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NASDAQ:AGEN

Forward-Looking Statements

This presentation contains forward-looking statements. These forward-looking statements are subject to risks and uncertainties, including the factors described under the Risk Factors section of our most recent Annual Report on Form 10-K or Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission and made available on our website at www.agenusbio.com. When evaluating Agenus' business and prospects, careful consideration should be given to these risks and uncertainties. These statements speak only as of the date of this presentation, and Agenus undertakes no obligation to update or revise these statements. This presentation and the information contained herein do not constitute an offer or solicitation of an offer for sale of any securities.

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Garo Armen, PhD, Chairman and CEO

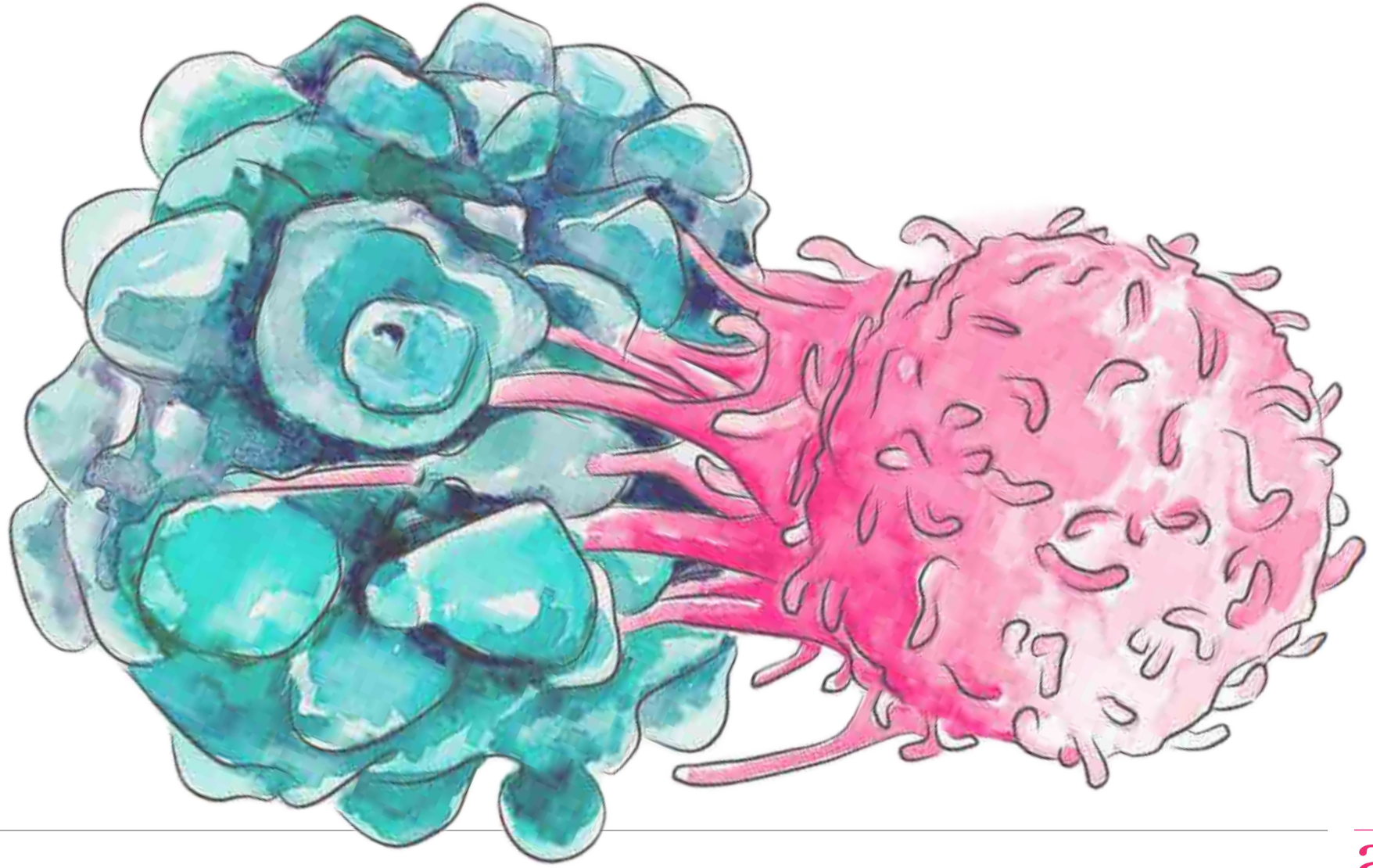
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agenus **R&D DAY**

New York

11:00 - 11:10am	Agenus Vision	Garo Armen, PhD
11:10 - 11:20am	Agenus: Who We Are And Where We are Going	Jennifer Buell, PhD
11:20 - 11:50am	Oncology: What Is Working and How Can We Improve? A Cervical Cancer Overview	Dr. Manuel Hidalgo
11:50 - 12:05pm	Agenus Zalifrelimab and Bastilimab in Cervical Cancer	Anna Wijatyk, MD
12:05 - 12:25pm	Audience Q&A with the panelists and presenters	Harshita Polishetty
12:30 - 1:00pm	The Revolution of Immuno-Oncology	Dr. Steven O'Day
1:00 - 1:15pm	NexGen CTLA-4, the AGEN1181 Advantage	Dhan Chand, PhD
1:15 - 1:30pm	Audience Q&A with the panelists and presenters	Harshita Polishetty
1:30 - 1:40pm	Agenus VISION Platform – Innovation Continues	Cailin Joyce, PhD
1:40 - 1:55pm	AgenTus - Allogeneic Cell Therapy Approach	Walter Flamenbaum, MD

Cancer and the Immune System - A Tug of War



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Agenus Is Set Up for Proprietary and Optimal Combinations

Checkpoint Antibodies

Neoantigen Cancer Vaccines

Cell Therapy

Immune Adjuvants

Agenus Has Several Notable Strategic Partners

*$2.4+ billion in potential milestones & royalties; **$500**M+ already received*

GILEAD	Incyte	UroGen Pharma	MERCK	gsk
$172.5M *received[1]*	**$145M** *received[2]*	**$10M** *received*	**$9M** *received*	**$190M** *received[3]*
Eligible • $1.7Bn milestones • Royalties	**Eligible** • $450M milestones • Royalties	**Eligible** • $200M milestones • Royalties	**Eligible** • $85M milestones • Royalties	**Eligible** • Up to $40M[4] receivable from royalty monetization

More detailed information available in Agenus SEC and 10k filings

[1] *Including $30M in equity investment*

[2] *Including $95M in equity investments*

[3] *$25.9 Million of this amount repayable and due in April 2021 if Shingrix does not meet certain sales targets in 2019 or 2020*

[4] *Eligible for two milestones ($15 Million and $25 Million) based on Shingrix meeting certain commercial sales targets metrics by 2024 and 2026*

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Imperative To Deliver Accessible Curative Combinations, Fast

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Transformation



1994-2014
Antigen vaccines
QS-21 (SHINGRIX)

2014
Antibodies

2015
Proprietary antigens

2015
GMP manufacturing

2016
Fc engineering
Cell line development

AgenTus THERAPEUTICS

2019
>14 proprietary programs
13 INDs & 12 Clinical combos 4 notable partners

GILEAD MERCK gsk Incyte

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Track
Annotate
News
Zoom
Normalized As Of 11/05/2018
.IO Equally weighted Portfolio 100.3576
.IO Market Cap weighted Portfolio 103.0921
AGEN US Equity - Last Price 171.8085
XBI US Equity - Last Price 99.5569
DRG Index - Last Price 102.8442
.IO MKTCA Index 02/28/19
Last Price 115.5769
200
180
160
140
120
80
171.8085
116.8412
103.0921
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
2018
03/01/19
2019

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Agenus: Who We Are And Where We are Going

Jennifer Buell, PhD, Chief Operating Officer

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Agenus Leadership Team



Garo Armen, PhD
Chief Executive Officer
- Founder of Agenus and pioneer in immuno-oncology
- Previously Chairman the Board at Elan and Protagenic Therapeutics



Jennifer Buell, PhD
Chief Operating Officer
- Led research and clinical efforts to advance 13 novel therapies to clinic
- Previously at BMS, Harvard Clinical Research Institute, Tufts



Julie DeSander
VP Business Development & Alliances
- Led $1.7B transaction with Gilead and multiple research collaborations
- Previously at Baxalta, Amgen, McKinsey



Don Vidic
VP Commercial
- 30 years experience in distribution, access, payor strategy, and sales
- Previously at CVS, Medco, McKesson, Walgreens



Anna Wijatik, MD
VP Clinical Development
- Led Phase III development and BLA filings for Asparlas, Replagal
- Previously at Shire, BMS, Baxter



Sunil Gupta, MD
VP Regulatory & Pharmacovigilance
- Led regulatory strategy and filings for Eloxatin, Jevtana
- Previously at Sanofi for 22 years



Alex Duncan, PhD
Chief Technology Officer
- Led Humira, Benlysta discovery and development
- Previously at AstraZeneca, Cambridge Antibody Technologies



Evan Kearns, JD
VP & General Counsel
- Expertise in corporate and securities law, financing transactions, corporate governance
- Previously at Goodwin Proctor



Christine Klaskin
VP Finance & Principal Accounting Officer
- Expertise in finance, accounting, and corporate treasury
- Previously at Arthur Anderson

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Agenus Drives Innovation with Record Speed

Operational Execution

- Pivotal trials - 200+ patients treated with AGEN2034 (PD-1) & AGEN1884 (First-Gen CTLA-4)
- 13 INDs filed in 3.5 years; novel discoveries advance
- Advanced proprietary combinations

Strategic Partnerships

GILEAD · MERCK · gsk · Incyte · UroGen Pharma

Pipeline

- Balstilimab and zalfrelimab BLA Filing 2020
- 6 First-in-Class Bispecifics (Undisclosed)
- Best-in-Class CTLA-4, TIGIT, CD137, GITR, OX40, TIM-3, LAG-3, ILT4, and undisclosed^

Discovery Platforms & Integrated Capabilities

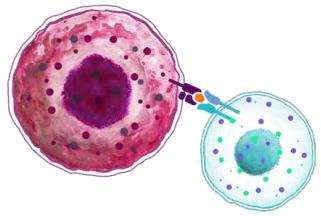
- Proprietary discovery engine that has generated 20+ clinical and preclinical compounds^
- In-house antibody & vaccine manufacturing — delivering at record speed
- Computational I-O platform enables high throughput discovery and translation

^ Includes proprietary and partnered pipeline

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Agenus Neoantigen Vaccines Expose Tumors for Immune Killing

Neoantigen Vaccines



Off-the-shelf vaccines

Proprietary QS-21

Remarkable activity in some patients with metastatic melanoma disease free 10+ yrs



Before Prophage



16 Months Post-Treatment



32 Months Post-Treatment

Belli F *et al.*, Clin Oncol 2002;20:4169-4180

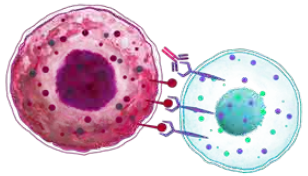
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Combinations are Critical for Robust & Durable Responses

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MERCK

CHECKPOINT ANTIBODIES



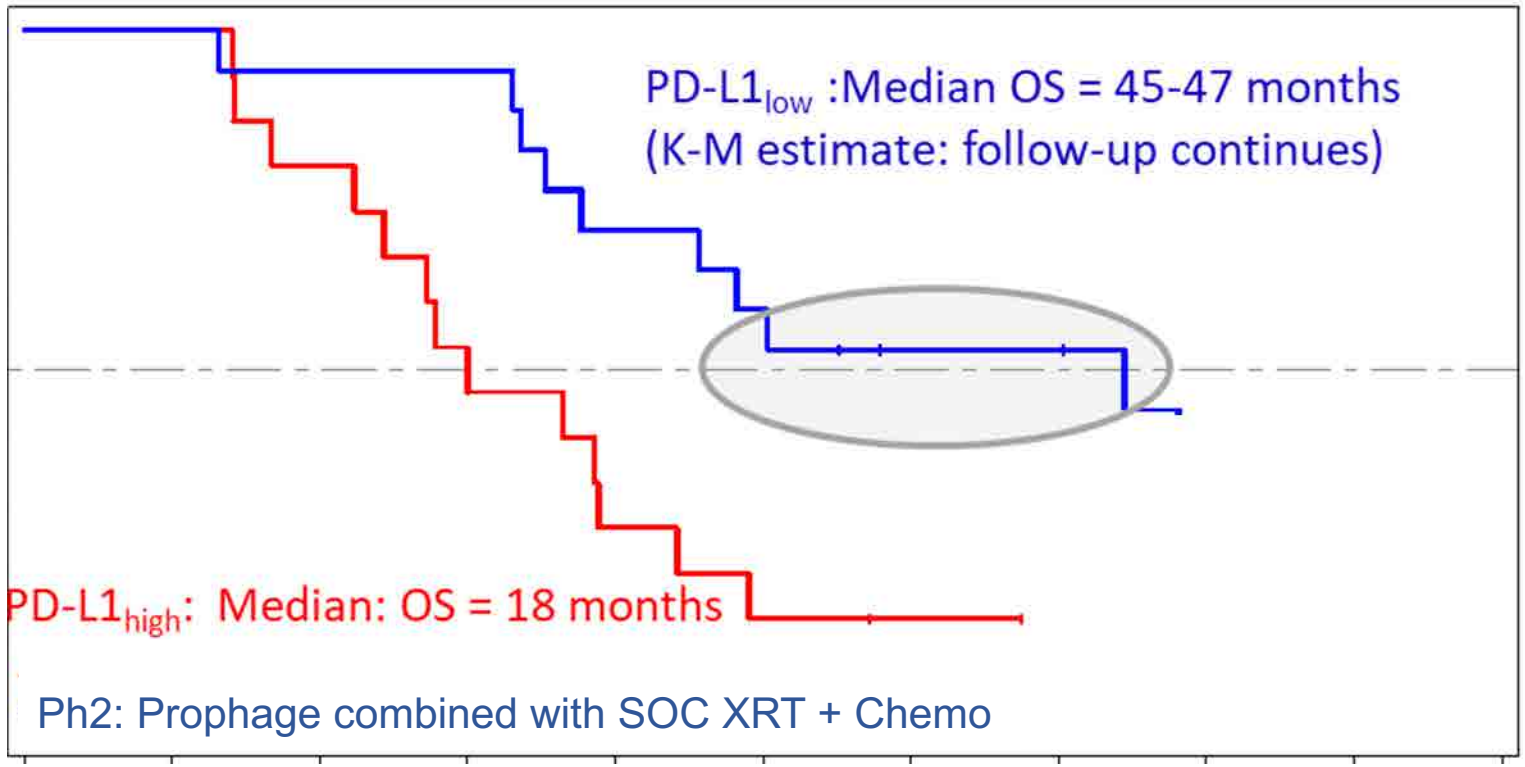
Fc engineering

Monospecifics

Bispecifics

Launched Ph 2: KEYTRUDA plus Agenus vaccine with SOC (GBM)

Funded by NIH BTTC; ongoing



Bloch et al. *Clin Cancer Res*. 2017:

Zalifrelimab is a Novel, Clinically Active, Anti-CTLA-4

zalifrelimab is advancing in a pivotal trial in combination with balstilimab in cervical cancer

- Phase 1 Clinical Trial with Zalifrelimab
- 62 y/o female with angiosarcoma of nose and cheeks had a complete and durable response (CR >2.8yrs)

Failed prior therapies

- Doxorubicin/ifosfamide
- Radiation therapy to 70 Gy
- Gemcitabine
- Rhinectomy
- High dose ifosfamide
- Pazopanib
- Phase I NOTCH inhibitor
- Temozolomide/bevacizumab
- Doxorubicin monotherapy

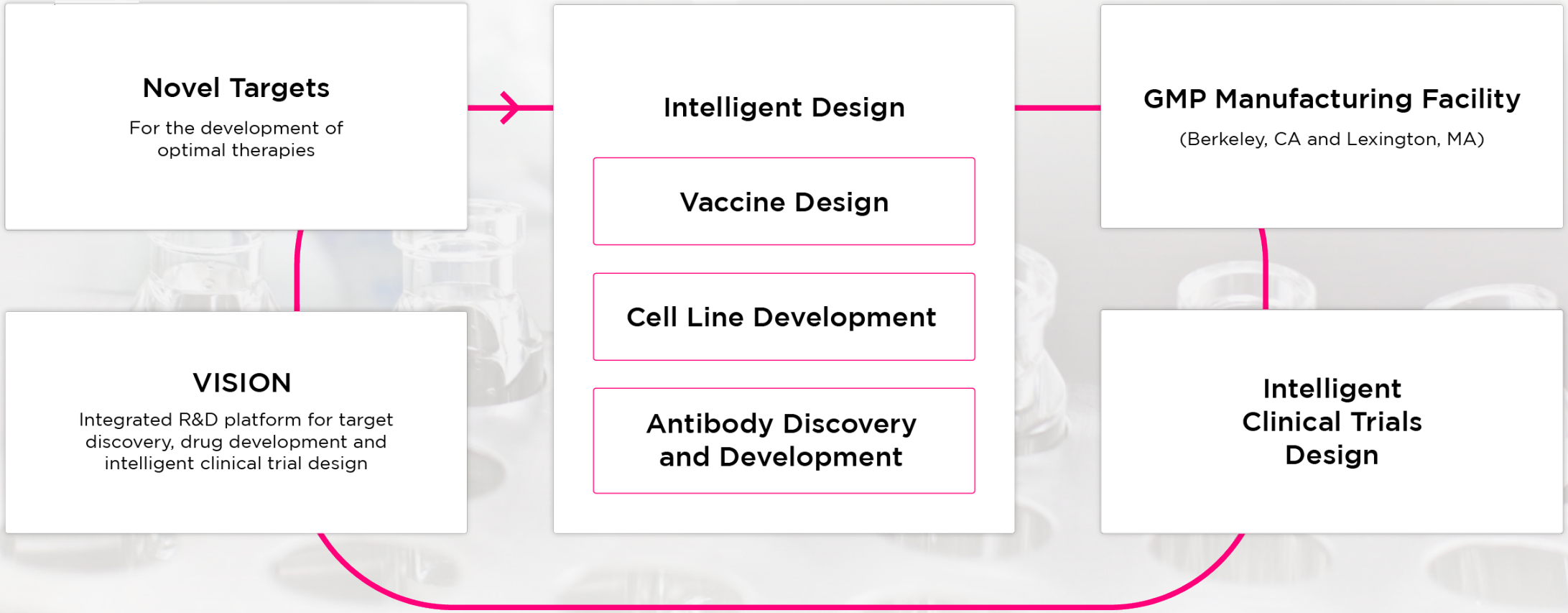




Patient profiled on CBS News Miami
Phase 1 study C-500-01 with PI Dr. Bree Wilky

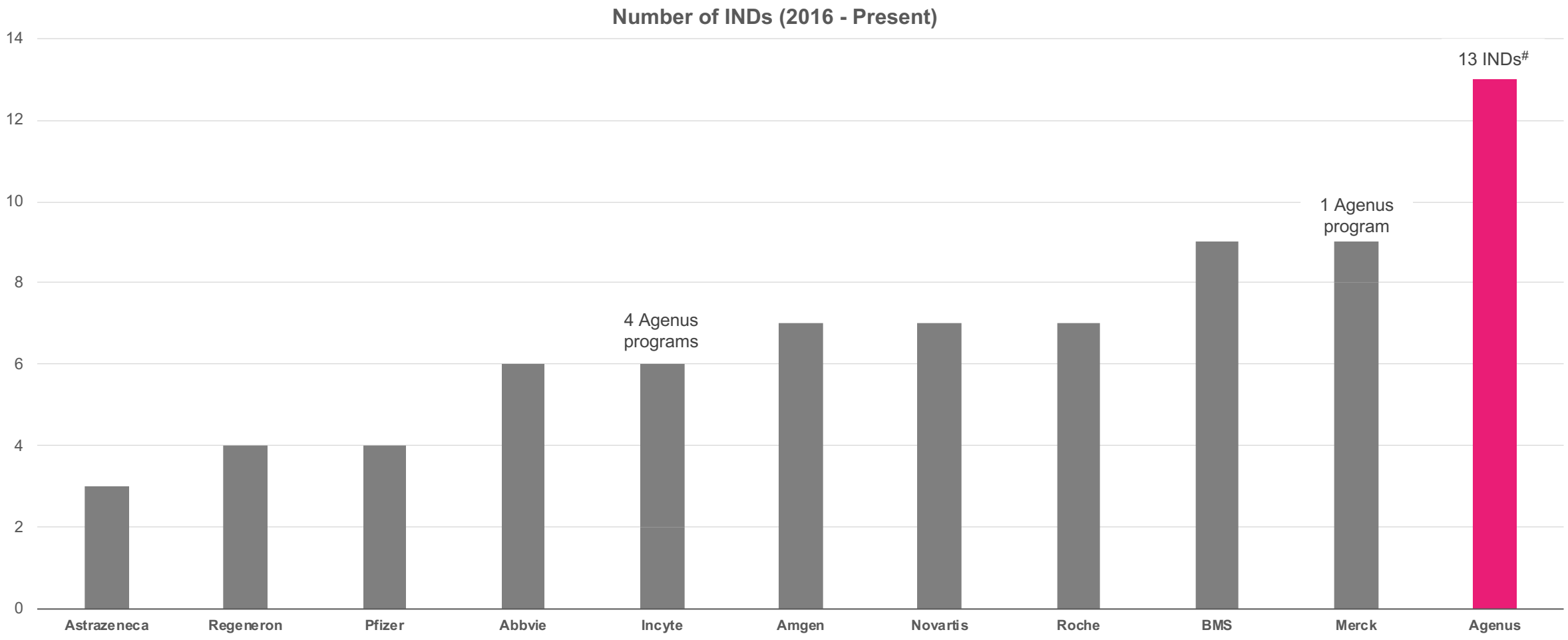
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Agenus is Fully Integrated From Concept to Clinic



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Agenus Outpaces Big Pharma in Advancing I-O Discoveries

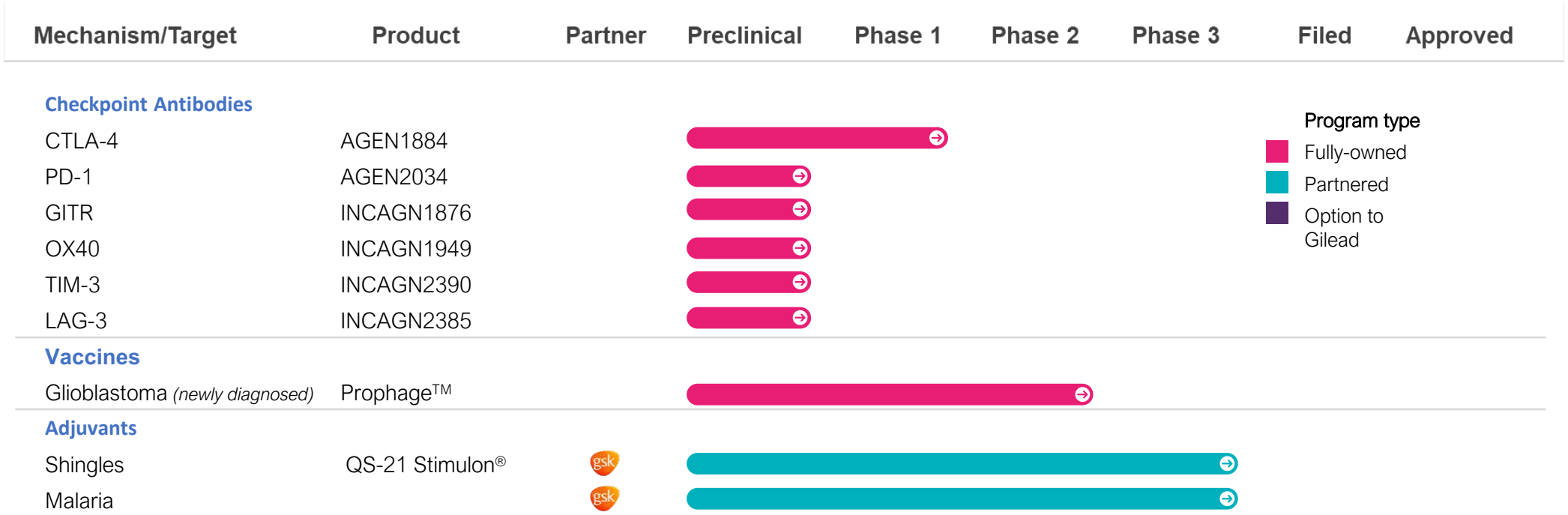


Analysis as of August 2019

INDs include programs partnered with Incyte, Merck and Gilead

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Agenus 2015



Notes: AGEN1884 and AGEN2034 are being evaluated in 2L cervical cancer and undisclosed tumors
Recepta Biopharma S.A. has exclusive rights to AGEN1884 and AGEN2034 in Brazil and five other South American countries

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Mechanism/Target	Product	Partner	Preclinical	Phase 1	Phase 2	Phase 3	Filed	Approved
Checkpoint Antibodies								
CTLA-4	AGEN1884							
PD-1	AGEN2034							
Next-generation CTLA-4	AGEN1181							
TIGIT								
Cytokine *(bispecific)*								
NK cell *(bispecific)*								
Stromal conditioning *(bispecific)*								
TME conditioning *(bispecific)*								
Tumor-associated macrophage								
CD137	AGEN2373	GILEAD						
Regulatory T cell depletion *(bispecific)*	AGEN1223	GILEAD						
TME conditioning *(bispecific)*	GS-1423	GILEAD						
GITR	INCAGN1876	Incyte						
OX40	INCAGN1949	Incyte						
TIM-3	INCAGN2390	Incyte						
LAG-3	INCAGN2385	Incyte						
Undisclosed		Incyte						
ILT4	MK-4830	MERCK						
Vaccines								
Glioblastoma *(newly diagnosed)*	Prophage™							
Cancers	AutoSynVax™							
Cancers	PhosphoSynVax™							
Adjuvants								
Shingles	QS-21 Stimulon®	gsk						
Malaria		gsk						
Adoptive Cell Therapy								
Cancers	Allogeneic iNKT	AgenTus						

Program type
- Fully-owned
- Partnered
- Option to Gilead

Agenus 2019

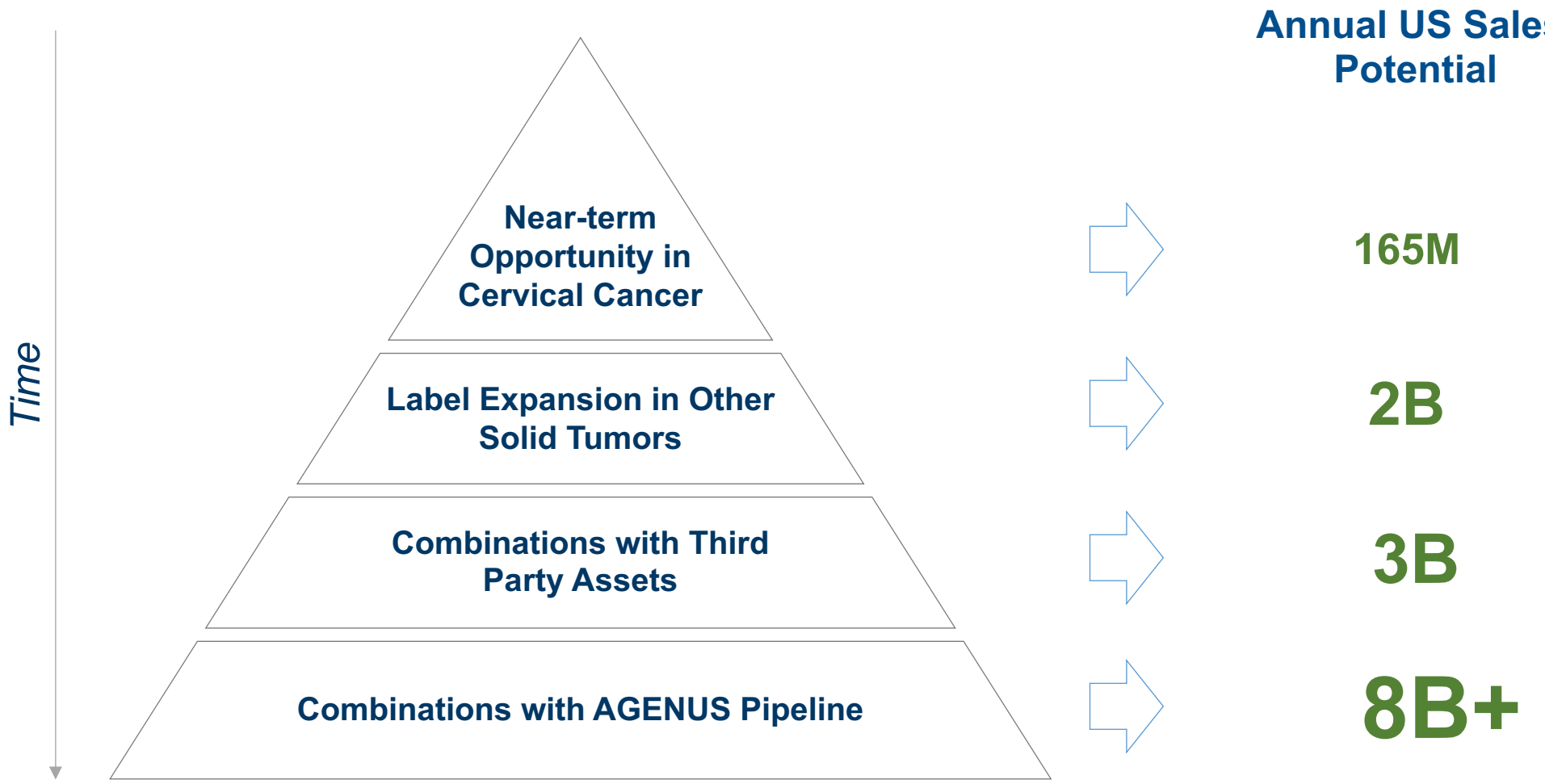
Notes: AGEN1884 and AGEN2034 are being evaluated in 2L cervical cancer and undisclosed tumors
Recepta Biopharma S.A. has exclusive rights to AGEN1884 and AGEN2034 in Brazil and five other South American countries

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Agenus First to Market Opportunity With CTLA-4 and PD-1

- PD-1s represent the largest oncology product category, with multiple blockbuster products
- Agenus' PD-1 antibody (balstilimab) is on track for a BLA filing in 2020
- Recent clinical data has solidified the opportunity for PD-1/CTLA-4 combos to fuel additional PD-1 growth
- Agenus will be the 2nd company to commercialize a PD-1 and CTLA-4 combination
- Balstilimab commercial opportunity is driven by
    - FDA approved indications,
    - NCCN guidelines (reimbursement), and
    - Superior combinations enabling label expansion with Agenus next-gen CTLA-4
- These development plans have the potential to yield beyond $8B in peak year sales (to start)

Balstilimab is Core to Agenus' & Partners' Combinations



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2019 Progress

2019 Progress in Proprietary Programs

Agenus Fully Owned Programs

- ✓ Pivotal combination zalifrelimab and balstilimab – accrual & planned interim analysis complete
- ✓ Pivotal trial with balstilimab – accrual and planned interim analysis *near* complete
- ✓ AGEN1181 in-clinic; PD-1 combos planned 4Q2019
- ✓ AGEN1223 (novel bispecific) and AGEN2373 (novel CD137) in clinic
- ✓ Allogeneic cell therapy IND on track for 4Q2019
- ✓ Initiation of 5+ first-in-class antibody/bispecific programs

FiC = First in Class

2019 Progress in Partnered Programs

Milestones exceed $22.5M in receivables

Partnerships

- ✓ FDA acceptance of GS-1423 (first-in-class bifunctional molecule) — **$7.5M**
- ✓ FDA acceptance of AGEN1223 (first-in-class bispecific molecule) — **$7.5M**
- ✓ FDA acceptance of AGEN2373 (potentially best in class anti-CD137) — **$7.5M**
- ✓ Gilead selected Agenus West as CMO for GS-1423 — **Undisclosed**
- ✓ GS-1423 in clinic

Eligible ~$1.7Bn

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What to Expect In The Next 12 Months

	2019 and 2020
Pipeline	**File (2) BLAs** **Clinical Data on 6 programs** • *Balstilimab, zalifrelimab*, AGEN1181, AGEN2373, AGEN1223, & allogeneic cell therapy **File (2) INDs with First/Best in class**
Partnerships	**Deliver milestones on current partnerships** • Expected ~$60M in cash milestones **Expand strategic partnerships**

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agenus **R&D DAY**

New York

Join us to hear the latest developments in Immuno-Oncology and Agenus pipeline of checkpoint antibodies, bispecifics, tumor micro environment conditioners and allogeneic cell therapies.

