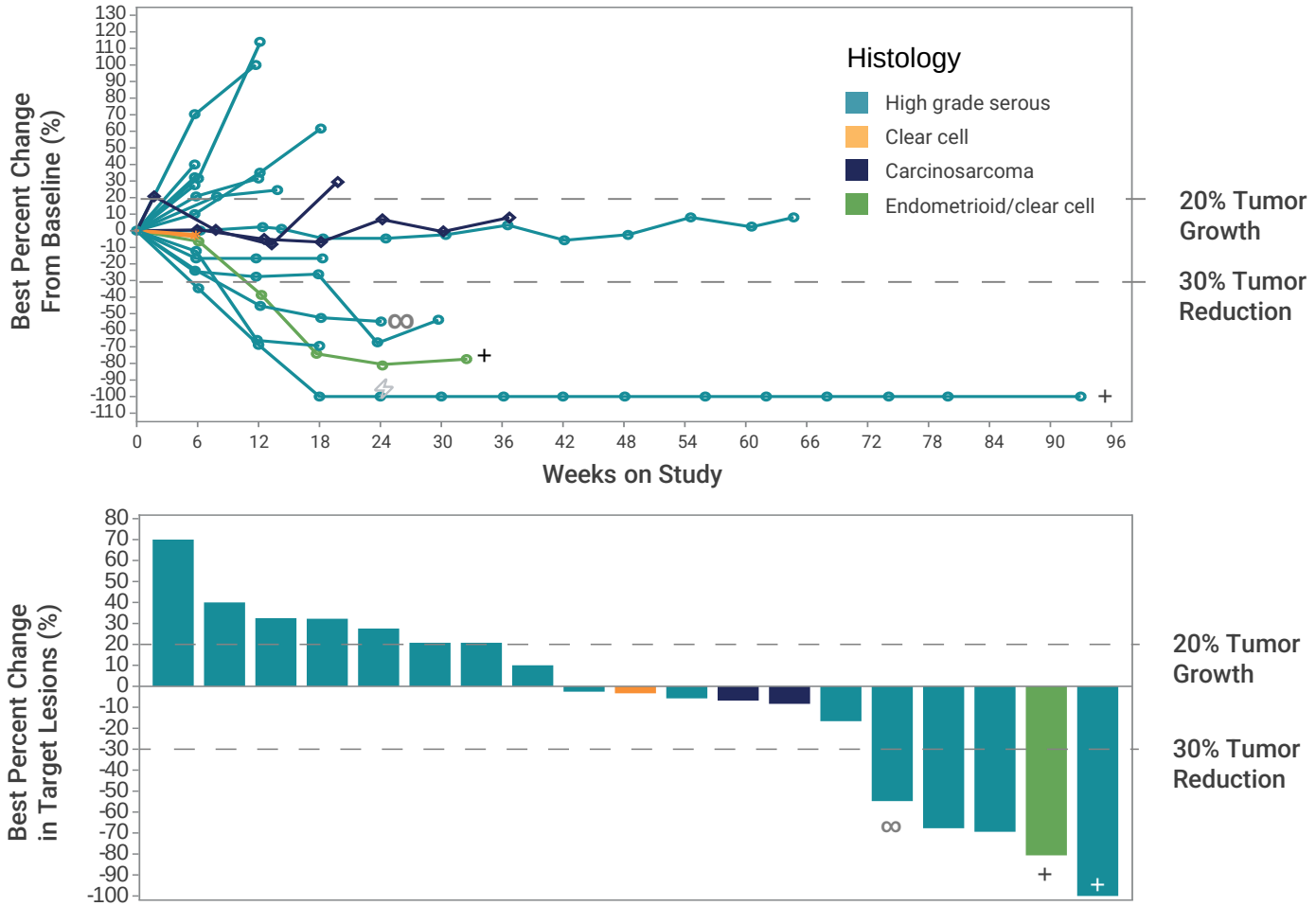
- 11/13 (85%) with 3L+ prior LOT
- 2/13 (15%) with prior I-O
- 13/13 (100%) MSS
- 0/10 (0%) TMB >10 mut/Mb
- 1/7 (14%) PD-L1 positive (≥1%)
- 9/13 (69%) RAS mutant
- 0/13
- 9/13 resp

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*Includes unconfirmed responses.
§SD by RECIST; metabolic CR by PET.

∞Resected target lesion showed complete pathologic response.
+Ongoing response.

Recurrent platinum refractory/resistant ovarian (n=19)



EFFICACY	
ORR, %*	**26%** (95% CI, 9-51%)
BOR, n (%)	
CR	1 (5)
PR	4 (21)
SD	7 (37)
PD	7 (37)
DCR (CR + PR + SD), %	**63%** (95% CI, 38-84%)
Median DOR, months	NR (95% CI, 4.2-NR)
Median F/U, months	6.5 (Range, 2.0-24.0)

Responder Characteristics (n=5)

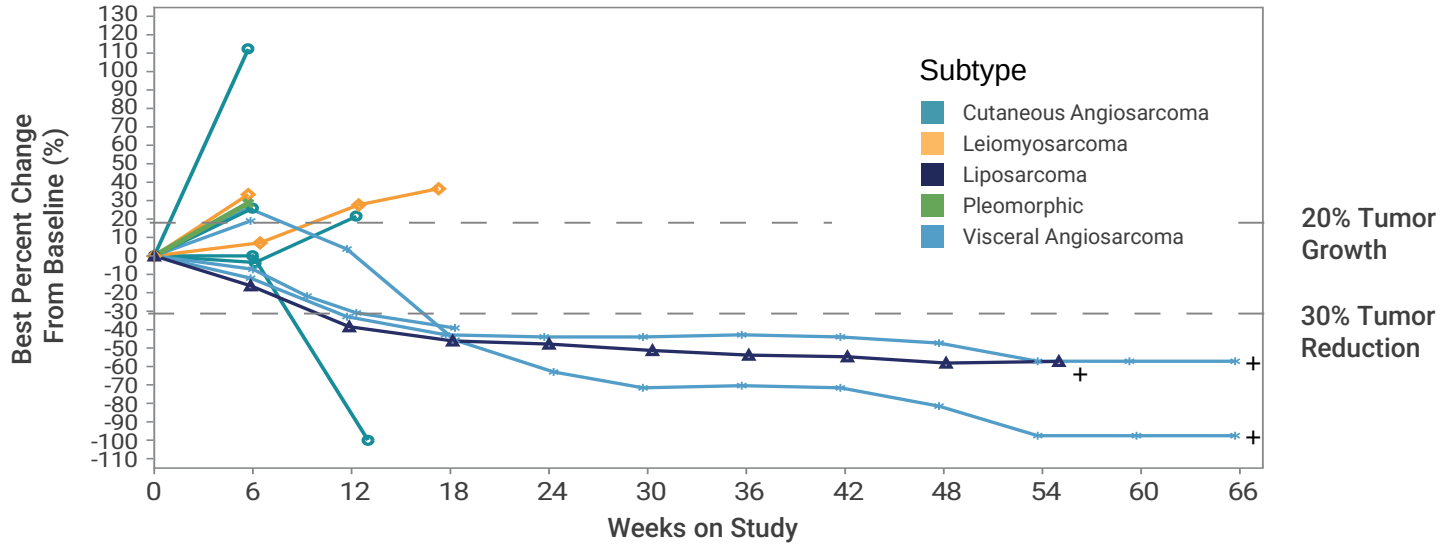
- 4 high grade serous (80%), 1 endometrioid/clear cell (20%)
- 3/5 (60%) with 3L+ prior LOT
- 1/5 (20%) with prior I-O (pembrolizumab/PI3Ki PD, nivolumab PD)
- 5/5 (100%) MSS
- 0/3 (0%) TMB >10 mut/Mb
- 3/3 (100%) PD-L1 positive (≥1%)
- 2/5 (40%) responses ongoing

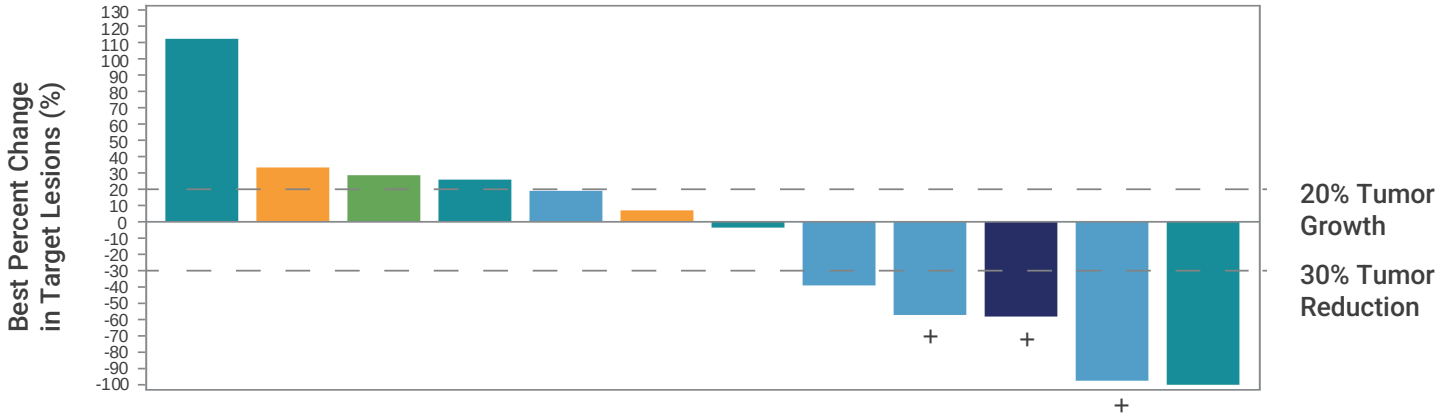
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*Includes unconfirmed responses.
∞ SD for 72 weeks on monotherapy prior to switching to combination.

+Ongoing response.
Received radiation, no evidence of disease.

Sarcoma (n=12)





EFFICACY	
ORR, %*	**42%** (95% CI, 15-72%)
BOR, n (%)	
CR	1 (8)
PR	4 (33)
SD	3 (25)
PD	4 (33)
DCR (CR + PR + SD), %	**67%** (95% CI, 35-90%)
Median DOR, months	NR (95% CI, 1.9-NR)
Median F/U, months	4.4 (Range, 1.1-19.6)

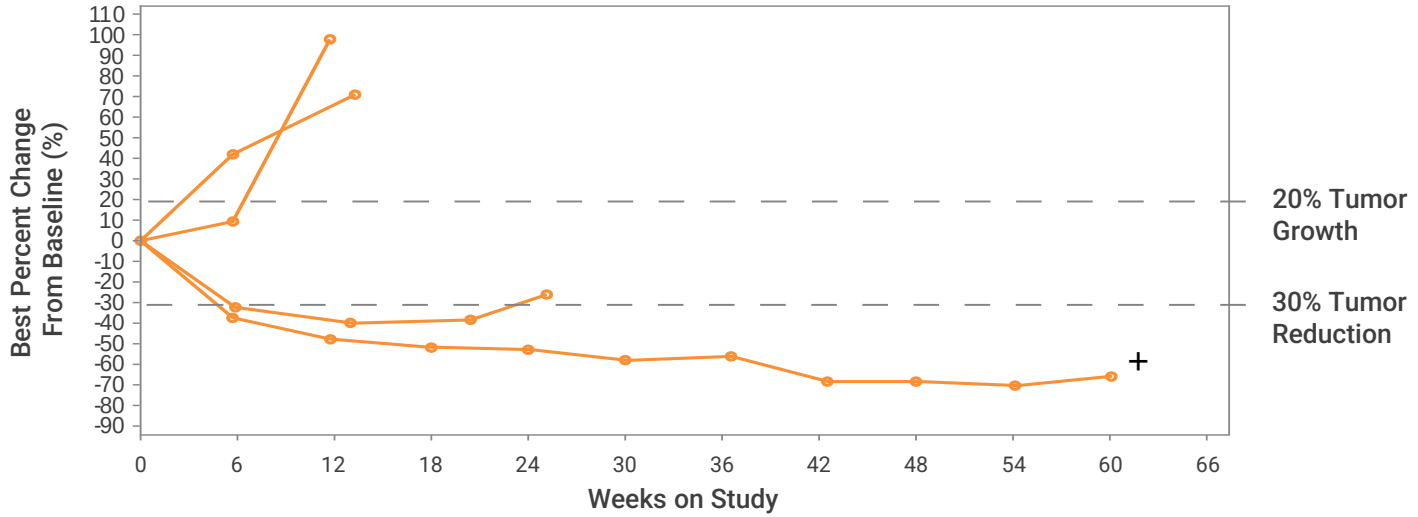
Responder Characteristics (n=5)

