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This version of the presentation includes corrections to errors in the original presentation contained on slide 22, clarifying footnotes on slides 20 & 21, and a post-meeting addition (slide 23).

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 and AgenTus' clinical development and regulatory plans and timelines, expected timing for clinical trials and releasing clinical data, anticipated milestones from partnership transactions, and goals for 2020. 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 filed with the Securities and Exchange Commission and made available on our website at www.agenusbio.com. Agenus cautions 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 undertakes 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.

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Investor Day

- Pivotal Trial Clinical Data on Balstilimab and Zalifrelimab
- AGEN1181: Beyond a Next-Generation CTLA-4
- New Discoveries

From the Experts



Charles Drake, MD, PhD

Co-Director, Cancer Immunotherapy Program, Columbia University Herbert Irving Comprehensive Cancer Center



Bradley Monk, MD, FACS, FACOG

Professor, Division of Gynecologic Oncology, Arizona Oncology (US Oncology Network), Co-Director of GOG Partners



Tyler Curiel, MD, MPH, FACP

The Daisy M. Skinner Professor of Cancer Immunology Research
Professor of Medicine, Microbiology, Immunology & Medical Genetics
UT Health San Antonio
Mays Cancer Center

From Agenus



Garo Armen, PhD

Chairman and CEO



Dhan Chand, PhD

Head of Drug Discovery



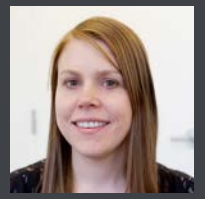
Jennifer Buell, PhD

President and COO



Mark Exley, PhD

Vice President Cellular Immunology



Julie DeSander

Vice President, Business Development & Alliance Management



Anna Wijatyk, MD

Head of Clinical Development

Delivering Some of Our 2020 Goals Today

- **6 Clinical Data Readouts**
  - ☑ **Zalifrelimab and Balstilimab**
  - ☑ **Balstilimab**
  - ☑ **AGEN1181**
  - ☐ AGEN1223
  - ☐ AGEN2373
  - ☐ GS-1423
- **2 INDs**
- **2 BLA filings**

*2020 Objectives Shared at Agenus' November 2019 R&D Day

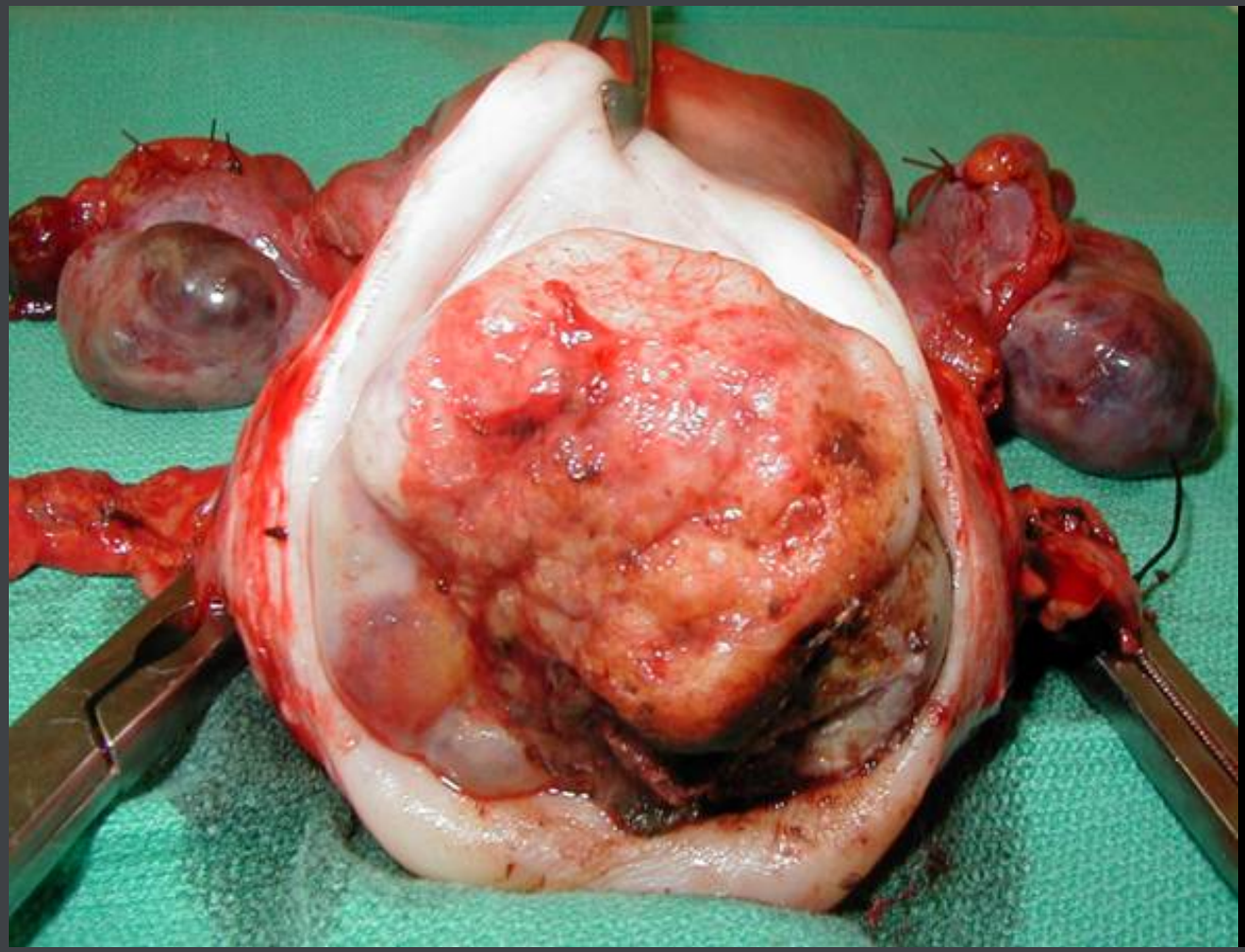


Dr. Bradley J. Monk

MD, FACOG, FACS

- Professor of Gynecologic Oncology
- University of Arizona
- Arizona Oncology (US Oncology Network)
- Co-Director > GOG Partners
- Chair Cervical Cancer Committee > Gynecologic Cancer Intergroup (GCIG)

The Enemy





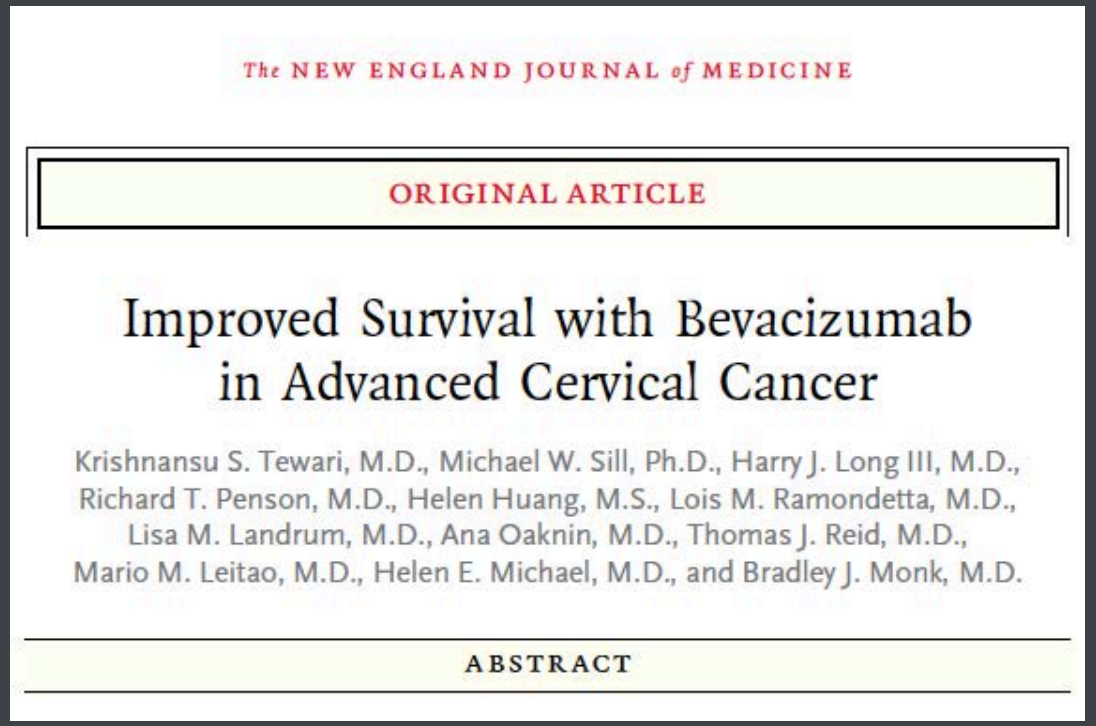
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Three Decades: Recurrent & Metastatic Cervical Cancer