From the Experts



Dr. Steven O'Day
Executive Director of the John Wayne Cancer Institute and Cancer Clinic



Dr. Manuel Hidalgo
Chief of Hematology & Medical Oncology, New York Presbyterian/Weill Cornell Medical Center

From Agenus



Dr. Garo Armen, PhD
Chairman and CEO



Dhan Chand, PhD
Head of Drug Discovery



Jennifer Buell, PhD
Chief Operating Officer



Anna Wijatyk, MD
Head of Clinical Development



Walter Flamenbaum, MD
CEO, AgenTus



Cailin Joyce, PhD
Innovation Discovery Engine



NewYork-Presbyterian

Weill Cornell Medicine

Dr. Manuel Hidalgo

Chief of the Division of Hematology and Medical Oncology at Weill Cornell Medicine and NewYork-Presbyterian/Weill Cornell Medical Center

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NewYork-Presbyterian

Weill Cornell Medicine

Immunotherapy for Cancer Treatment
What is Working and What is Not

Manuel Hidalgo, M.D., Ph.D.

July 2019

AMAZING THINGS ARE HAPPENING HERE

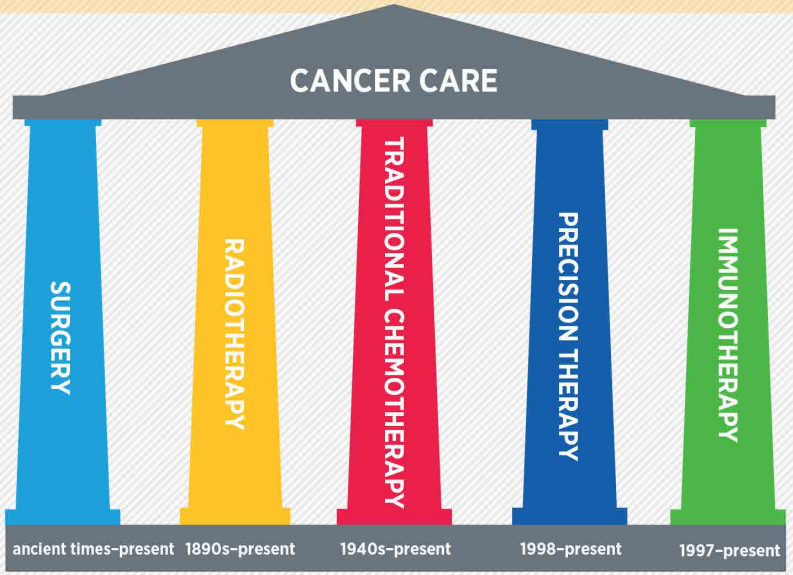
Disclosure

- **Founder and stock holder:** Champions Oncology, Inc.
- **Research support from:** Celgene, Pfizer, Bioline, Asana, Erytech, Bicycle, Berg, Oncomatrix, BioExcell.
- **Honorarium from:** Celgene, Bioline, Erytech, Agenus, SOBI, Pharmacyte, Bayer, Targovax, Oncomatrix, BioOncotech.
- **Royalties:** Myriad for PALB2 patent.

Pillars of Cancer Treatment

FIGURE 4

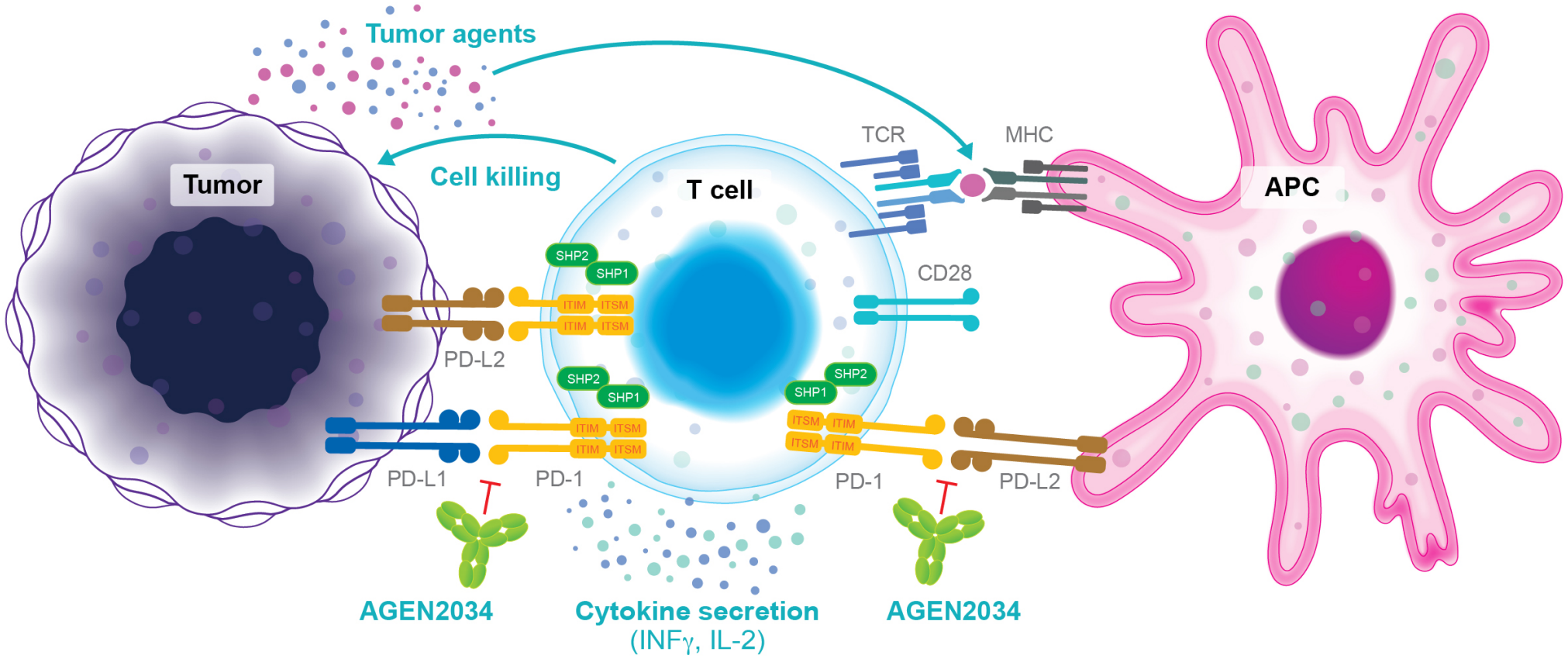
MORE OPTIONS FOR CANCER CARE



Physicians often refer to the "pillars" of cancer treatment. For thousands of years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, traditional chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and traditional chemotherapy–continue to be mainstays of cancer care. In the late 1990s, the first precision therapeutics were introduced, leading to the fourth pillar, precision therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent pillars of cancer care has increased dramatically in the past five years.

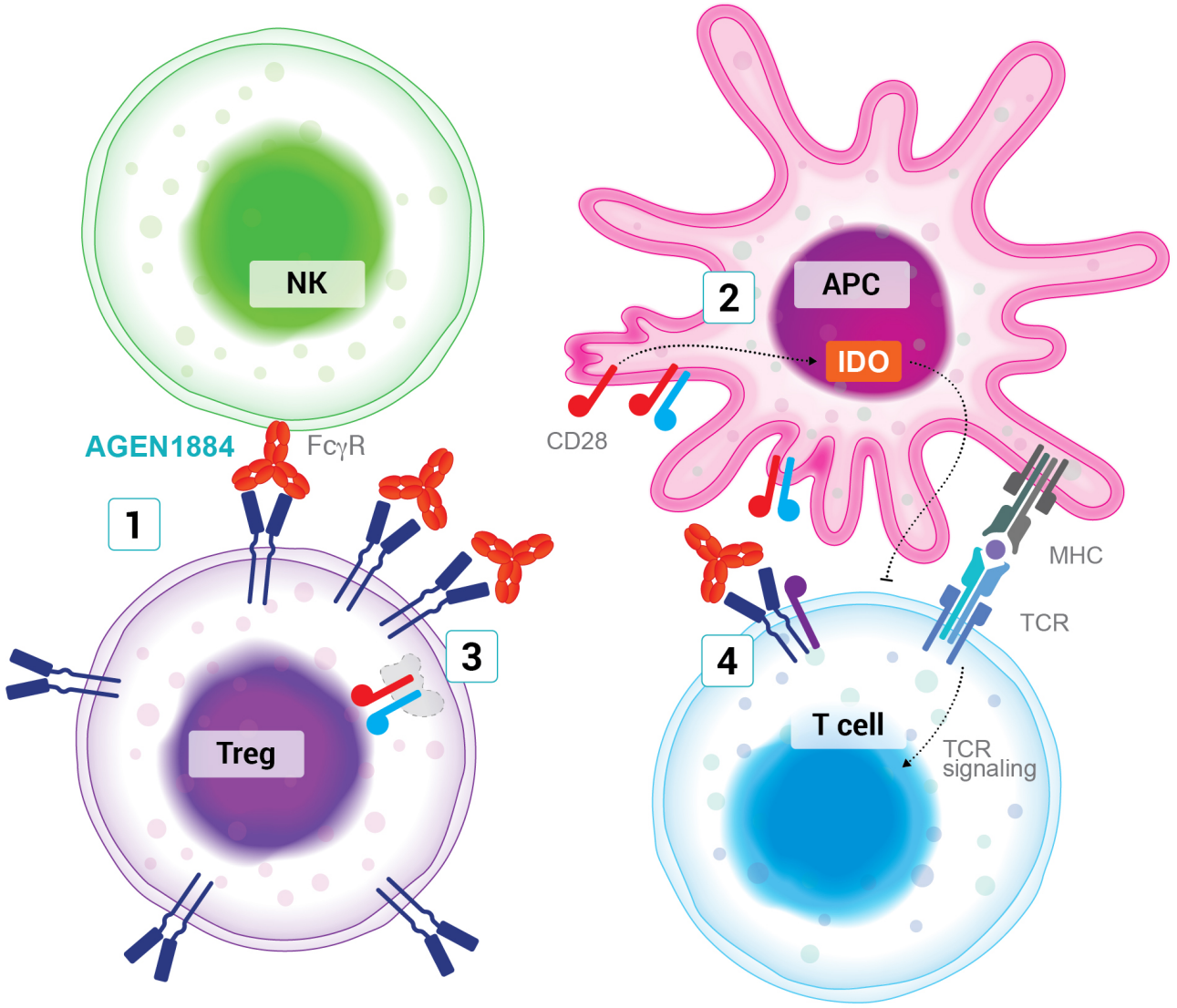
American Association for Cancer Research Cancer Progress Report 2015

Mechanism of Action of Check Point Inhibitors (Anti-PD-1)



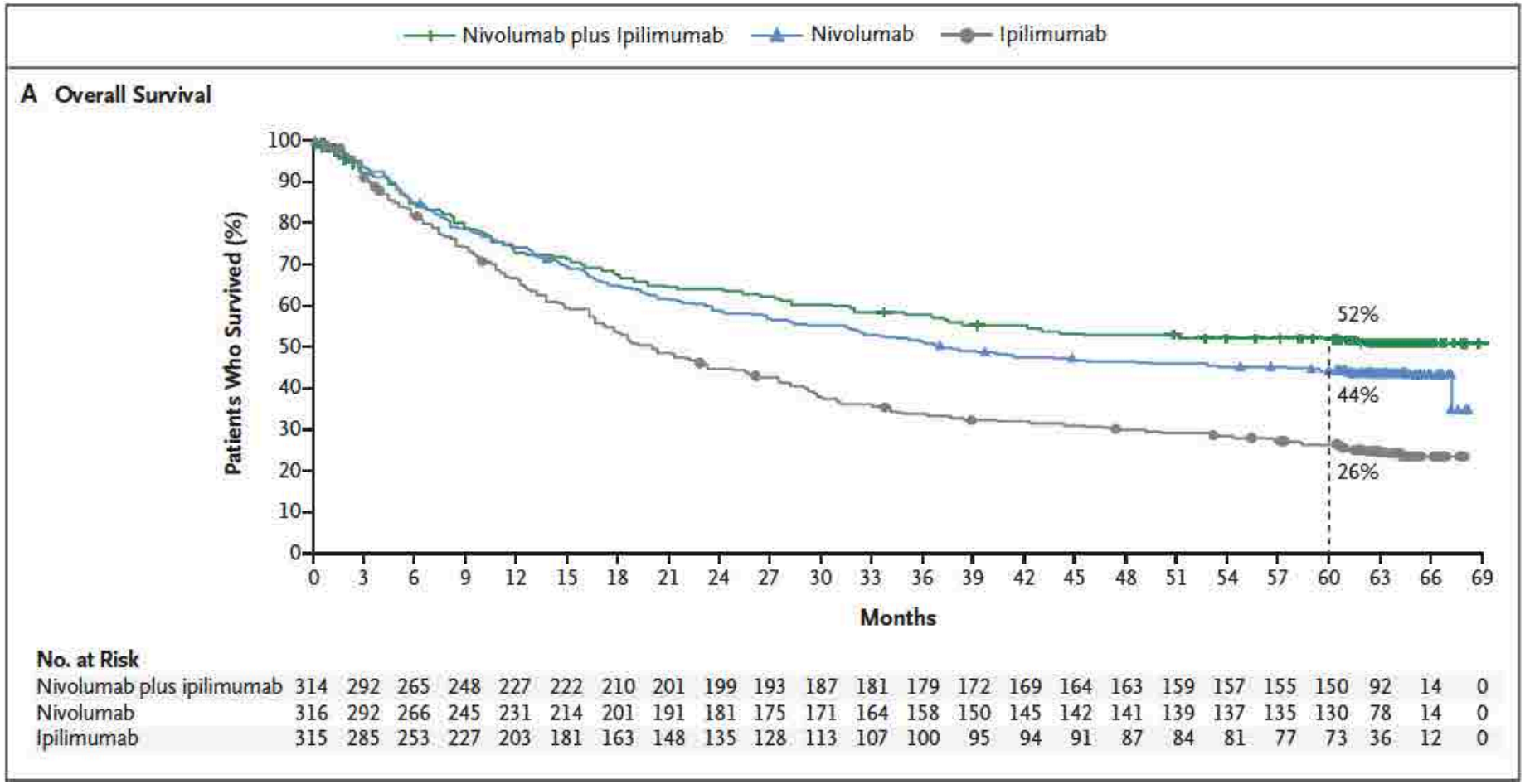
NewYork-Presbyterian Weill Cornell Medicine

Mechanism of Action of Check Point Inhibitors (Anti-CTLA-4)



Weill Cornell Medicine

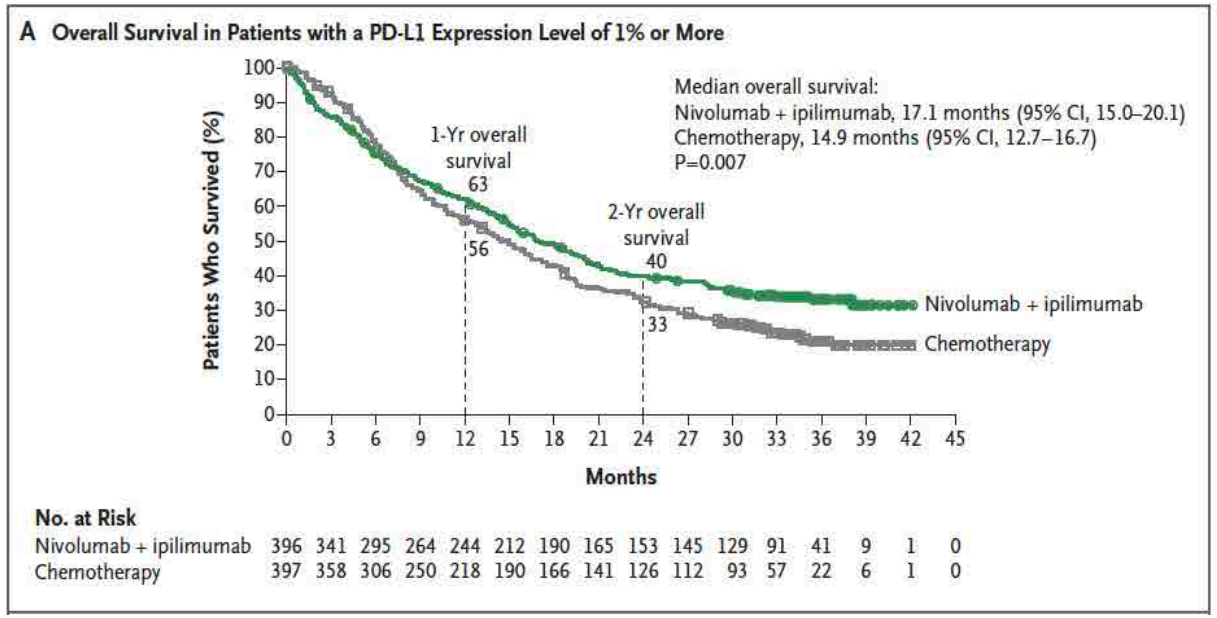
Ipi + Nivo in Advanced Melanoma

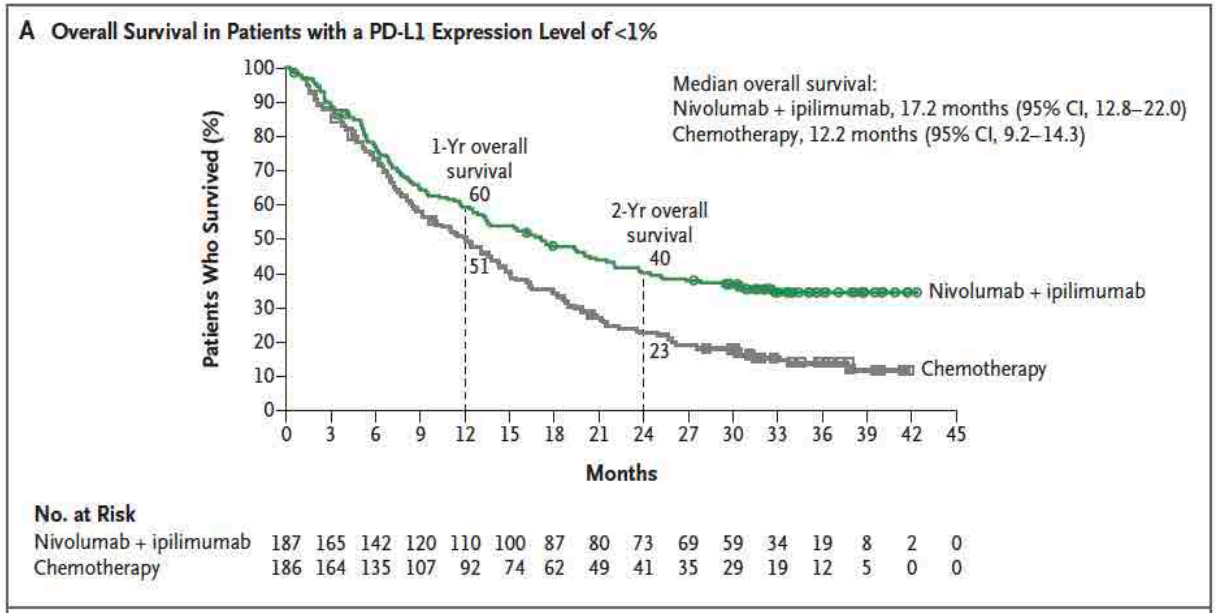


No. at Risk																								
Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

Larkin at al, NEJM 2019

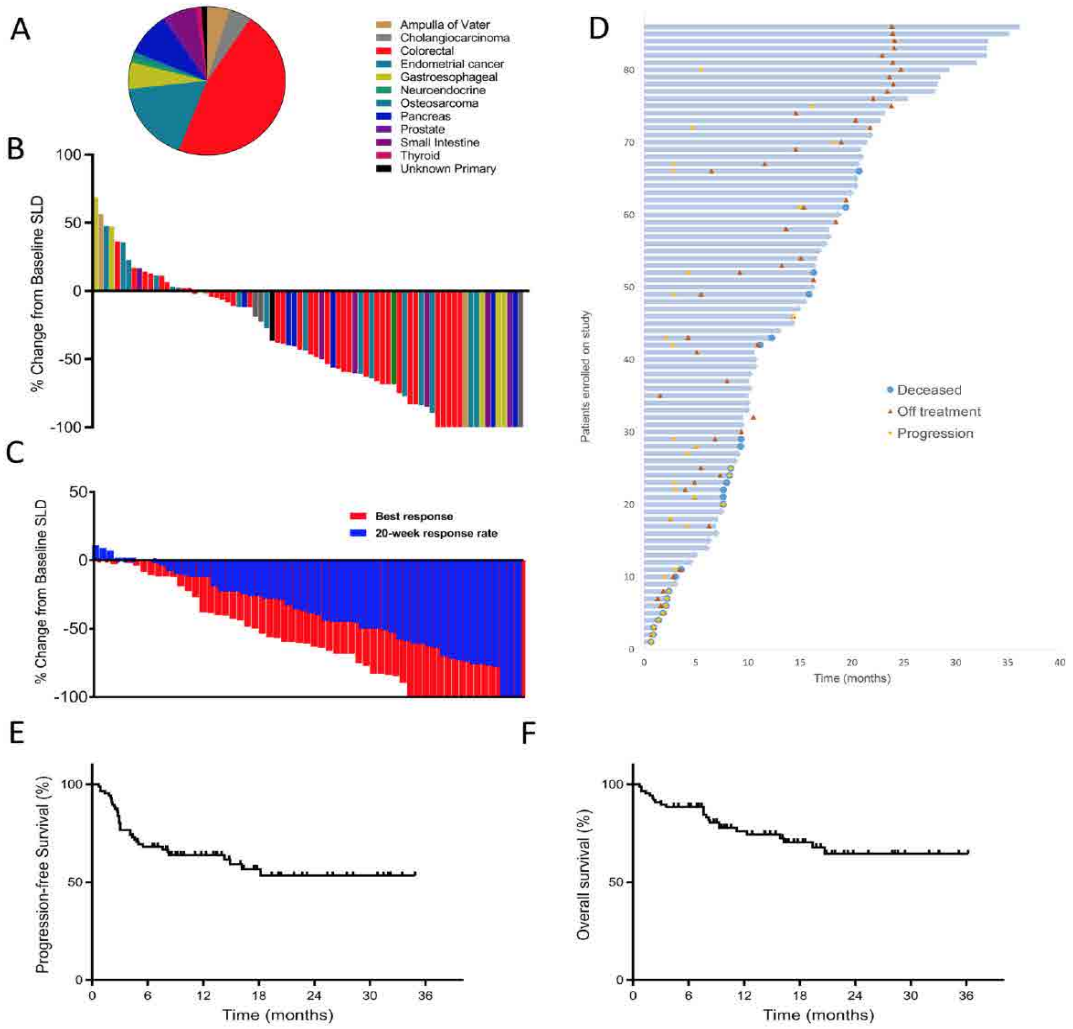
PDL1- Expression and Outcome





Hellman at al, NEJM 2019

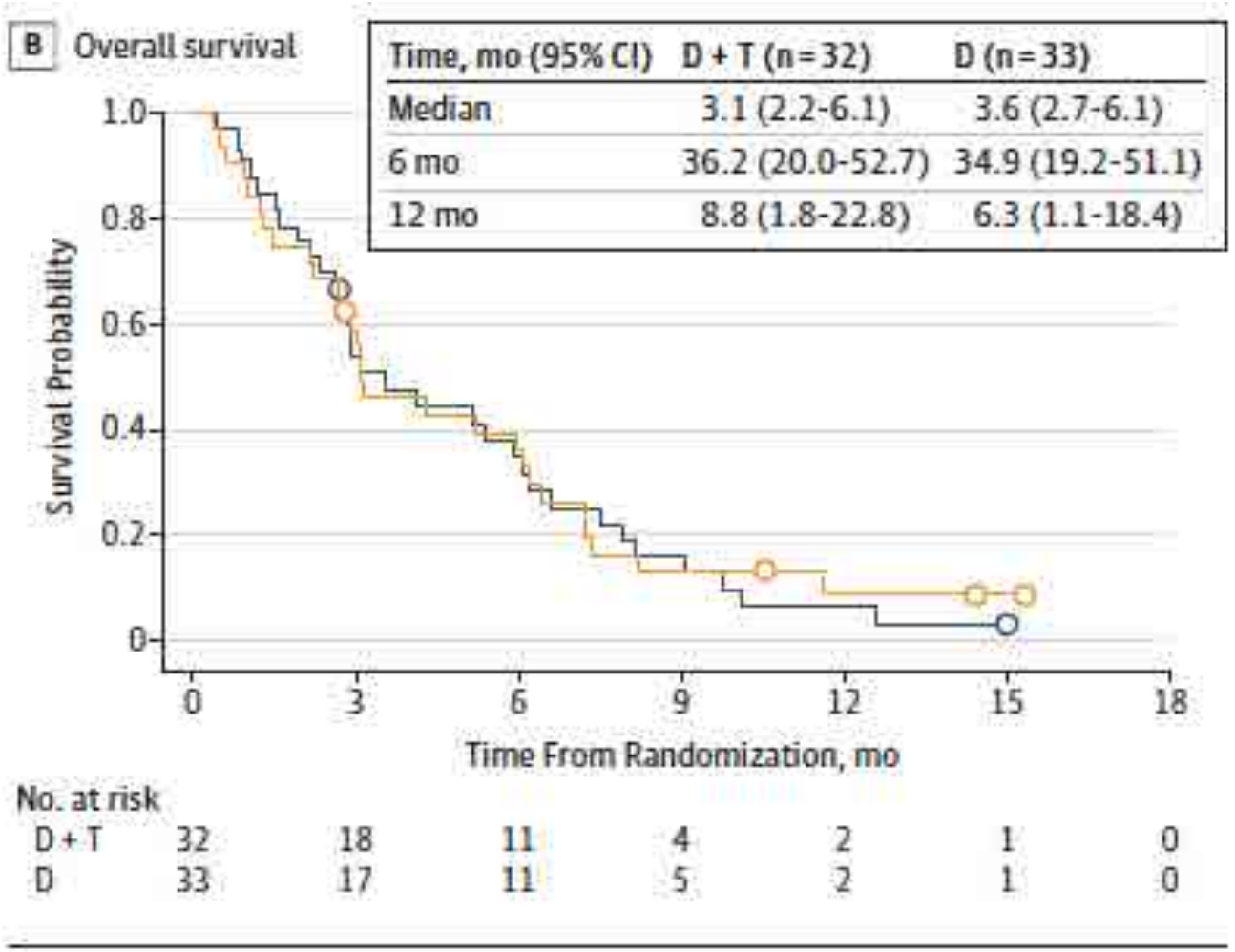
PD1 Blockade in MSI Cancers



Le et al., Science 2017

NewYork-Presbyterian Weill Cornell Medicine

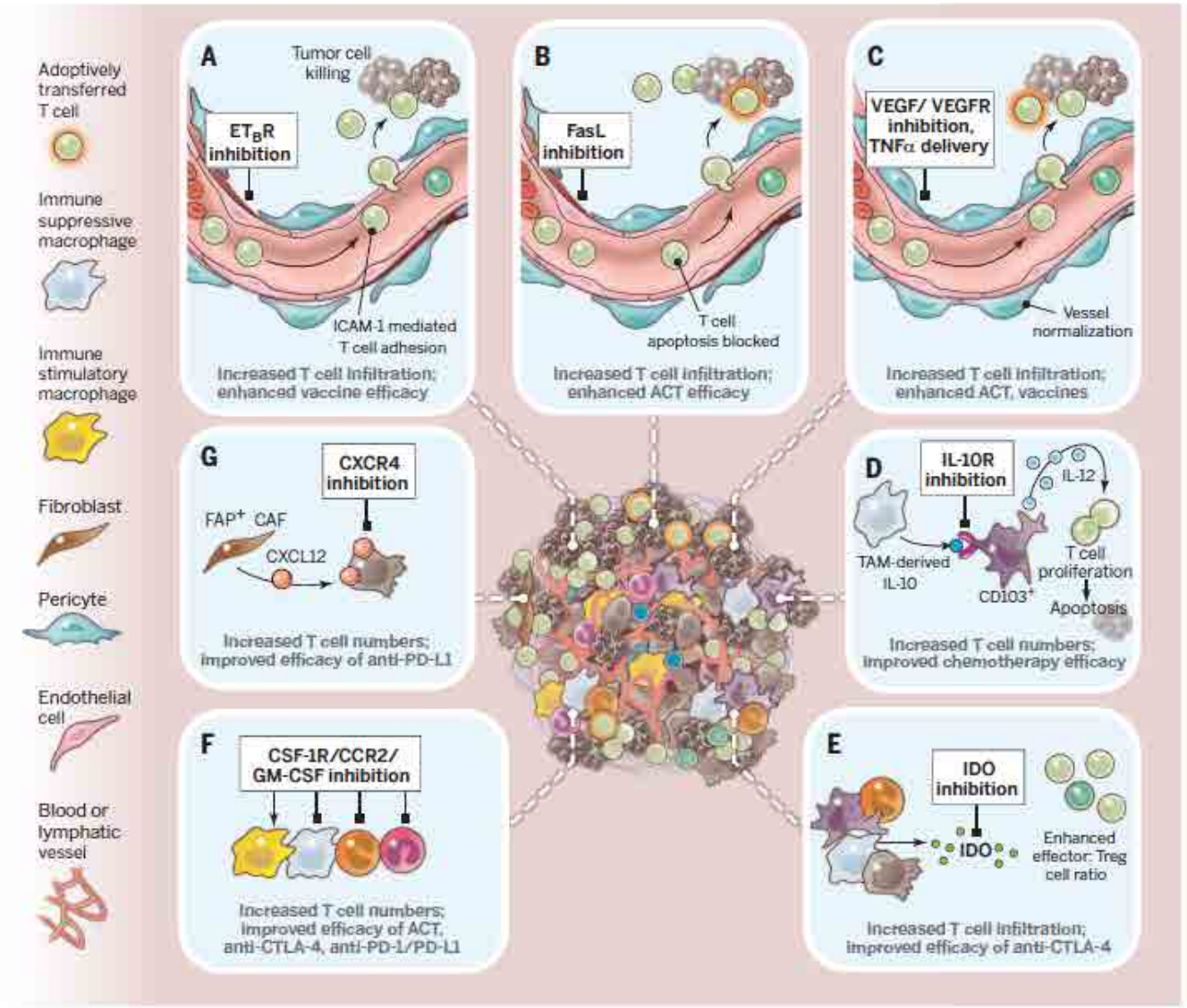
CPI in PDAC



O'Reilly et at JAMA Onc 2019

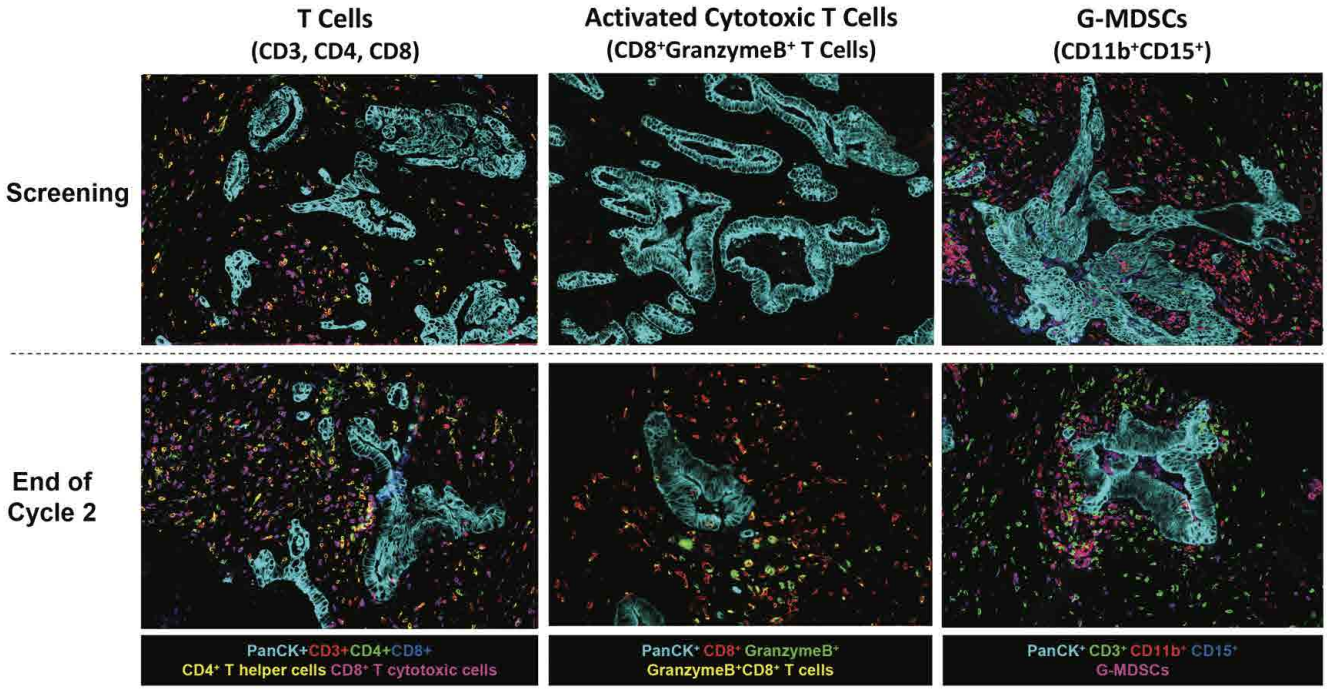
NewYork-Presbyterian Weill Cornell Medicine