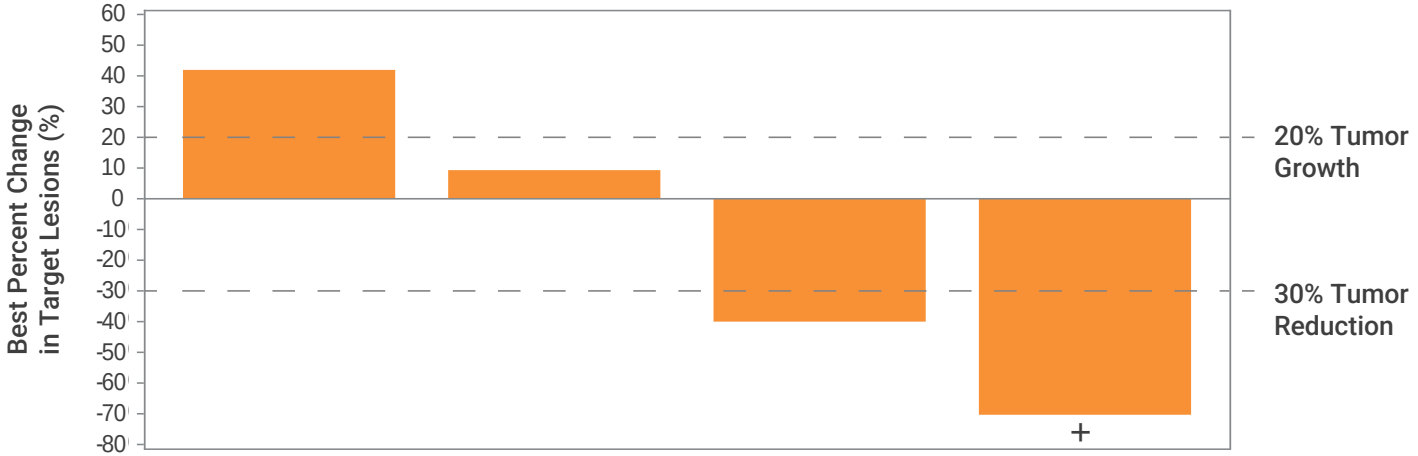
- 1 cutaneous angiosarcoma (20%), 3 visceral angiosarcoma (60%), 1 liposarcoma (20%)
- 3/5 (60%) with 3L+ prior LOT
- 4/4 (100%) MSS
- 1/4 (25%) TMB >10 mut/Mb (TMB=15, visceral angiosarcoma)
- 3/4 (75%) PD-L1 positive (≥1%)
- 3/5 (60%) responses ongoing

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*Includes unconfirmed responses.
+Ongoing response.

Anti-PD-(L)1 NSCLC (n=4)





One additional confirmed PR since the data cutoff, ORR 60% (3/5)

EFFICACY	
ORR, %	**50%** (95% CI, 7-93%)
BOR, n (%)	
CR	0 (0)
PR	2 (50)
SD	1 (25)
PD	1 (25)
DCR (CR + PR + SD), %	**75%** (95% CI, 19-99%)
Median DOR, months	NR (95 % CI, 4.5-NR)
Median F/U, months	5.3 (Range, 3.3-16.2)

Responder Characteristics (n=2)†

- *Patient 1*:
  - PD-L1 negative (0%)
  - Prior I-O: Carboplatin/paclitaxel/ **pembrolizumab**, **pembrolizumab** (PD)
  - Response ongoing
- *Patient 2*:
  - PD-L1 negative (0%)
  - Prior I-O: Carboplatin/pemetrexed/ **pembrolizumab**, pemetrexed/ **pembrolizumab** (PD)

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*Includes unconfirmed responses.
†One additional evaluable patient since the data cutoff (ongoing confirmed PR).
+Ongoing response.

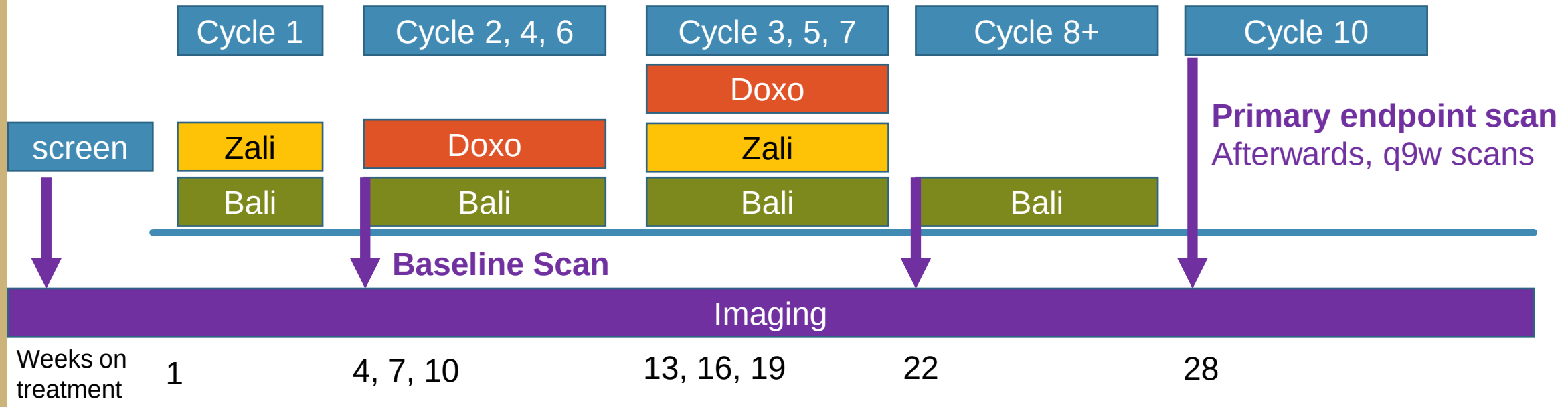
Investigator-Sponsored Trials

1) Doxorubicin/zalifrelimab/balstilimab
2) Doxorubicin/botensilimab/balstilimab

Doxorubicin/zalifrelimab/balstilimab

ICI priming prior to chemo start
4 cycles CTLA-4

Drug	Schedule
Balstilimab 300 mg flat	q3weeks up to 2 years
Zalifrelimab 1 mg/kg	q6weeks x 4
Doxorubicin 75 mg/m2 (bolus/zinecard)	q3weeks x 6, starts at C2



NCT04028063, PI: Wilky

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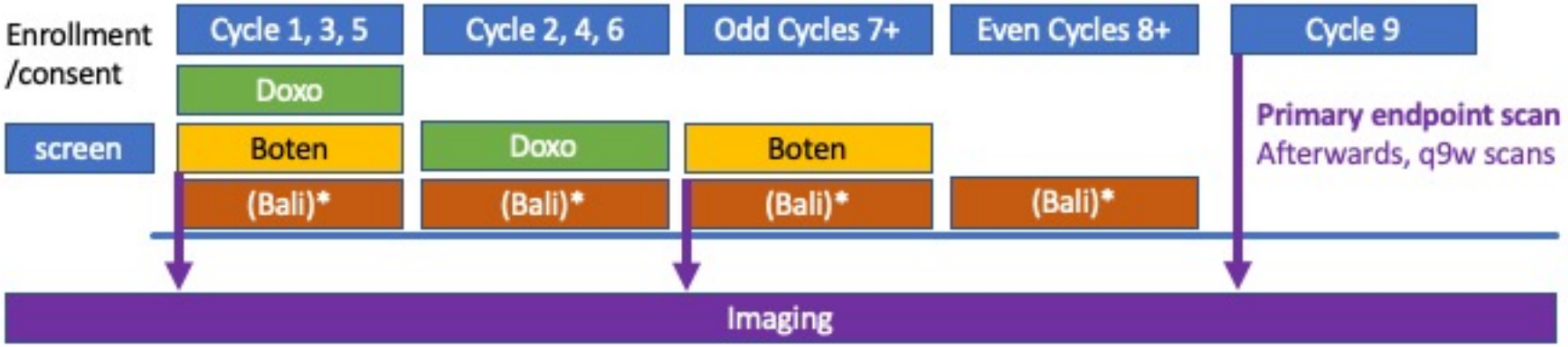
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Doxorubicin/**botensilimab**/balstilimab

NCT04028063, PI: Wilky

Patients will be assigned to dose-levels following time to Bayesian optimal interval design (TITE-BOIN).

Treatment Cohort	Drug	Schedule
-1 (De-escalation)	Doxorubicin 50 mg/m2 Botensilimab 75 mg	q3weeks x 6 doses q6weeks up to 2 years
1 (Starting level)	Doxorubicin 60 mg/m2 Botensilimab 75 mg	q3weeks x 6 doses q6weeks up to 2 years
2	Doxorubicin 75 mg/m2 Botensilimab 75 mg	q3weeks x 6 doses q6weeks up to 2 years
3	Doxorubicin 75 mg/m2 Botensilimab 75 mg Balstilimab 450 mg	q3weeks x 6 doses q6weeks up to 2 years q3weeks up to 2 years



Research Correlative Samples:
Tumor Biopsy: Screening, C2D5, progression (optional)
Peripheral Blood: Screening, C2D1, C2D5, C4D1, progression

* For cohort 3 only

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Acknowledgements



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Allison Christians, MS
Joseph Magno, PhD Candidate

Dexiang Gao/Junxiao Hu
HIMSR Core Facility
Clinical Research Staff
Oncology Clinical Research Support Team

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Sarcoma Foundation of America SFA finding the cure in our time

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SYLVESTER COMPREHENSIVE CANCER CENTER UNIVERSITY OF MIAMI HEALTH SYSTEM

American Cancer Society

University of Colorado Cancer Center



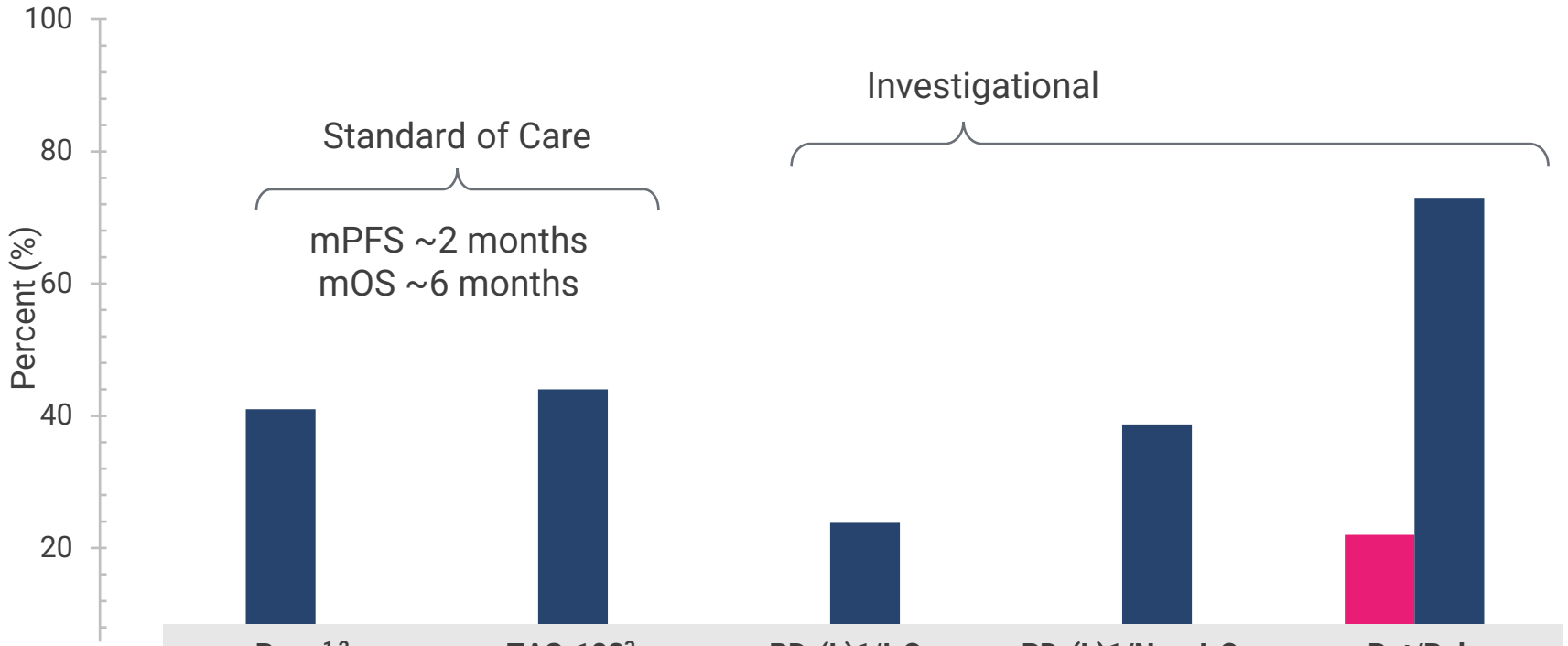
Email: breelyn.wilky@CUAnschutz.edu. Twitter: @breelynwilkyMD