- Seven randomized phase 3 trials
- Cisplatin (Cis) 50 mg/m2 plus paclitaxel (Pac) 135 mg/m2 IV over 24 hrs standard therapy
- Median overall survival (OS) ≤12 months
- Majority of patients with recurrent cervical cancer pre-treated with cisplatin-based chemoradiation for locally advanced disease (1999 onwards)

Tewari KS, et al. *Curr Oncol Rep.* 2005;7(6):419-434. Monk BJ, et al. *J Clin Oncol.* 2007;25(20):2952-2965. Tewari KS, et al. *Onkologie.* 2008;32(10):552-554. *Monk BJ, et al. *J Clin Oncol.* 2009;27(28):4649-4655. Tewari KS, et al. *Semin Oncol.* 2009;36(2):170-180. Tewari KS, et al. *Clin Adv Hematol Oncol.* 2010;8(2):108-115. Tewari KS. *Am J Hematol Oncol.* 2010;9:31-34. Tewari KS. *Clin Ovarian Cancer.* 2011;4:90-93.

New England Journal of Medicine and THE LANCET



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

ABSTRACT

THE LANCET

Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240)

Krishnansu S Tewari, Michael W Sill, Richard T Penson, Helen Huang, Lois M Ramondetta, Lisa M Landrum, Ana Oaknin, Thomas J Reid, Mario M Leitao, Helen E Michael, Philip J DiSaia, Larry J Copeland, William T Creasman, Frederick B Stehman, Mark F Brady, Robert A Burger, J Tate Thigpen, Michael J Birrer, Steven E Waggoner, David H Moore, Katherine Y Look, Wui-Jin Koh, Bradley J Monk

NRG ONCOLOGY™

FDA approved for 1-L metastatic disease Aug 14 2014

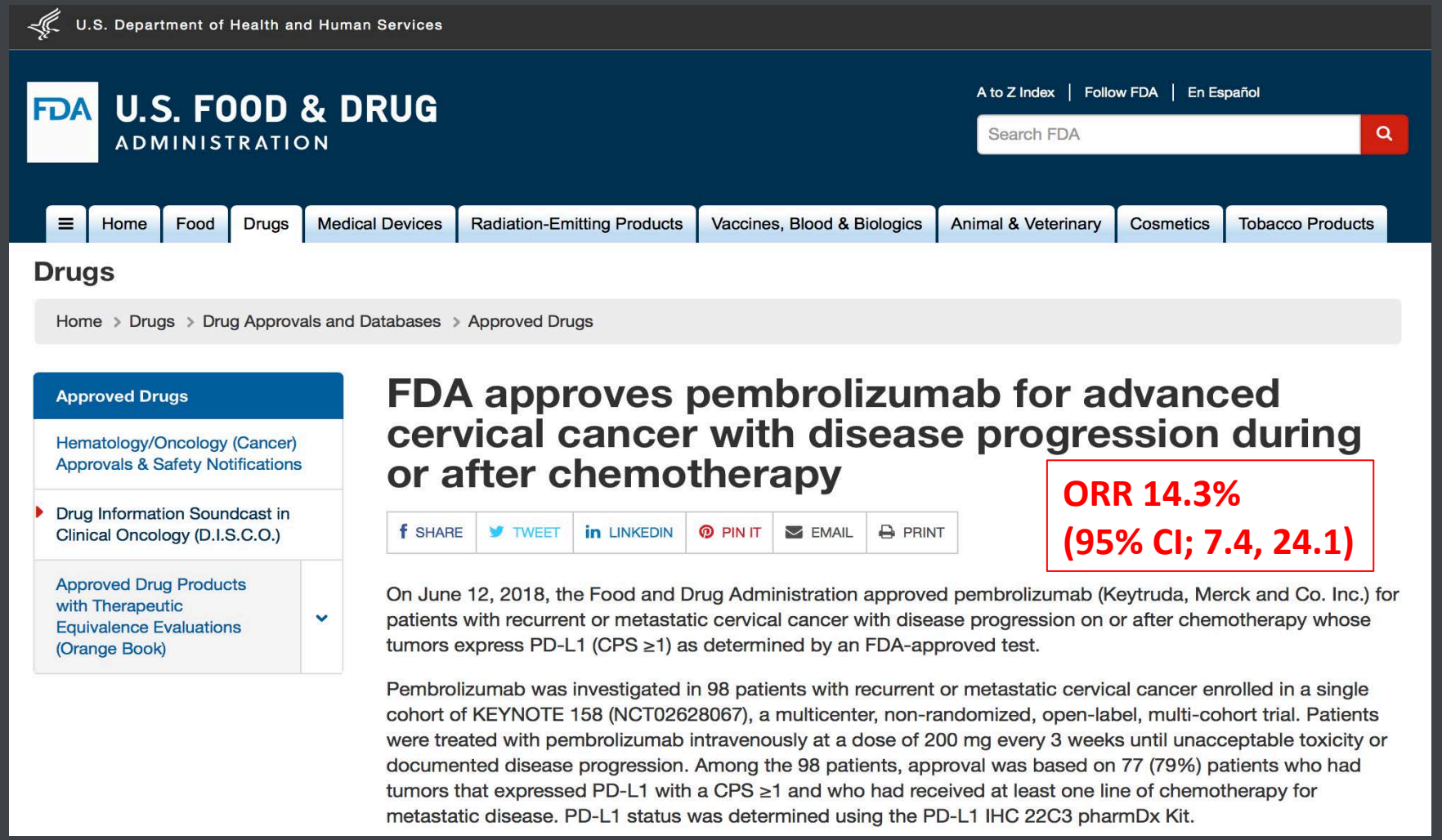
FDA U.S Food and Drug Administration

Tewari KS, et al. *N Engl J Med*. 2014;370(8):734-743.

Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

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FDA Accelerated Approval of Pembrolizumab
(June 12, 2018)



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

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ORR 14.3%
(95% CI; 7.4, 24.1)

On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had tumors that expressed PD-L1 with a CPS ≥1 and who had received at least one line of chemotherapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.

Companion Diagnostic
PD-L1 IHC 22C3
CPS≥1

FDA Press Release. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610572.htm. Accessed October 31, 2019.