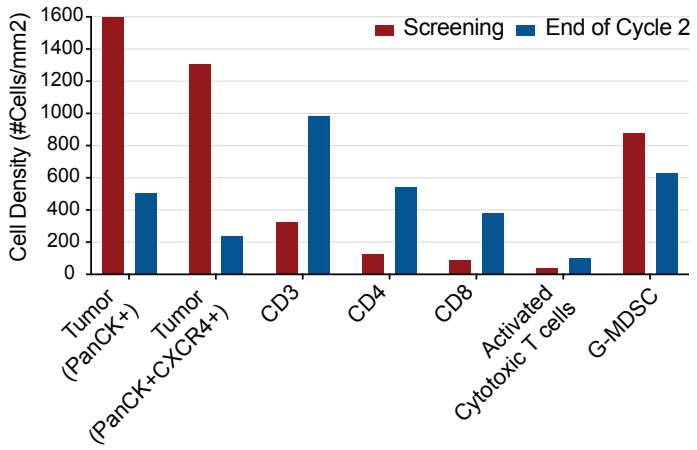
Overview of IO Therapeutic Strategies



Joyce at al, Science 2015

Effects on T cell Infiltrate in Tumor Tissues

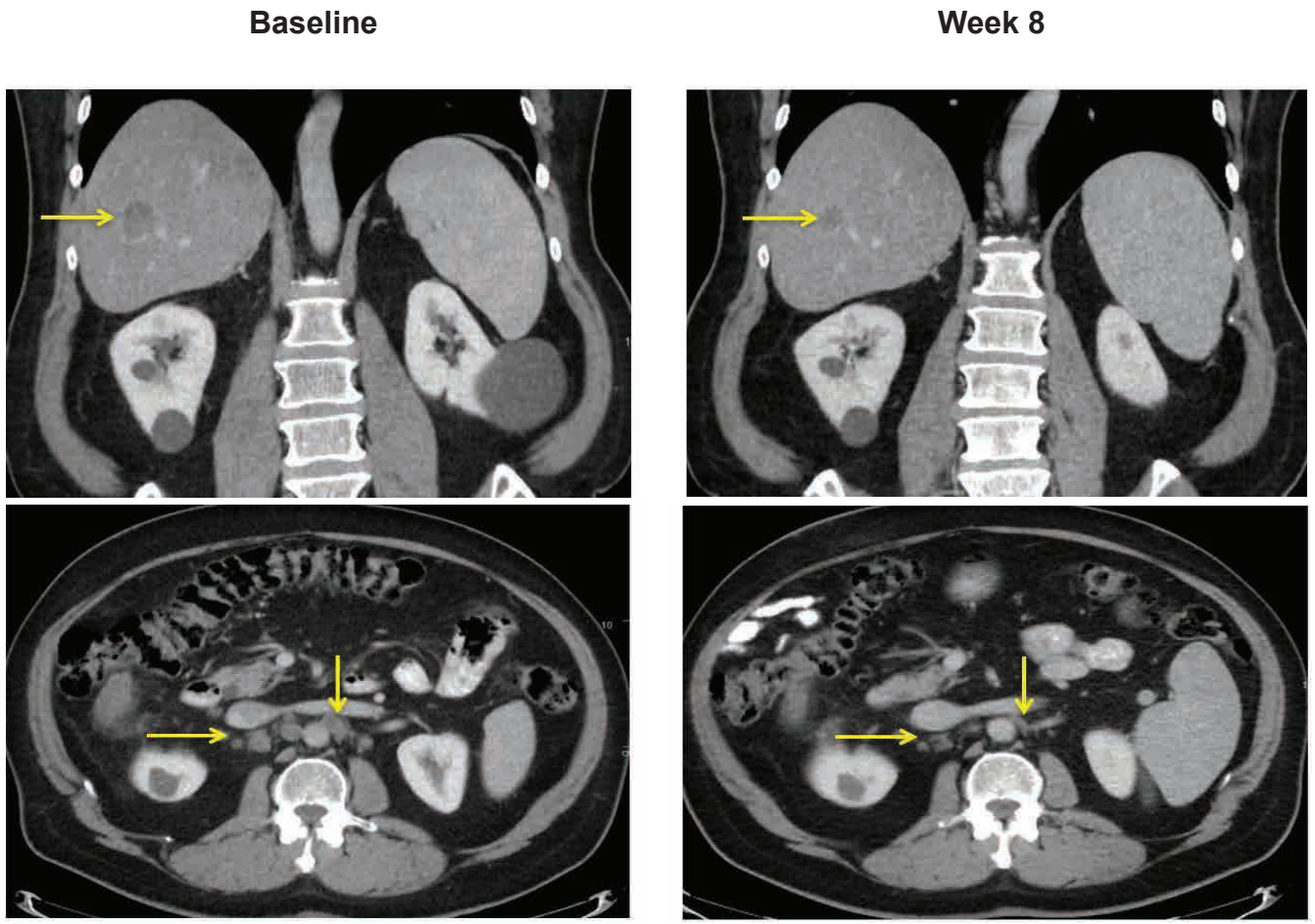




Hidalgo et al, ESMO 2018

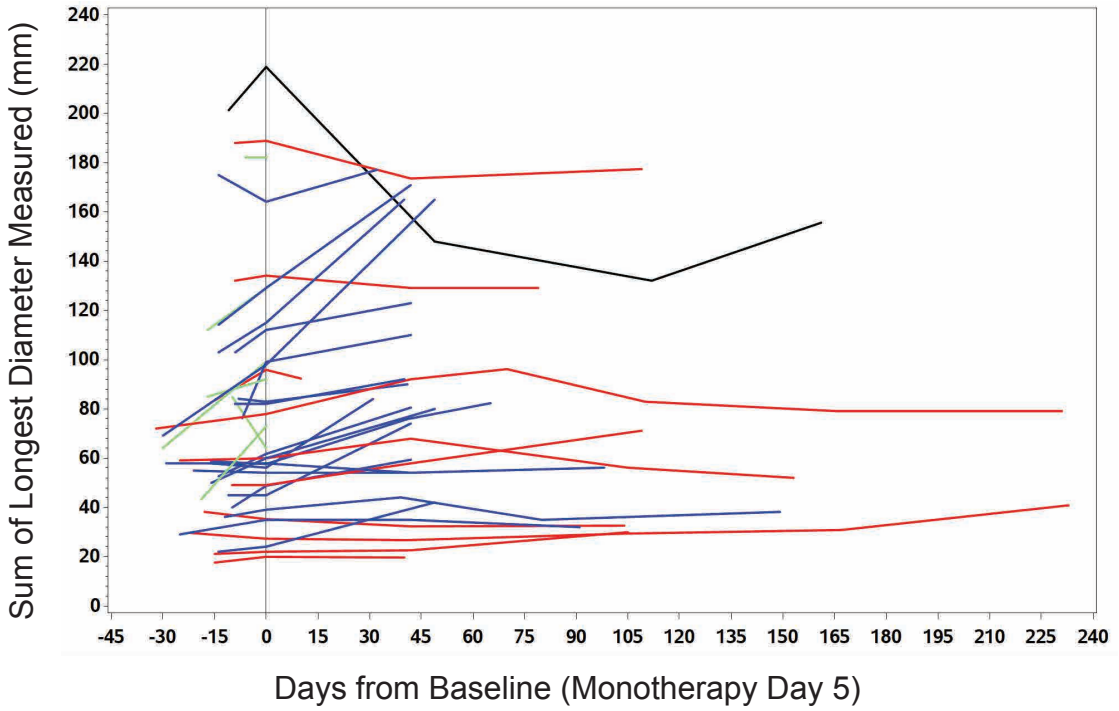
NewYork-Presbyterian Weill Cornell Medicine

Representative Case



Hidalgo et al, ESMO 2018

Individual Patient Outcome



Hidalgo et al, ESMO 2018

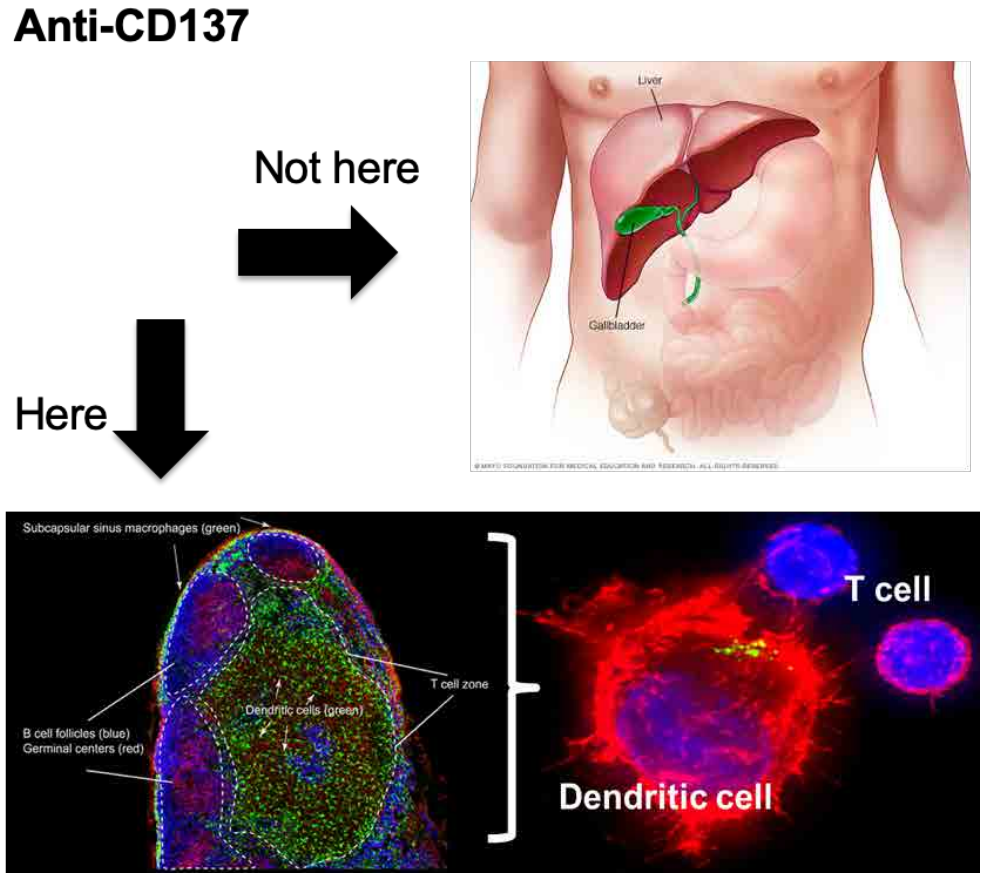
Co-stimulatory Potential of CD137 Agonists: AGEN2373

Potent co-stimulator of the immune synapse

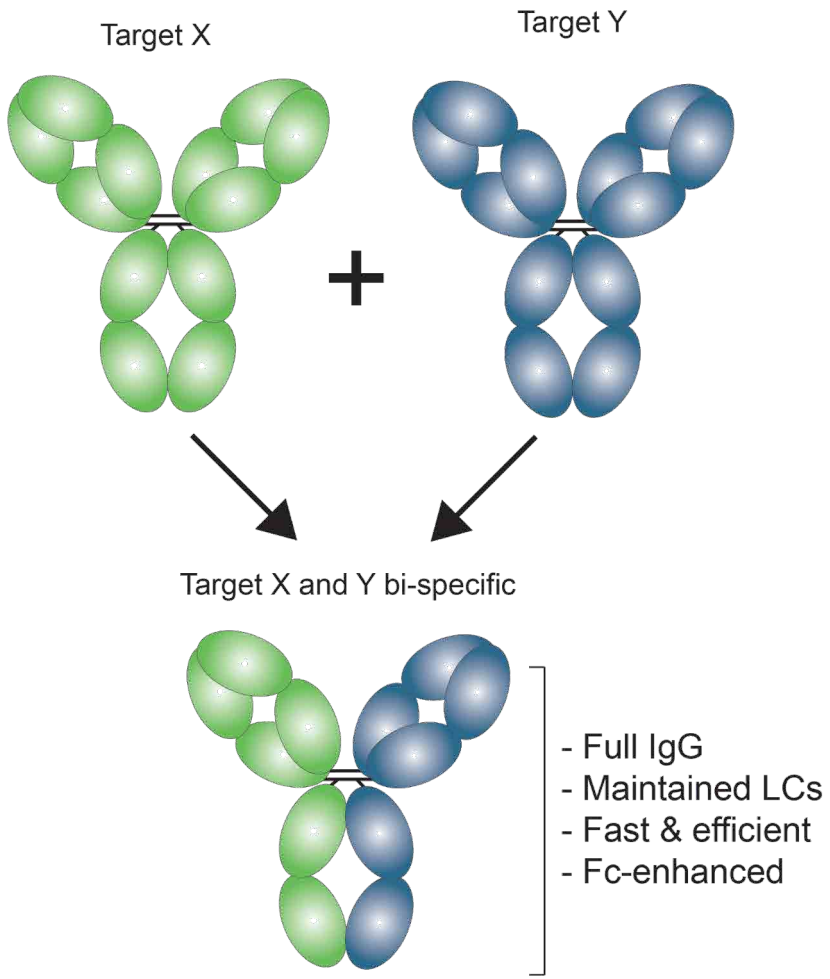
- ✓ Potent T cell activation and effector function
- ✓ Enhanced NK cell cytotoxicity
- ✓ IgG1 Fc backbone to realize full receptor agonism

Improved Safety (expected)

- ✓ Conditionally active agonist avoid off-site toxicity
- ✓ No evidence of liver toxicity



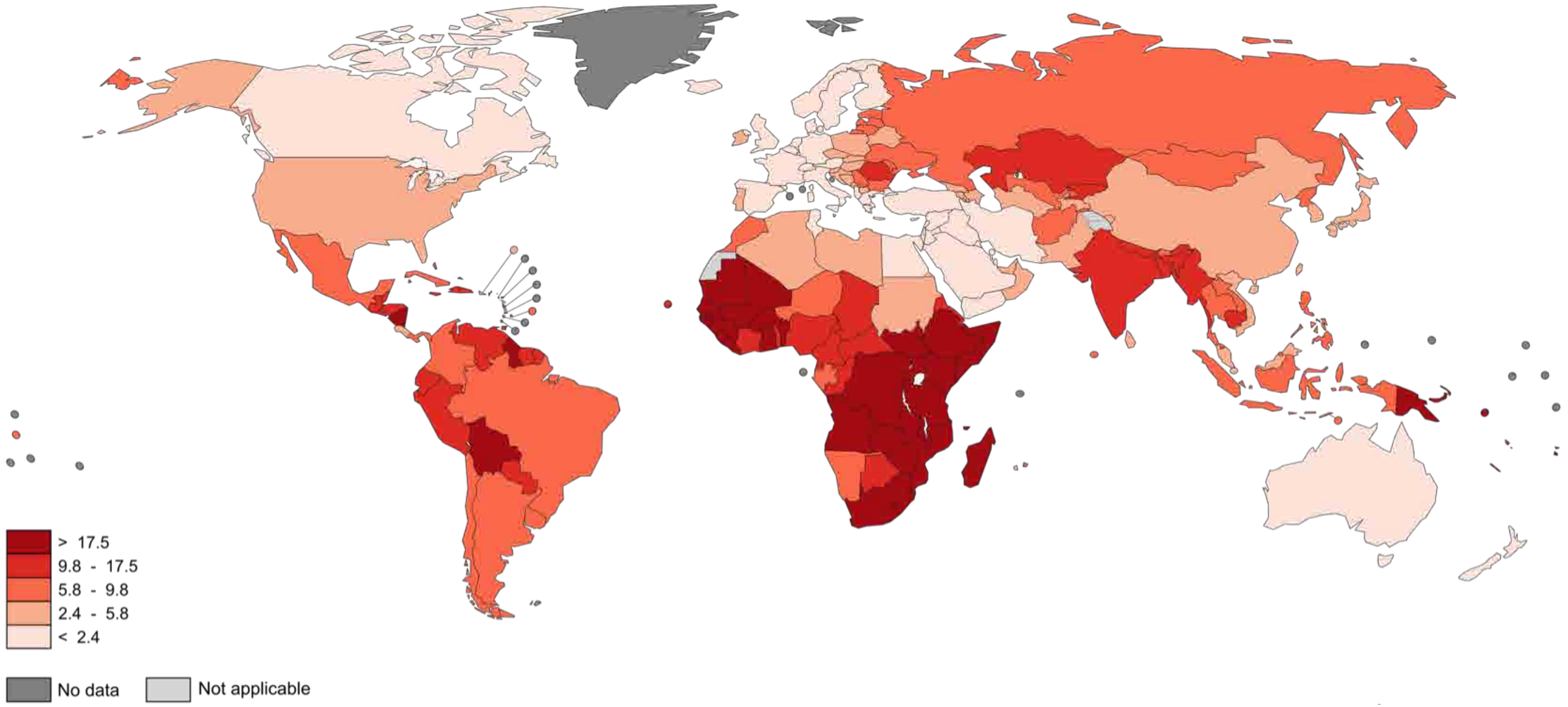
AGEN1223 - A First-in-Class Bi-specific Designed to Deplete Regulatory T cells in TME



- Boosts cancer-fighting T effector cells
- Spares important *peripheral* T regs
- Targets co-expression of antigens on tumor-infiltrating T regs

These important mechanisms not addressed with current therapies

Cervical Cancer Burden ~12,500 new cases in US annually

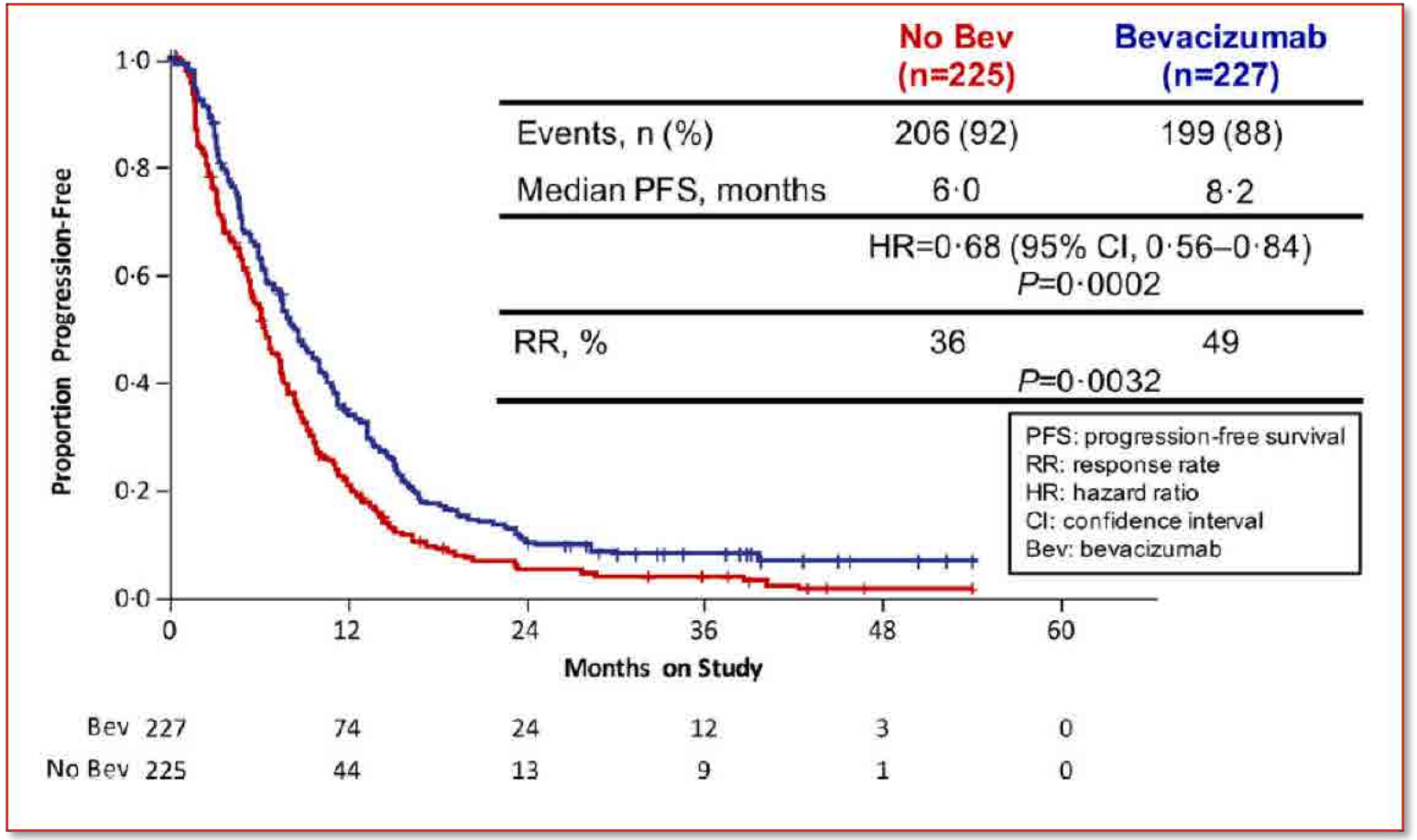


Cervical Cancer Facts



Prior treatment history

- SURGERY
- RADIATION
- CHEMOTHERAPY

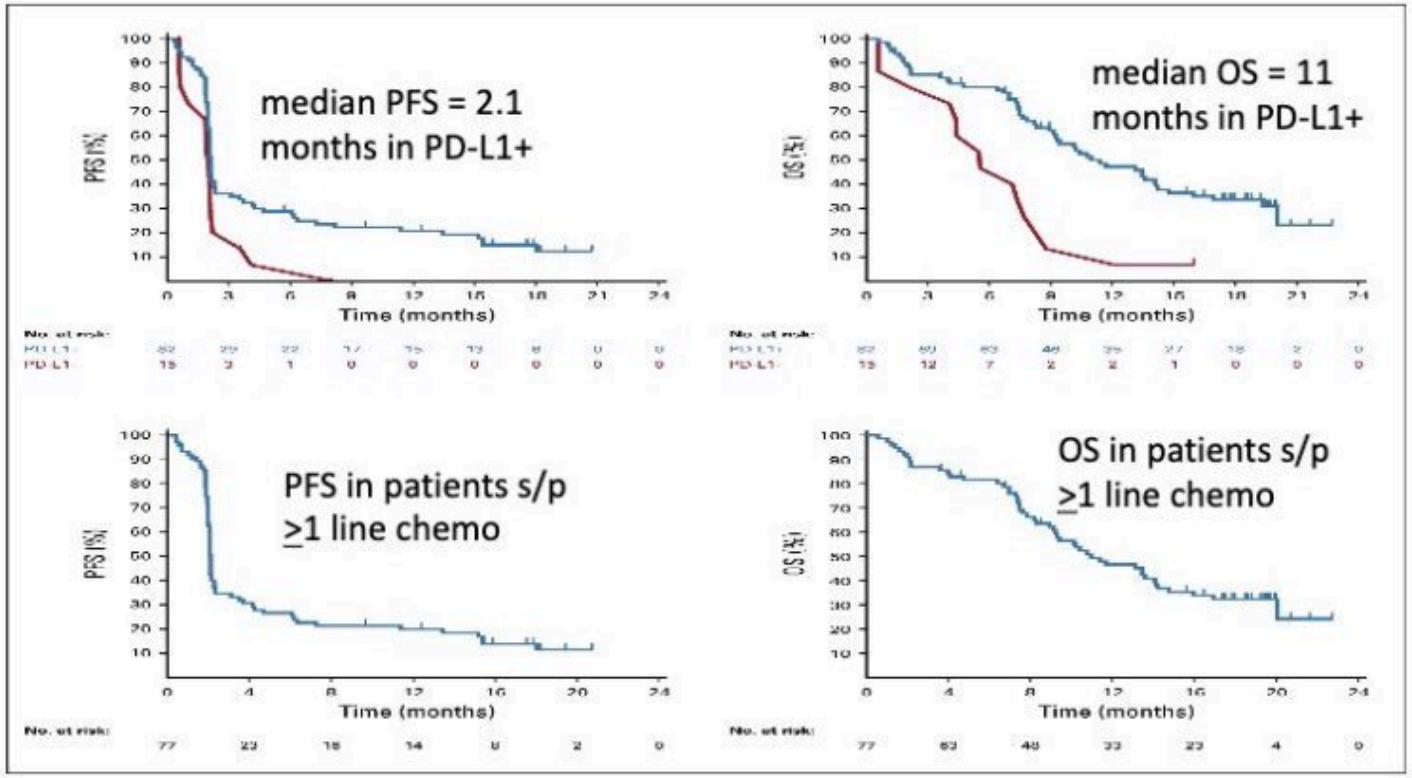


GOG 240

NewYork-Presbyterian Weill Cornell Medicine

CPI (Anti-PD-1) in Cervical Cancer: Keynote 158 based on 14% RR in PD-1+ tumors (CPS>1)

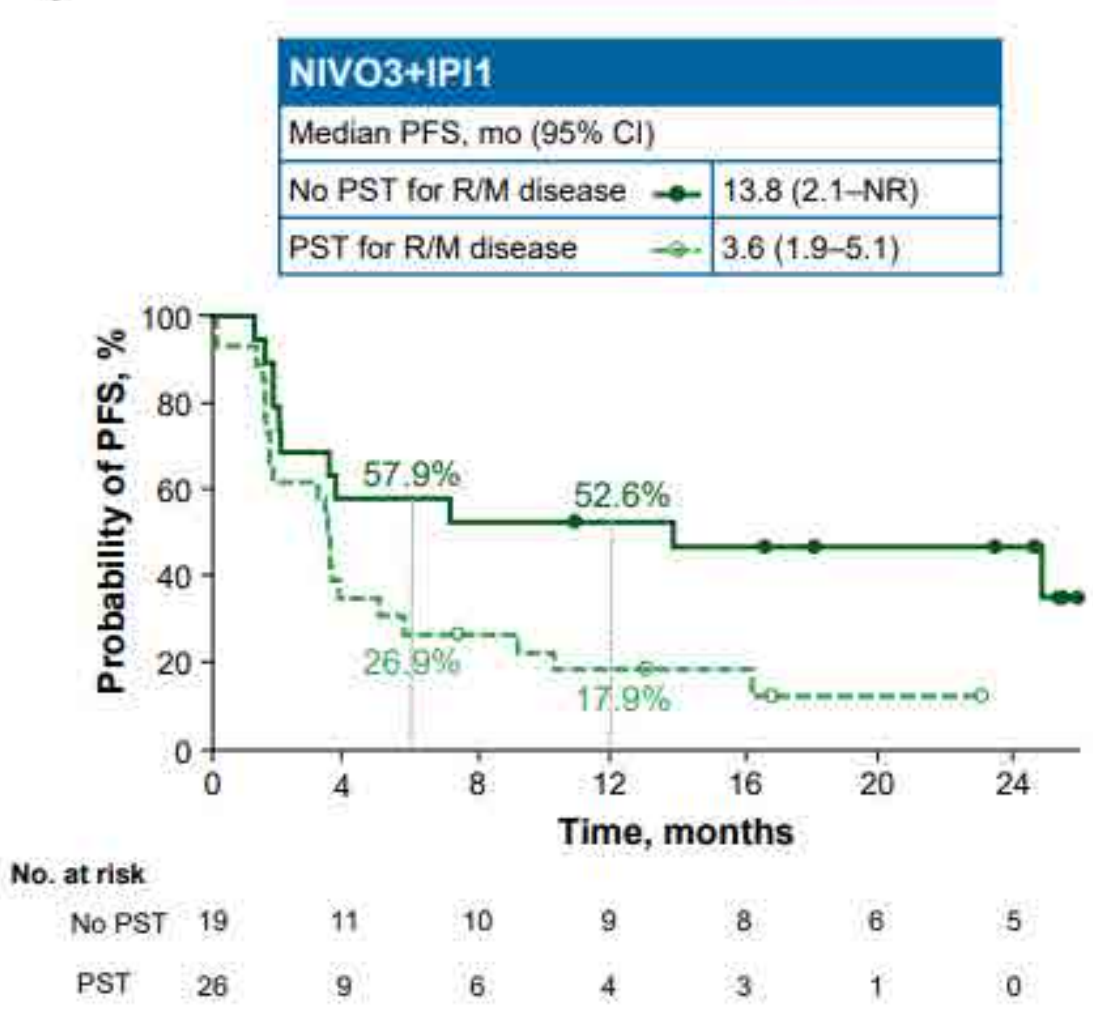
Keynote 158: Phase 2 Study of Single Agent Pembrolizumab in Advanced Cervical Cancer

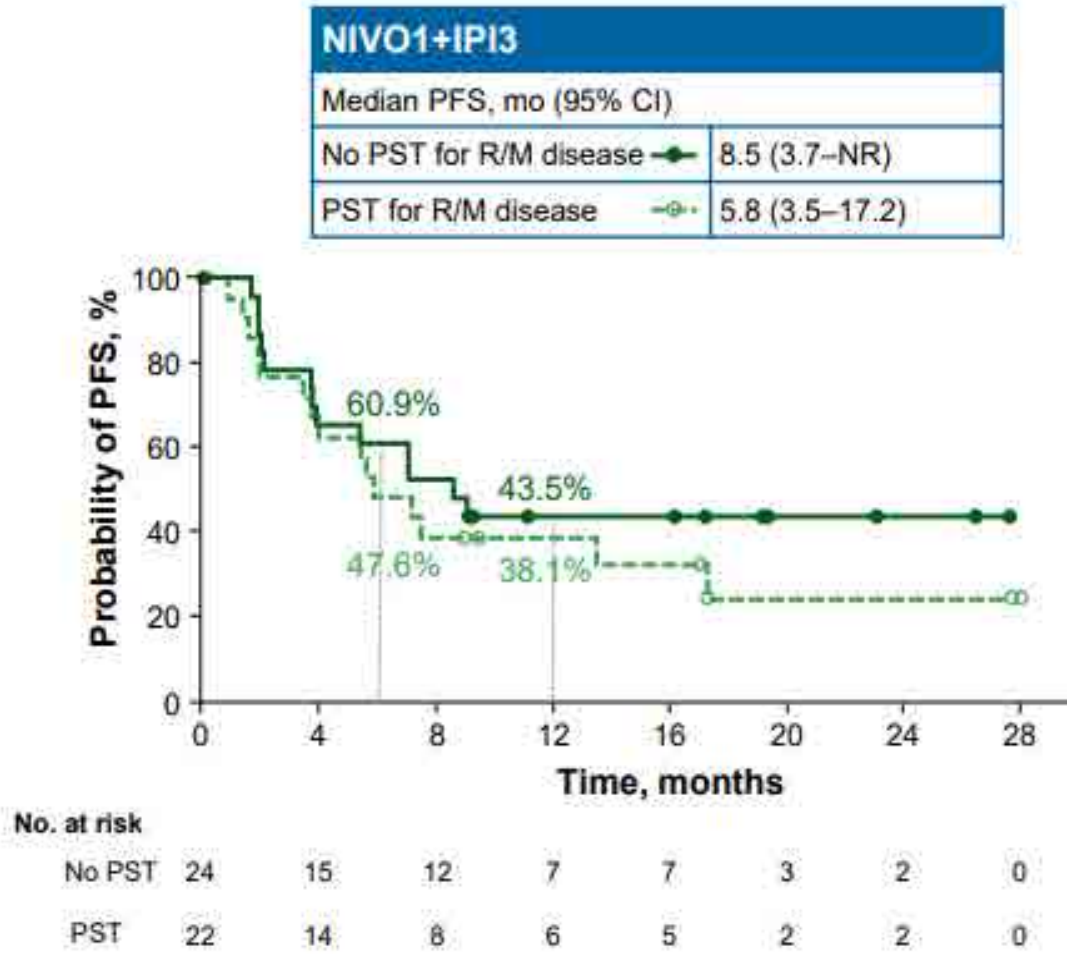


Chung HC et al. J Clin Oncol 2019: 37: epub

NewYork-Presbyterian Weill Cornell Medicine

CPI in Cervical Cancer: Checkmate 358





Oaknin et al, ESMO 2019

NewYork-Presbyterian Weill Cornell Medicine

Conclusions

- **PD 1 and CTL4 inhibition results in clear OS improvement is some cancer types (malignant melanoma, RCC, NSCLC).**
  - ✓ **Biomarkers**
  - ✓ **Toxicity**
  - ✓ **Sequence**
  - ✓ **Cost**