BOTENSILIMAB – A TRANSFORMATIVE TREATMENT FOR CRC

Joseph Grossman, MD
Vice President, Exploratory Medicine

CURRENTLY APPROVED TREATMENTS AND EXPERIMENTAL IMMUNOTHERAPIES OFFER LIMITED EFFICACY IN 2L+ MSS CRC



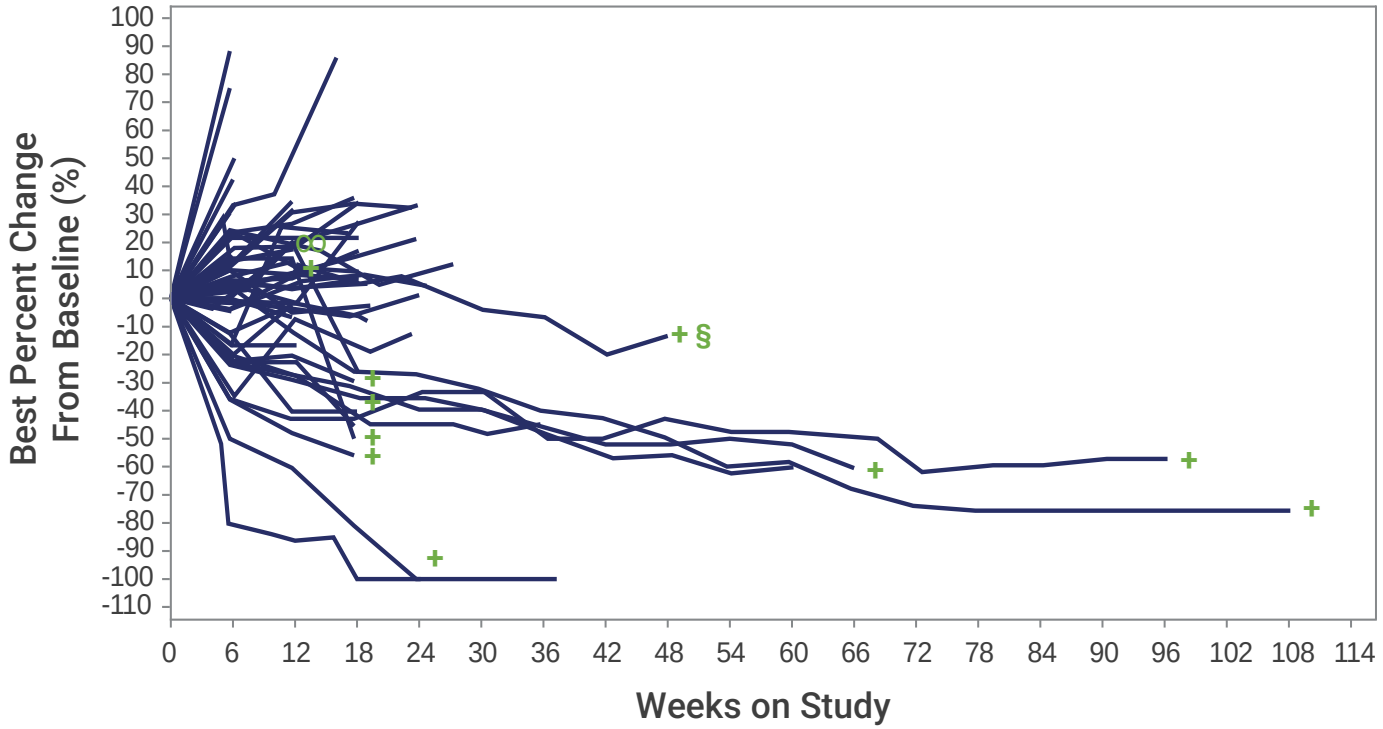
	Rego[1,2] (n=505)	TAS-102[3] (n=502)	PD-(L)1/I-O Combos (n=219)	PD-(L)1/Non-I-O Combos (n=95)	Bot/Bal (n=59)
ORR (%)	1	2	4	5	**22**
DCR (%)	41	44	24	39	**73**
mPFS (mo.)	1.9	2.0	1.8	2.1	**4.1**

- ~95% of metastatic colorectal cancer is microsatellite stable (MSS CRC)
- Limited efficacy with regorafenib and TAS-102
- I-O-only responses are rare
- PD-(L)1/I-O and Non-I-O Combos: variable efficacy and durability

Advanced, metastatic or treatment-resistant CRC

Wilky et al. SITC 2022
Abrams et al. ASCO GI 2022 Poster 121
Gomez-Roca et al. ASCO 2021 Poster 3564
Fakih et al. ASCO 2021 Poster 3560
Cousin et al. CCR 2021
Barzi et al. ASCO GI 2022 Poster 15
Garralda et al. ASCO 2021 Poster 3584
Chen et al. JAMA Oncol. 2020
Eng et al. Lancet Oncol 2019
Bendell et al. Ann Oncol 2018
Grothey et al. Lancet 2013
Mayer et al. NEJM 2015
Overman et al. ASCO 2016
Naing et al. ESMO 2019

SPIDER PLOT (N=59)



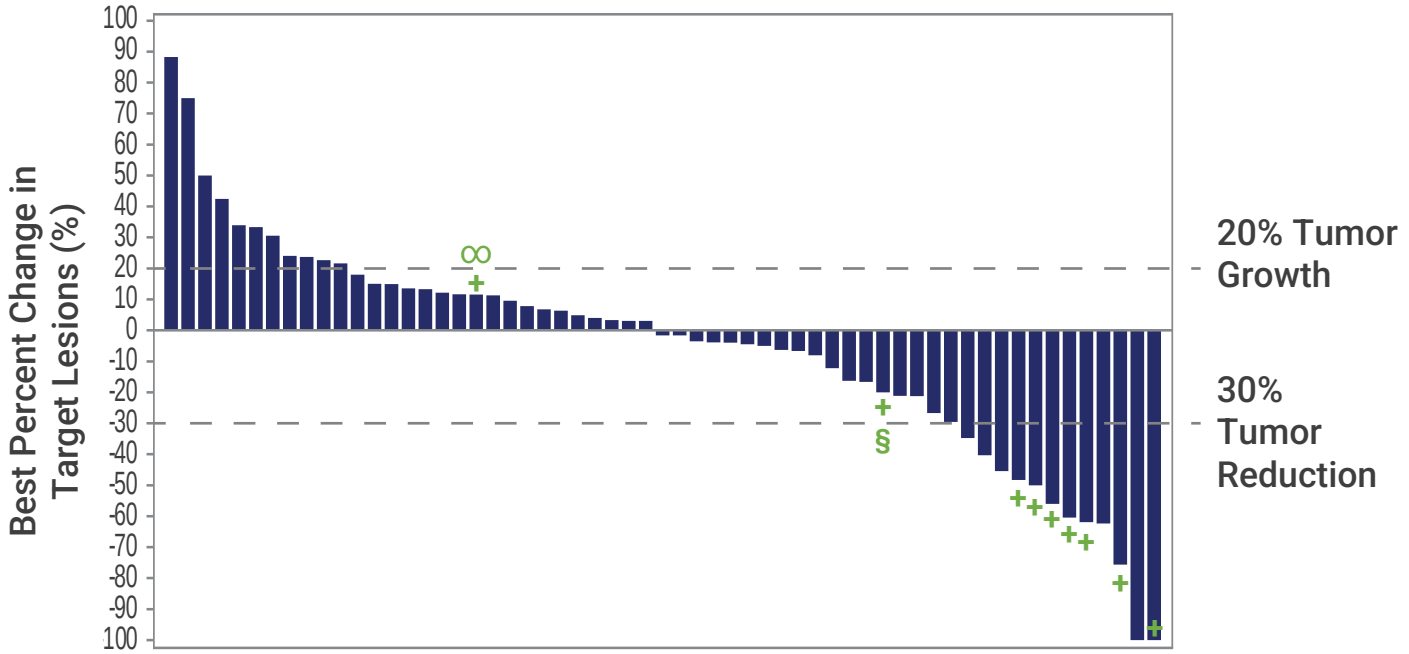
Responder Characteristics (n=13)

- 11/13 (85%) with 3L+ prior LOT
- 2/13 (15%) with prior I-O
- 13/13 (100%) MSS
- 0/10 (0%) TMB >10 mut/Mb
- 1/7 (14%) PD-L1 positive (≥1%)
- 9/13 (69%) RAS mutant
- 0/13 (0%) BRAF mutant
- 9/13 (69%) with ongoing responses

Efficacy	
ORR, %*	**22%** (95% CI, 12-35%)
BOR, n (%)	
CR	1 (2)
PR	12 (20)
SD	30 (51)
PD	16 (27)
DCR (CR + PR + SD), %	**73%** (95% CI, 60-84%)
Median DOR, months	NR (95% CI, 2.8-NR)
Median PFS, months	4.1 (95% CI, 2.7-4.4)
Median OS, months	NR (95% CI, 9.4-NR)
12-month OS, months	60% (95% CI, 42-75%)
Median F/U, months	6.2 (Range, 1.6-29.3)

*Includes unconfirmed responses.
§SD by RECIST; metabolic CR by PET.
∞Resected target lesion showed complete pathologic response.
+Ongoing response.

WATERFALL PLOT (N=59)



Responder Characteristics (n=13)

- 11/13 (85%) with 3L+ prior LOT
- 2/13 (15%) with prior I-O
- 13/13 (100%) MSS
- 0/10 (0%) TMB >10 mut/Mb
- 1/7 (14%) PD-L1 positive (≥1%)
- 9/13 (69%) RAS mutant
- 0/13 (0%) BRAF mutant
- 9/13 (69%) with ongoing responses

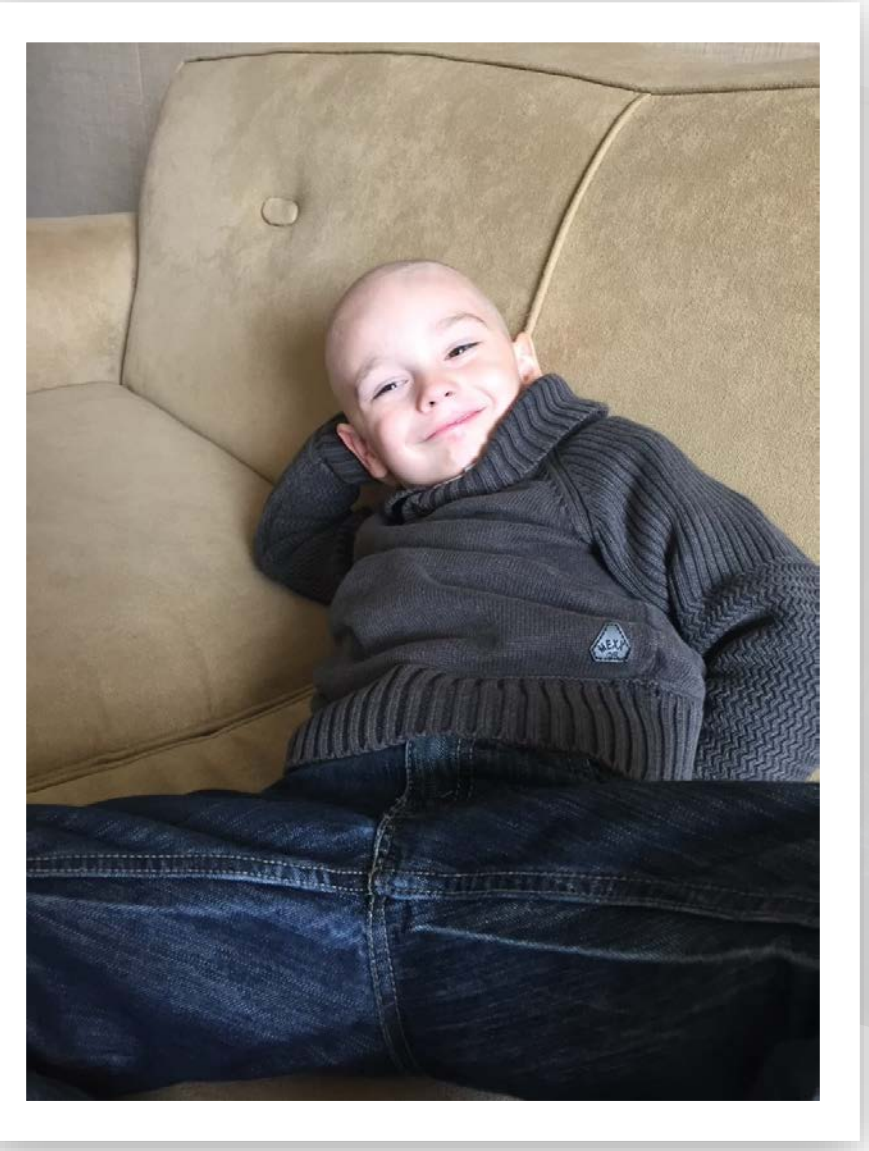
Efficacy	
ORR, %*	**22%** (95% CI, 12-35%)
BOR, n (%)	
CR	1 (2)
PR	12 (20)
SD	30 (51)
PD	16 (27)
DCR (CR + PR + SD), %	**73%** (95% CI, 60-84%)
Median DOR, months	NR (95% CI, 2.8-NR)
Median PFS, months	4.1 (95% CI, 2.7-4.4)
Median OS, months	NR (95% CI, 9.4-NR)
12-month OS, months	60% (95% CI, 42-75%)
Median F/U, months	6.2 (Range, 1.6-29.3)

*Includes unconfirmed responses.
§SD by RECIST; metabolic CR by PET.
∞Resected target lesion showed complete pathologic response.
+Ongoing response.