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Efficacy and Safety of Nivolumab + Ipilimumab in Patients with Recurrent/Metastatic Cervical Cancer: *Results From CheckMate 358*

BARCELONA 2019 ESMO congress

Proof of Concept for Combo PD-1 + CTLA-4 in Cervical

R. Wendel Naumann[1*], Ana Oaknin[2*], Timothy Meyer[3], Jose Maria Lopez-Picazo[4], Christopher Lao[5], Yung-Jue Bang[6], Valentina Boni[7], William H. Sharfman[8], Jong Chul Park[9], Lot. A. Devriese[10], Kenichi Harano[11], Christine H. Chung[12], Suzanne L. Topalian[8], Kamarul Zaki[3], Tian Chen[13], Junchen Gu[13], Bin Li[13], Adam Barrows[13], Andrea Horvath[13], Kathleen N. Moore[14]

[1]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [2]Vall d´Hebron University Hospital, Vall d´Hebron Institute of Oncology, Barcelona, Spain; [3]University College London, London, UK; [4]Clinica Universidad de Navarra, Navarra, Spain; [5]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [6]Seoul National University Hospital, Seoul, South Korea; [7]START Madrid CIOCC Hospital Madrid Norte Sanchinarro, Madrid, Spain; [8]Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD, USA; [9]Dana Farber Cancer Institute, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston, MA, USA; [10]Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [13]Bristol-Myers Squibb, Lawrence, NJ, USA; [14]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA and Sarah Cannon Research Institute, Nashville, TN, USA

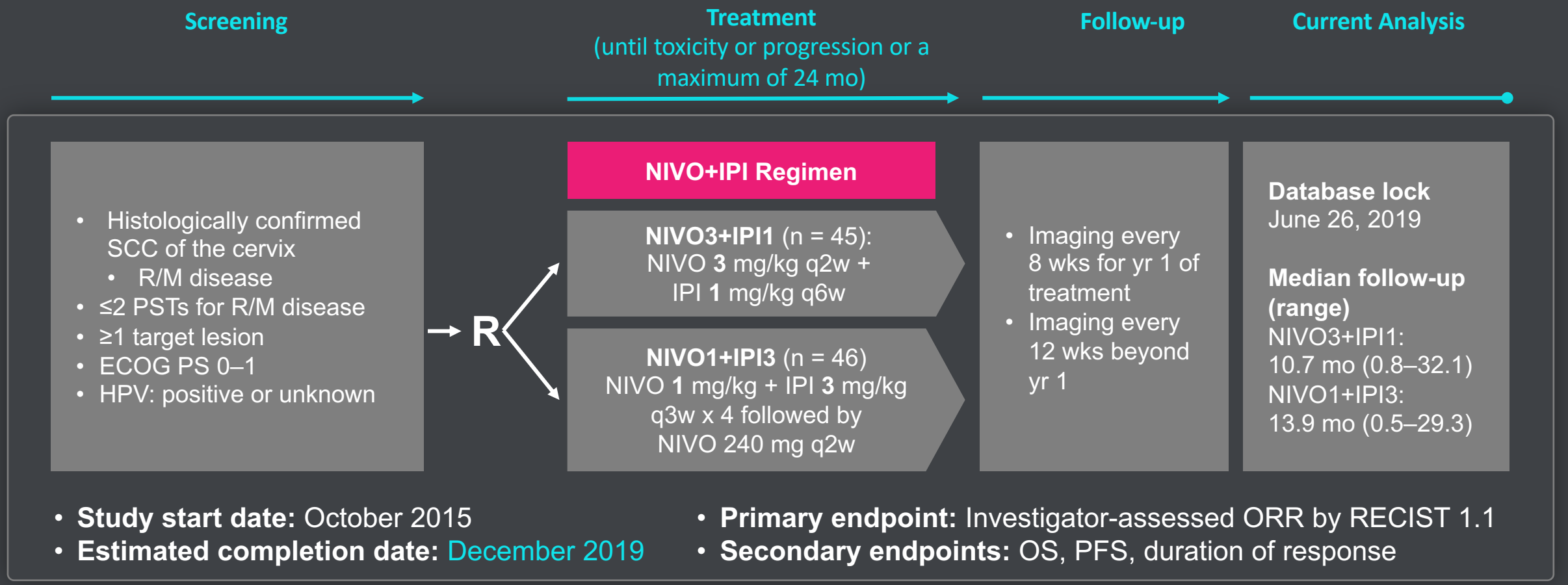
 * Colead authors

Abstract Number 5630

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Study Design and Current Analysis

Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease



- **Study start date:** October 2015
- **Estimated completion date:** December 2019
- **Primary endpoint:** Investigator-assessed ORR by RECIST 1.1
- **Secondary endpoints:** OS, PFS, duration of response

ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival; PS, performance status; PST, prior systemic therapy; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; SCC, squamous cell carcinoma.

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Patient Characteristics

Baseline characteristics	NIVO3+IPI1 (n = 45)	NIVO1+IPI3 (n = 46)
Age, median (range), y	48.0 (32–76)	44.5 (26–74)
ECOG PS, n (%)		
0	23 (51.1)	26 (56.5)
1	22 (48.9)	20 (43.5)
AJCC stage, n (%)		
II (A–B)	3 (6.6)	0 (0.0)
III (A–C)	1 (2.2)	8 (17.4)
IV (A–B)	41 (91.1)	38 (82.6)
Tumor cell PD-L1 expression, [*†] n (%)		
Evaluable	37 (82.2)	34 (73.9)
≥1%	23 (62.2)	23 (67.6)
<1%	14 (37.8)	11 (32.4)
Not evaluable/not reported	8 (17.8)	12 (26.0)

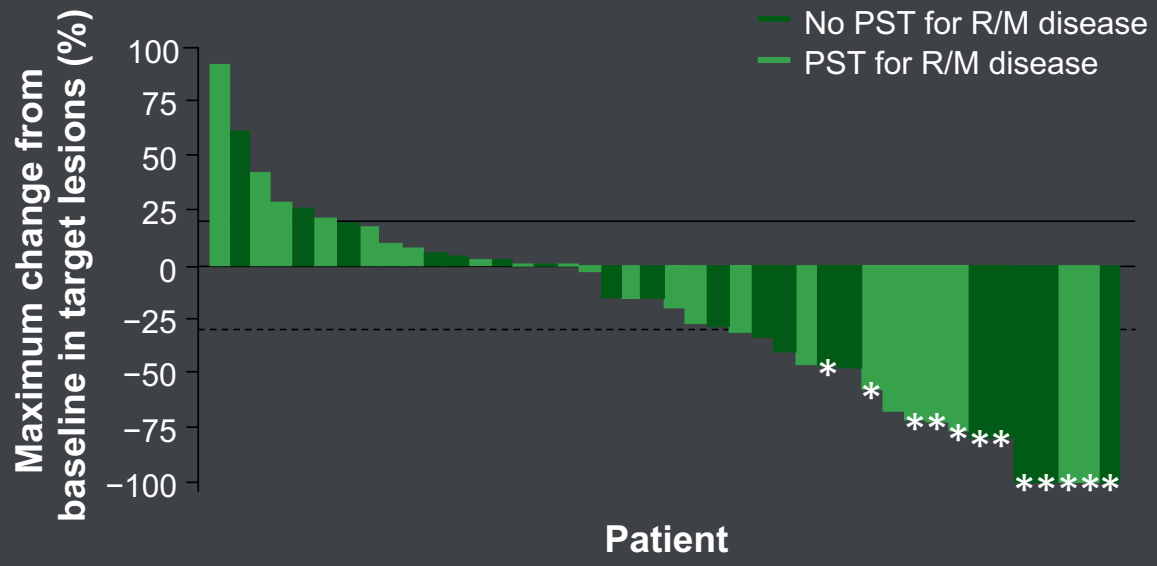
Prior therapies	NIVO3+IPI1 (n = 45)	NIVO1+IPI3 (n = 46)
Prior therapy, n (%)		
Platinum	39 (86.7)	42 (91.3)
Bevacizumab	24 (53.3)	25 (54.3)
Prior radiotherapy, n (%)	38 (84.4)	39 (84.8)
Prior systemic therapy in the R/M setting, n (%)		
0	19 (42.2)	24 (52.2)
≥1	26 (57.8)	22 (47.8)

Prior systemic therapy (PST) in the recurrent/metastatic (R/M) setting

[*] Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity. [†] Assessed in pretreatment (archival or fresh) tumor biopsy specimens with the use of a validated, automated immunohistochemical assay using the rabbit antihuman PD-L1 clone 28-8 (Phillips T, et al. *Appl Immunohistochem Mol Morphol* 2015;23:541-549).
AJCC, American Joint Committee on Cancer.