- **PD-1 and CTLA 4 resistant patients/tumors need:**
  - ✓ **Better drugs**
  - ✓ **Other targets**
  - ✓ **Combination strategies**
  - ✓ **New strategies: ACT and ACT combinations**

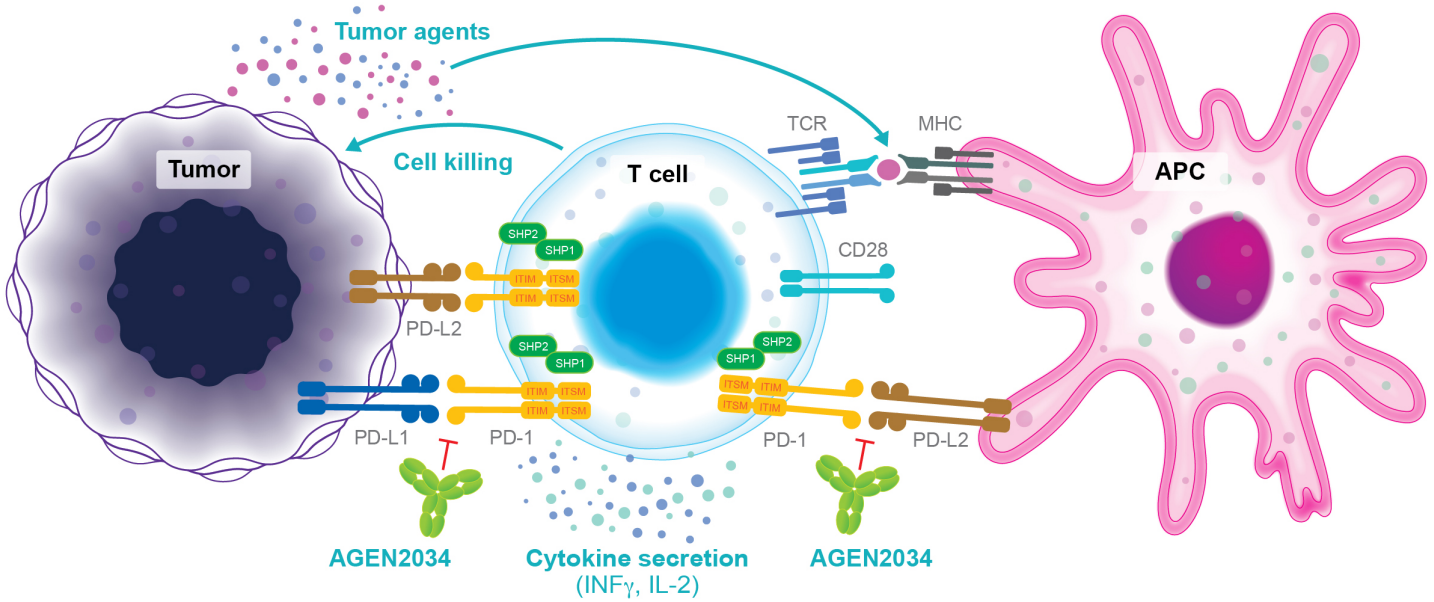
- **Adding CTLA 4 blockaded to PD-1 intermediate sensitive tumors is an strategy to improve outcome in these patients/diseases.**

Balstilimab (anti-PD-1) & *Zalifrelimab* (anti-CTLA-4) Are Clinically Active and Advancing in Pivotal Trials

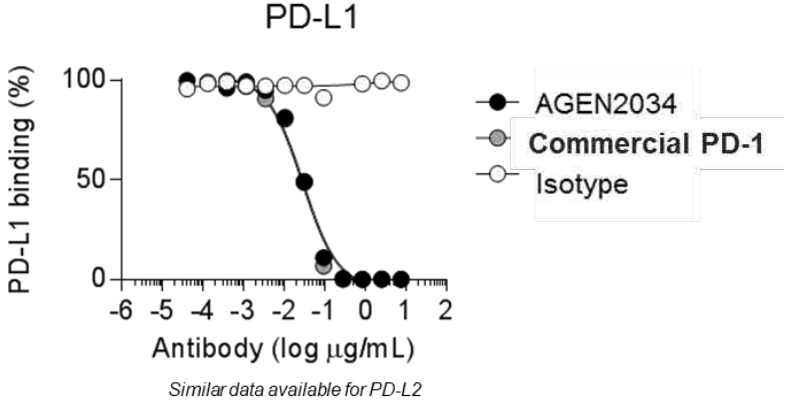
Anna Wijatyk, MD, Head of Clinical Development and Operations

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Balstilimab (AGEN2034) is Comparable to Commercial PD-1

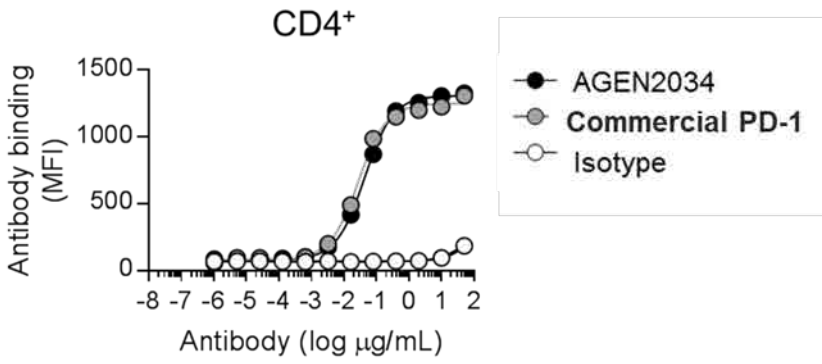


AGEN2034 completely blocks PD-1 ligand interactions



Similar data available for PD-L2

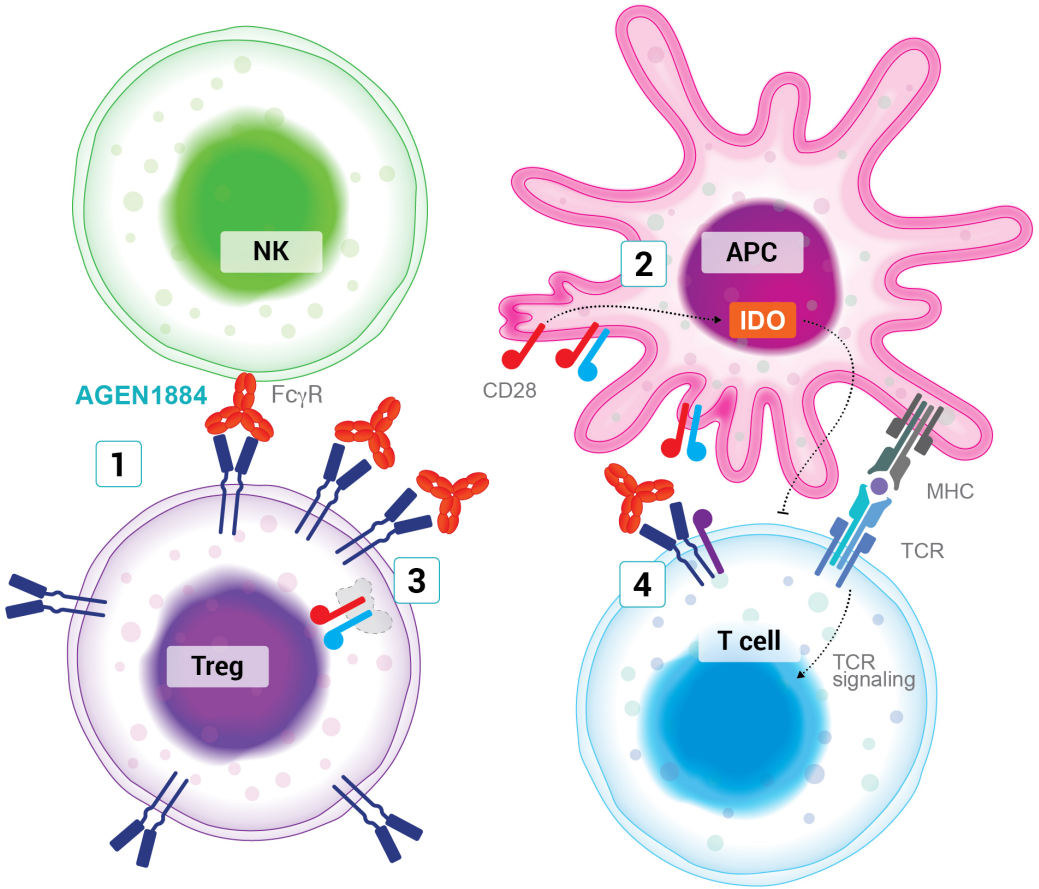
Potent cell binding to primary human T cells

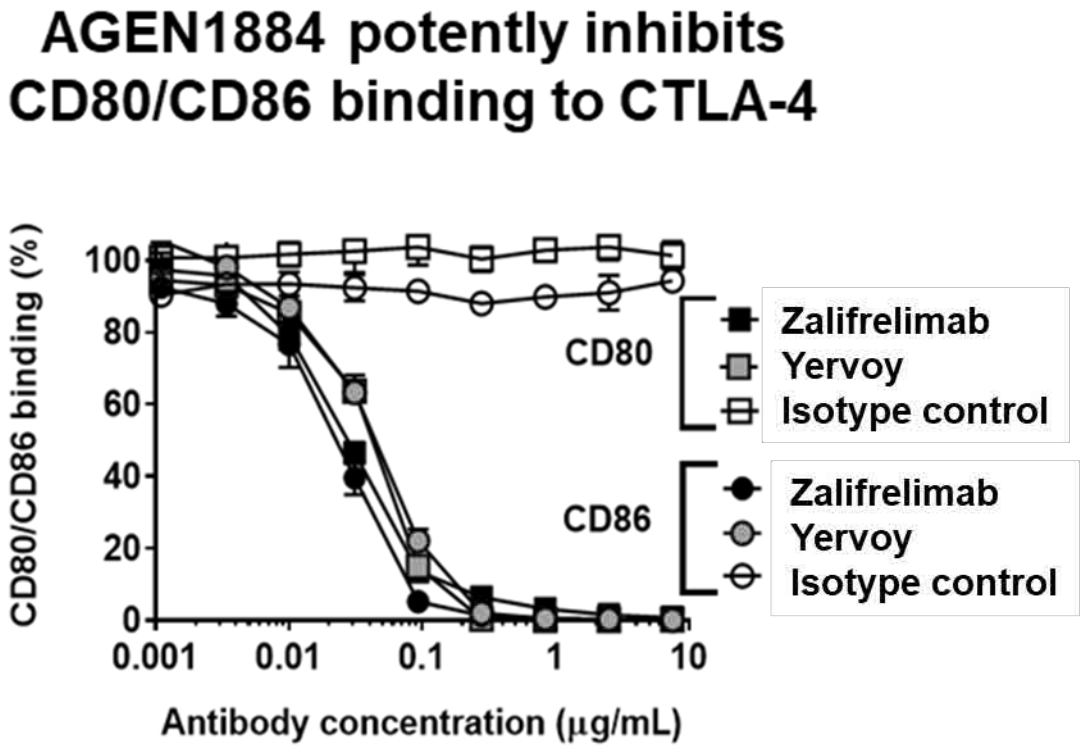


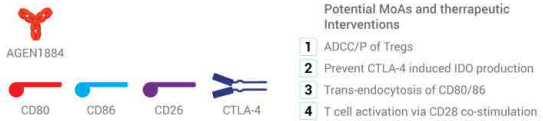
Similar data available for CD8+ T cells

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Zalifrelimab is a Novel Anti-CTLA-4 Designed to be Comparable to Commercial CTLA-4







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Balstilimab in Patients with Solid Tumors & Relapsed/Refractory Cervical Cancer

Anna Wijatyk, MD, Head of Clinical Development and Operations

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Balstilimab Demonstrates Benefit in >60% of Patients in Multiple Tumors

Data reported at ESMO 2018

Partial Response	Durable disease stabilization (>12 weeks)	
Ovarian Cancer	Ovarian Cancer	Ovarian Cancer
Cervical Cancer	Ovarian Cancer	Ovarian Cancer
Breast Cancer	Cervical Cancer	Ovarian Cancer
	Cervical Cancer	Cervical Cancer
	Endometrial Cancer	Cervical Cancer
	Endometrial Cancer	Endometrial Cancer
	Endometrial Cancer	Breast Cancer
	Endometrial Cancer	Cholangiocarcinoma
	Ewing Sarcoma	Vaginal Cancer
	Prostate Cancer	Soft Tissue Sarcoma
	Adenoid Cystic Cancer	Leimyosarcoma
	Pancreatic Cancer	Leimyosarcoma
	Duodenal Cancer	
	Colon Cancer	

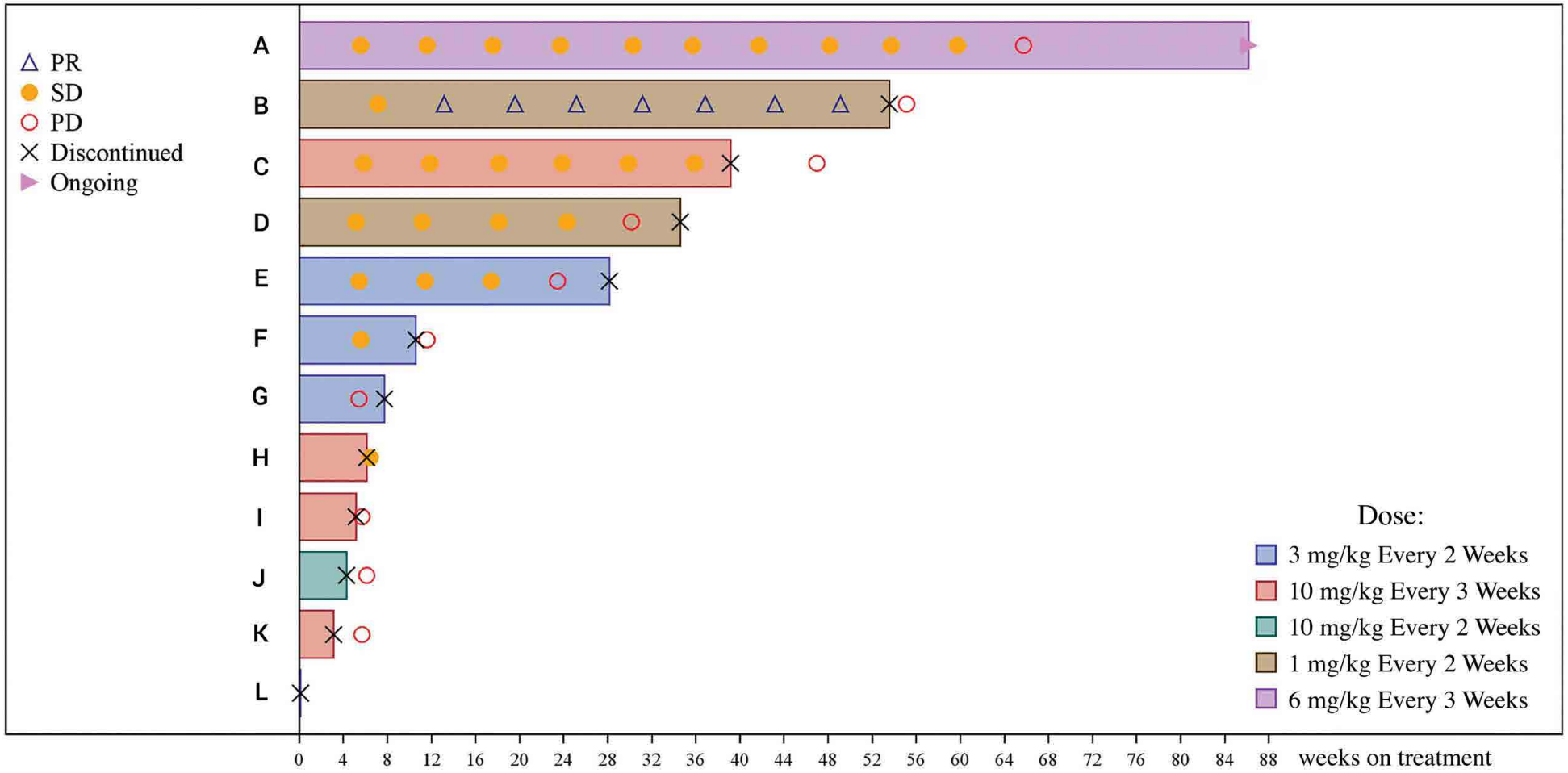
Safety and pharmacology profile is consistent with drug class

Phase 1, open-label, dose-escalation trial in subjects with metastatic or locally advanced solid tumors, and Phase 2 expansion to evaluate efficacy in subjects with recurrent, unresectable, or metastatic (advanced) cervical cancer that has progressed after a platinum doublet. Reported on first 50 patients treated. NCT03104699. Investigator Reported Data. Interim analysis for pivotal trial underway (NOV2019)

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Balstilimab Shows Durable Responses & Disease Control in Ovarian

Phase 2 dose of 3mg/kg Q2W or 300mg Q3W



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Zalifrelimab Designed to Be Comparable to Commercial Agents

Zalifrelimab is advancing in a pivotal trial in combination with balstilimab in cervical cancer

Phase I Overview

- Tolerable to 6mg/kg Q3W
- Monotherapy was clinically active across a range of tumors (ACC, mBCC, Breast, ependymoma)
- Zalifrelimab demonstrated a curative response in refractory angiosarcoma

Overall Response	Cancer Type
Complete Response	Angiosarcoma nose/cheek
Stable disease	ACC
Stable disease	Metastatic Breast Cancer
Stable disease	Breast cancer
Stable disease	Ependymoma (anaplastic)

Complete Response – Durable beyond 2.8yrs and ongoing

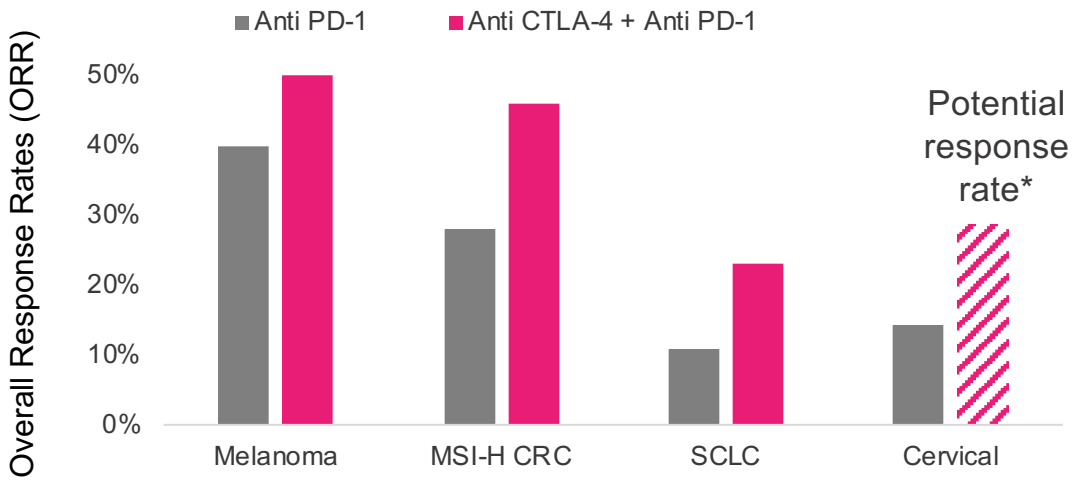




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Where PD-1 is Active, CTLA-4 Expands Response & Durability

CTLA-4 enhances the efficacy of anti PD-1s, doubling it in some cancers



Source: Agenus Events and Presentations, Keytruda® label
* For illustrative purposes only

CTLA-4 enhances durability of response

1L melanoma data from Checkmate-067 (n=945)
I-O combination in patients previously on chemotherapy

	PD-1 (N=316)	PD-1 + CTLA-4 (N=314)
mPFS	6.9 months	**11.7 months**
mOS	36.9 months	**Not Reached**

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Two Paths For Fast Approval with Potential Best In Class Efficacy

Rapid Path to BLA
2L Cervical Cancer

- Accelerated FDA approval validated by Merck/others with monotherapy and combination
- Endpoint - Response rates/duration of response

Target BLA submission
2020

Additional studies
Multiple Cancers

- Potential to substantially expand initial market by moving to 1L cervical cancer
- Multiple rapid approval pathways in indications where AGEN2034 and AGEN1884 have demonstrated clinical activity
- Combinations with Agenus next-gen I-O and partner portfolio agents

Target BLA submissions
2022+

Pivotal Trial of *Balstilimab* Monotherapy in Advanced Tumors and Relapsed/Refractory Cervical Cancer

Key Inclusion Criteria

- Histologically or cytologically confirmed locally advanced or recurrent , metastatic squamous cell carcinoma or adenocarcinoma of cervix
- IO naive
- Measurable disease per RECIST 1.1
- Relapsed after platinum based treatment (First line)
- ECOG 0 or 1 and life expectancy ≥3 months.
- Adequate organ and marrow function

Dose Escalation (phase 1)*

Part I: AGEN2034 1,3,10 mg/kg q2w

Part II: AGEN2034 6,10 mg/kg q3w

Recommended Phase 2 Dose (RP2D)
AGEN2034 3mg/kg q2w

Dose Expansion (phase2)

Cervical Cancer Expansion cohort

Phase 2

Primary endpoints:
Objective Response Rate (ORR) per RECIST 1.1 per IERC**

Secondary endpoints:
Safety, PK, DOR, DCR, PFS, OS

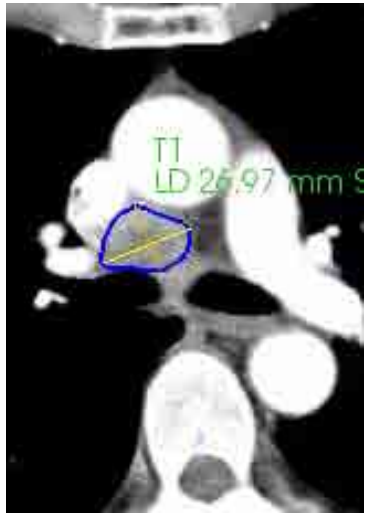
*Dose de-escalation arm was permitted but not used
**Tumors were assessed by Independent End Point Review Committee (IERC) and local investigator.
ECOG: Eastern Cooperative Oncology Group Performance Score RECIST, response evaluation criteria in solid tumors

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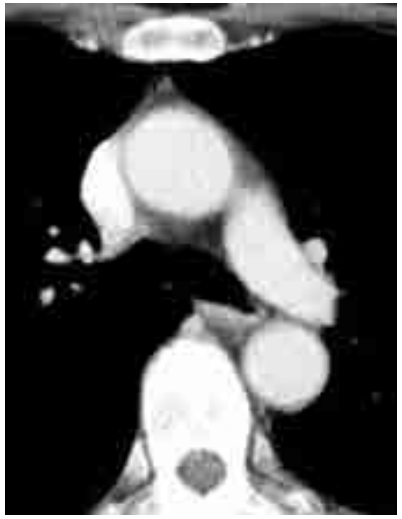
C-700-001 Study Responders

Patient #1 – Continuing on treatment since May 2018

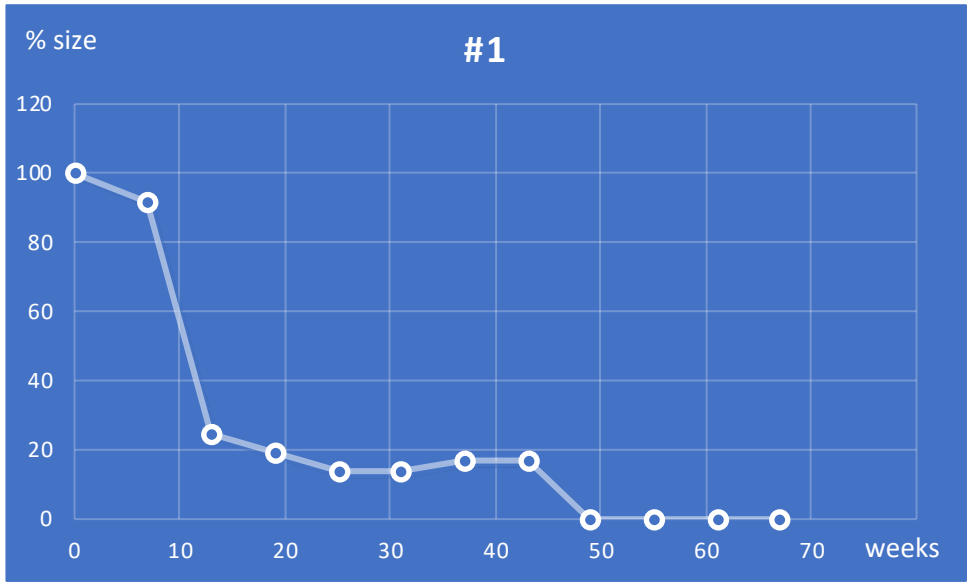
Central review



Screening



Cycle 36 – CR



Demographics	64 y.o.; White
Primary tumor	FIGO-IIIa; SCC,
Prior treatment	carbo/tax in 2016

	Baseline	On-treatment
Target lesions	mediastinal l.ns. 36 mm	CR from cycle 6 on
Non-t lesions	none	

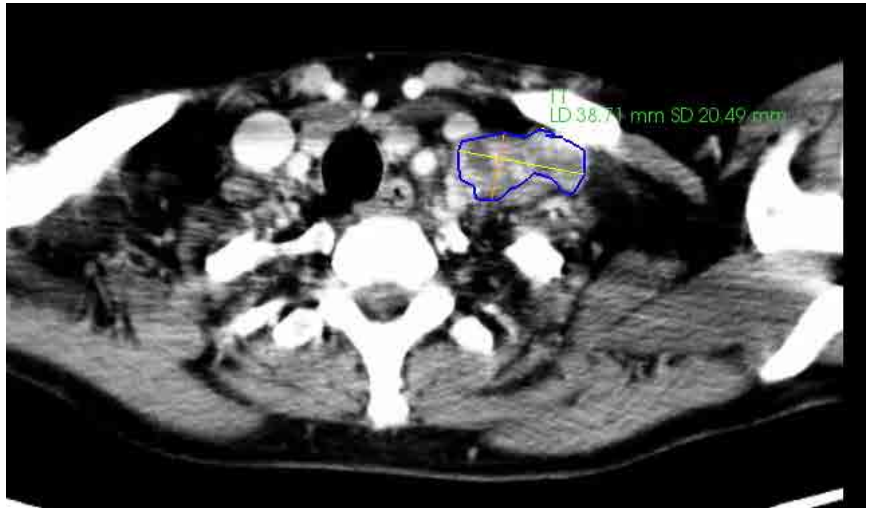
Related AEs	G2 mucosal inflammation, G1 maculo-popular rash, G1 lichen planus

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C-700-001 Study Responders

Patient #2 – Treated for 52 weeks (until development of breast ca)

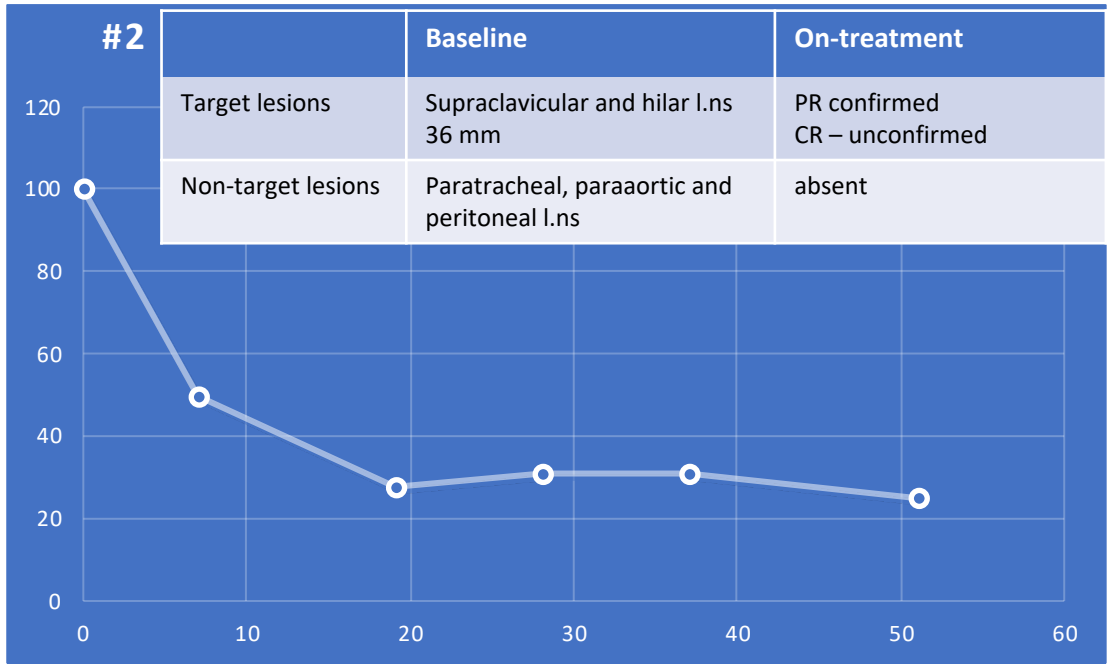
Central review



Screening



End of treatment – CR



Demographics	55 y.o.; white
Primary tumor	FIGO IIB SCC
Prior treatment	CRT in 2018
Related AEs	No related AEs