THE PATH TO BOTENSILIMAB APPROVAL

Dr. Patricia Carlos
Chief of Regulatory, Quality and Safety



THE PATH TO APPROVAL



HOW CAN WE DELIVER BOTENSILIMAB PLUS BALSTILIMAB TO PATIENTS AS FAST AS POSSIBLE

- ***Early and often*** engagement strategy with global regulators
- Expedited approval mechanisms for patients with limited treatment options for serious disease
- Comprehensive approach to Safety, Efficacy and Optimal Dosing, and SOC comparison
- Multipronged approach that we hope will lead to approval and reimbursement in multiple regions simultaneously
- Leverage data from multiple studies to expedite label expansion after inital approval

FIRST FILING

- *Anticipate that first filing will be in MSS CRC in 2024*
- *Planning for multiple supplemental filings in years to follow*

The ROADTAKEN | agenus

THE FUTURE OF CANCER IMMUNOTHERAPY

Dr. Alexander M.M. Eggermont

Professor Clincal&Translational Immunotherapy
University Medical Center Utrecht
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Princess Maxima Center for Pediatric Oncology
Utrecht, Netherlands
Board Comprehensive Cancer Center Munich
Emeritus Professor, Surgical Oncology
Erasmus University Roterdam, NL
& Paris-Saclay University, FR

Immunotherapy Revolution: Lessons from Melanoma: From Advanced to Adjuvant to NEO-Adjuvant

Agenus R&D, Boston, November 2022

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Princess máxima center pediatric oncology

UMC Utrecht

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER

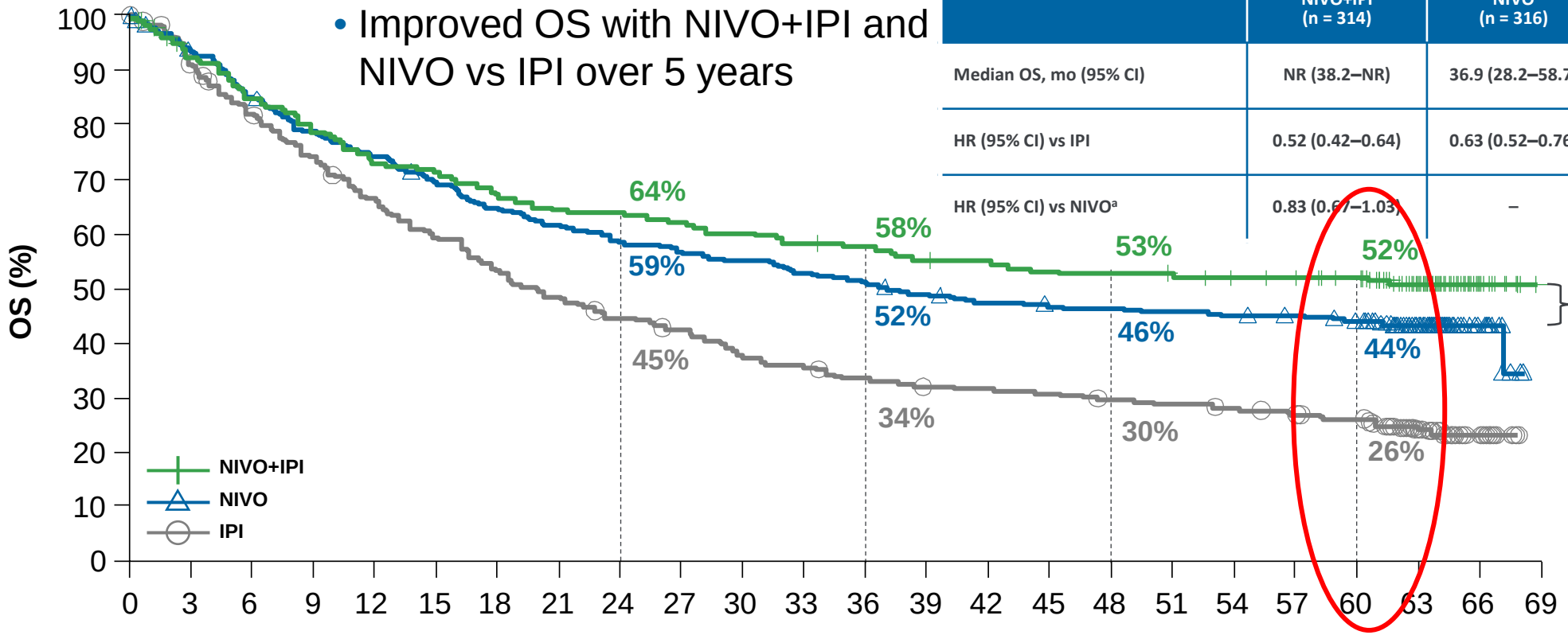
Short List of Statements

1) Anti-PD1 is a core necessity as it protects CTL function at tumor site
2) Anti-CTLA4 is core necessity to prime Tcells and Provide Tcell clone diversity
3) **Anti-CTLA4 is here to stay**
4) Anti-LAG3 prolongs CTL function but has less Tcell clone diversity power
5) The anti-PD1 ceiling is sooo hard to break
    - Examples
    - Time for a Macrophage Checkpoint-Inhibitor
6) From Advanced Disease to Adjuvant Therapy : consistent translation of efficacy
7) **NEOADJUVANT Immunotherapy will change "everything"**
    - More cures
    - Shorter Tx Cycles
    - Less Surgery
    - Insert neoadjuvant cohorts for Better Drug Development
    - **ANTI-CTLA4 + ANTI-PD1: DOUBLES pCR RATE**

Checkmate-67 NIVO + IPI: 5 Year Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

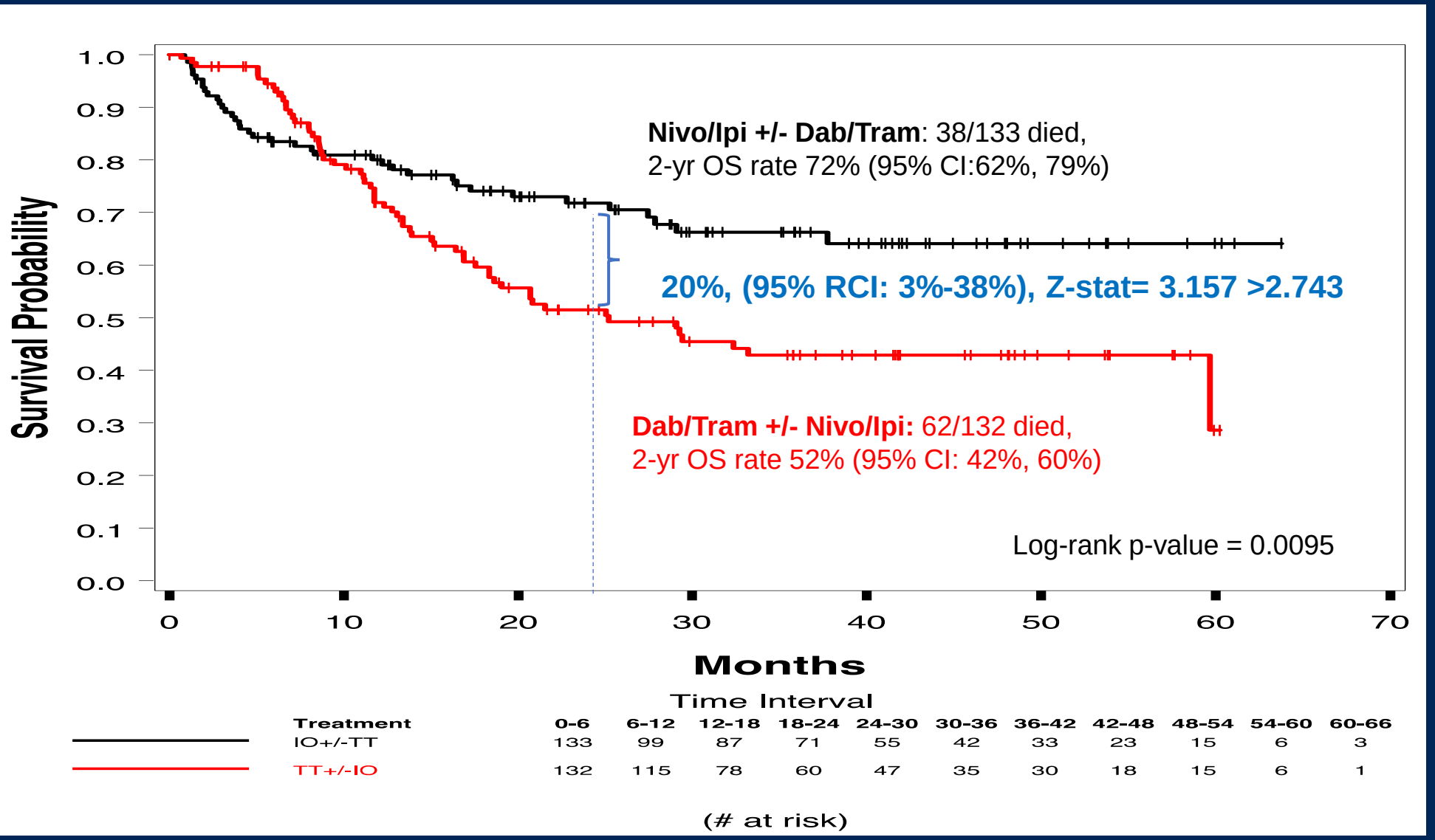


No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Dreamseq Overall Survival (OS): Step 1 +/- Step 2

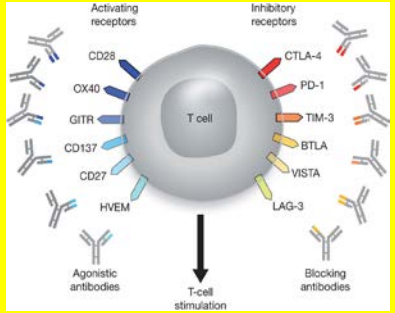


PRESENTED BY: Michael B. Atkins, MD

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Soooo hard to break the anti-PD1 ceiling
RECENT FAILURES



Agonistic mAbs

CD137, ICOS-1, STING,……

Anti-IDO drug Epcadostat

ECHO-301/KN-252: Pembrolizumab + Epcadostat vs Pembrolizumab

IT(intratumoral) Treatments: Oncolytic Virus TVEC and TLR Tilsolimod

MASTERKEY-265 : Pembrolizumab+TVEC vs Pembrolizumab

ILLUMINATE-301 : Ipilimumab+Tilsolimod vs Ipilimumab

cytokines

PIVOT-01: Nivolumab + BEMPEG vs Nivolumab (ESMO 2022)

IMMUNE SYSTEM BLOCKED AT MULTIPLE LEVELS

- 1) **CTL PRIMING**
  - e.g. CTLA4 ……. - **Unblock: anti-CTLA4**
- 2) **CTL EFFECTOR Function**
  - e.g. PD-1 / PDL-1…… - **Unblock: anti-PD1/anti-PDL1**
- 3) **MACROPHAGES in Tumor Infiltrate (TAM)**
  - **e.g. Macrophages; MDSC - anti-FcγRII Mabs: avoid anti-PD1 neutralization**
    - **Fc-modulation: optimize ICI (e.g. LaLa mut: Prolgolimab)**
    - **M2-M1 repolarization agents (CCR5; CCR5/CCR2)**
    - **anti-CD47 : RBCs+++, Platelets +++: MEGA DOSE: anemia/thrombopenia**
    - **anti-SIRPα : SAME CD47 blocking without anemia/thrombopenia**

THE OLD AND NEW ERA
Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2011)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

New Era (2015–2018)

		HR	Stage	FDA/EMA
Ipilimumab (US)[2,3,4]	HR_{RFS}(Ipilimumab vs. Placebo)=**0.75**		III	(2015)
Nivolumab[5,6]	HR_{RFS}(Nivolumab vs. **Ipilimumab**)=**0.65**	± 0.50	IIIB/IV	(2017)
Dabrafenib plus Trametinib[7,8]	HR_{RFS}(Dab+Tra vs. Placebo)=**0.47**	± 0.50	III	(2018)
Pembrolizumab[9,10,11]	HR_{RFS}(Pembrolizumab vs. Placebo)=**0.57**	± 0.50	III	(2018)

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27;
[2]Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30 ; [3]Eggermont AM, et al. *NEJM 2016; 375: 1845-55* [4;] Eggermont AM, et al. *Eur J Cancer 2019;119:1-10*
[5]Weber J, et al. *NEJM* 2017;377:1824-35; [6]Ascierto, PA et al. *Lancet Oncology* 2020; 21:1465-1477
[7]Long GV, et al. *NEJM* 2017;377:1813-23; [8]Dummer R et al. *NEJM* 2020;383:1139-1148
[9]Eggermont AM, et al. *NEJM* 2018;379:1879-1891; [10]Eggermont AM, et al. *JCO* 2020;38:3925-3936;
[11]Eggermont AM, et al. *Lancet Oncology* 2021;22:643-654; [9]Eggermont AM, et al. *NEJM Evidence* 2022; on line