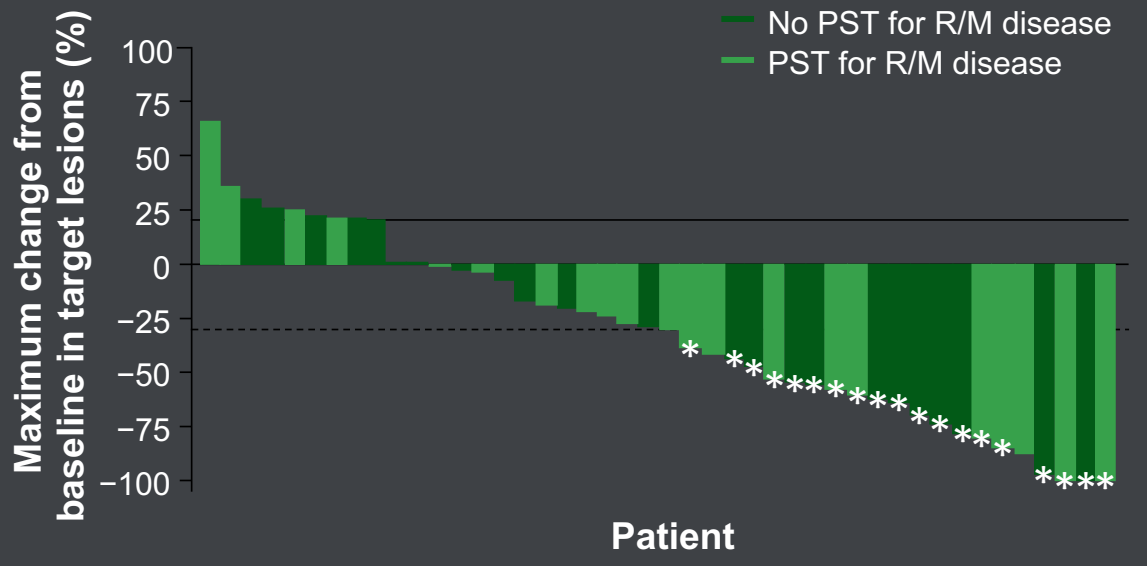
Change from Baseline in Target Lesion Size

NIVO3+IPI1



ORR 23.1% (9.0–43.6) PST for R/M disease

NIVO1+IPI3



ORR 36.4% (17.2–59.3) PST for R/M disease

Bars with asterisks represent confirmed responses (complete or partial response).
PST, prior systemic therapy.

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Complete Response to Treatment with Nivolumab + Ipilimumab



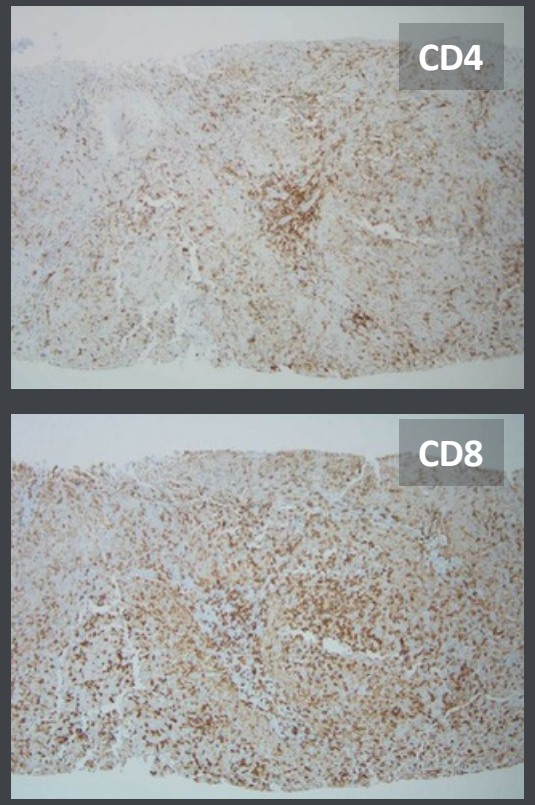
42-year-old woman with recurrent stage IIA (with lung metastases) HPV positive SCC of the cervix; ECOG PS 1; tumor cell PD-L1 <1%

Before CheckMate 358

- First diagnosed with localized disease January 2016
- Prior therapies
  - WPRT + cisplatin
  - HDRB, completed April 2016
  - Carboplatin + paclitaxel + bevacizumab, completed January 2017
    - Documented disease progression

CheckMate 358

- Treated with NIVO3+IPI1
- Complete response; time to response: 7.7 mo
- Biopsy at wk 7 showed only necrosis
- Stopped treatment after 2 years
- No evidence of disease as of August 2019 (7 mo post-treatment completion)



Biopsy (wk 7) showing extensive infiltration of CD8 cells with a high CD8/CD4 ratio

All images provided by Dr Naumann, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA.
HDRB, high dose rate brachytherapy; SCC, squamous cell carcinoma; WPRT, whole pelvic radiotherapy.

CheckMate 358 Safety Summary

Event, n (%)	NIVO3+IPI1 (n = 45)		NIVO1+IPI3 (n = 46)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs	36 (80.0)	13 (28.9)	38 (82.6)	17 (37.0)
Treatment-related SAEs	12 (26.7)	8 (17.8)	16 (34.8)	10 (21.7)
TRAEs leading to treatment discontinuation	6 (13.3)	2 (4.4)	9 (19.6)	6 (13.0)
Treatment-related SAEs leading to treatment discontinuation	2 (4.4)	1 (2.2)	5 (10.9)	5 (10.9)

- No new safety signals
- Higher incidence of TRAEs and treatment-related SAEs leading to treatment discontinuation in NIVO1+IPI3 compared with NIVO3+IPI1
- No treatment-related deaths

SAE, serious adverse event; TRAE, treatment-related adverse event.