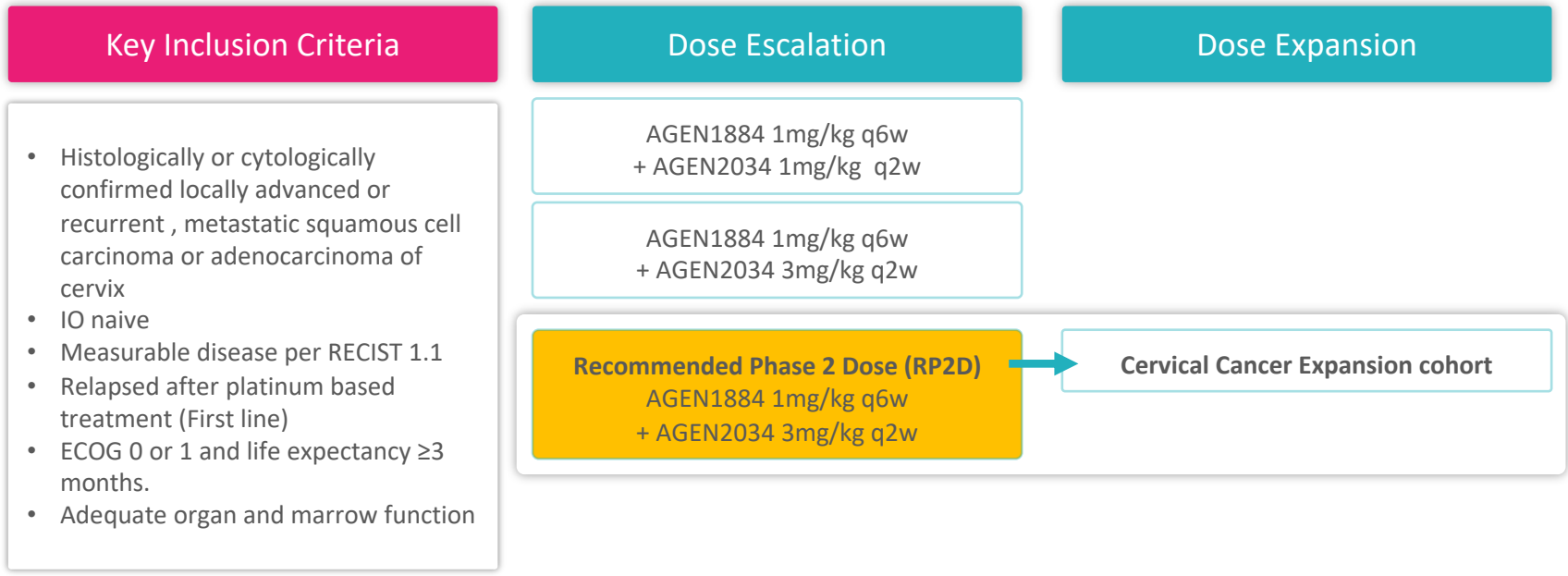
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Zalifrelimab and Balstilimab in Patients with Solid Tumors & Relapsed/Refractory Cervical Cancer

Anna Wijatyk, MD, Head of Clinical Development and Operations

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Pivotal Trial of *Balstilimab & Zalifrelimab* Combination Therapy in Advanced Tumors and Relapsed/Refractory Cervical Cancer



Phase 2

Primary endpoints:

Objective Response Rate (ORR) per RECIST 1.1 as determined by the Independent End Point Review Committee (IERC)**

Secondary endpoints:

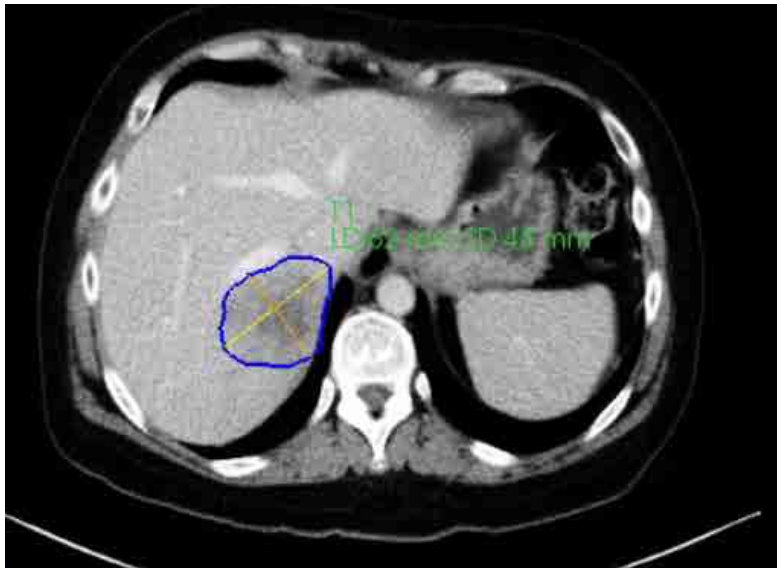
Safety
Pharmacokinetics
Duration of Response (DOR)
Disease Control Rate (DCR)
Progression Free Survival (PFS)
Overall Survival (OS)

*Dose de-escalation arm was permitted but not used
**Tumors were assessed by Independent End Point Review Committee (IERC) and local investigator.
ECOG: PS Eastern Cooperative Oncology Group Performance Score RECIST, response evaluation criteria in solid tumors

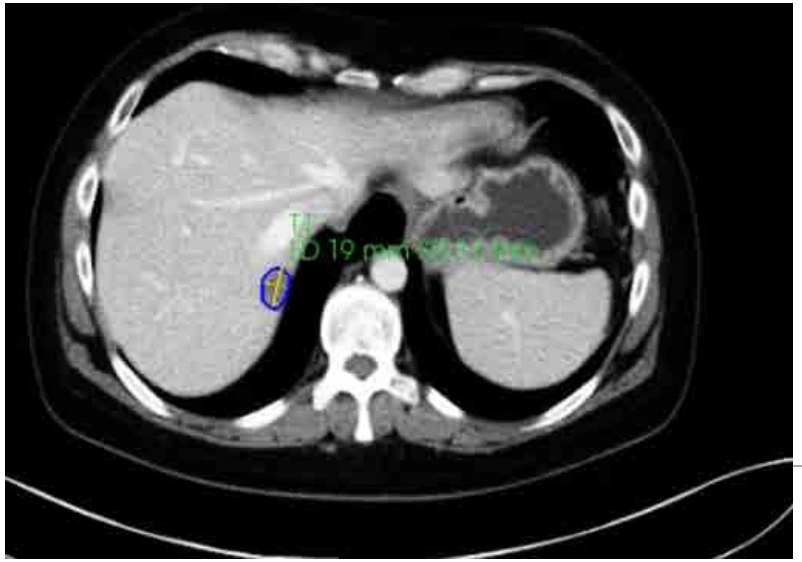
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C-550-001 Study Responders

Patient #3 – Continuing on treatment since Jan 2019 central review

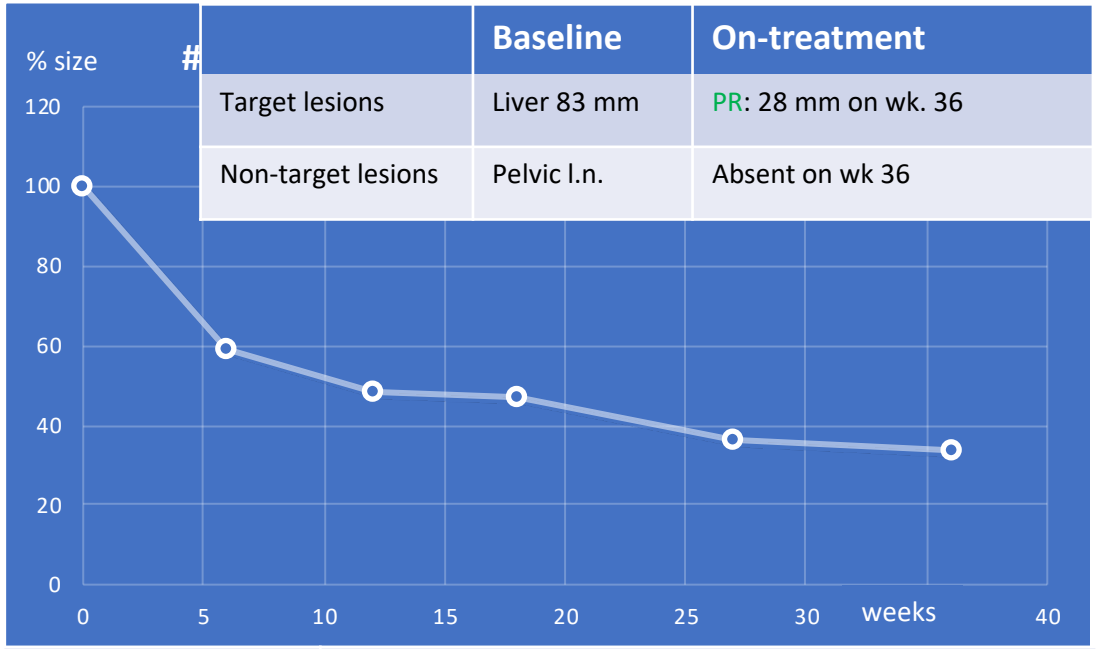


Screening



PR on week 36

	Baseline	On-treatment
Target lesions	Liver 83 mm	PR: 28 mm on wk. 36
Non-target lesions	Pelvic l.n.	Absent on wk 36



Demographics	38 y.o.; black
Primary tumor	FIGO-IIIB; SCC, moderately diff.
Prior treatment	CRT in 2018; adjuvant carbo/tax in 2018
Related AEs	G1 anemia, G1 pruritus, G2 hypopituitarism

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C-550-001 Study Responders

Patient #4 – Continuing on treatment since Mar 2019

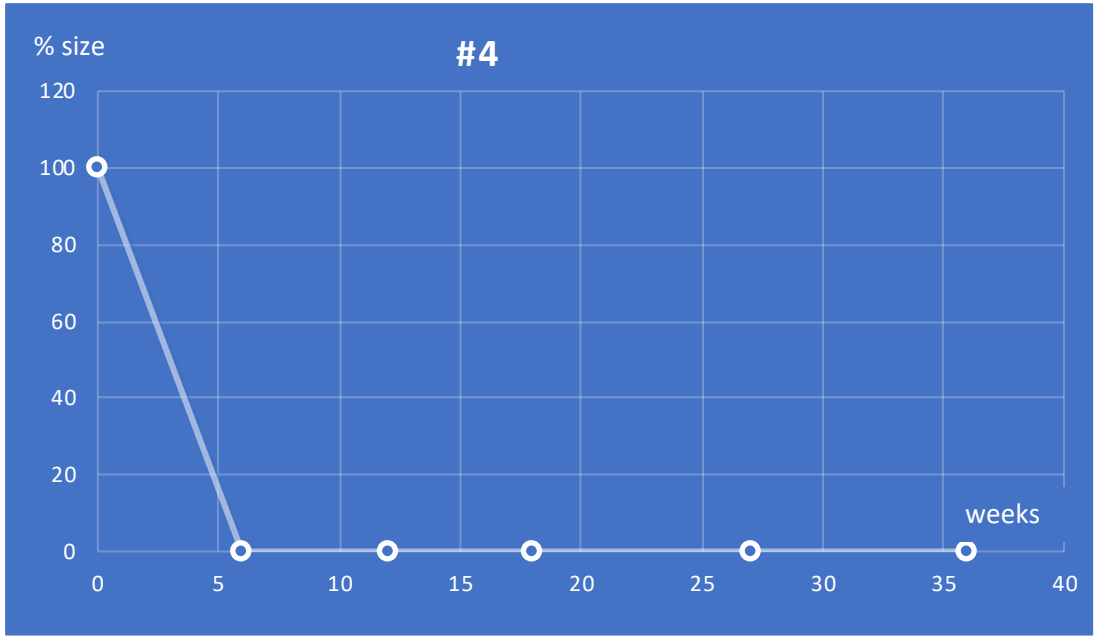
Site review



Screening



Week 27 – CR
from week 6-on



Demographics	57 y.o.; white
Primary tumor	FIGO-IIIB; SCC nonkeratinizing
Prior treatment	Hysterectomy and CRT in 2015; 1st line carbo/tax in 2018

	Baseline	On-treatment
Target lesions	Vaginal stump 47 mm; inguinal l.n. 19 mm	CR on wk 6
Non-target lesions	none	-
Related AEs	G2 hypothyroidism	

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Upcoming Catalysts for *Balstilimab and Zalifrelimab*

2019*	2020
Complete Accrual for BLA trials	File (2) BLAs
Complete planned interim analysis	Accelerate combination of balstilimab & AGEN1181 (NexGen CTLA-4)
Commercial supply ready	Additional strategy clinical collaborations

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Dr. Steven J. O’Day

Executive Director of the John Wayne Cancer Institute and Cancer Clinic

Director of Providence Los Angeles Regional Research

Professor of Medical Oncology and Director of Immuno-Oncology
Co-Director of Melanoma and Cutaneous Oncology Research Program

JOHN WAYNE CANCER INSTITUTE
at Providence Saint John's Health Center

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The Revolution of Immuno-Oncology
Past, Present and Future

Steven O'Day MD

Professor of Medical Oncology
Executive Director
Director Clinical Research
The John Wayne Cancer Institute
Providence Saint John's Health Center
Santa Monica, CA

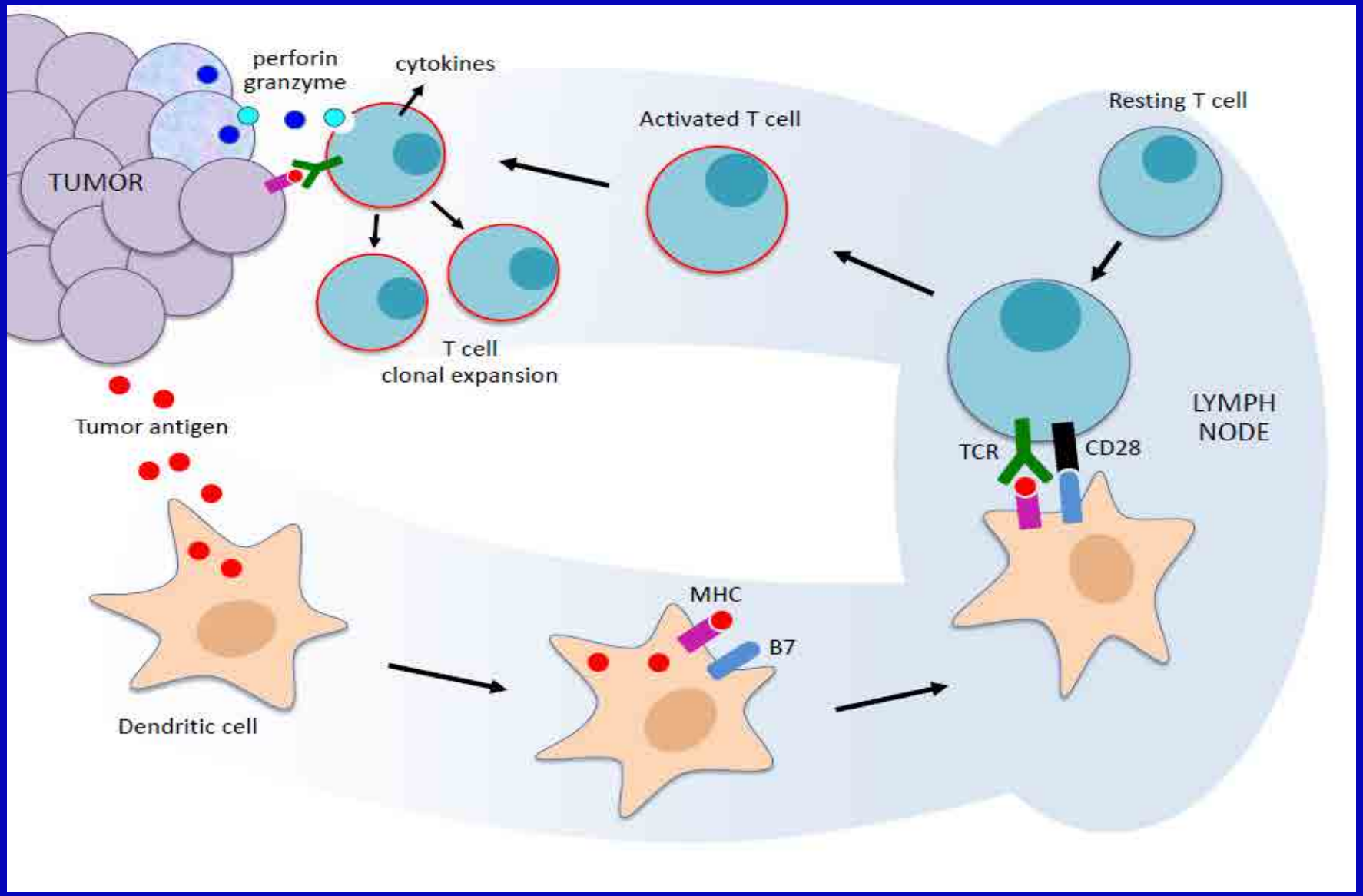
Outline

- Revolution Immune Oncology
- Resurgence of CTLA-4 Blockade
- Complex Tumor and Immune Dance
- Forward Progress

Immune System

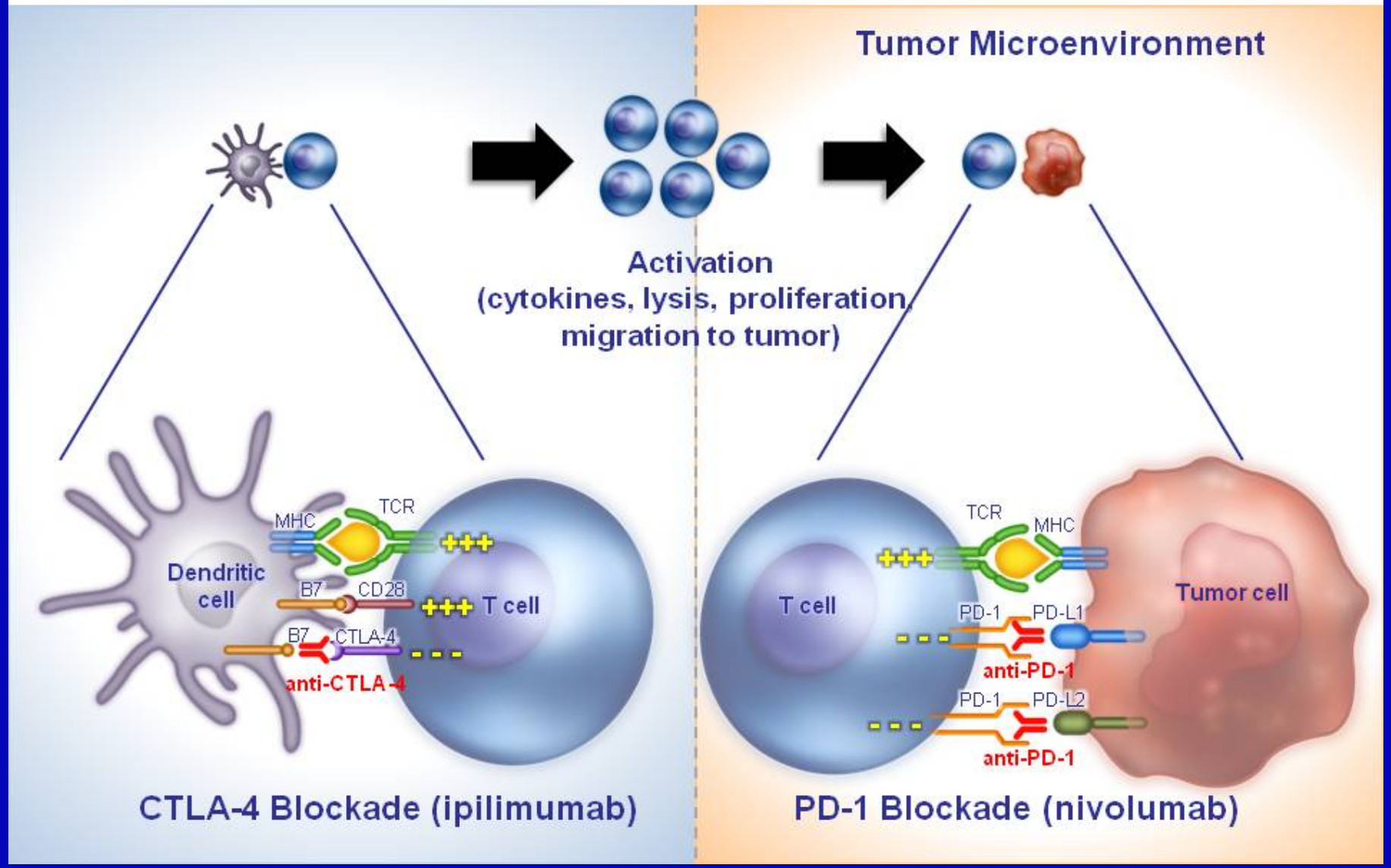
- Power
- Adaptability
- Memory

Tumor Immunology: Overview

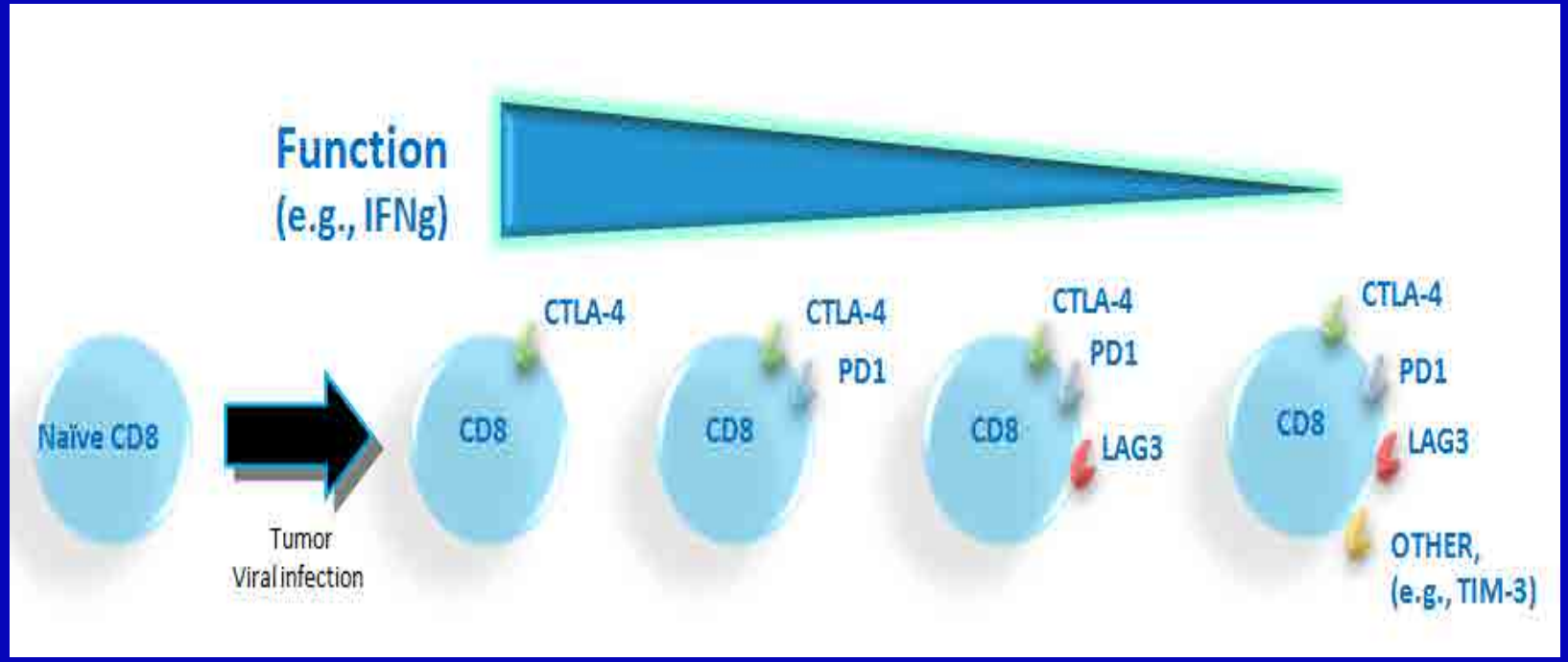


Courtesy of Scott Gettinger, MD – Yale

Blocking CTLA-4 and PD-1



Targeting the Exhausted T-cell Phenotype

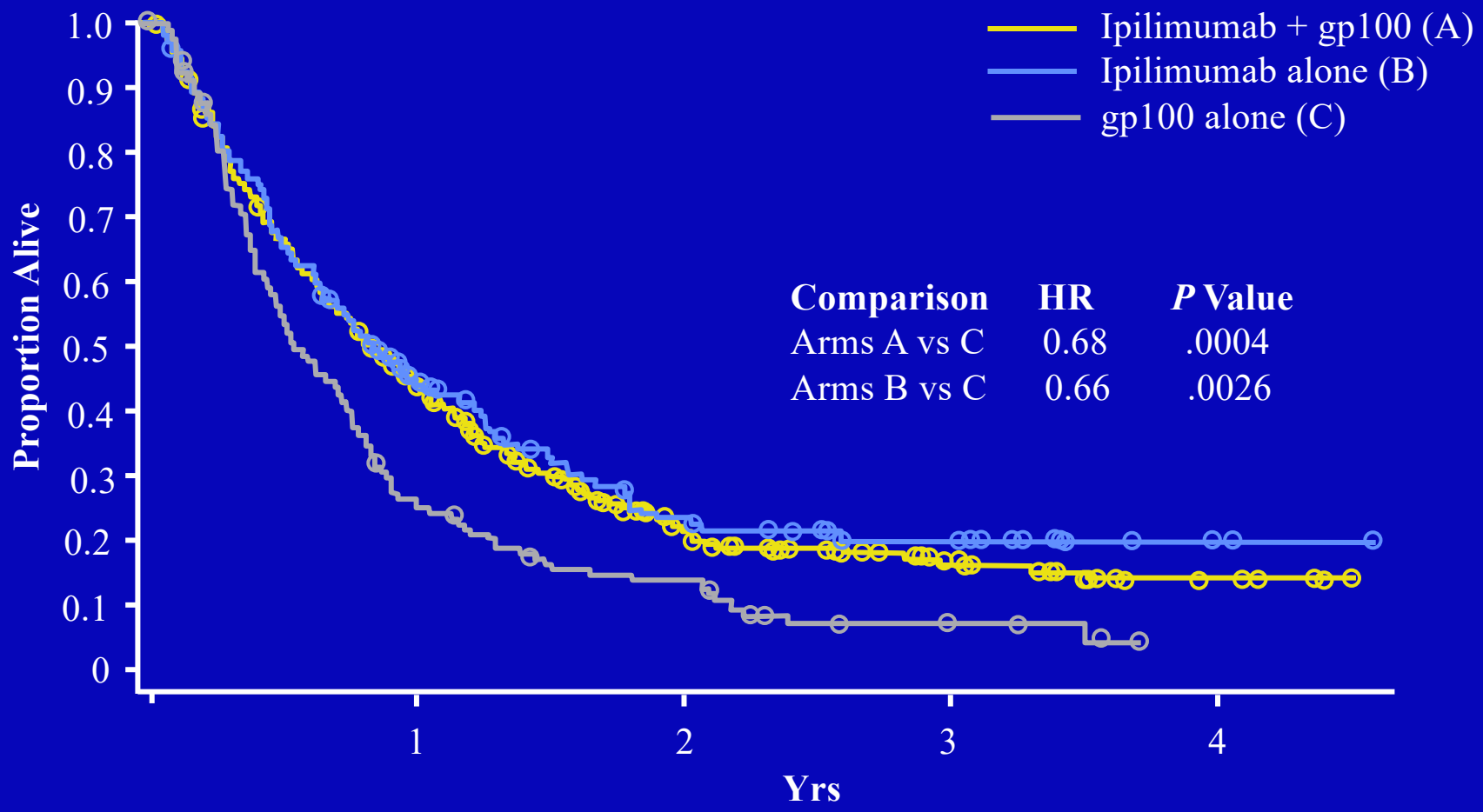


- T cell exhaustion characterized by up-regulation of inhibitor checkpoint markers (CTLA-4, PD-1, LAG3..)
- Exhaustion is proportional to # inhibitory markers
- Blockade of these inhibitory receptors may restore functionality to T cells

Adapted from Wherry et al., *Nat Immunol.* 2011.

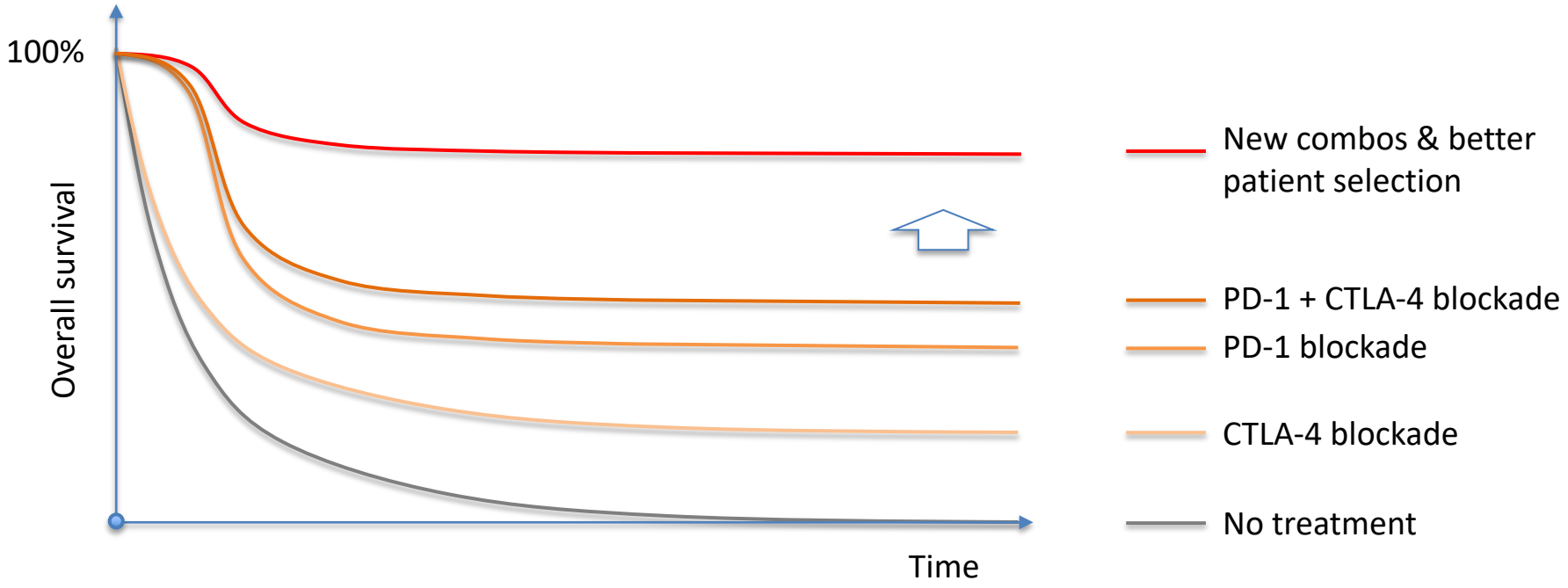
Pr Proprietary

Phase III Study of Ipilimumab, gp100, or Both in Advanced Melanoma: Survival



Hodi FS, O'Day S et al. N Engl J Med. 2010;363:711-723.