The importance of Anti-CTLA4 also in combination adjuvant

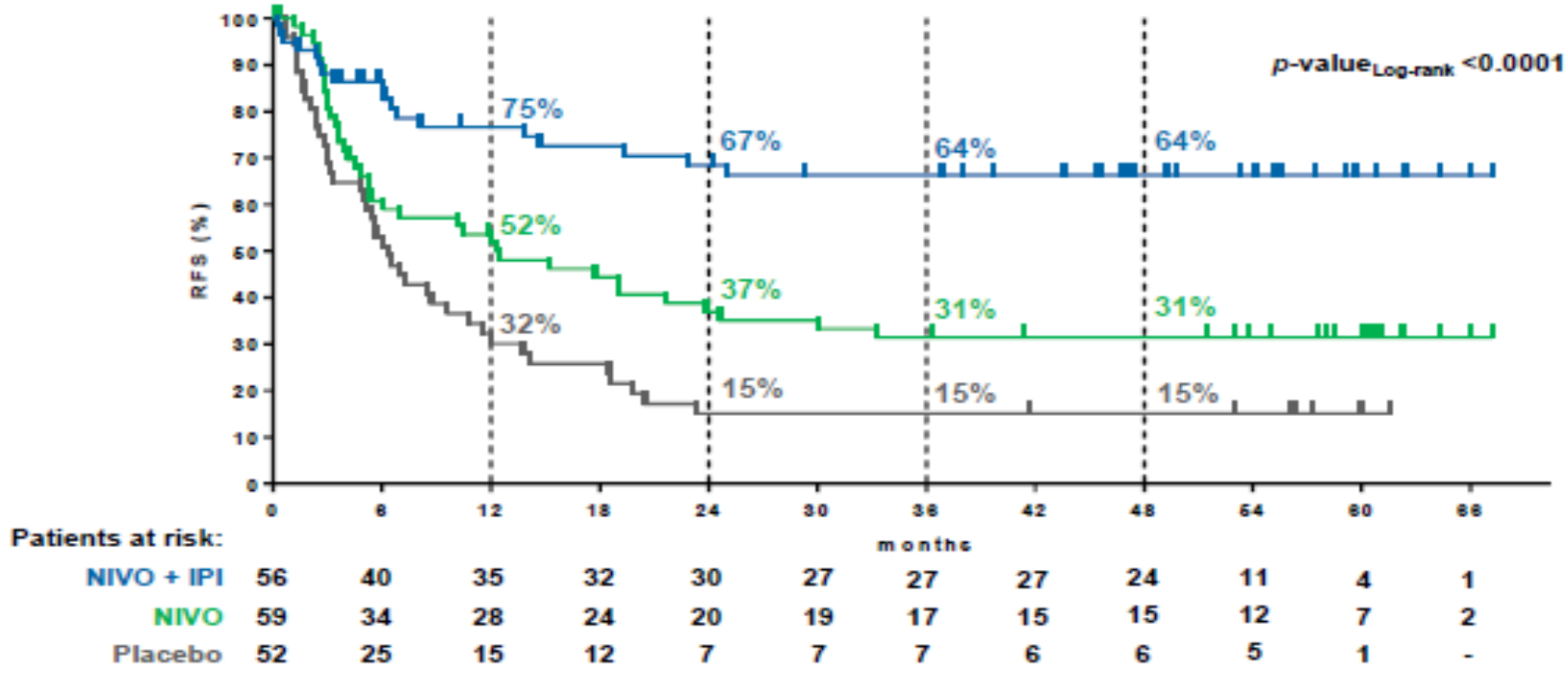
THE IMMUNED STUDY

IPI 3mg/q3wk + NIVO 1mg vs NIVO vs PBO in RESECTED STAGE IV

Data cut-off date Sep 23, 2021
Median follow-up time: 49.2 months

	NIVO+IPI (n=56)	NIVO (n=59)	Placebo (n=52)
Median RFS, mo (95% CI)	NR[1] (25.0, NR)	12.3 (5.3, 23.9)	6.3 (3.3, 9.6)
HR (97.5% CI) vs placebo	0.25 (0.13, 0.48)	0.60 (0.36, 1.00)	-
HR (97.5% CI) vs NIVO	0.41 (0.22, 0.78)	-	-

[1]NR: not reached



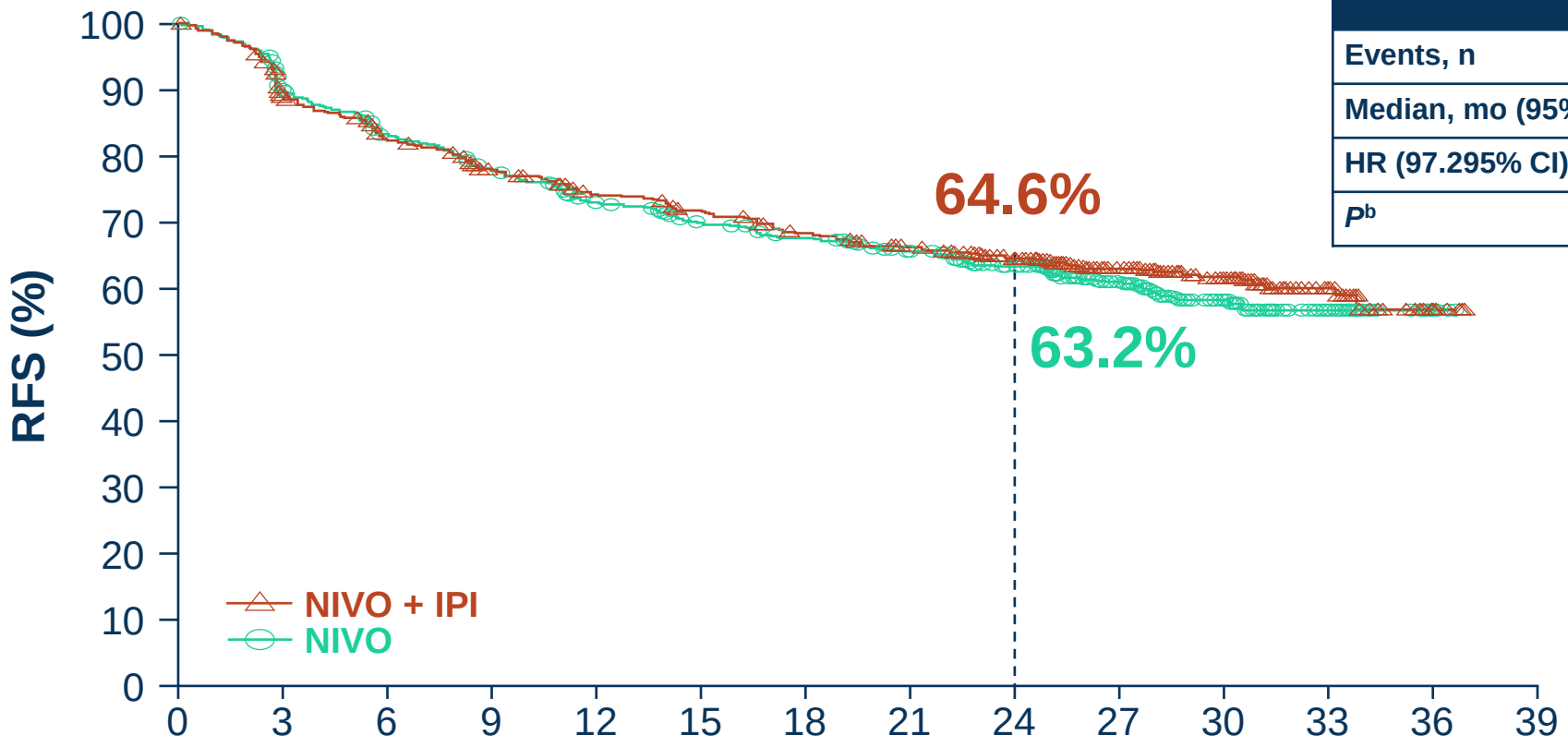
congress

Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01654-3/fulltext

d for re-use.

Checkmate 915: IPI 1mg/q6wk + Nivo vs Nivo
RFS in ITT population

	NIVO + IPI (n = 920)	NIVO (n = 924)
Events, n	327	347
Median, mo (95% CI)	NR	NR
HR (97.295% CI)[a]	0.92 (0.77–1.09)	
***P*[b]**	0.269	



No. at risk

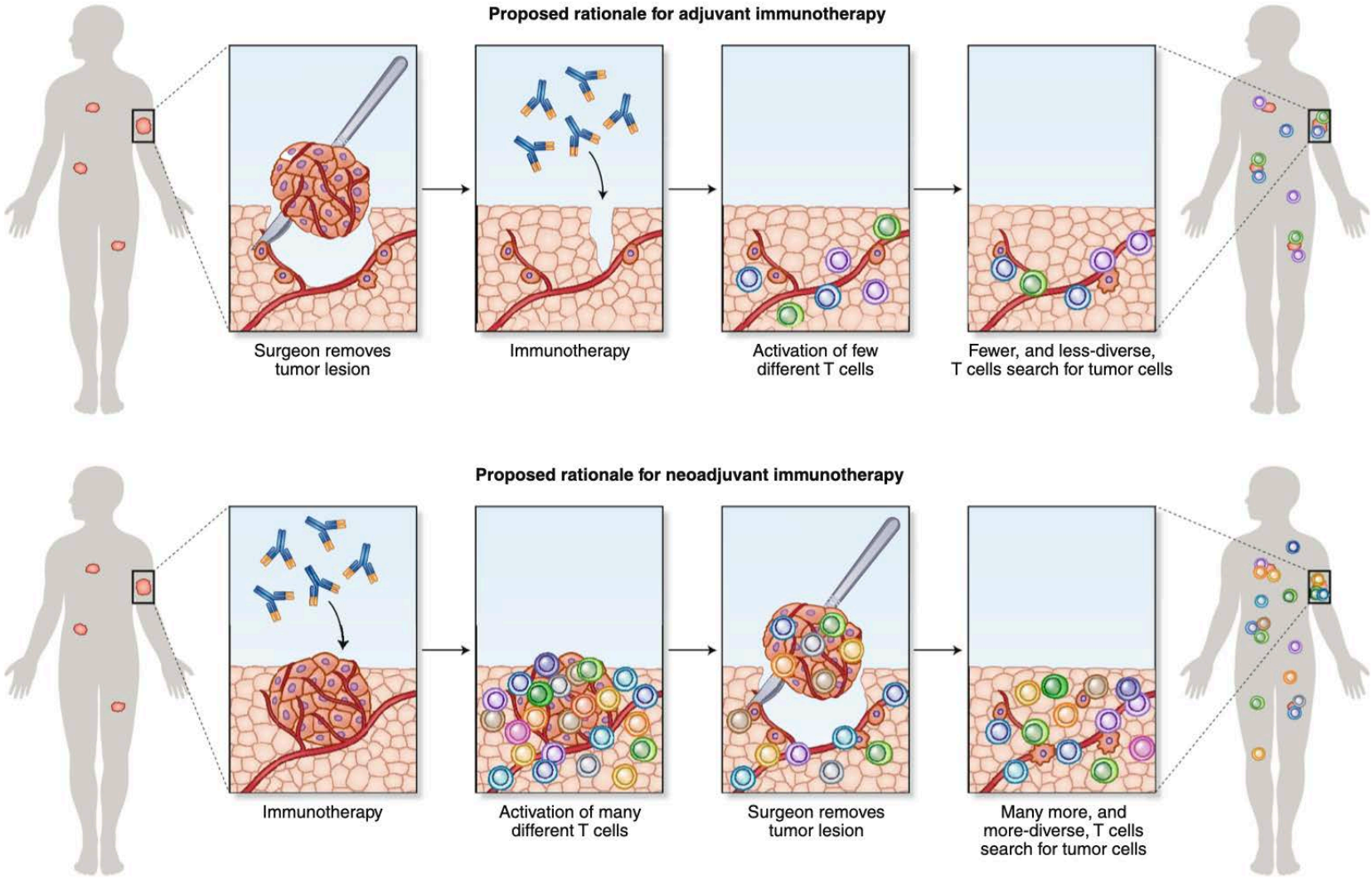
NIVO + IPI	920	783	720	669	630	605	572	547	505	371	193	74	9	0
NIVO	924	793	721	669	615	578	554	525	476	362	181	69	5	0

NEOADJUVANT IMMUNOTHERAPY REVOLUTION

More Cures / Shorter TXs / Less Surgery

- **Palpable/Macroscopic Stage III Melanoma**
- **Resectable Stage IV Melanoma**
- **MSI ColoRectal Cancer**
- **Locally advanced CSCC (face/head/neck)**
- T3 Bladder Cancer
- Multiple other trials (Lung, H&N,GEJ,TNB,GBM)

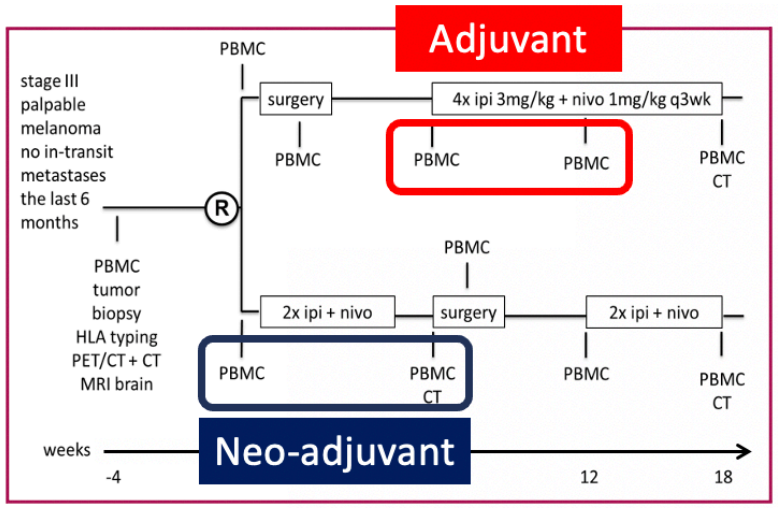
The Concept of Neoadjuvant Immunotherapy