CheckMate 358 TRAEs with Incidence ≥5%*

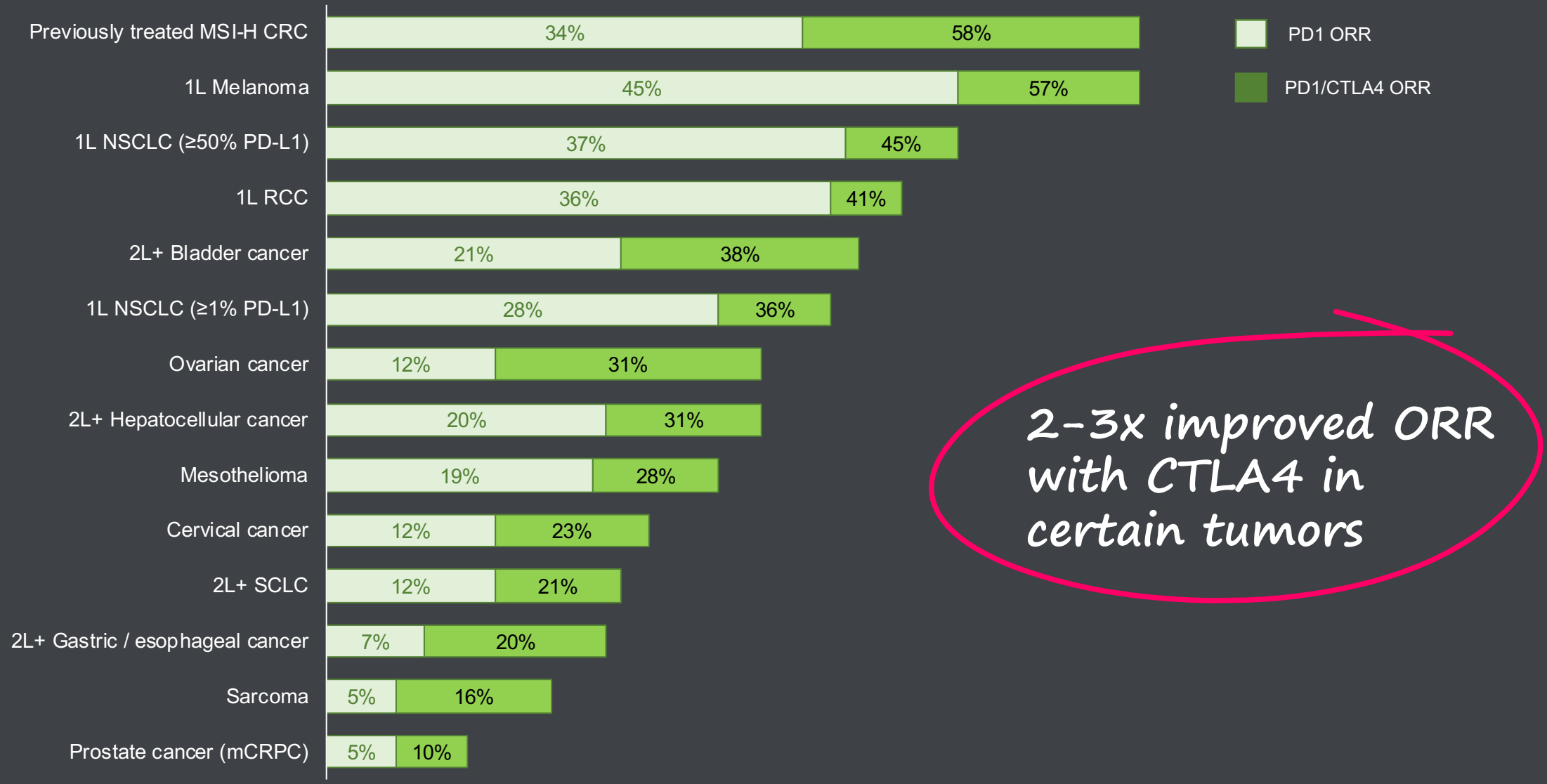
	NIVO3+IPI1 (n = 45)		NIVO1+IPI3 (n = 46)	
TRAEs, by SOC, n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4
General/administration site	17 (37.8)	0	20 (43.5)	0
Gastrointestinal	16 (35.6)	4 (8.9)	26 (56.5)	6 (13.0)
Skin	16 (35.6)	0	16 (34.8)	2 (4.3)
Laboratory investigations	15 (33.3)	5 (11.1)	17 (37.0)	9 (19.6)
Endocrine	13 (28.9)	2 (4.4)	20 (43.5)	0
Pulmonary	6 (13.3)	1 (2.2)	6 (13.0)	1 (2.2)
Metabolism	5 (11.1)	1 (2.2)	5 (10.9)	0
Nervous system	4 (8.9)	0	6 (13.0)	0
Musculoskeletal	2 (4.4)	1 (2.2)	9 (19.6)	0
Hepatobiliary	2 (4.4)	2 (4.4)	3 (6.5)	2 (4.3)

- Higher incidence of treatment-related gastrointestinal events in NIVO1+IPI3 compared with NIVO3+IPI1; this could be due to higher ipilimumab dose
- Of the 6 patients with grade 3–4 treatment-related gastrointestinal events, colitis was reported in 4 patients, and diarrhea, nausea, vomiting, and gastritis were reported in 1 patient each

*TRAEs with incidence <5% included the following SOCs: blood, cardiac, ear, eye, infections, injury, psychiatric, renal, reproductive system/breast, and vascular.
SOC, system organ class.

Why CTLA-4 and PD-1 have Best-in-Class Potential

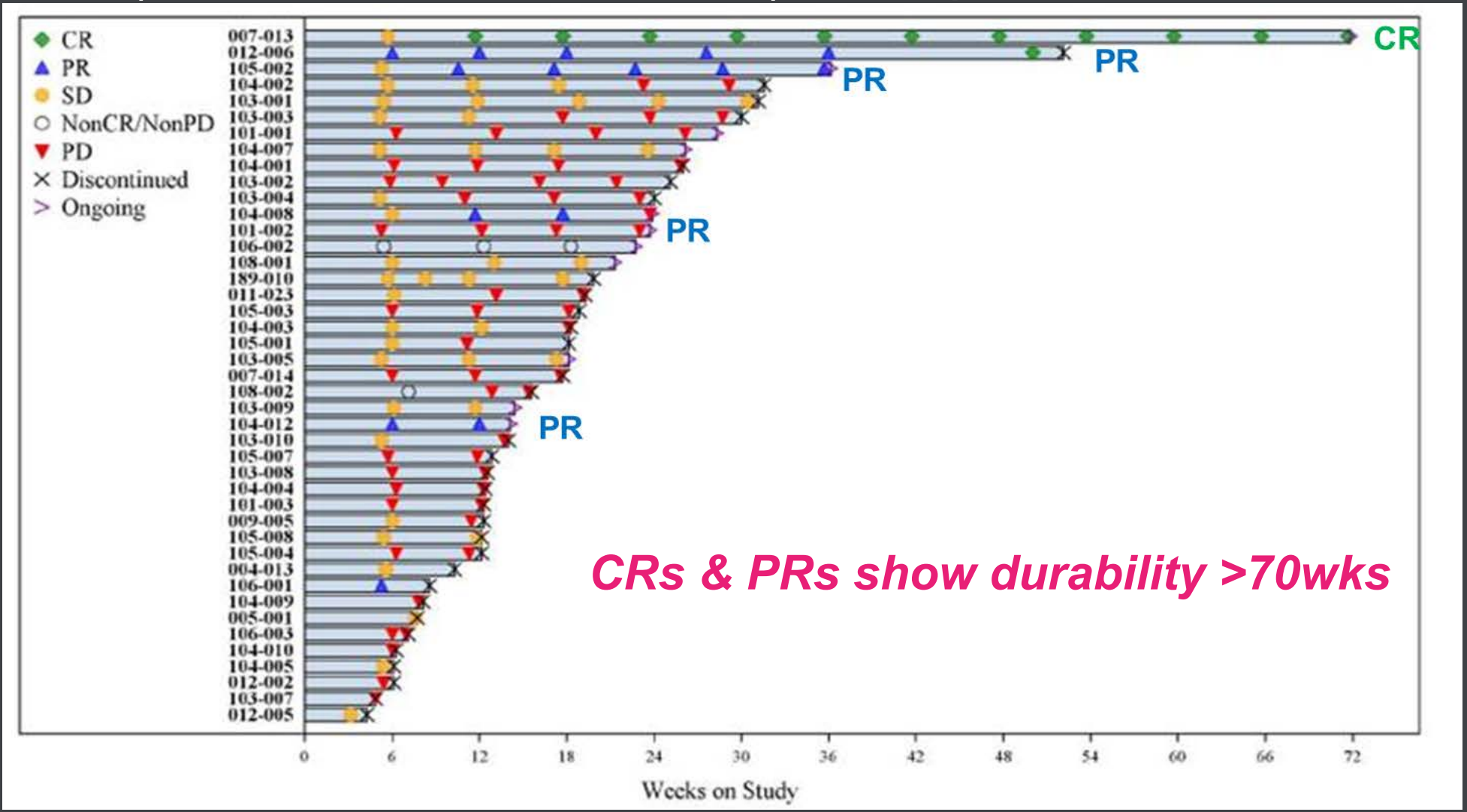
CTLA-4 Improves PD-1 Responses & Durability in Multiple Tumors