New combinations and better patient selection



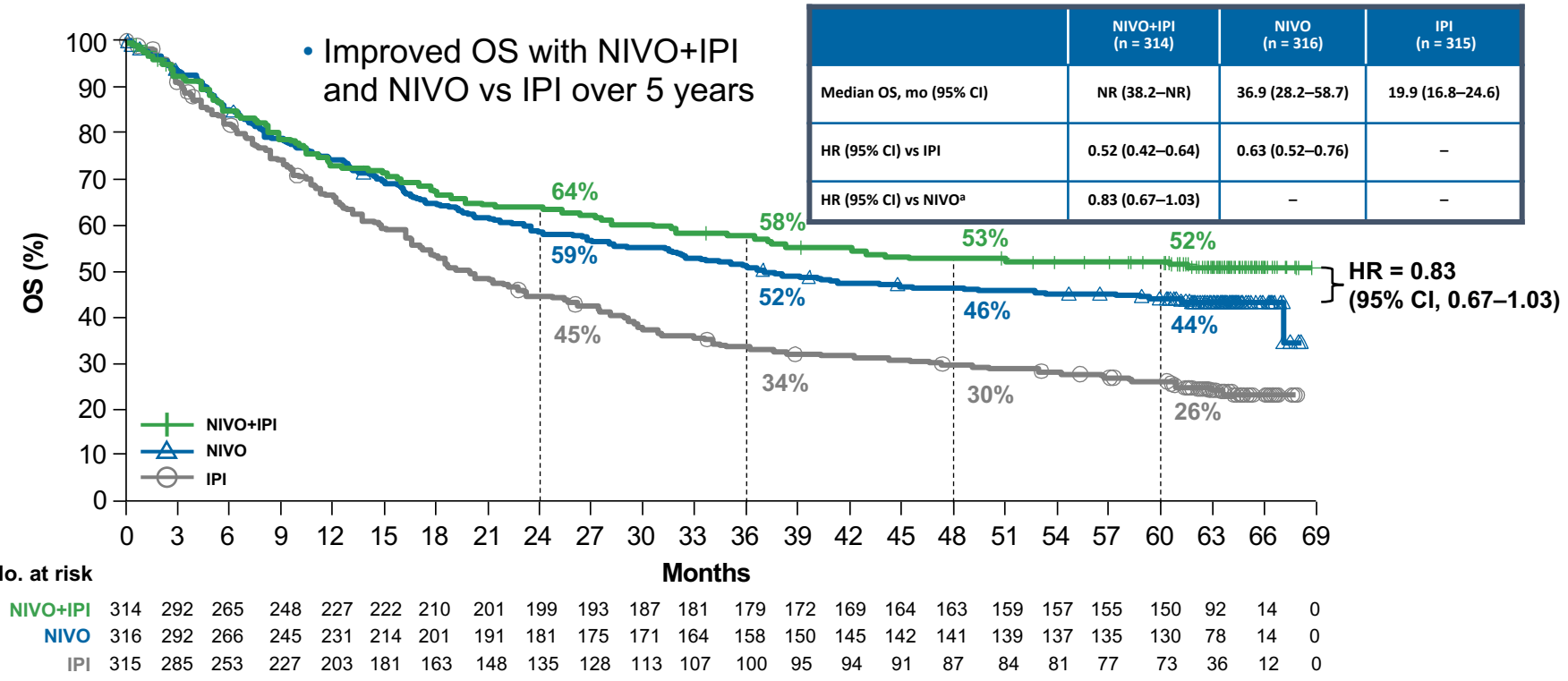
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao, C.L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, C. Lebbé, G. McArthur, P.A. Ascierto, G.A. Daniels, G.V. Long, L. Bastholt, J.I. Rizzo, A. Balogh, A. Moshyk, F.S. Hodi, and J.D. Wolchok

Overall Survival



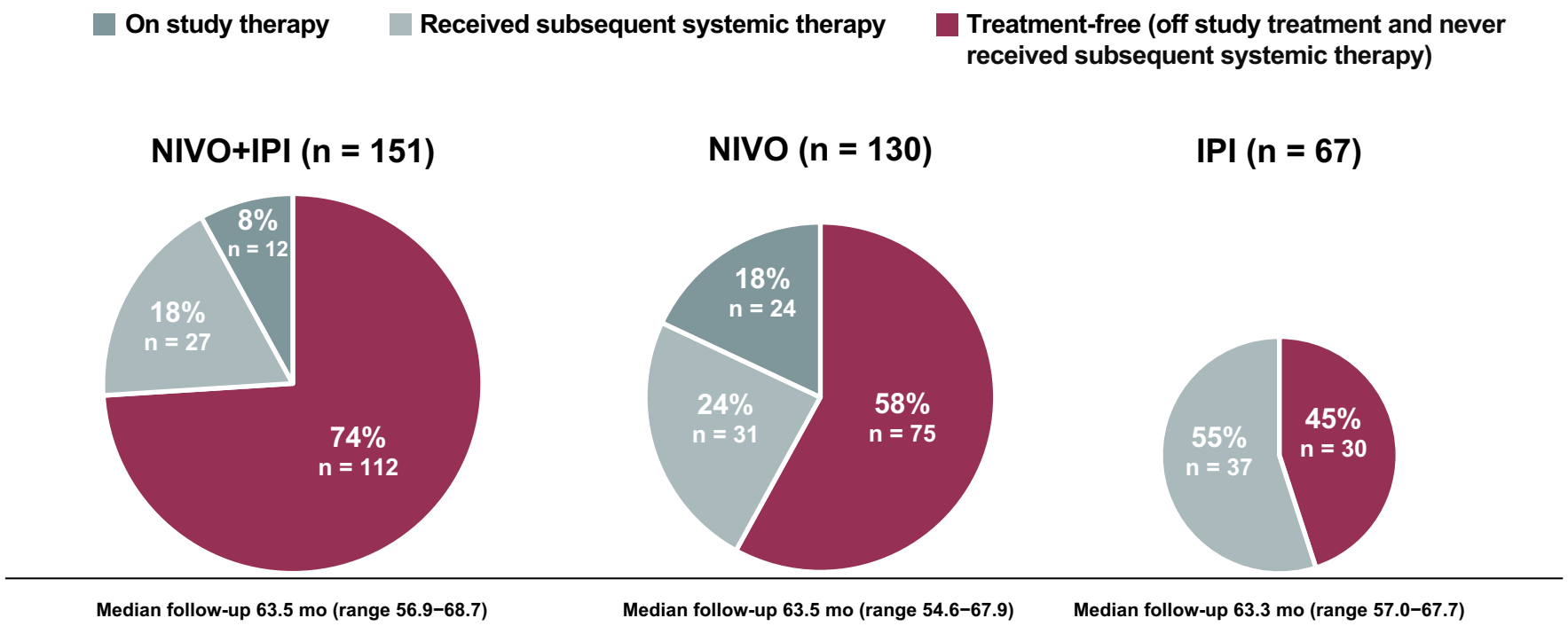
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

[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.

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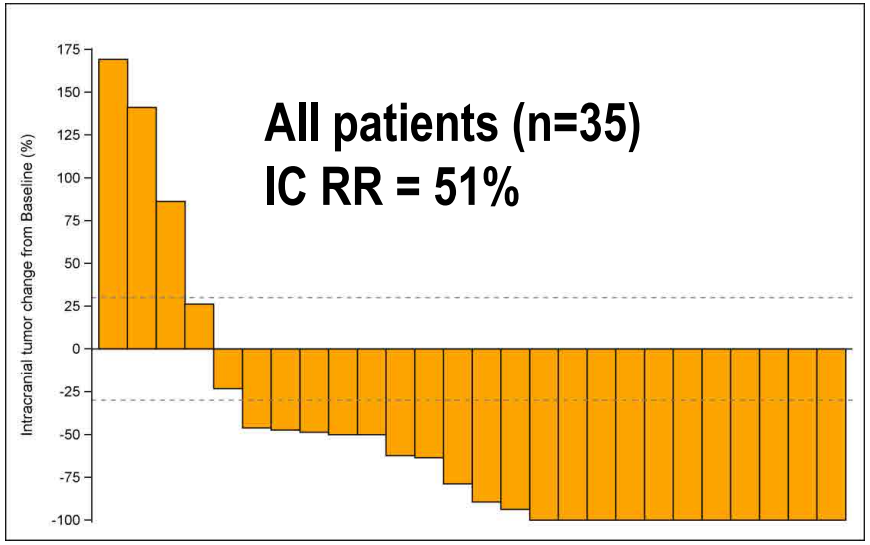
Higher Proportion of Patients Alive and Treatment-Free at 5 Years With NIVO+IPI[a]

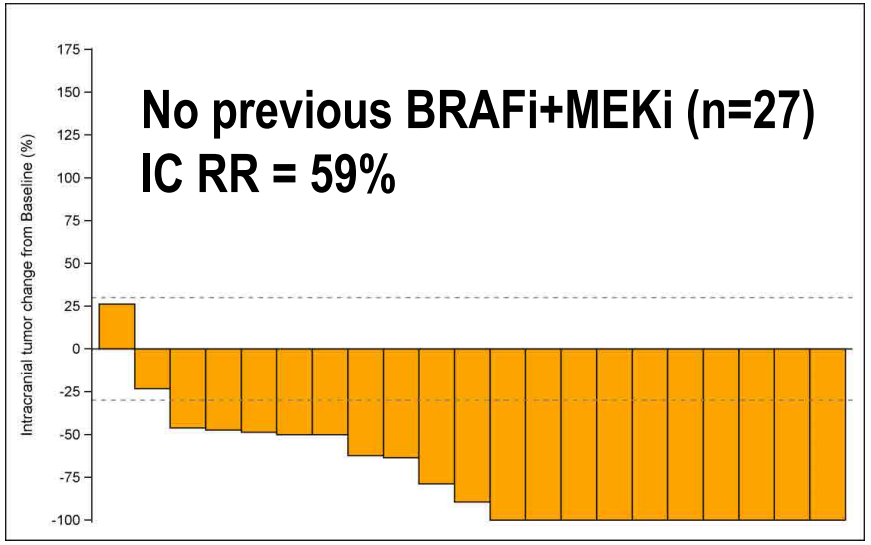
Population analyzed: patients who were alive and followed on study



[a]Post-hoc analysis.

Cohort A: Nivolumab + Ipilimumab Intracranial Response



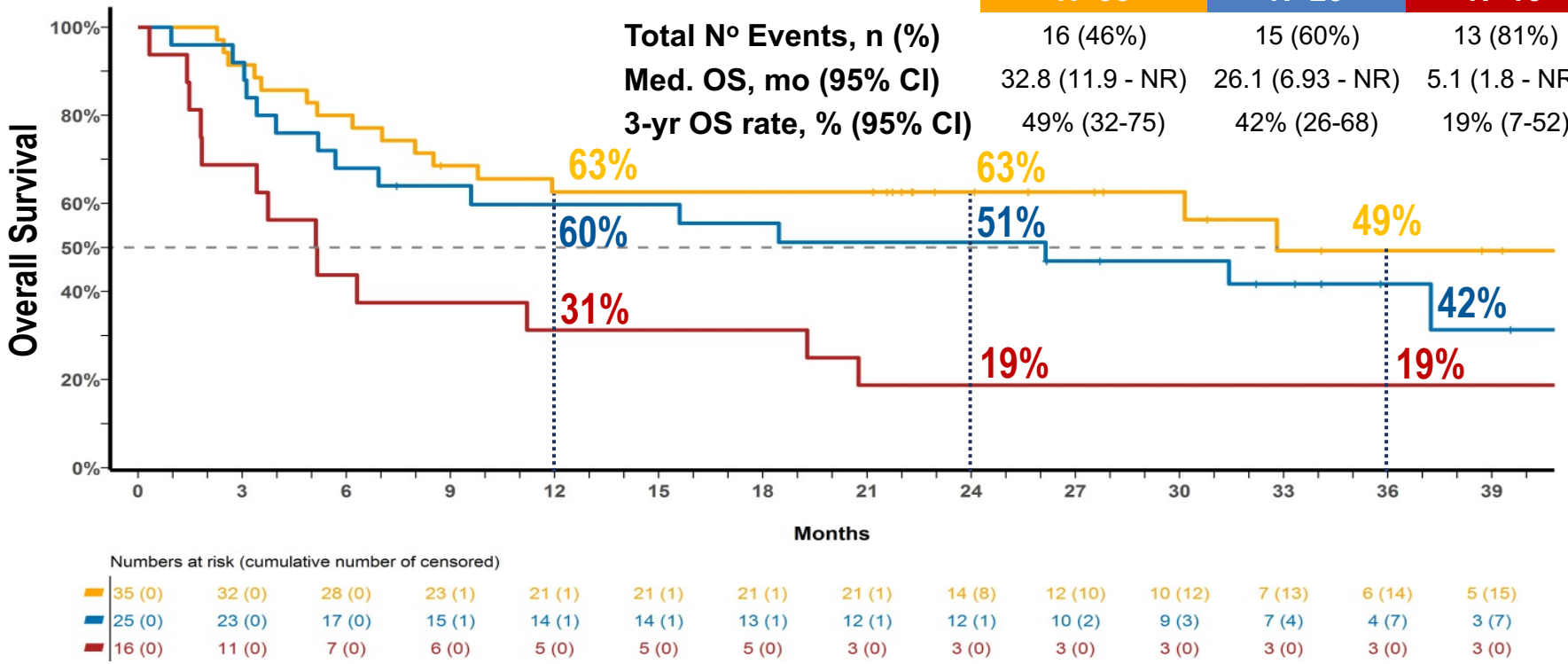


Previous BRAFi+MEKi
ORR = 25% (2/8)

Presented by Georgina V Long @ProfGLongMIA

Overall Survival

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	16 (46%)	15 (60%)	13 (81%)
Med. OS, mo (95% CI)	32.8 (11.9 - NR)	26.1 (6.93 - NR)	5.1 (1.8 - NR)
3-yr OS rate, % (95% CI)	49% (32-75)	42% (26-68)	19% (7-52)



Presented by Georgina V Long @ProfGLongMIA

Returning to CTLA-4

- Improving Efficacy
- Reduced Toxicity

PD1/CTLA-4 Platform

- Full dose PD1
- Low Dose CTLA-4
  - 1 mg/kg Q 3-12 weeks
- Preserved Efficacy, Reduced Toxicity
- Melanoma, RCC, NSCLC

Going Forward
Optimal IO Development

- First Line Combination
  - PD1/CTLA-4/New Drug
  - PD1/New Drug

- Second Line Combination
  - PD1/CTLA-4/New Drug
  - PD1/New Drug
  - CTLA4/New Drug

Going Forward
Optimal IO Clinical Trial Design

- **Metastatic Disease**
  - 12-18 month Landmark PFS plateau
- **Neoadjuvant**
  - pCR, RFS
- **High Risk Adjuvant**
  - RFS

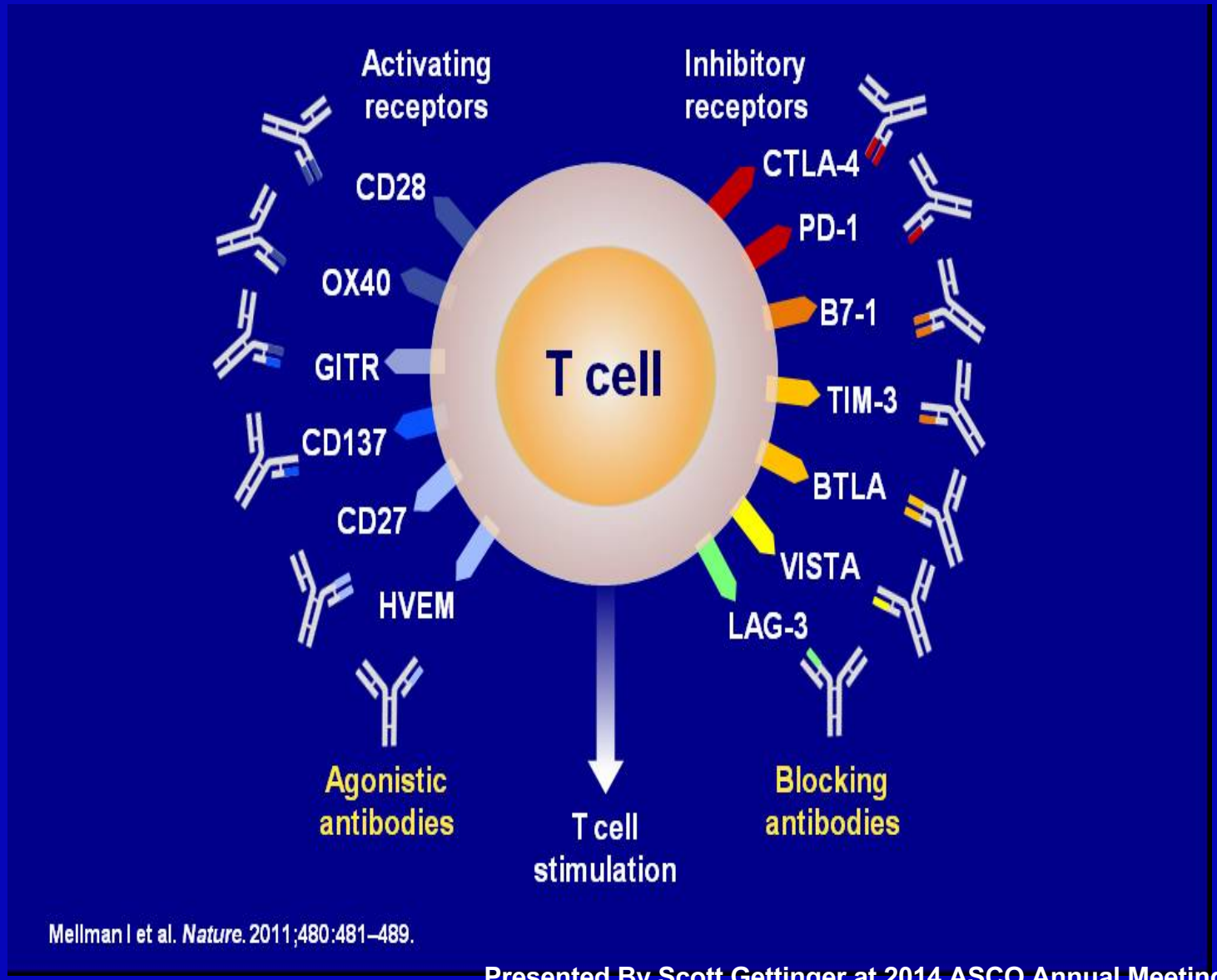
Future Clinical Trials

- Biology Driven and Translational
- Adaptive and Smart
- Clinically Meaningful Endpoints

Moving Forward:
IO Platform Combinations:

- T Cell Optimization
- Priming Response
- TME

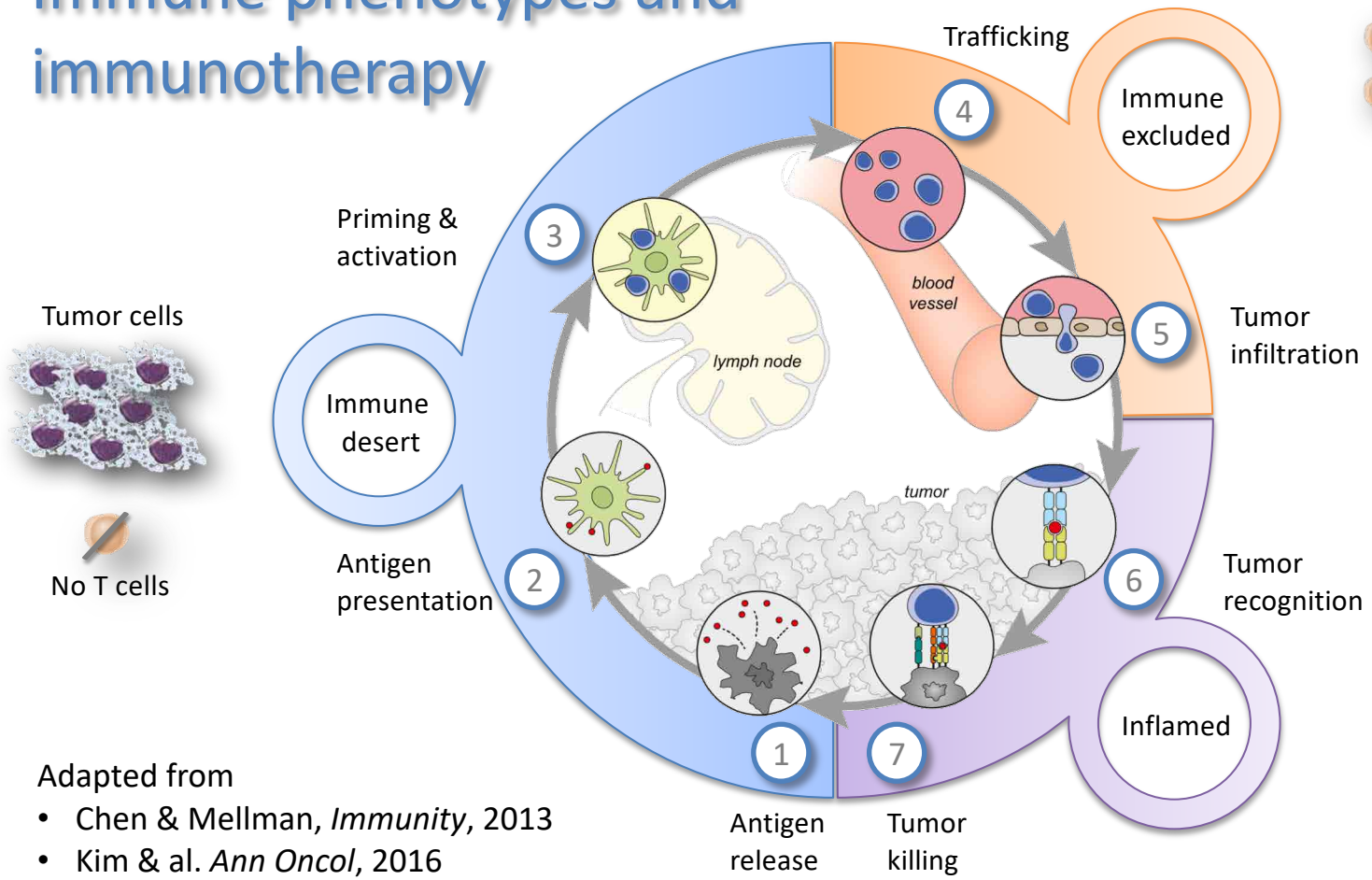
T-Cell Immune Checkpoints

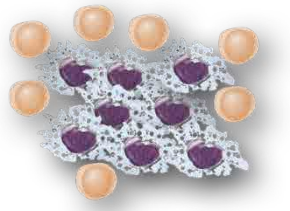


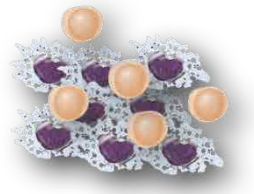
Presented By Scott Gettinger at 2014 ASCO Annual Meeting

Pr Proprietary

Immune phenotypes and immunotherapy



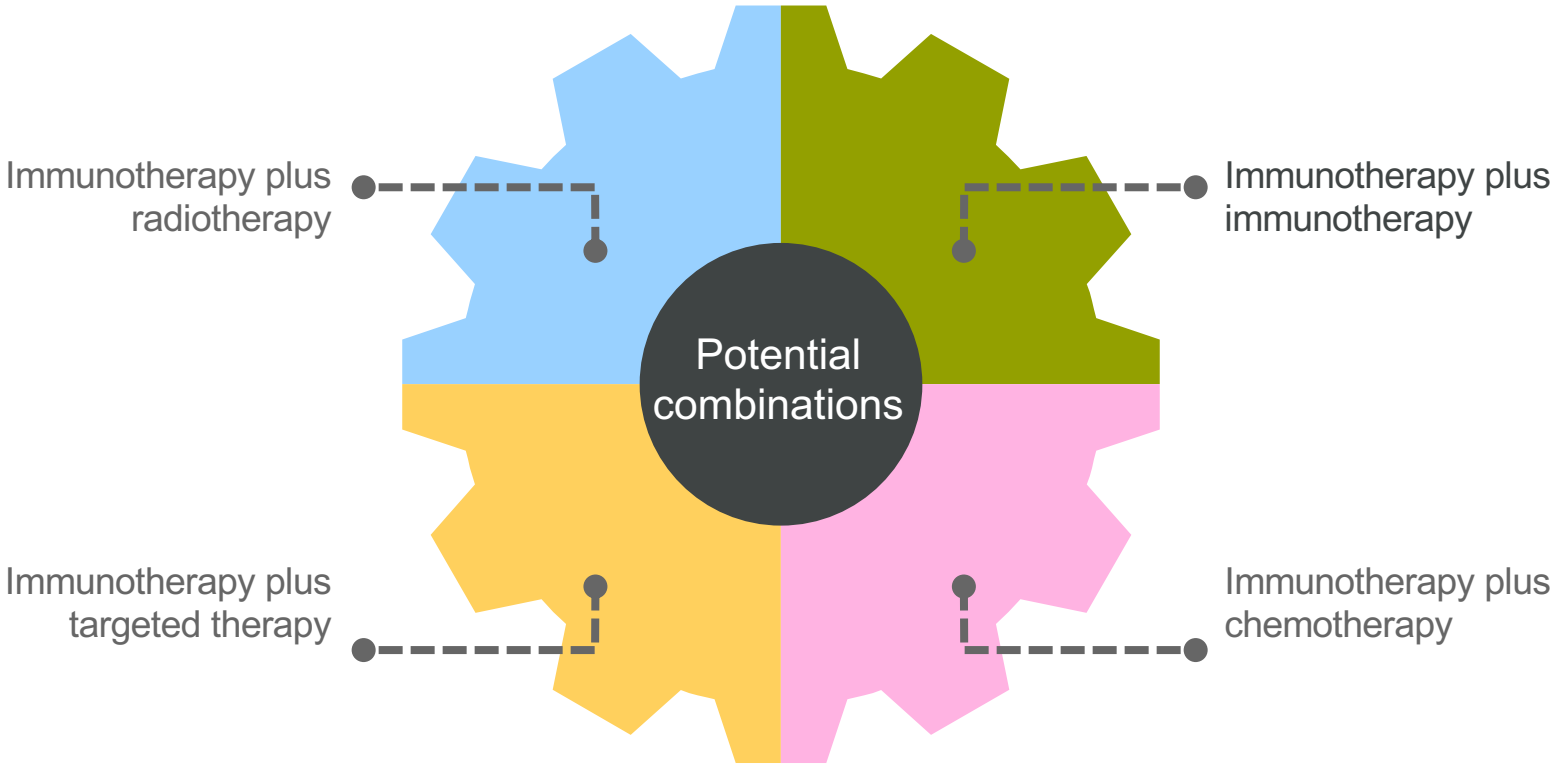




Adapted from

- Chen & Mellman, *Immunity*, 2013
- Kim & al. *Ann Oncol*, 2016

Potential combination strategies for the treatment of cancer



Final Thoughts

- The Immune Cascade is Complex and Beautiful in its Memory, Adaptability and Durable Power
- Cancer Cell Directed Therapies Can Be Effective But Fraught with Peril Due To Genetic Heterogeneity and Resistance
- Going Forward, Short Bursts of Cancer Cell Directed Therapy in Combination with an Optimal Immune Activation will Change the Landscape of Cancer

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AGEN1181- Next Generation Anti-CTLA-4:

Translating new insights into high-impact drug discovery

Dhan Chand, PhD, Head of Drug Discovery

agenus

AGEN1181 Competitive Advantage - Monospecific Approaches

	AGEN1181	YERVOY®
T cell activation	++	+
Treg Depletion	+	?
Enhanced T cell priming and Memory	+	-
Safety	+	-

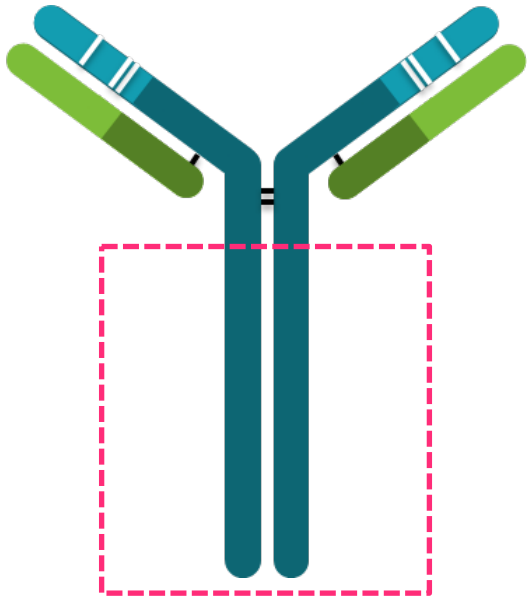
AGEN1181 Competitive Advantages vs. CTLA-4 Bispecific Approaches

	AGEN1181	CTLA-4 BISPECIFICS
Target Cells	+	Limited
Dosing	Flexible	Limited
Optimal priming and Treg depletion via novel Fc mechanism	+	-
Therapeutic Reach	++	Limited

agenus

2nd Generation I-O: Optimizing CTLA-4 Therapeutic Benefit (AGEN1181)

AGEN1181
Next-Generation CTLA-4



Fc-enhanced "back-end"

Enhanced Potency

- ✓ Enhanced T cell priming/activation
- ✓ Increased intratumoral Treg depletion
- ✓ Improved combination efficacy anticipated (PD-1 and others)

Improved Safety (expected)

- ✓ Reduced risk of CDC (C1q binding)
- ✓ Broader therapeutic index – no clinical abnormalities detected in NHP models (up to 100mg/kg)

Expanded Patient Reach

- ✓ Potential to reach a broader patient population untouched by a conventional IgG1 format (ipilimumab)
- ✓ Expected to significantly increase the response rates vs. ipilimumab

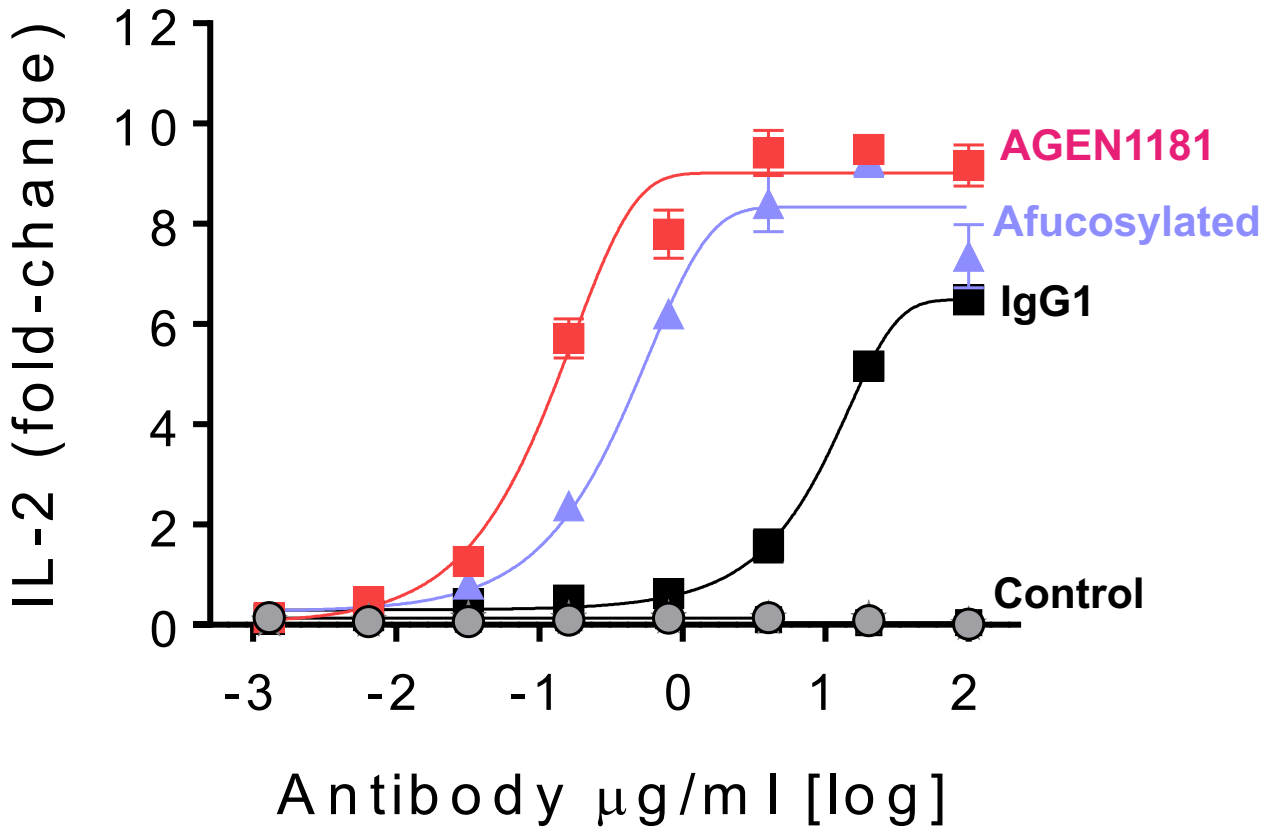
Phase I initiated April 2019

PD-1 combo studies to start imminently (2H2019)