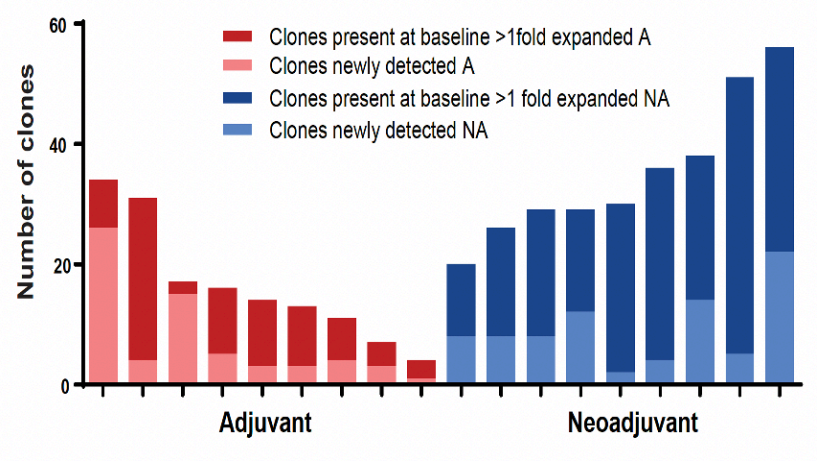


Versluis, Long, and Blank, Nat Med 2020

Neoadjuvant is Superior to Adjuvant Immunotherapy

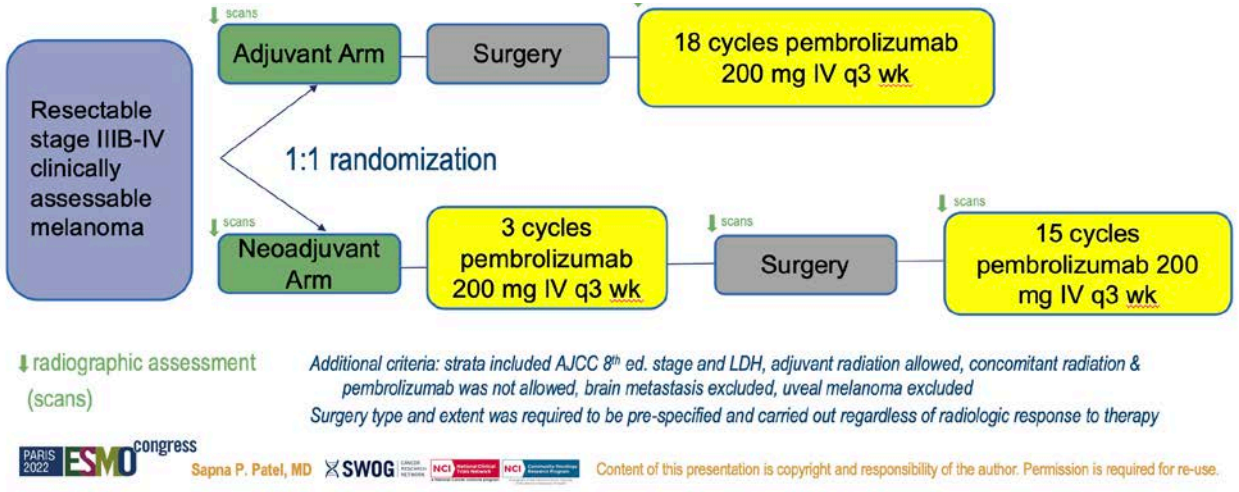
OpACIN (Phase 1)

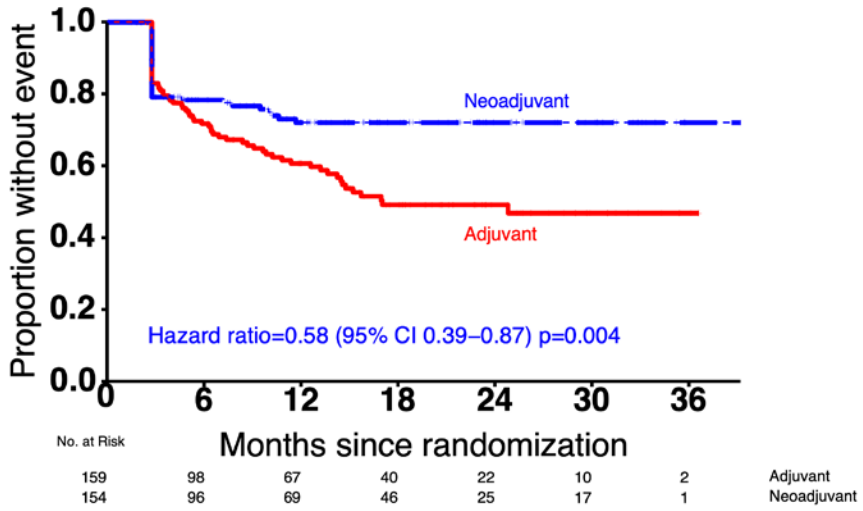




Blank et al., Nat Med 2018

SWOG S1801 (Phase 2)

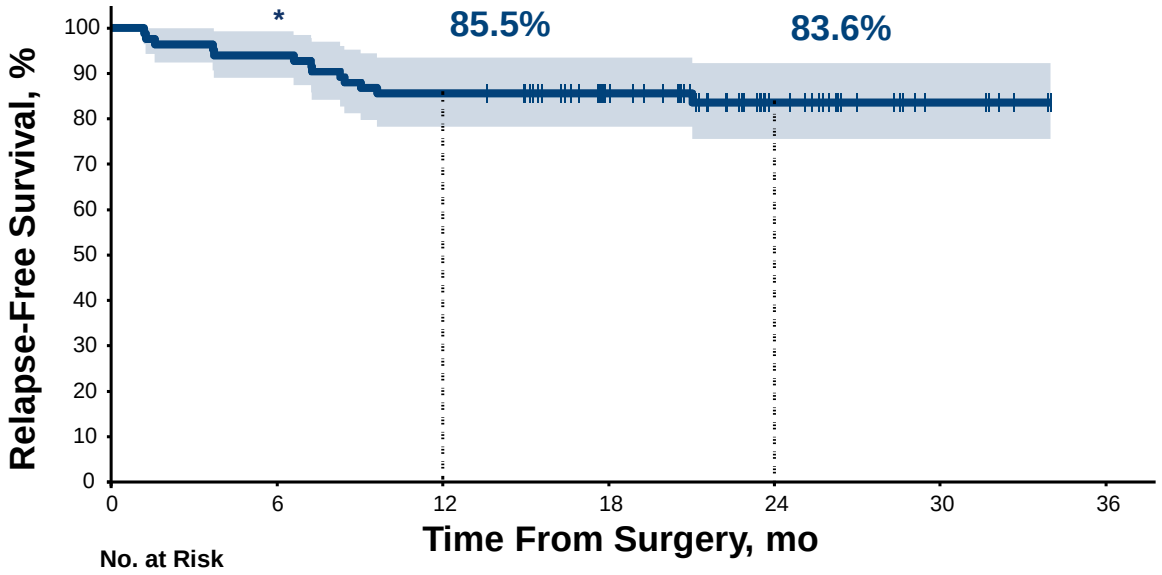


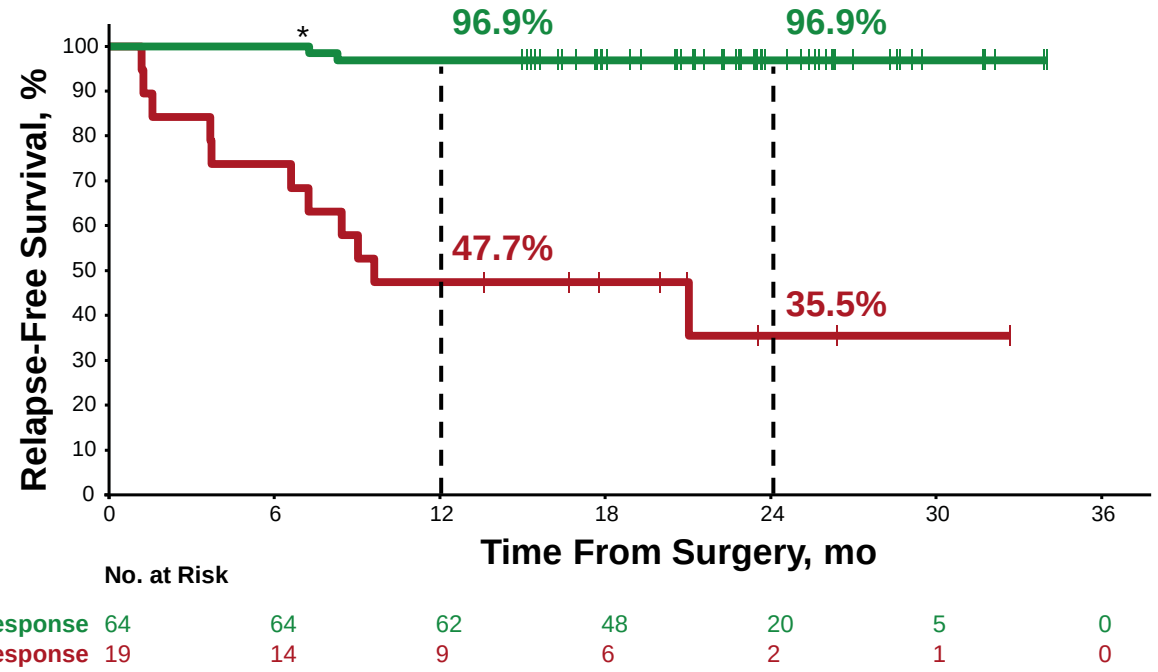


Patel et al., LBA6 ESMO 2022

OpACIN-neo (2 cycles Ipi1/Nivo3): RFS After 2.5 Years FU and Pathologic Response Predicts Outcome[1]

- OpACIN-neo: after a median follow-up of 24.6 months, only 1/64 (2%) patient with pathologic response has relapsed







Christian BLANK

Rozeman et al., ASCO 2020
Rozeman et al., Nat Med 2021

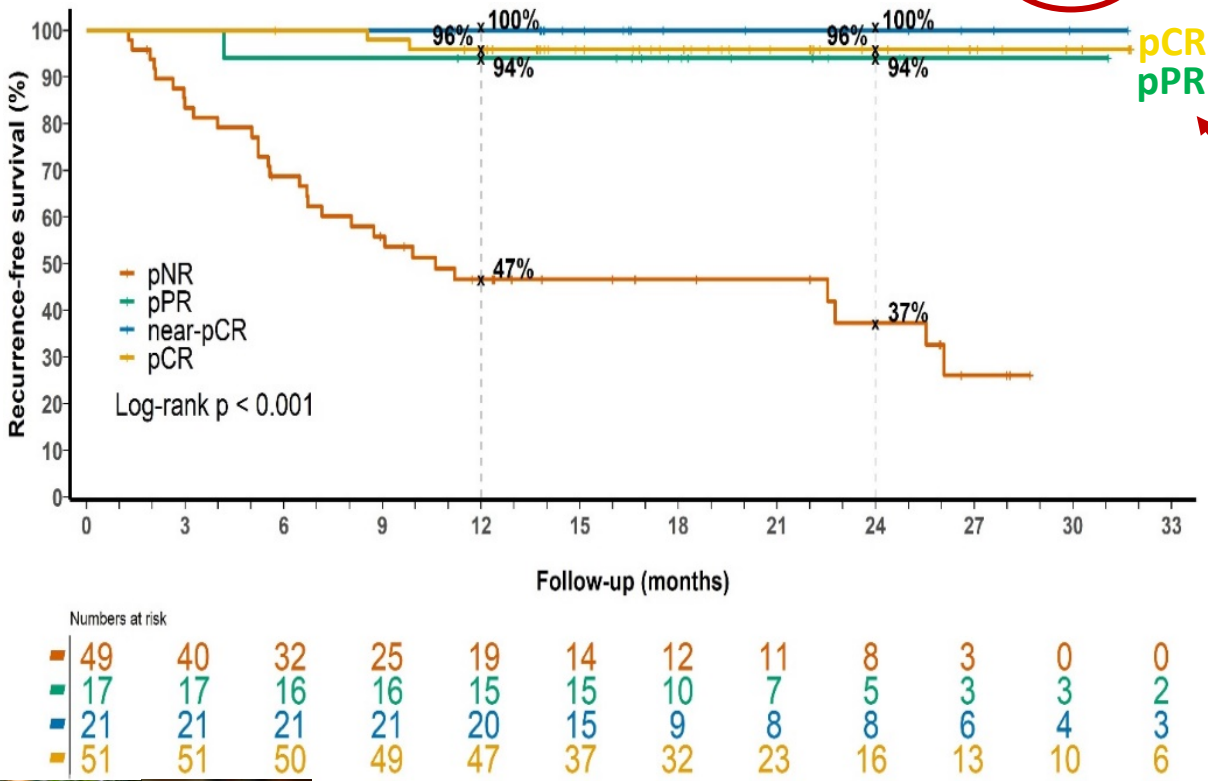
Pooled Analysis: Neoadjuvant Therapy in Stage III Melanoma