2-3x improved ORR with CTLA4 in certain tumors

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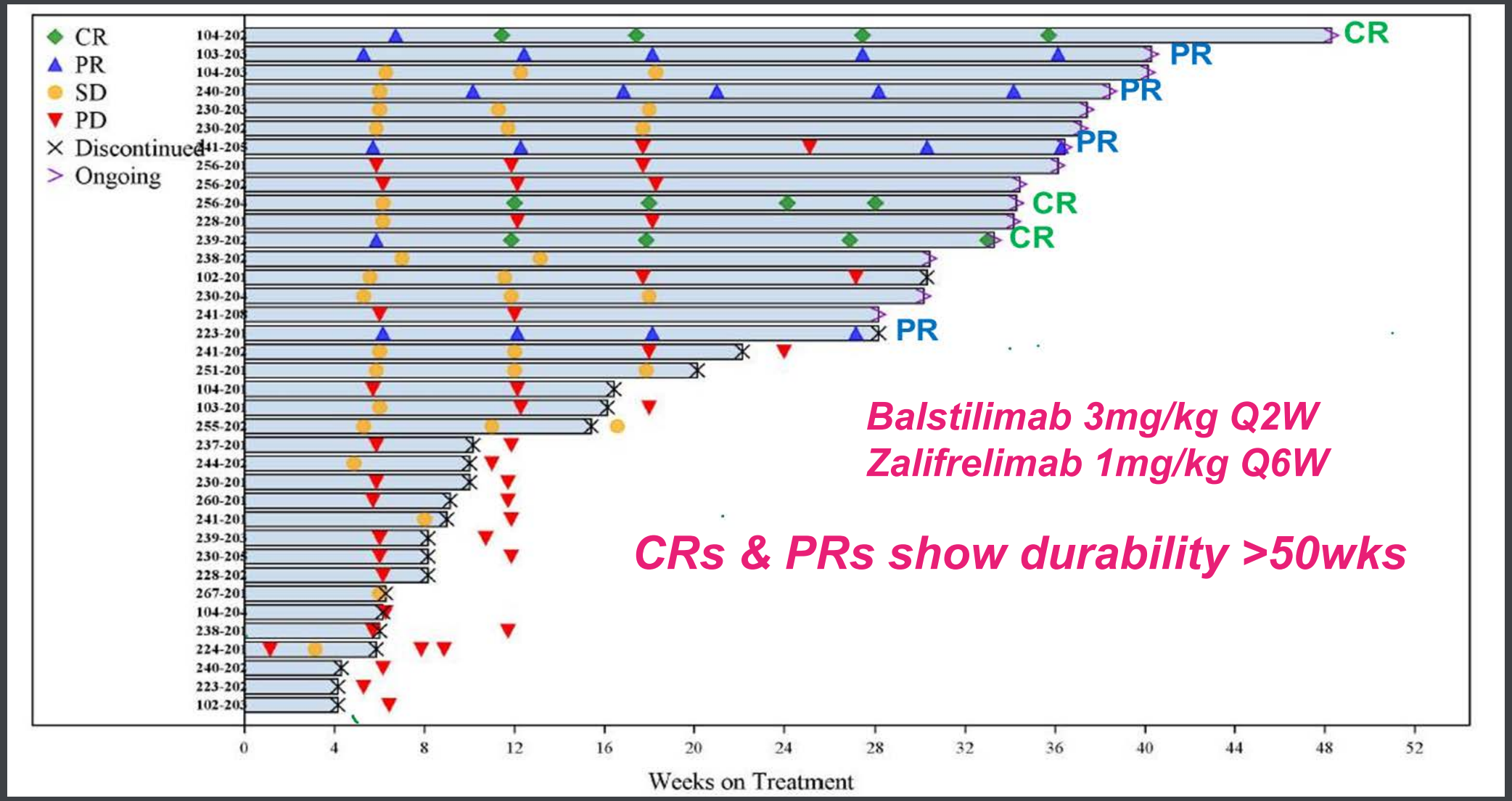
Balstilimab (anti-PD-1) Alone is Active and Durable in 2L Cervical Cancer (11.9% ORR;1 CR, 4 PRs)*, Independent Reads



*Agenus data: C-700-01 interim analysis data cut off 16 Oct 2019. Estimates for efficacy set (n=42) – all patients with measurable disease at baseline dosed as of 15 Jul 2019.
Notes: Plot shows all patients with on-study tumor assessments at the time of interim analysis including patients without measurable disease. 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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Balstilimab (anti-PD-1) + Zalifrelimab (anti-CTLA-4) may be a Best-in-Class Option in 2L Cervical Cancer (20.6% ORR, 3 CR, 4PR)*, Independent Reads



*Agenus data: C-550-01 interim analysis data cut off 12 Jul 2019 with 1 Nov 2019 update on patients with response. Estimates for efficacy set (n=34) – all patients with measurable disease at baseline dosed as of 31 Mar 2019. Notes: Plot shows all patients with on-study tumor assessments at the time of interim analysis including patients without measurable disease. 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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Balstilimab (anti-PD-1) plus zalifrelimab (anti-CTLA-4) may be the most promising & clinically advanced off-the-shelf treatment option with an acceptable safety profile

Sponsor	Agent	# of Patients	ORR	CR	PR	Related AEs (Grade 3+)
Agenus	Balstilimab*	42	14.3%	2.4%	11.9%	9.1%
Merck	Pembrolizumab***	98	12.2%	3.1%	9.2%	12.2%
Agenus	Balstilimab + Zalifrelimab*	34	26.5%	11.8%	14.7%	14.6%
BMS	Ipilimumab + Nivolumab	26	23.1%	3.8%	19.2%	28.9%
Seattle Genetics / Genmab	Tisotumab vedotin	55	22%	2%	20%	56%**
Iovance	LN-145	27	44.4%	11.1%	33.3%	96.3%**

*Data from pre-planned interim analysis; ** Sponsor reported as Treatment-Emergent Adverse Events; ***Chung, HC, et al. 2019. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 37(17):1470-1478. Data presented for full population (no biomarker restrictions for comparison).

Addition to original presentation: UPDATED DATA APR2020

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Agenus CTLA-4 & PD-1 Potential Best-in-Class Option for 2L Cervical Cancer

Sponsor	Treatment	# of Patients	Complete Response	Partial Response	Overall Response Rate
Combination of PD-1 and CTLA-4					
Agenus	Balstilimab + Zalifrelimab*	34	8.8%	11.8%	20.6%
BMS	Ipilimumab + Nivolumab[1]	26	3.8%	19.2%	23.1%
PD-1 Monotherapy					
Agenus	Balstilimab **	42	2.4%	9.5%	11.9%
Merck	Pembrolizumab[2]	98	2.6%	11.7%	14.3%

*Agenus data: C-550-01, Interim analysis data cut off 12 July 2019, n=34, efficacy set (patients with measurable disease at baseline); ** Agenus data: C-700-01, Interim analysis data cut off 16 Oct 2019, n=42, efficacy set (patients with measurable disease at baseline); [1]Naumann RW et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934; [2]Chung HC et al., J Clin Oncol. 2019 Jun 10;37(17):1470-1478

Corrected Slide

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Clinical Benefit with Tolerability in 2L Cervical Cancer Studies with Balstilimab (anti-PD-1) and Zalifrelimab (anti-CTLA-4)

	Balstilimab*+ Zalifrelimab (N=41)	Balstilimab** (N=44)
Serious on-treatment AEs, n (%) [#AEs]	15 (36.6%) [24]	22 (50.0%) [44]
Grade 3+ on-treatment Adverse Events, n (%) [#AEs]	18 (43.9%) [36]	25 (56.8%) [84]
Any on-treatment AEs leading to discontinuation	1 (2.4%) [1]	2 (4.5) [2]
Immune-related on-treatment by investigator, n (%) n (%) [#AEs]	18 (43.9%) [47]	10 (22.7%) [16]