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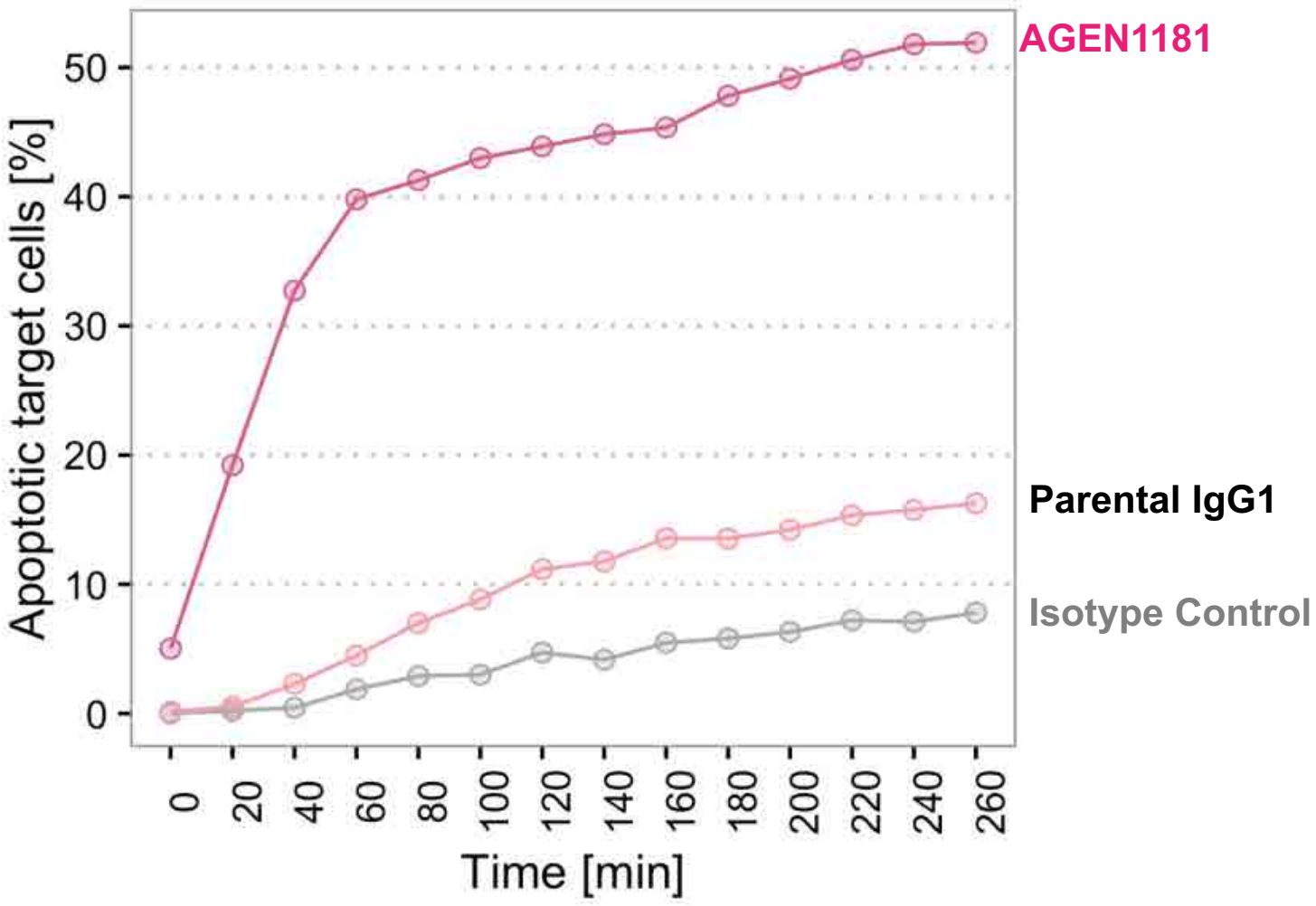
AGEN1181 Promotes Superior T cell Priming and Activation

Increased binding to FcγRIIIA enhances T cell responsiveness



Source: Agenus Data

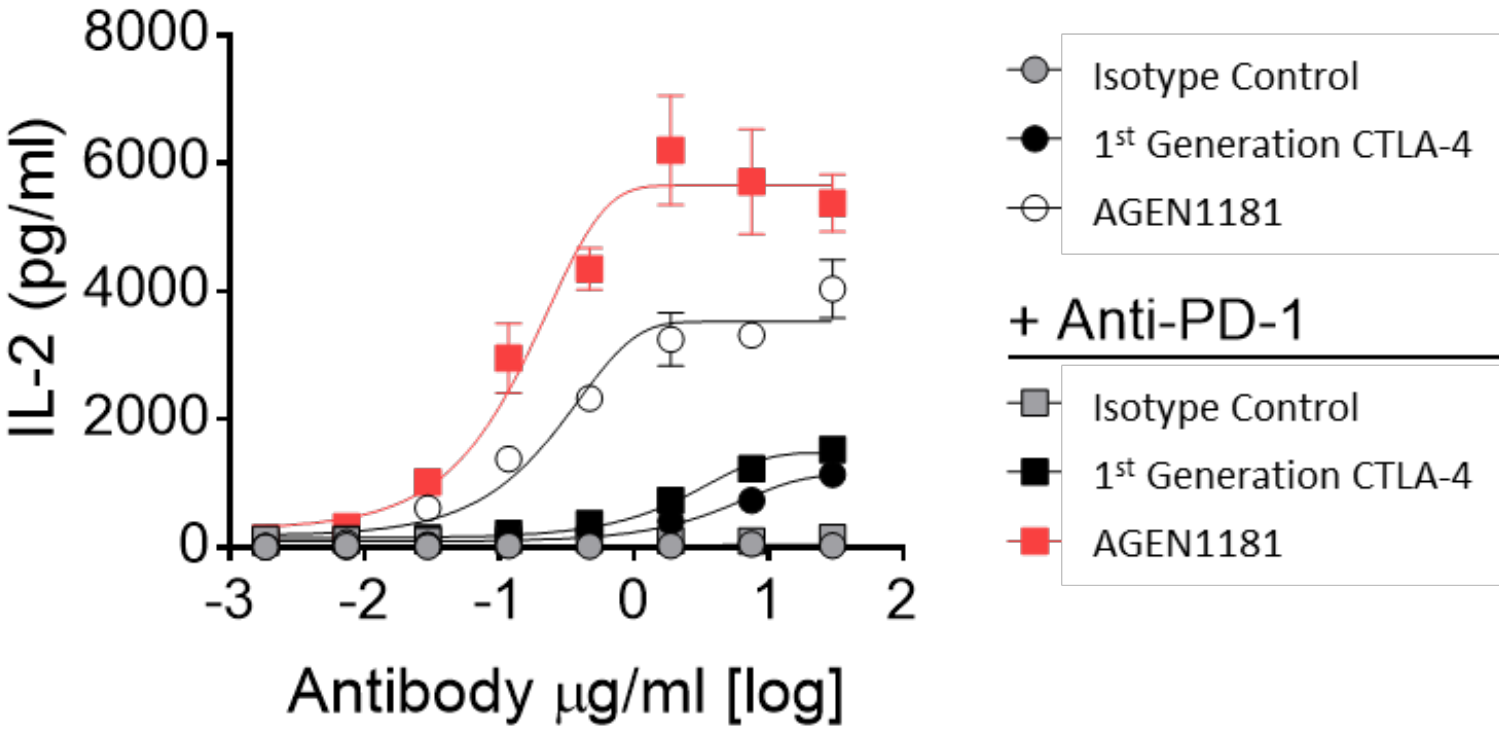
AGEN1181 is Optimally Designed to Enhance Treg Depletion



Source: Agenus Data

Superior Combination Activity with PD-1 Blockade

A comparison to first-generation anti-CTLA-4



1. Enhances antibody function
2. Increases combination potential
3. Harnesses a novel MoA

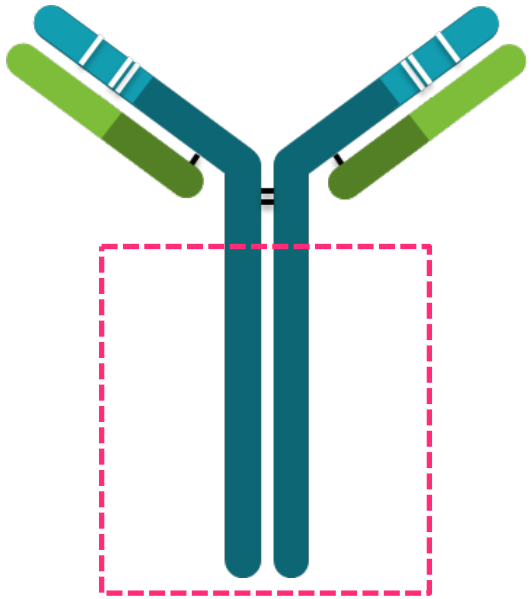
Source: Agenus data

Waight *et al.*, Cancer Cell 2018

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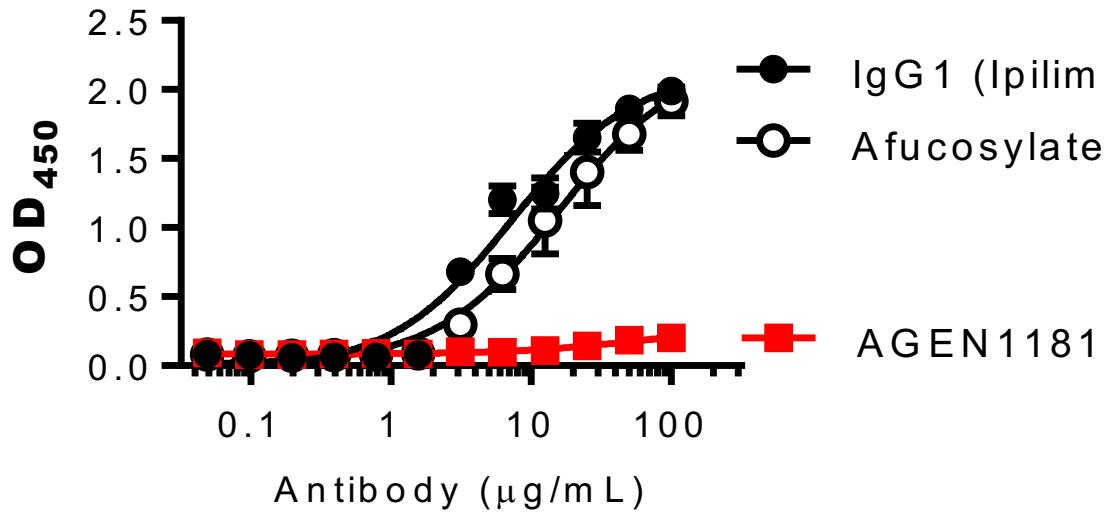
Phase I initiated April 2019

PD-1 combo studies to start imminently (2H2019)

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AGEN1181 is Designed to Avoid the Risk of CDC-mediated AEs

Advantage relative to IgG1 and afucosylated next-gen (BMS) approaches



Eur J Endocrinol. 2015 Feb;172(2):195-204. doi: 10.1530/EJE-14-0845. Epub 2014 Nov 21.

Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma.

Albarel F[1], Gaudy C[2], Castinetti F[1], Carré T[2], Morange I[1], Conte-Devolx B[1], Grob JJ[2], Brue T[3].

- **Anticipated to improved safety and tolerability over competitor anti-CTLA-4 agents**
- Complement fixation by Ipilimumab has been associated with chronic inflammation of the pituitary gland *(Iwama et al., Sci Transl Med. 2014)*

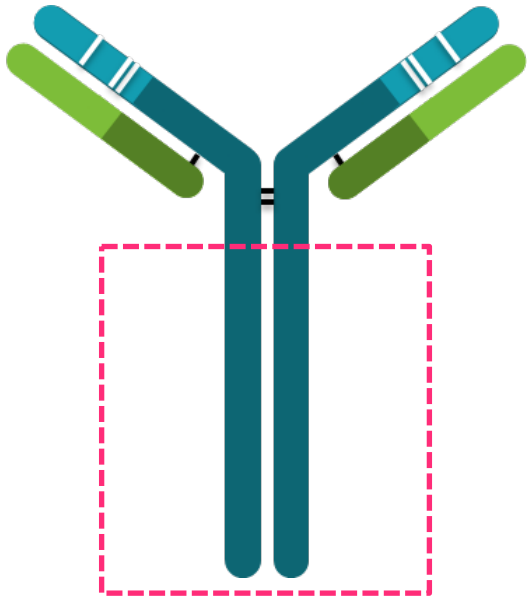
Full study report: TRL-0095

Source: Agenus data

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AGEN1181
Next-Generation CTLA-4



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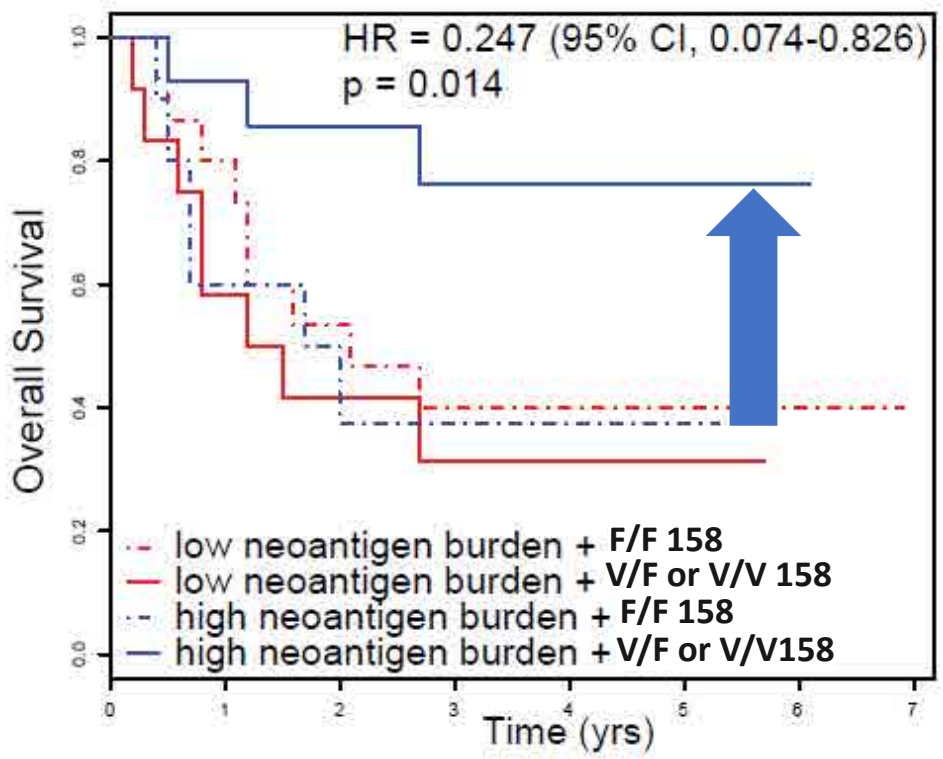
Phase I initiated April 2019

PD-1 combo studies to start imminently (2H2019)

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AGEN1181 is Designed to Expand Benefit of Anti-CTLA-4

FcγRIIIA polymorphism and neoantigen burden contributes to the activity of anti-CTLA-4



Arce-Vargas et al., Cancer Cell 2018

AGEN1181 is designed to benefit ~60% of patients *(with & without the genetic polymorphism)*

- ~20% of patients have curative benefit with anti-CTLA-4 alone
- ~40% of patients have limited response due to a genetic polymorphism

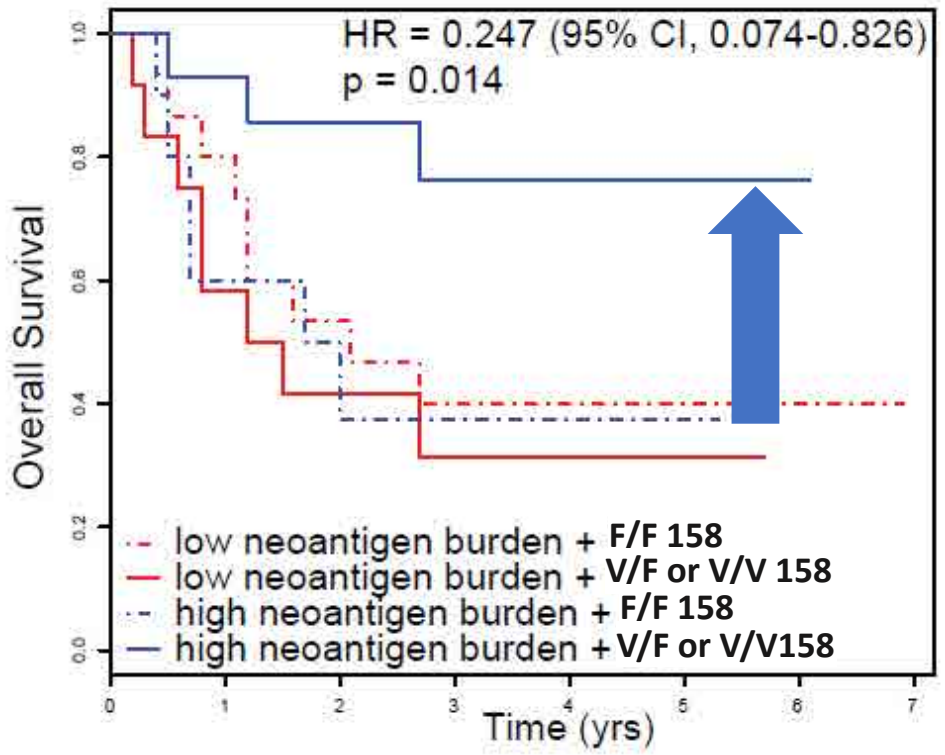
F - low affinity allele
V - high affinity allele

[1]*Larkin et al. 2019*
[2]*Arce-Vargas et al., Cancer Cell 2018*

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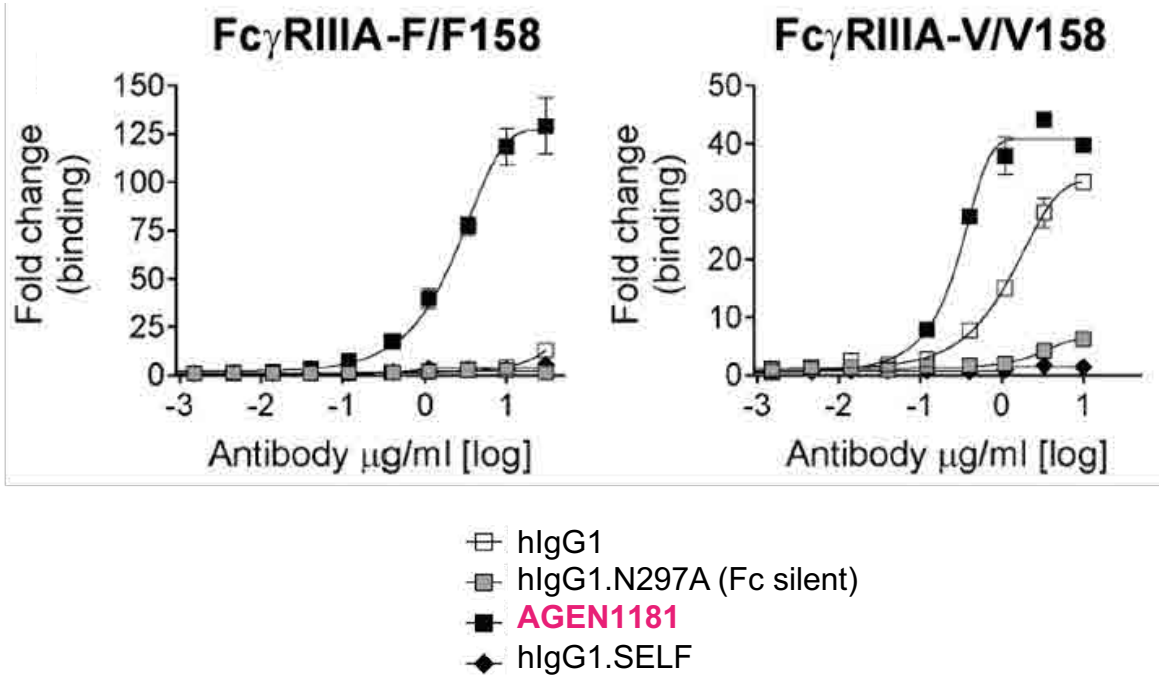
AGEN1181 is Designed to Expand Benefit of Anti-CTLA-4

FcγRIIIA polymorphism and neoantigen burden contributes to the activity of anti-CTLA-4



Arce-Vargas et al., Cancer Cell 2018

AGEN1181 demonstrates enhanced binding to both the low and high-affinity FcγRIIIA



F - low affinity allele
V - high affinity allele

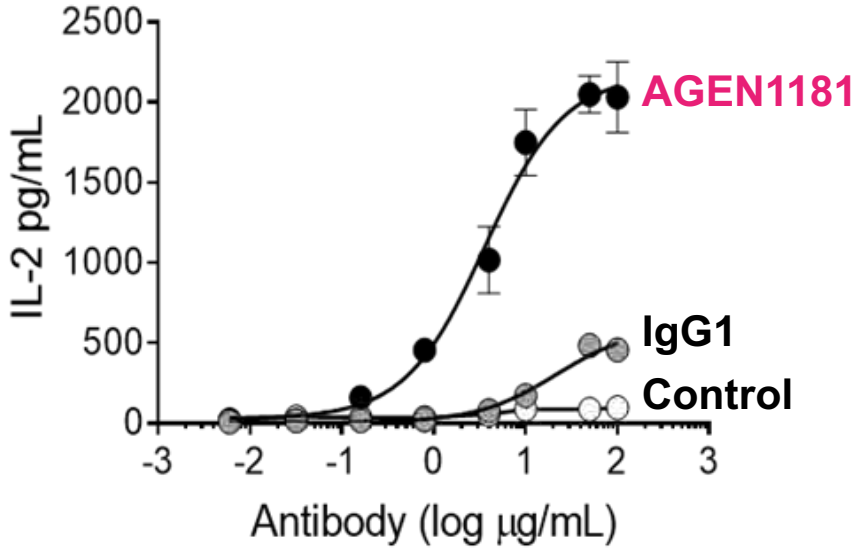
Waight *et al.*, Cancer Cell 2018

[1]*Larkin et al. 2019*
[2]*Arce-Vargas et al., Cancer Cell 2018*

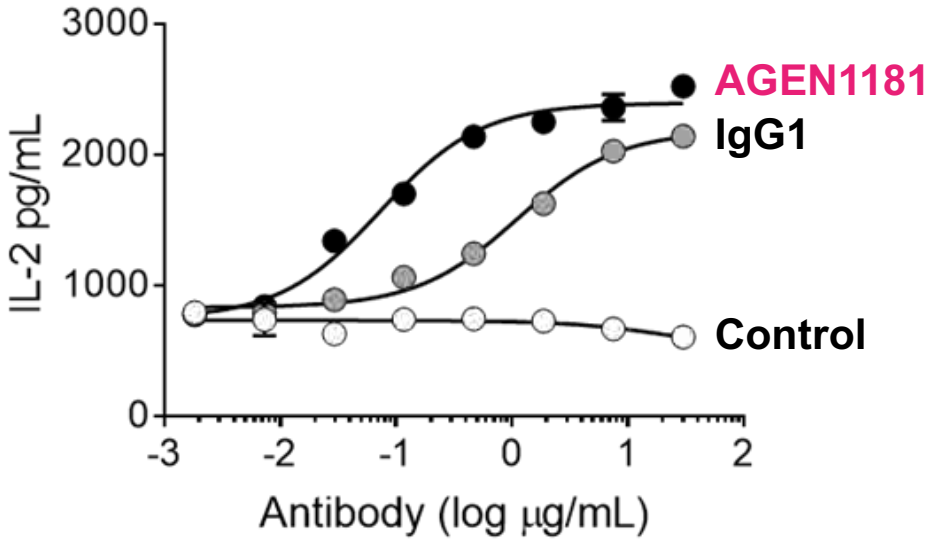
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AGEN1181 Outperforms an IgG1 Analog in Donors That Express the Low Affinity FcγRIIIA 158F Allele

FcγRIIIA 158 F/F donor



FcγRIIIA 158 V/F donor



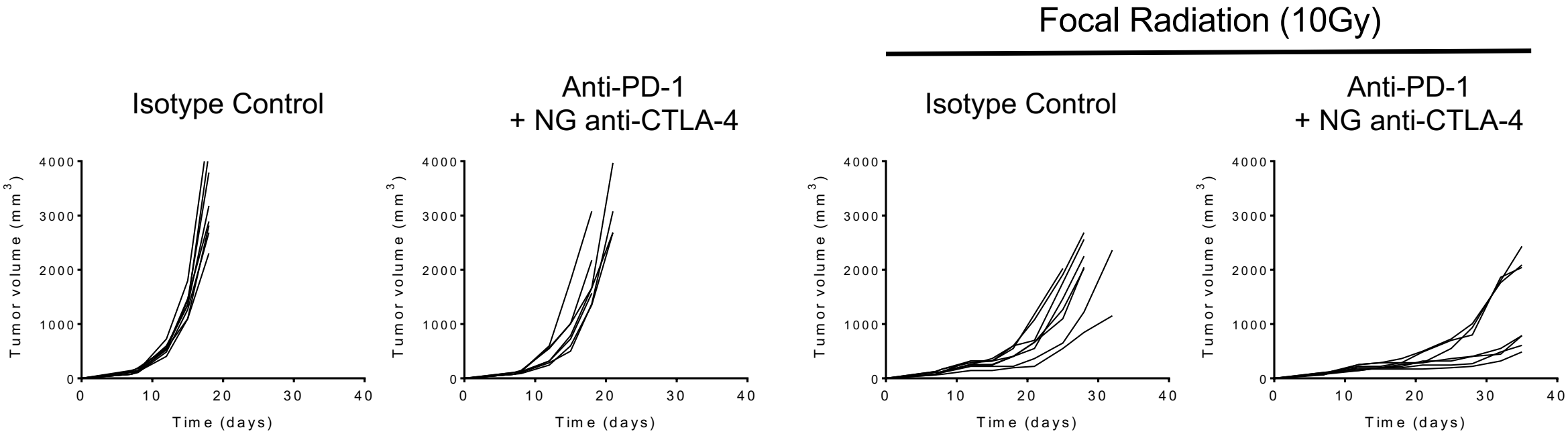
F - low affinity allele
V - high affinity allele

Source: Agenus Data

agenus

Rational Combinations Can Expand Therapeutic Benefit

Focal Radiation combines with NexGen CTLA-4 and PD-1 blockade to enhance tumor control *(B16F10 tumor model)*



Source: Agenus Data

agenus

AGEN1181 is Optimally Designed for Monotherapy and Combination Superiority

Two distinct and rapid paths to BLA approval

1. **Monotherapy with deeper responses** compared to first-generation CTLA-4 with expanded benefit in patients that are unresponsive due to a FcγR genetic polymorphism

2. **Superior combination with anti-PD-1** with opportunistic paths to approval in major indications like melanoma and lung cancer

Upcoming Catalysts:

- Initiation of combo trials with anti-PD-1 (2H2019)
- Early Ph1 clinical and combination readout (1H2020)

VISION I-O Discovery Platform

Cailin Joyce, PhD, Business Development & Alliance Management

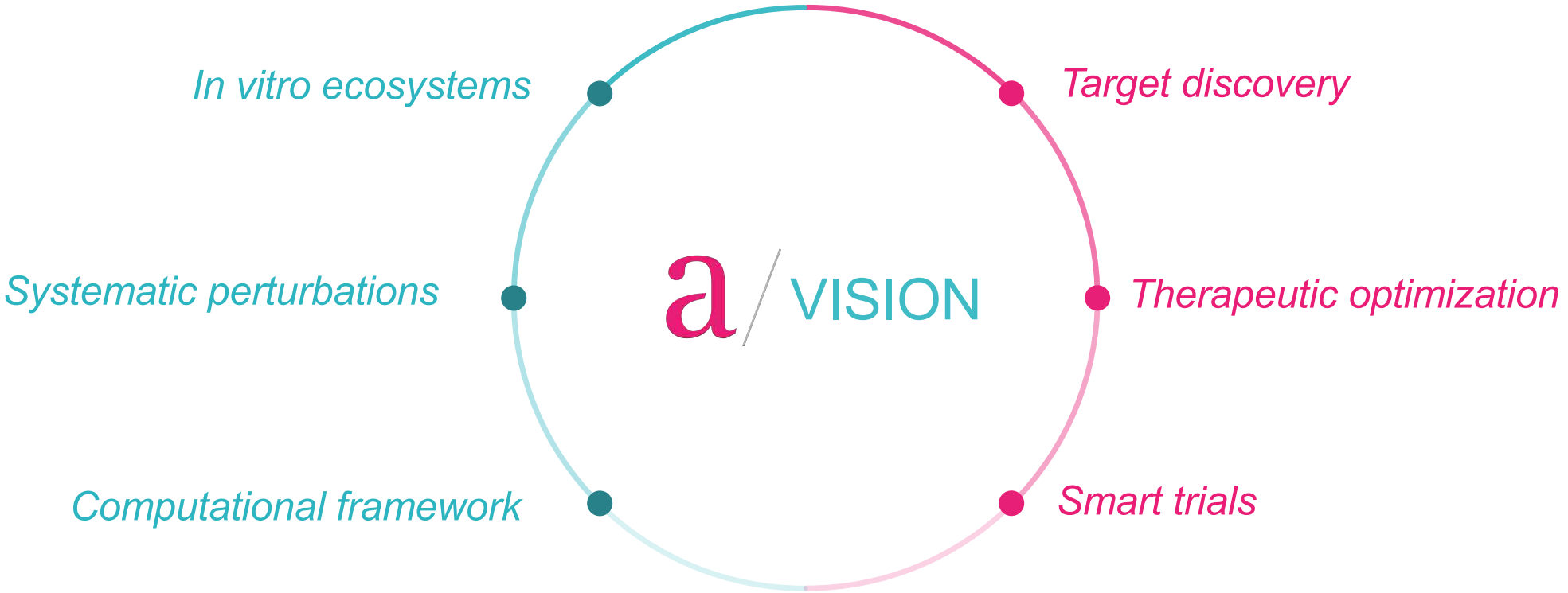
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3.4%

Rate of approvals from oncology clinical trials

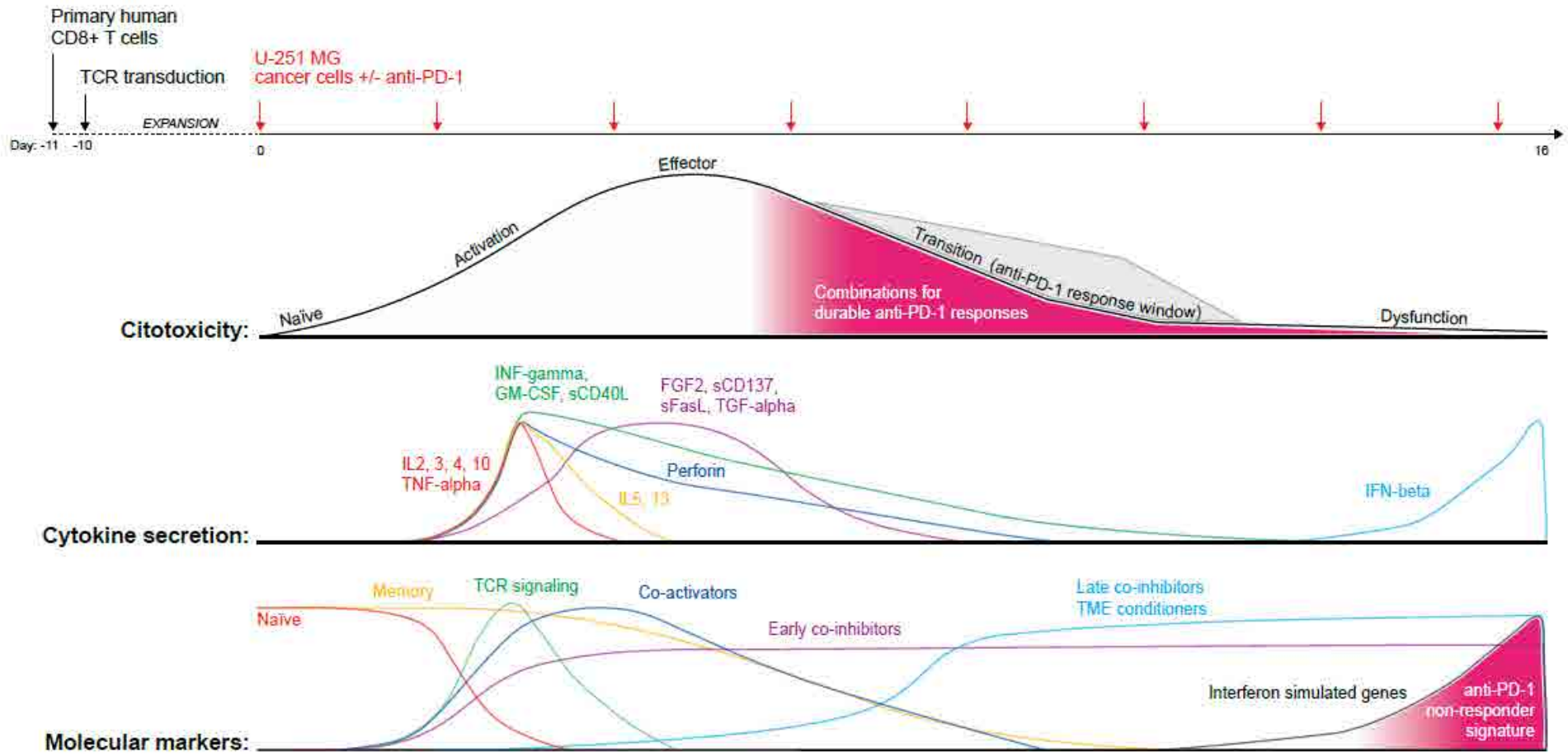
Source: Wong, et al. *Biostatistics* 2019