RFS by Pathological Response : SUPERIORITY IMMUNOTHERAPY

IMMUNOTHERAPY

Anti-PD1 pCR = 20%

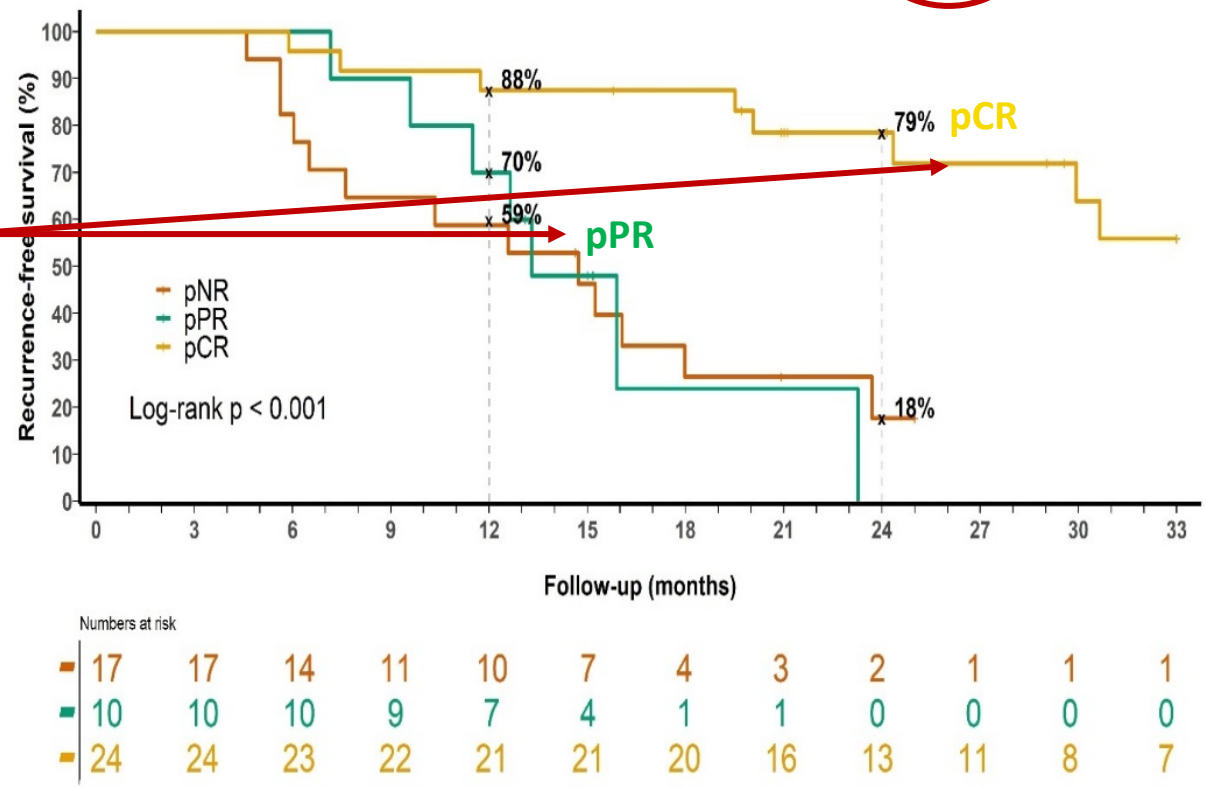
Anti-PD1 + Anti-CTLA4 pCR = 43%



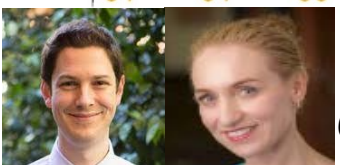
Med f/u 19.3 mo

Targeted Therapy

Dabrafenib + Trametinib pCR = 47%



Med f/u 25.9 mo



@ProfGLongMIA

Alexander Menzies et al Nat Med 2021



ASCO 2020: PRADO (The First 99 Patients)[1]

NEOADJUVANT IPI+NIVO REDUCE TLND RATES: LESS SURGERY

Personalized Response-Driven Adjuvant Therapy After Combination of Ipilimumab and Nivolumab in Stage IIIB/C Melanoma

Stage IIIB/C de novo or recurrent melanoma RECIST 1.1; measurable (≥1.5 cm short diameter) PA proven

Lymph Node Marker placement

2 courses **ipilimumab** 1 mg/kg + **nivolumab** 3 mg/kg Q3W

Resection of marked lymph node

- pCR or pathological near pnCR (0%-10% vital tumor cells) → **No CLND 60% of PTS** → Follow-up CT Q12W → Follow-up[c]
- pPR (10%-50% vital tumor cells) → CLND → Follow-up CT Q12W → Follow-up[c]
- No pathological response (pNR) (>50% vital tumor cells) → CLND → **NIVO** or D+T 52 wk RT[b] CT Q12W → Follow-up[c]

Week	-4	0	6	12	64
	Lab	Marked lymph node removal CT Lab Feces collection		CT Lab Ultrasound LN (no CLND arm only)	CT Lab Ultrasound LN (no CLND arm only)

[a] BRAF + MEK inhibition in *BRAF* V600E/K patients is allowed according to patient's and treating physician's decision when available. [b] Adjuvant radiotherapy according to patient's and physician's decision. [c] According to institute's standard.

1. Blank CU et al. ASCO 2020. Abstract 10002.

NEOADJUVANT IMMUNOTHERAPY WILL BE #1 TOPIC IN THE NEXT 5 YEARS: *More Cures—Less Surgery!*

MELANOMA palpable lymph nodes

- Nivolumab 3 + ipilimumab 1: 70% pathologic CR!
- **No more TLND in >50%** of patients with palpable nodes in 5 years
- S1801 Neoadjuvant-Adjuvant Pembrolizumab in Stage III: New Standard of Care

BLADDER CANCER

- 50% pCR for T3 bladder cancers: wait and see
- **Reduction cystectomies**

MSI COLORECTAL CANCER

- **19/20 p(n)CR for MSI CRC! (Chalabi……Haanen et al. *Nature Medicine*. 2020) NICHE 1**
- **107 PTS MSI CRC dMMR: ESMO 2022: NICHE 2: almpost 100% OR:**
- **In Future in case of p(n)CR: NO more (rectal) surgery, but endoscopy + MRI**

LUNG, HEAD and NECK, ESOPHAGEAL and GASTRIC, BREAST, GBM



NICHE 1: Chalabi, ----- Haanen, NKI Amsterdam

Neoadjuvant treatment of dMMR colon cancers

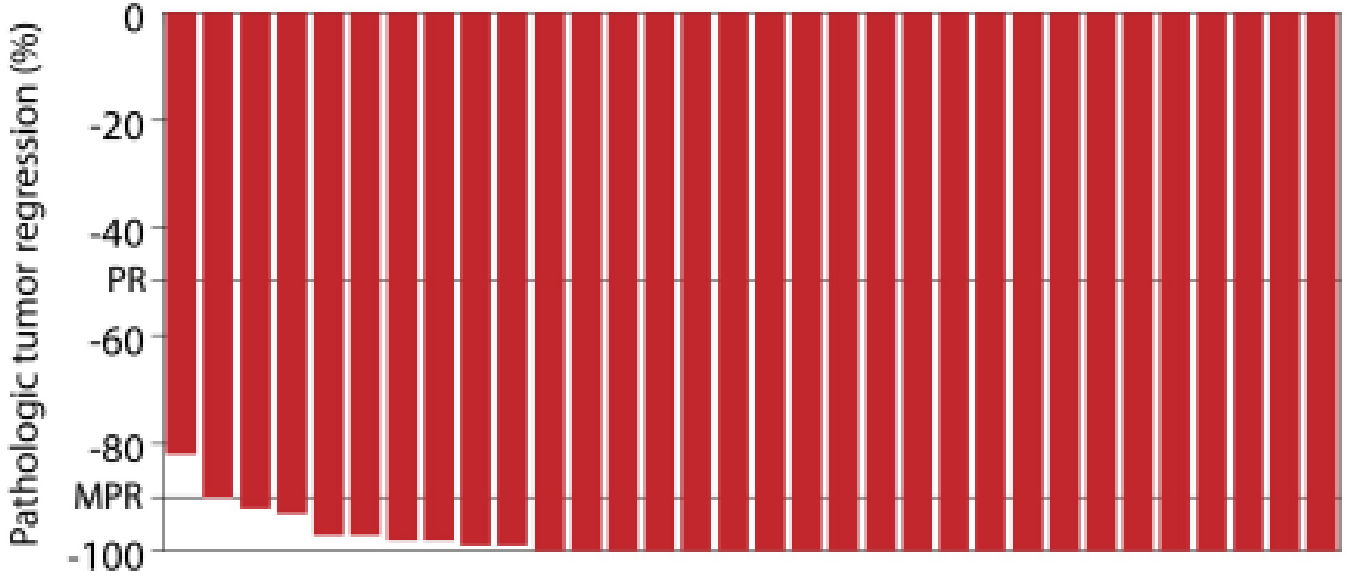
Previous data from NICHE-1 (*n*=32) show that immune checkpoint blockade is highly effective in non-metastatic dMMR colon cancers

- 100% pathologic responses and 60% pathologic complete responses

ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[2,5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17] and John B. Haanen[2,3,17]



PARIS 2022 ESMO congress

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Chalabi et. al, Nat Med 2020; Verschoor et. al, ASCO 2022

NICHE 2 (107 T3T4 pts): Chalabi et al. : NO MORE RECTUM RESECTIONS !

Major pathologic response in 95% of patients; 67% pCR

Pathologic response (RVT)		Patients *n*= 107
Yes	**(≤ 50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

RVT = residual viable tumor

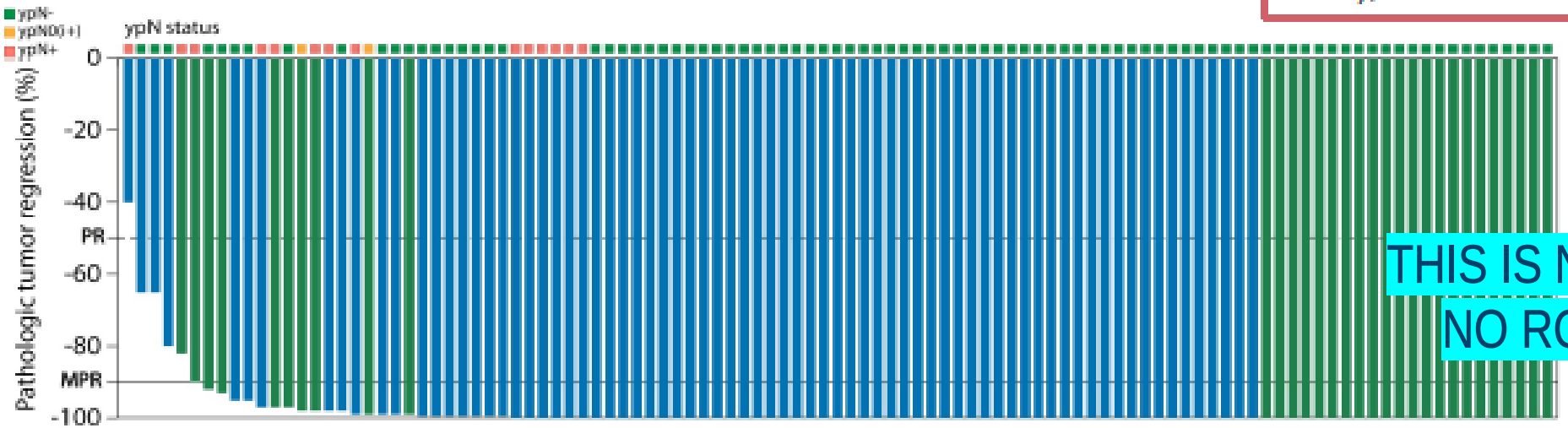
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

THIS IS NEW STANDARD OF CARE:
NO RCT PLEASE (Eggermont)

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ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

70 Locally advanced CSCC : NEOADJUVANT CEMIPLIMAB
Gross et al. (NEJM 2022)



- Neoadjuvant cemiplimab is highly active in resectable CSCC
  - 63.3% combined pathologic response rate (pCR + MPR)
  - 68.4% ORR by RECIST 1.1
    - Most classified partial response (PR)

- Imaging underestimated pathologic response
  - 50.6% pCR rate versus 6.3% imaging CR

- No new safety signals & Function-preserving surgery enabled in some cases

COMMENT: THIS IS NEW STANDARD OF CARE: NO RCT PLEASE (Eggermont)

CR, complete response; CSCC, cutaneous squamous cell carcinoma; ICPR, independent central pathology review, MPR, major pathologic response; ORR, objective response rate; pCR, complete pathologic response; RECIST 1.1., Response Evaluation Criteria in Solid Tumors version 1.1.