On treatment AEs: AEs occurring after study treatment initiation, and within 30/90 days of study drug discontinuation
*C-550-01, Interim analysis data cur 12 July 2019
**C-700-01, interim analysis data cut 16 October 2019

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Conclusions

1. Recurrent cervical cancer is an area of high unmet need
2. Accelerated approval from small single arm clinical trials is established as a pathway to the clinic
3. Anti PD-L1 has activity (ORR) between 10-15%
    a) Including Balstilimab
4. Adding anti CTLA-4 to anti PD-L1 increases clinical activity with acceptable safety
    a) Including Zalifrelimab to Balstilimab
5. I believe that accelerated approval of Balstilimab alone and Balstilimab + Zalifrelimab in those with PST for R/M cervical cancer is likely

WE AIM TO HAVE CANCER PATIENTS LIVING LONGER AND BETTER

Anna Wijatyk, MD
Head of Clinical Development

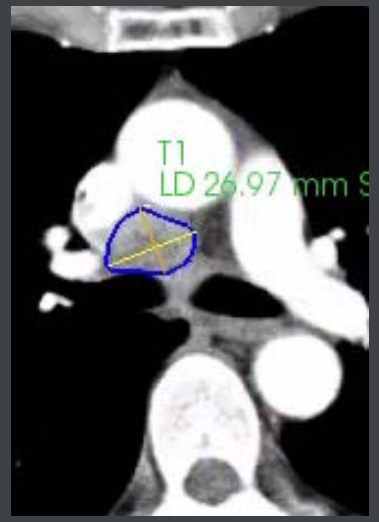
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On Track to Deliver 2 BLAs: Balstilimab & Zalifrelimab

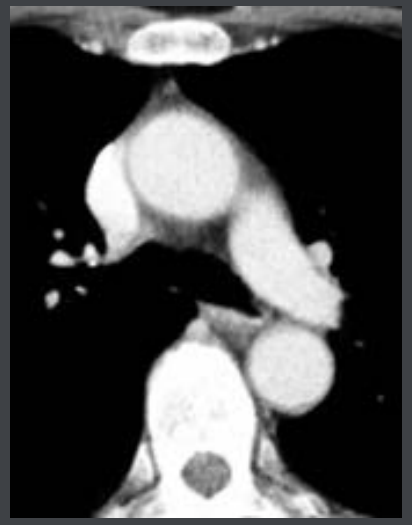
Balstilimab (PD-1) Monotherapy Complete Response Case

Patient #1 – Continuing on treatment since May 2018

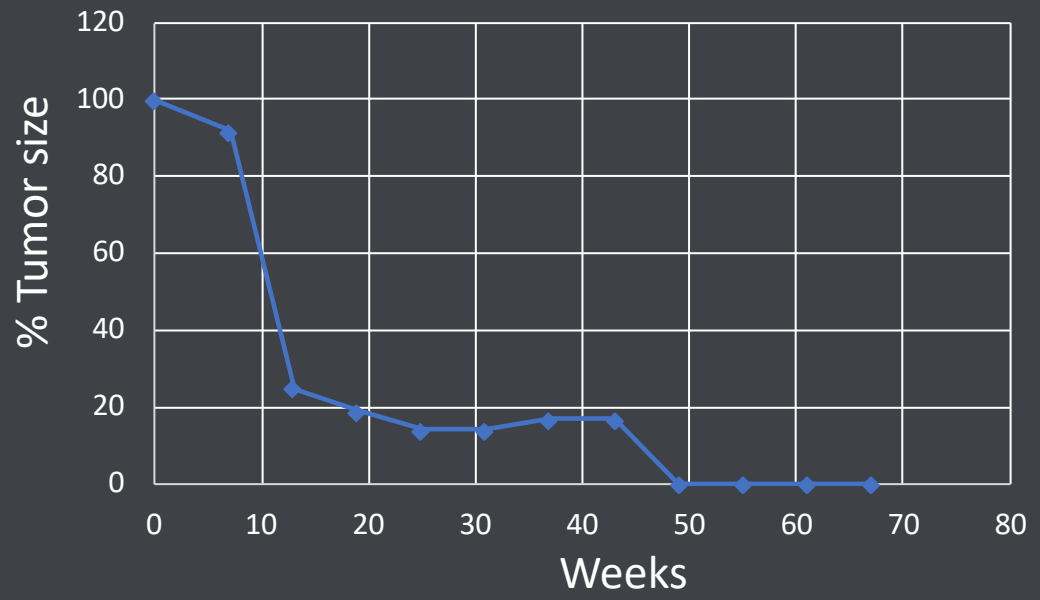
Independent review



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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Combination Balstilimab (PD-1) & Zalifrelimab (CTLA-4)

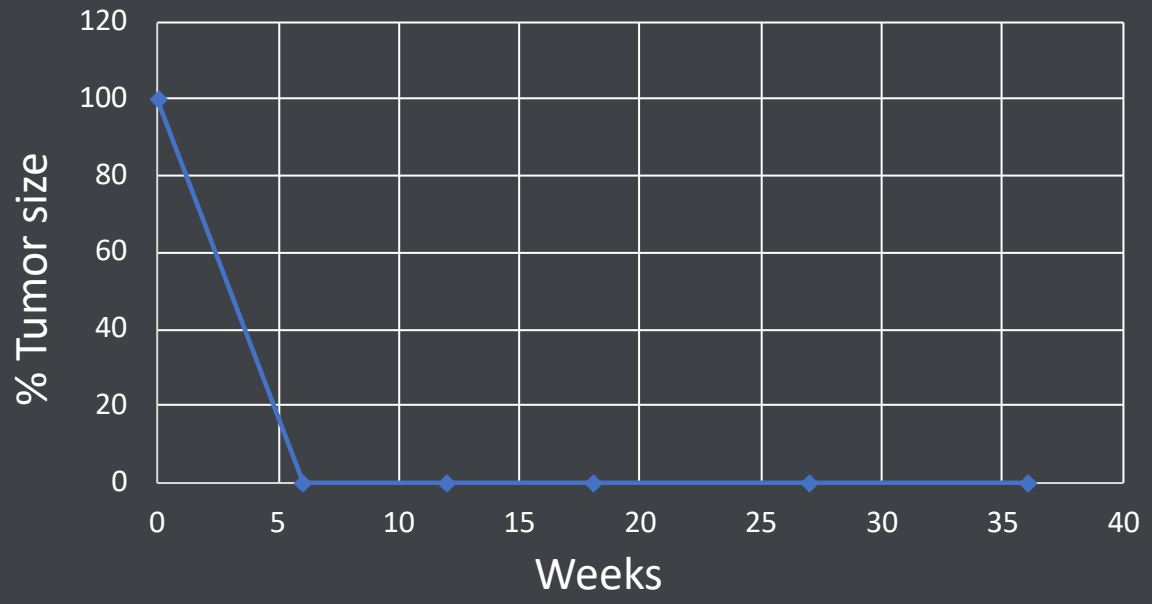
Complete Response (Overall 3 CRs; 4 PRs)



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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Clinical Development and Operations

2 Interim Analyses
Pivotal Trial Analysis Underway

~300 Patients Treated

8 Studies Open

25 Countries
120 Sites

54 Agenus Team Members

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Deliver Clinical Data on Multiple Discoveries

Balstilimab

Balstilimab + Zalifrelimab

AGEN1181

AGEN1223

AGEN2373

New Discoveries to Patients with Path-breaking Speed

IND Cleared → Sites Activated → Patients Dosed

Industry Standard: 168 days

Agenus timelines - 65 Days

Speed to clinic, speed to patients, speed to market

Agenus

Jennifer Buell, PhD
President and COO

Agenus Discoveries In The Clinic

	Agenus	Partners
Commercial		QS-21 (SHINGRIX)[1]
Pivotal (Planned BLA 2020)	Balstilimab (PD-1) Balstilimab + Zalifrelimab (CTLA-4)	
Phase 1/2	AGEN1181 AGEN1223* AGEN2373*	GS-1423 MK-4830 INCAGN1876 INCAGN1949 INCAGN2390 INCAGN2385