VISION Capabilities and Applications



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Deep, Integrative Profiling of the Tumor-immune Interface In Vitro

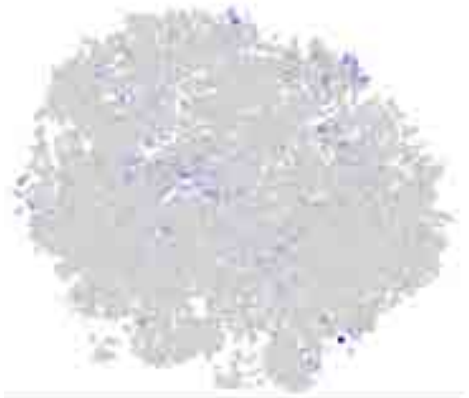


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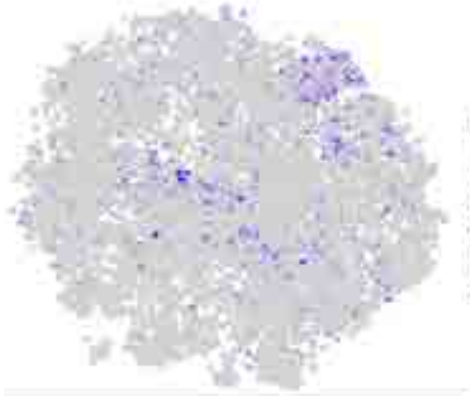
Discovery: Combinations for Durable Anti-PD1 Response

VISION T cell dysfunction
Target expression on an activated, PD-1 responsive T cell subset

Isotype



Anti-PD1

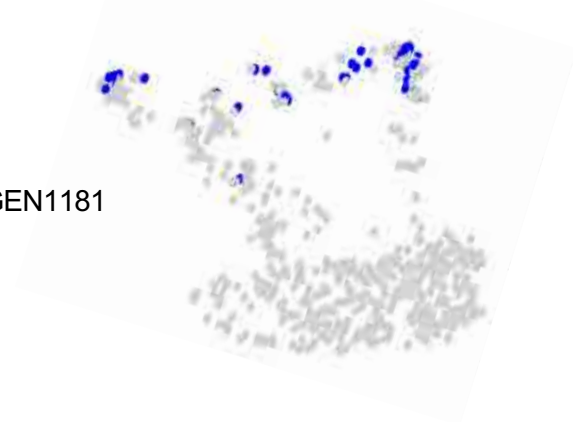


VISION SEA assay
Upregulated on activated T cells in presence of AGEN1181

Isotype



AGEN1181



Public scRNA-seq data
Enriched in intratumoral CD8⁺ T cells

Peripheral CD8+



Intratumoral



Source: Agenus Data

agenus

Smart Trials: Predictive Signature for PD-1 Response

In vitro dysfunction signature
231 genes
(**Agenus**)

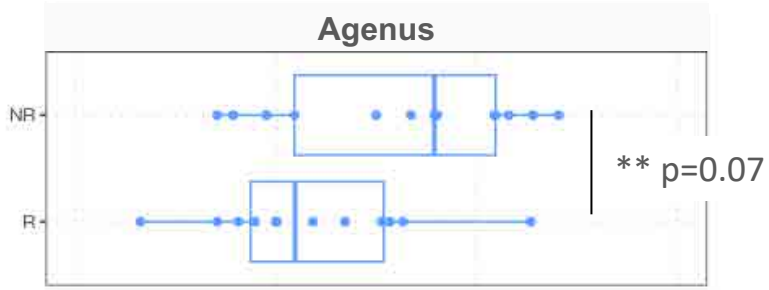
Melanoma TIL dysfunction signature
1088 genes
(Feldman et al., 2016)

Melanoma TIL dysfunction signature
28 genes
(Tirosh et al., 2016)

Bulk RNA-sequencing data from melanoma tumors

- 14 PD-1 responders
- 13 PD-1 non-responders

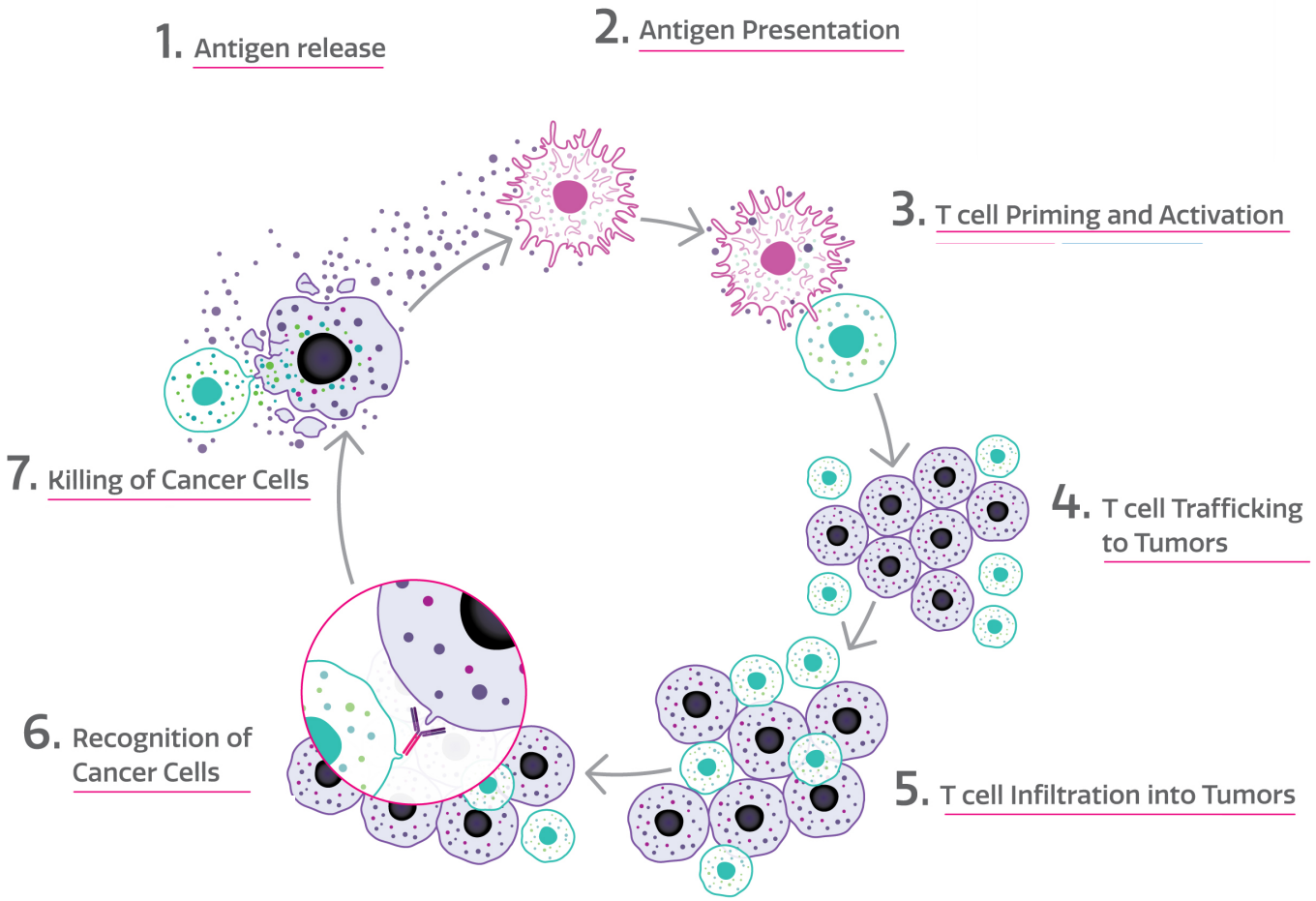
(Hugo *et al.* 2016)



Source: Agenus Data

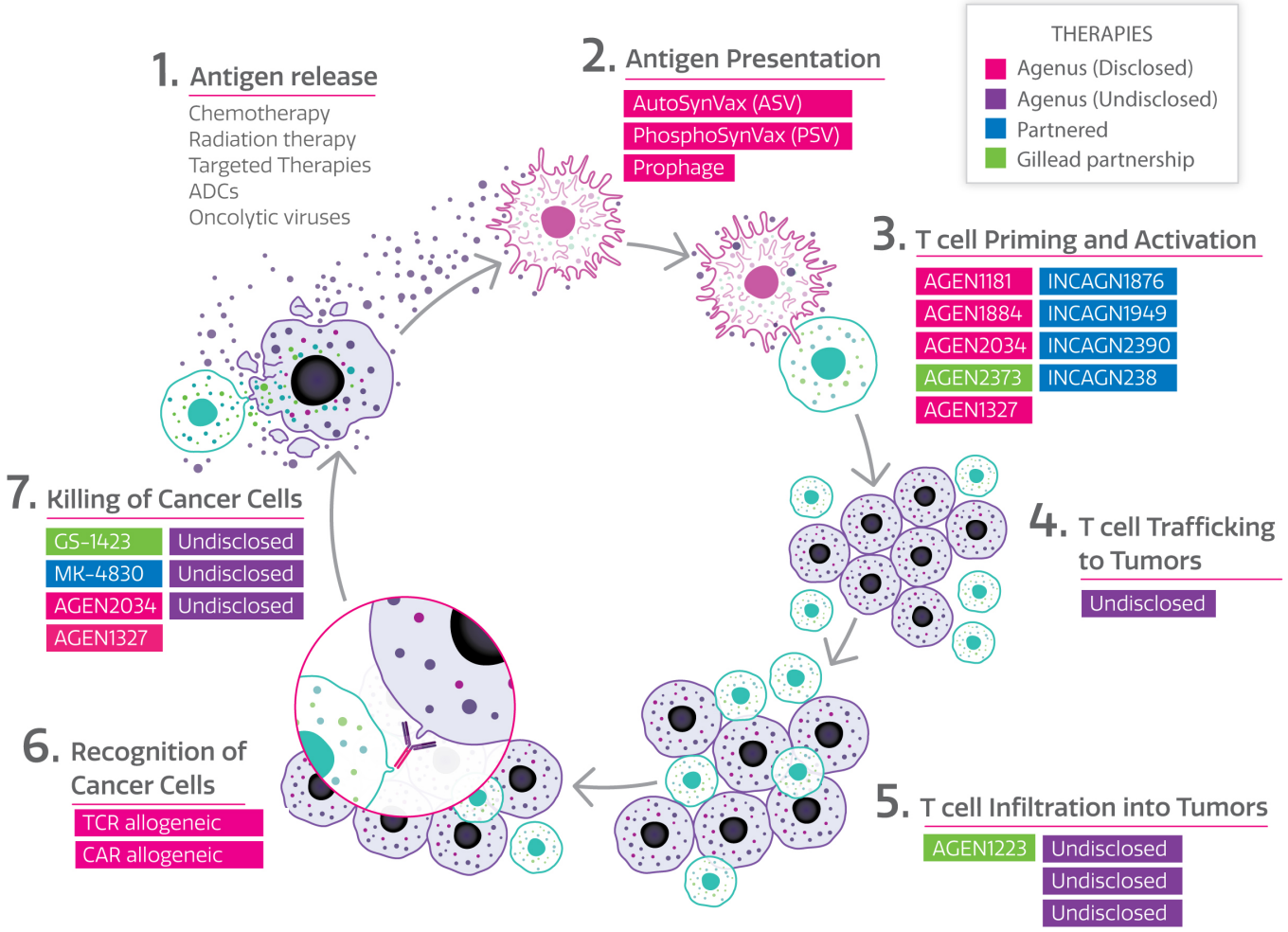
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VISION Helps Develop a Broad Clinical Pipeline



agenus

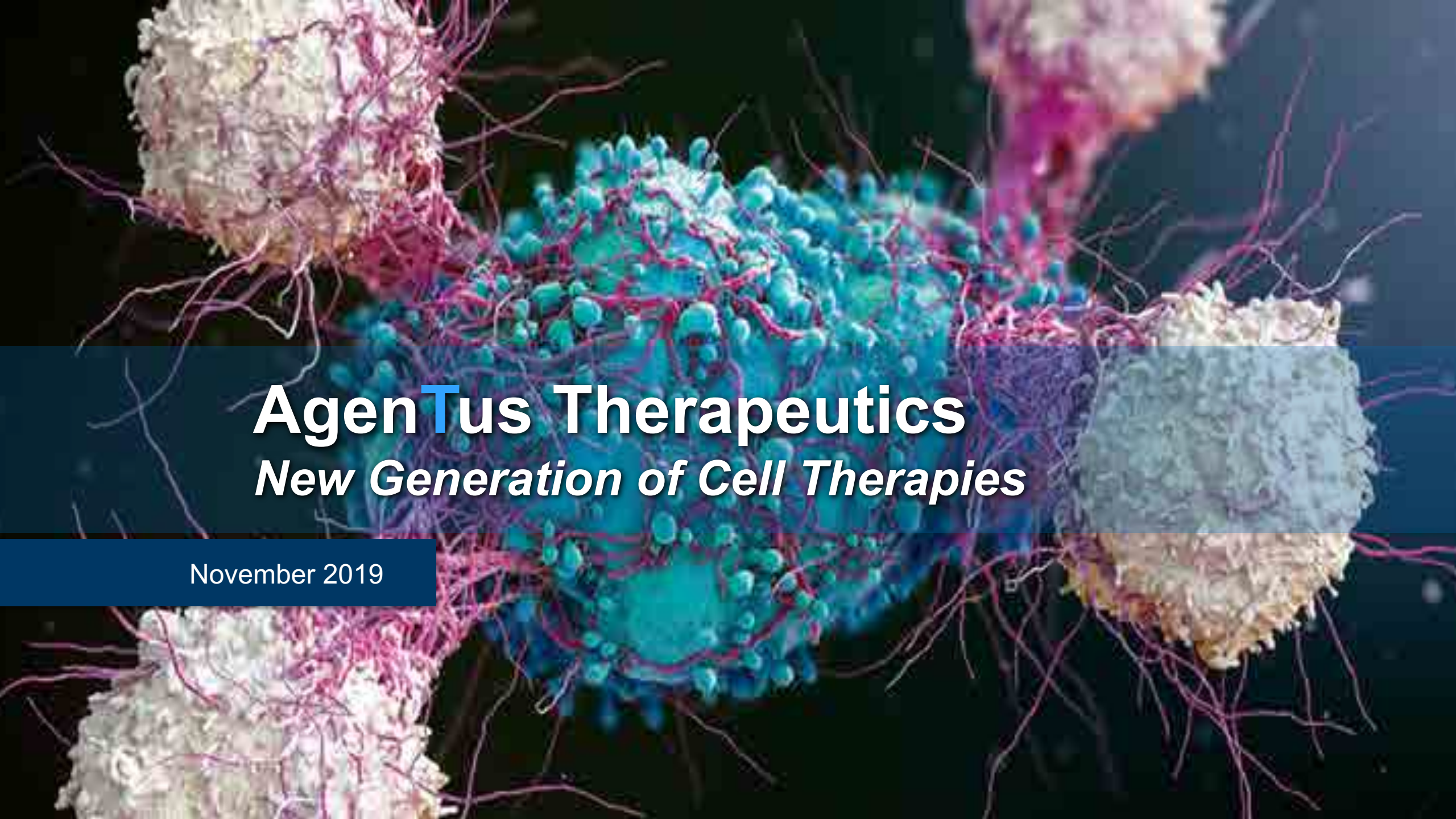
VISION Helps Develop a Broad Clinical Pipeline



agenus

VISION Catalyzes Development and Discovery

- ✓ Improve durability of PD-1 responses
- ✓ Deep read on AGEN1181 mechanisms of action
- ✓ Maximize potential of iNKT cells & other next-generation agents



AgenTus Therapeutics

New Generation of Cell Therapies

November 2019

AgenTus Leadership team



Walter Flamenbaum M.D.
Chief Executive Officer



Peter Suenaert, M.D., PHD
Head of Global Clinical Development



Andy Hurwitz, PhD
Head of Preclinical Research



Marc van Dijk, PhD
Head of Platform Development



Mark Exley, PHD
Head of Cellular Immunology



Michael Plater, PhD
Chief Administrative Officer



Alain Pralong, PHD
Head of Manufacturing and Process Development

AgenTus THERAPEUTICS

Leading with New Generation Cell Therapies

Our cell therapies are designed to:

- Be safer and more effective
- Be more affordable
- Target solid tumor cancers – not treated with currently approved cell therapies
- Achieve durable responses when used with Agenus checkpoint antibodies

AgenTus advantages:

- Access to I-O combination therapies – through Agenus
- Expertise in allogeneic “off-the-shelf” cell formats
- Proprietary IP and know-how
- World-class Immuno-Oncology and Cell Therapy experts

First Generation Cell Therapies

Have significant limitations and challenges

Current cell therapies

- Only two approved therapies
- Both are autologous CAR-T cell based
- Both address only B-cell leukemias and lymphomas
- Harmful side effects
- Cost incompatible for IO combinations

Product	Cost (US)	Production Time
KYMRIAH®	$475,000	22 days
YESCARTA®	$373,000	26 - 29 days

Total treatment costs ~ $1 million

AgenTus THERAPEUTICS

First Generation Cell Therapies

Great when they work but…..

Positives

- Unprecedented efficacy and durability in “liquid” cancers

Hurdles

- Must be individually made - for each patient
- Take a month to manufacture
- Costly - up to $1M total treatment cost per patient
- Failure to manufacture - one third of patients
- Complicated patient management

Challenges

- Work only in liquid tumors - less than 10% cancers
- Deadly side effects - Cytokine Release Syndrome
- Recurrence of cancers in 30-50% patients

AgenTus THERAPEUTICS

Making Cell Therapies More Effective, Safer, Cheaper and Broadly Applicable requires…

NEED TO HAVE

1. A Superior Cell Format
2. Optimal Receptors
3. New Targets
4. Low Manufacturing Cost

Current efforts generally aim to improve on just one aspect of these which is not sufficient to achieve the desired outcomes

AgenTus THERAPEUTICS

AgenTus Advantage: a NEW GENERATION Adoptive Cell Therapy ("ACT")

OUR CAPABILITIES

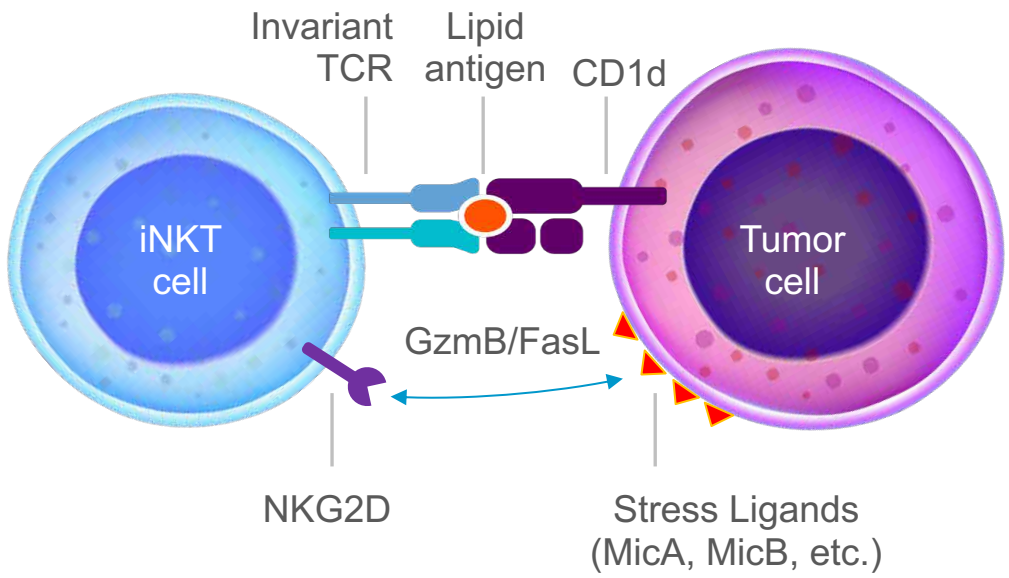
1 Potent cancer-killing with our flexible **CELL FORMAT**	2 Our precision engineered **RECEPTORS**	3 Our proprietary novel TARGETS	4 Rapid, lower cost **PRODUCTION PROCESS**
iNKT cells	T-Rx™, Intrepid ™, T-Sprint™, & CARDIS™	Phosphopeptide Tumor Targets (PTTs)	Allogeneic iNKT process

5 Plus breadth of I-O knowledge and privileged access to **Agenus'** Check Point Antibodies

AgenTus THERAPEUTICS

Natural Killer T Cells ("iNKTs"): Powerful Multipurpose Cancer Killers

AgenTus THERAPEUTICS *spearheading iNKTs for 3rd generation ACT*

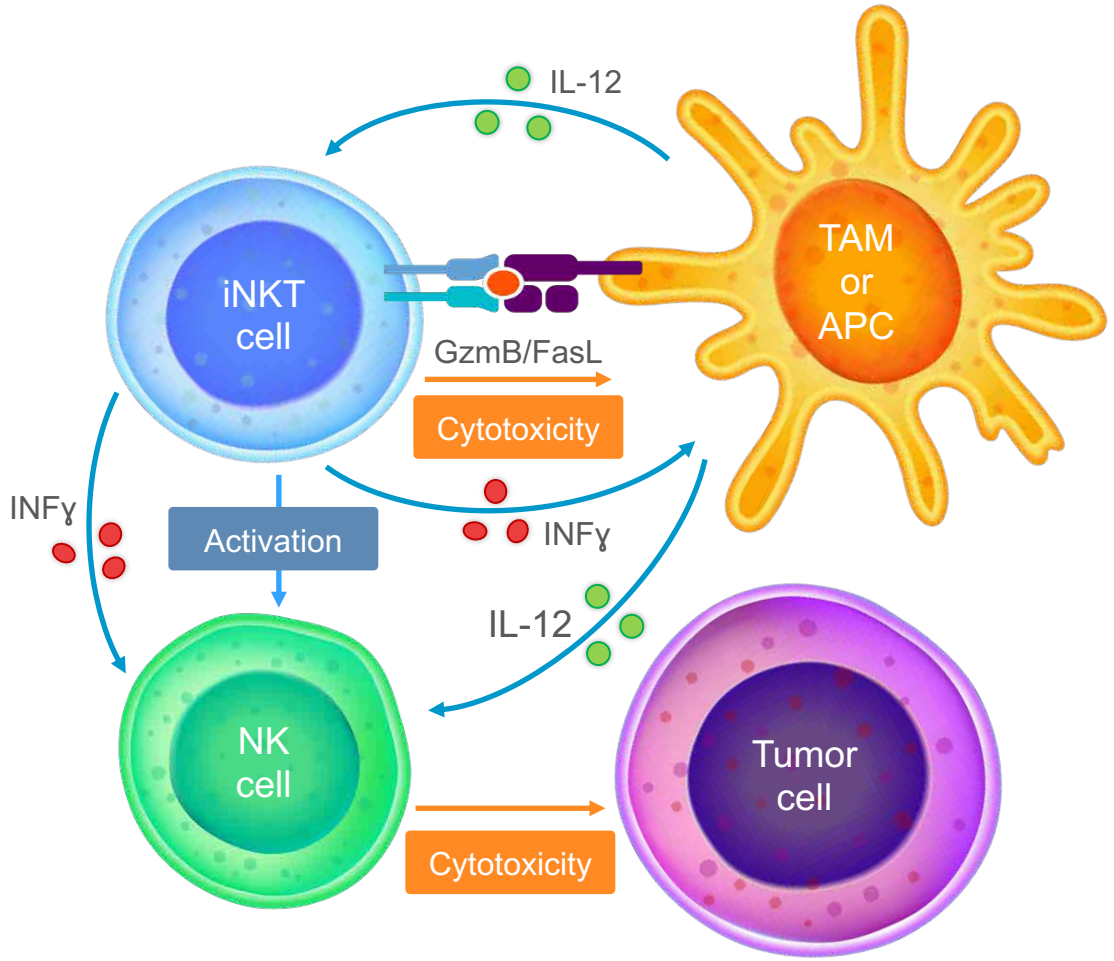


- **Have two natural mechanisms for killing cancer cells**
  - Invariant T Cell Receptor ("iTCR") detects tumor target CD1d & kills
  - NKG2D detects Stress Ligands & kills
- **Home to tissues / tumors spontaneously**
  - Unlike T cells, which must be activated, iNKTs are designed to kill naturally AND,
  - May make lymphodepletion unnecessary

Adapted from: Wolf BJ et al. Front Immunol. 2018 Mar 2;9:384. PMID: 29559971 Free PMC Article

AgenTus THERAPEUTICS

iNKT Cells Also Significantly Boost Immune Response Naturally



- **Recondition Tumor Micro-Environment** ("TME")
  - Strong interferon gamma secretion boosts effector T cell recruitment
- **Activate antigen presenting cells** for better recognition of tumors by targeting multiple antigens which helps
  - block tumor escape
  - block tumor recurrence
- **Recruit Natural Killer (NK) cells**
  - improves the activity of checkpoint antibodies
  - blocks tumor escape by loss of MHC expression

Adapted from: Wolf BJ et al. Front Immunol. 2018 Mar 2;9:384. PMID: 29559971 Free PMC Article

AgenTus THERAPEUTICS

iNKT Cells are Ideally Suited to Treat All Types of Late Stage Cancers

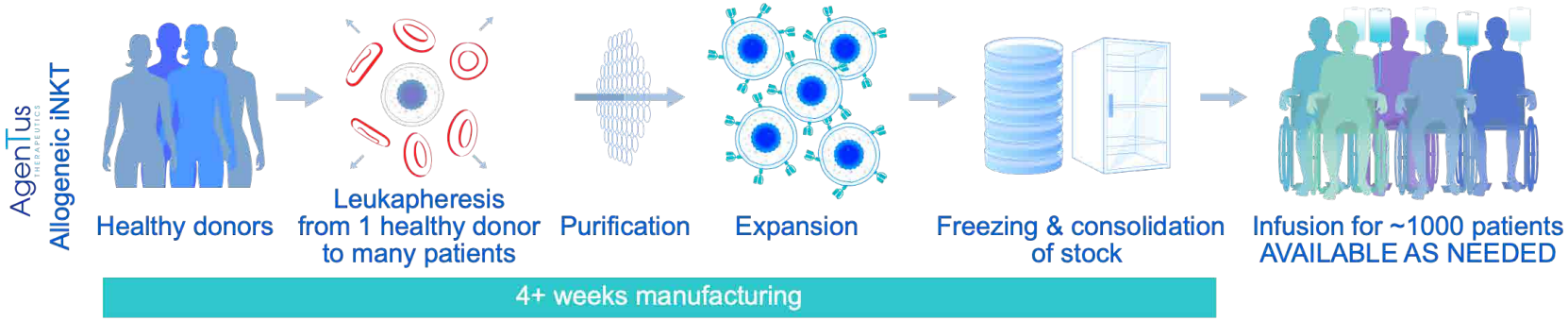
Allogeneic iNKTs IND 4Q 2019, with clinical trials for mono and combinations in 2020

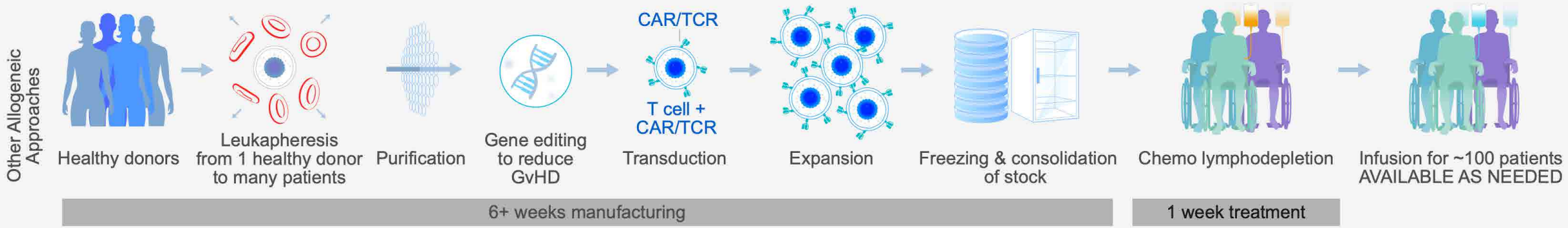
- **Optimal Treatment :** Allogeneic iNKT + Agenus checkpoint antibodies
- Designed to treat most late-stage cancer patients - 1st and 2nd gen cell therapies target a fraction of cancers
  - Our iNKTs are produced in a simple streamlined process vs. current cell therapies
  - Our treatment will be at much lower prices than current cell therapies

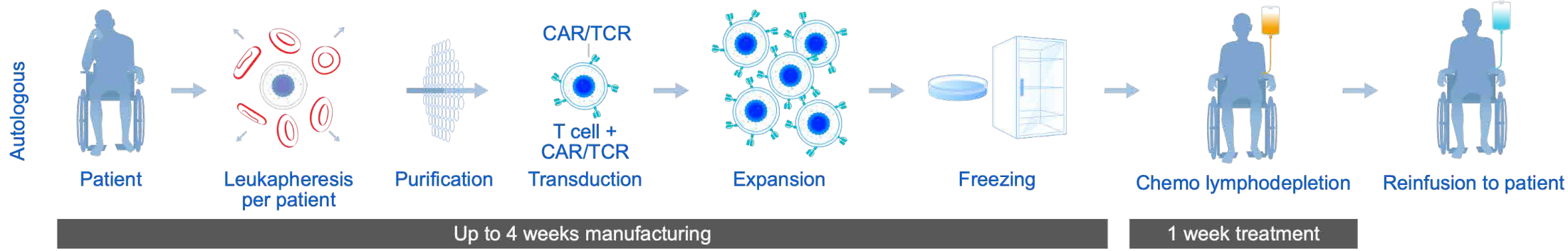
2019	2020
1st IND	**2nd IND: Combination trials**
• Allogeneic iNKTs • Multiple Myeloma • At Dana Farber Cancer Center	• Allogeneic iNKTs with… • Agenus checkpoint Antibodies – AGEN2034 (PD-1) – AGEN1884 (CTLA-4) or – AGEN1181 (next gen CTLA-4)

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Allogeneic iNKT Cells







Clinical Plans to Provide Optimal, Stepwise Validation of AgenTus Cell Therapy

1. Potent cancer-killing, Flexible **CELL FORMAT**
2. Precision engineered **receptors**
3. New targets
4. Fast, cost-effective **production process**
5. Optimal combinations

Clinical Trial Plan

Allogeneic iNKT cells	• Efficacy against solid and liquid tumors • Off the shelf, rapid, and affordable • Safer (No Graft versus Host Disease, lymphodepletion)	1 4
CARs in Allogeneic iNKT cells	• More efficacious than CAR-T cells • Safer (No GvHD, lymphodepletion not required)	1 2 4
TCRs in Allogeneic iNKT cells	• **Efficacy against solid and liquid tumors** • **Three ways to kill cancer for superior efficacy** • **Safer, faster, affordable**	1 2 3 4
ACT Combinations with CPMs	• Supercharges ACT & fosters endogenous anti-tumor immunity • Broader anti-tumor activity & memory to complement allogeneic formats • Superior efficacy and durability	2 5

AgenTus THERAPEUTICS



AgenTus Therapeutics

Third Generation Cell Therapies

R&D Day Presentation

For additional information please contact:
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