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- **S1801 Neoadjuvant-Adjuvant Pembrolizumab in Stage III: NEW STANDARD OF CARE**
- **NEW : NEOADJUVANT CEMIPLIMAB IN CUTANEOUS SCC**: **NEW STANDARD OF CARE: NO RCT PLEASE**

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- **NEW STANDARD OF CARE: NO RCT PLEASE !!!!!**

LUNG, HEAD and NECK, ESOPHAGEAL and GASTRIC, BREAST, GBM



NSCLC: NEOADJUVANT Nivo+Chemo vs Chemo

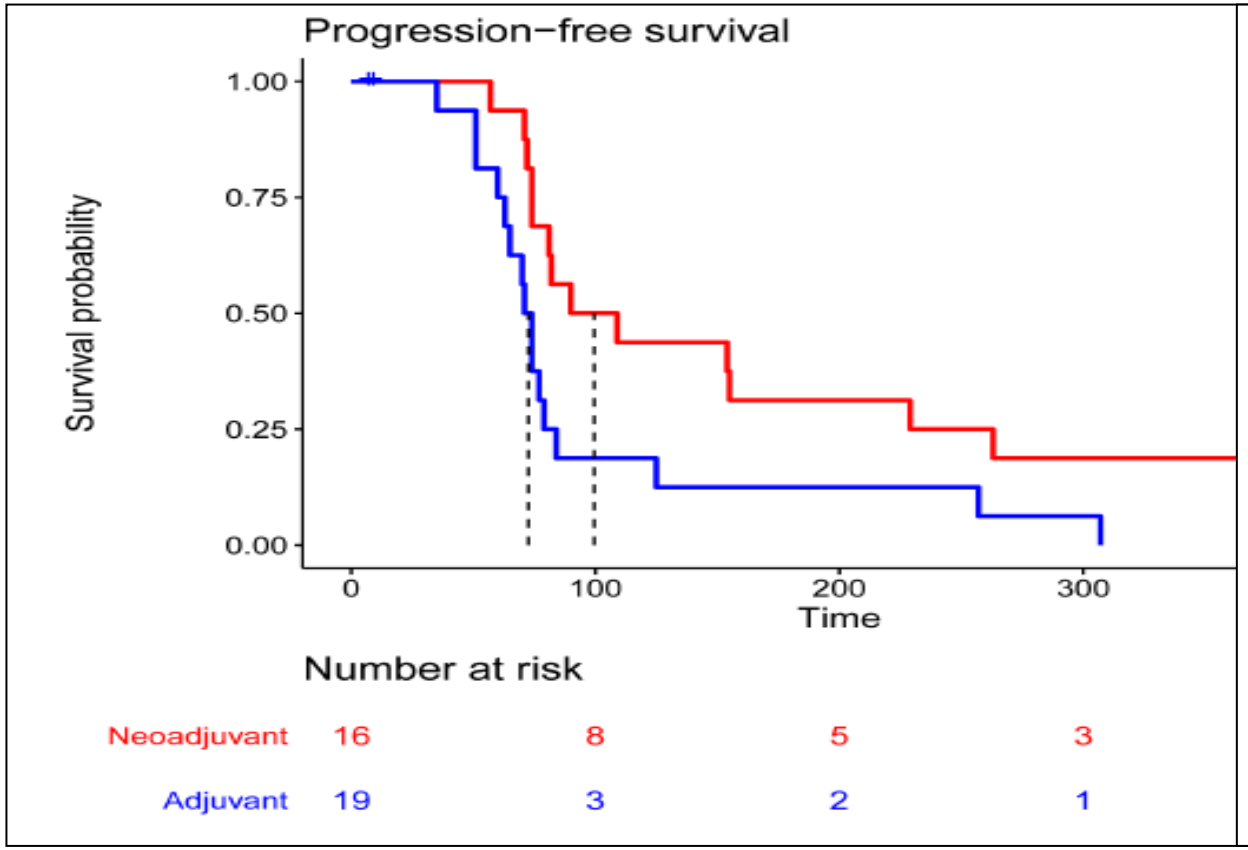
Checkmate-816

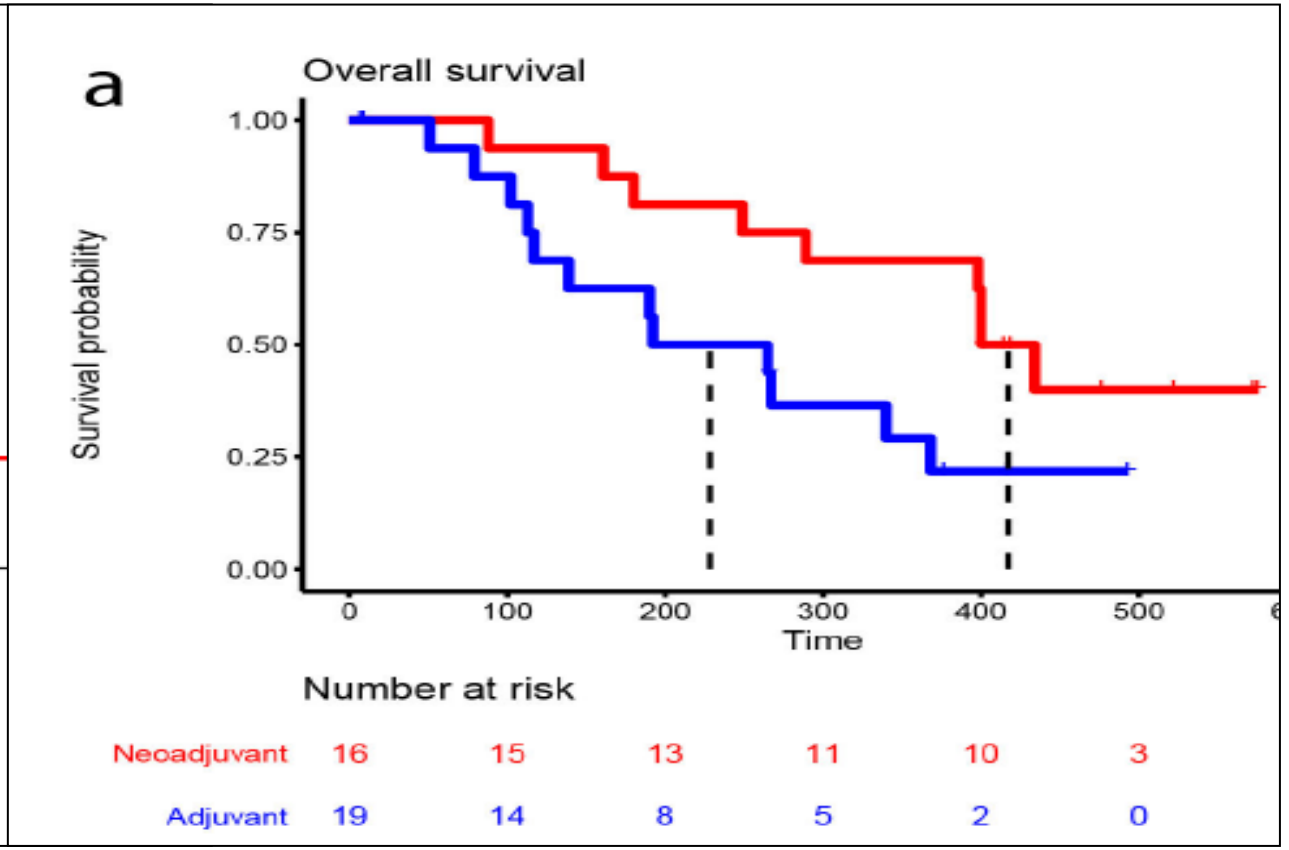
FDA APPOVAL 3/2022

- 37% Reduction Relapses: RFS (HR, 0.63; *P* =.0052)
- mRFS Nivo+chemo 31.6 mts vs 20.8 mts for chemo

- pCR rate combi vs mono: 24% vs 2% (*P* <.0001)
- IA for OS : HR 0.57 (95% CI, 0.38-0.87)

Impact of Only 1 Dose Neo-Adjuvant Anti-PD1 for Recurrent GBM





Median PFS: 72.5 – 99.5 days
HR: 0.43; P2 =0.03

Median OS: 228.5 days – 417 days
HR: 0.39; P2 = 0.04

PREDICTIONS
APPROVED and TO BE Approved (NEO) ADJUVANT TX

1) **MELANOMA**
2) **RCC**
3) **BLADDER**
4) **LUNG**
5) **ESOPHAGEAL / GEJ**
6) **GEJ /GASTRIC**
7) **HCC**
8) **CRC dMMR / MSI**
9) **MERKEL**
10) **cSCC**
11) **TNBC**
12) **H&N ?**
13) **GBM ?**


Princess
máxima
center
pediatric oncology
UMC Utrecht
CCC MÜNCHEN
COMPREHENSIVE
CANCER CENTER

Thank You

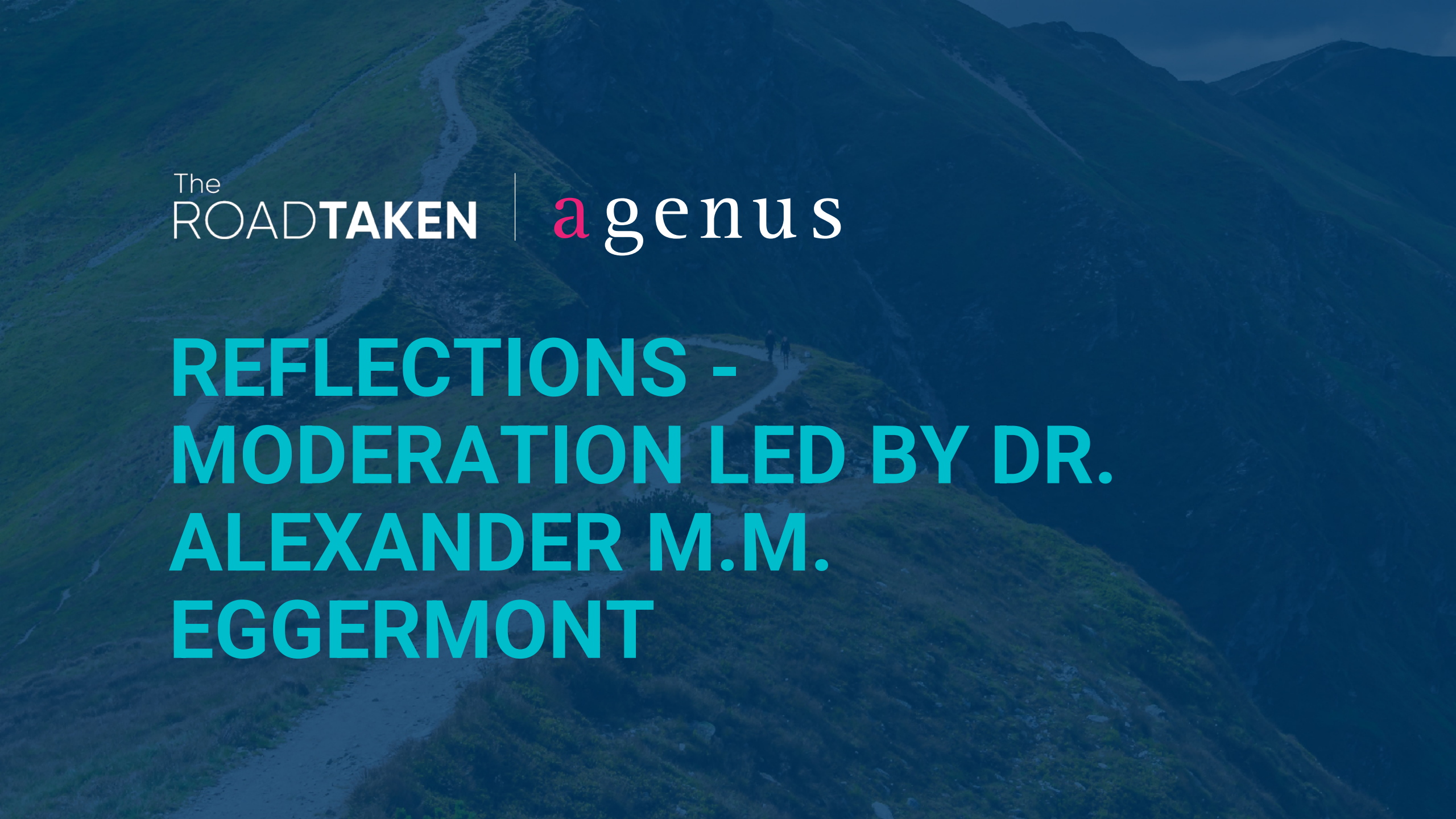
AGENUS PORTFOLIO CAN REACH UNTAPPED I-O MARKET



Current I-O market

$47B

Source: Evaluate Pharma 2022 global revenue estimates, Agenus analysis


The ROADTAKEN
agenus
REFLECTIONS - MODERATION LED BY DR. ALEXANDER M.M. EGGERMONT

The ROADTAKEN | agenus

AGENUS NEXT:
QUESTIONS & ANSWERS AND CONCLUSIONS

Todd Yancey, MD

Senior Global Clinical Development,
Medical Affairs and Commercial Advisor



SITC R&D Day

November 12, 2022