*Option programs w GILD

More detailed information available in Agenus SEC and 10k filings

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



NewYork-Presbyterian

COLUMBIA | COLUMBIA UNIVERSITY HERBERT IRVING COMPREHENSIVE CANCER CENTER

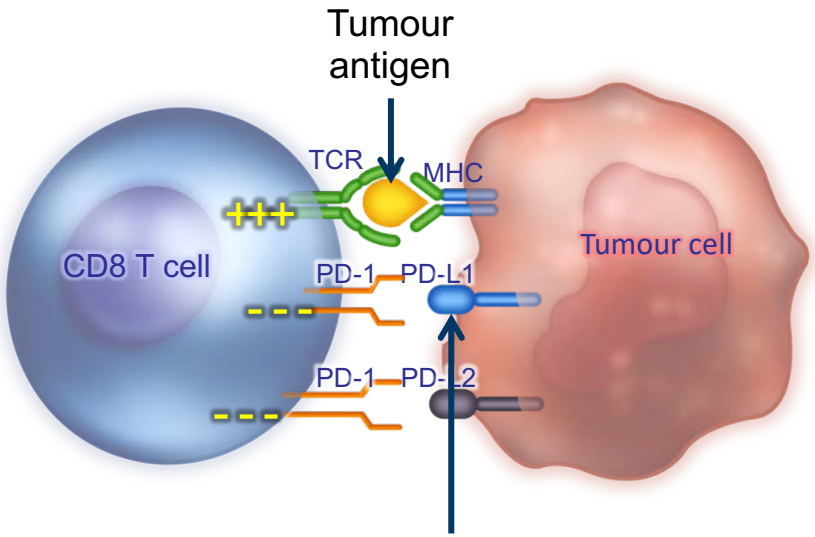
Dr. Charles Drake

MD, PhD

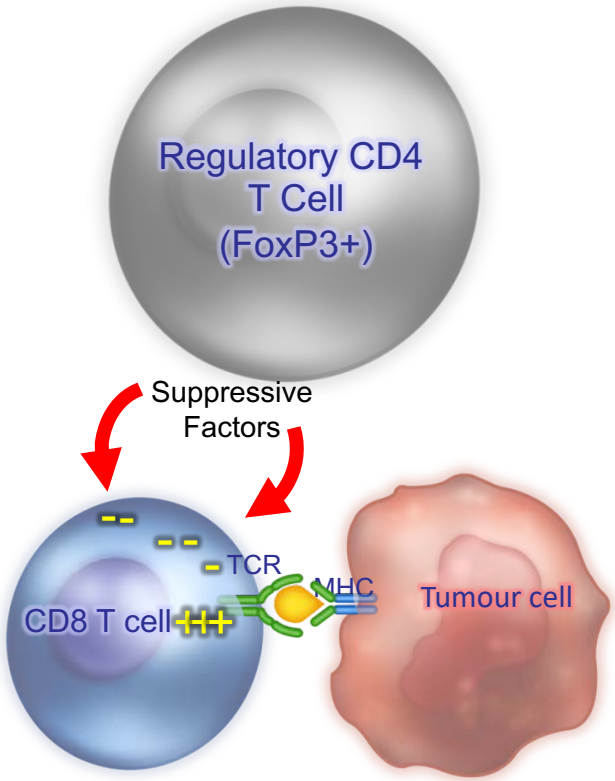
- Professor of Medicine
- Co-Director, Cancer Immunotherapy Programs
- Co-Leader, Tumor Biology and Microenvironment
- Faculty Director – Human Immune Monitoring Core
- Division Director – GU Oncology

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Regulatory T Cells (Treg) Are Prevalent in the Tumor Microenvironment

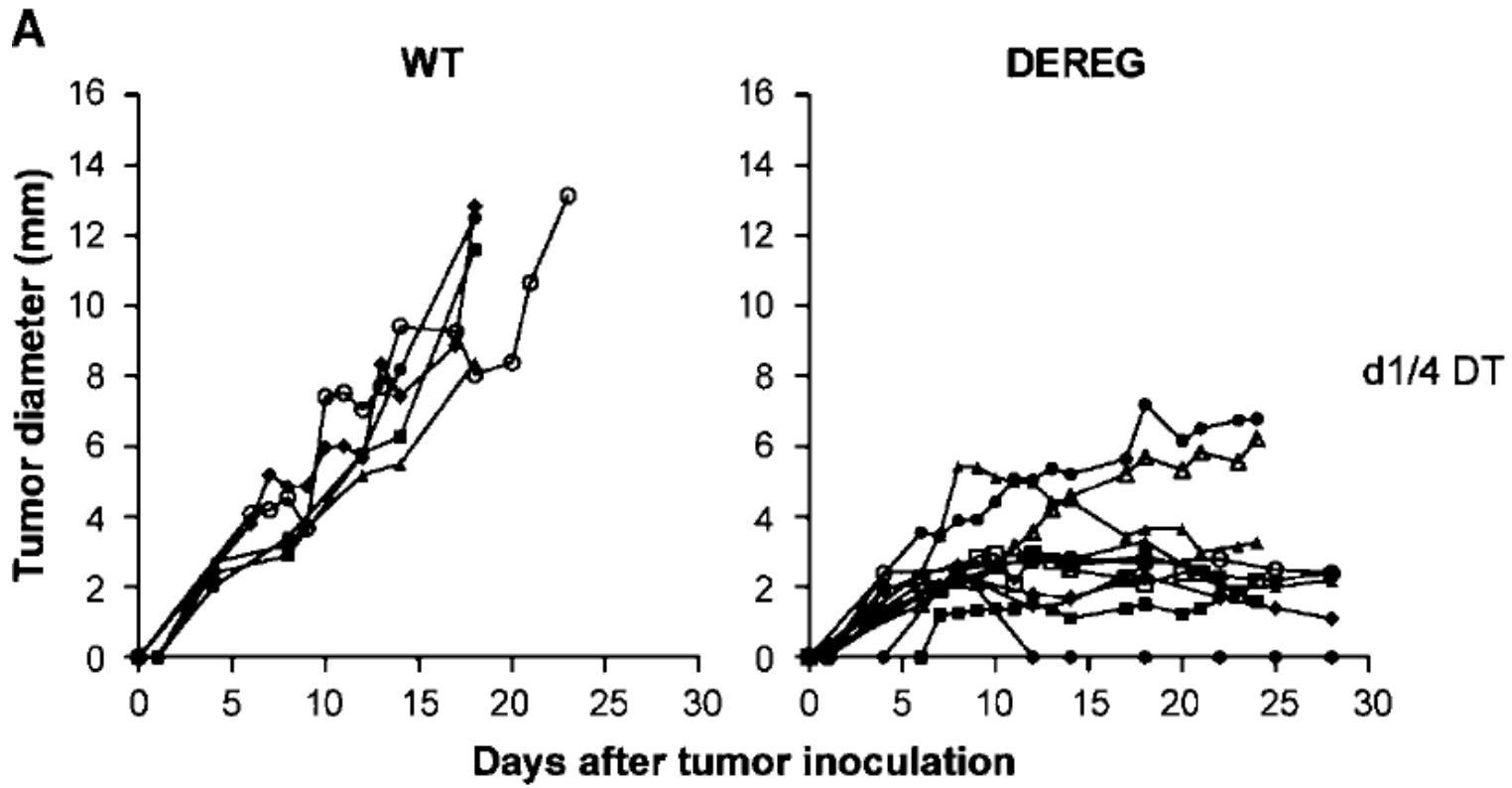


PD-L1 expression on tumor cells
OR
Myeloid cells SEND a negative signal



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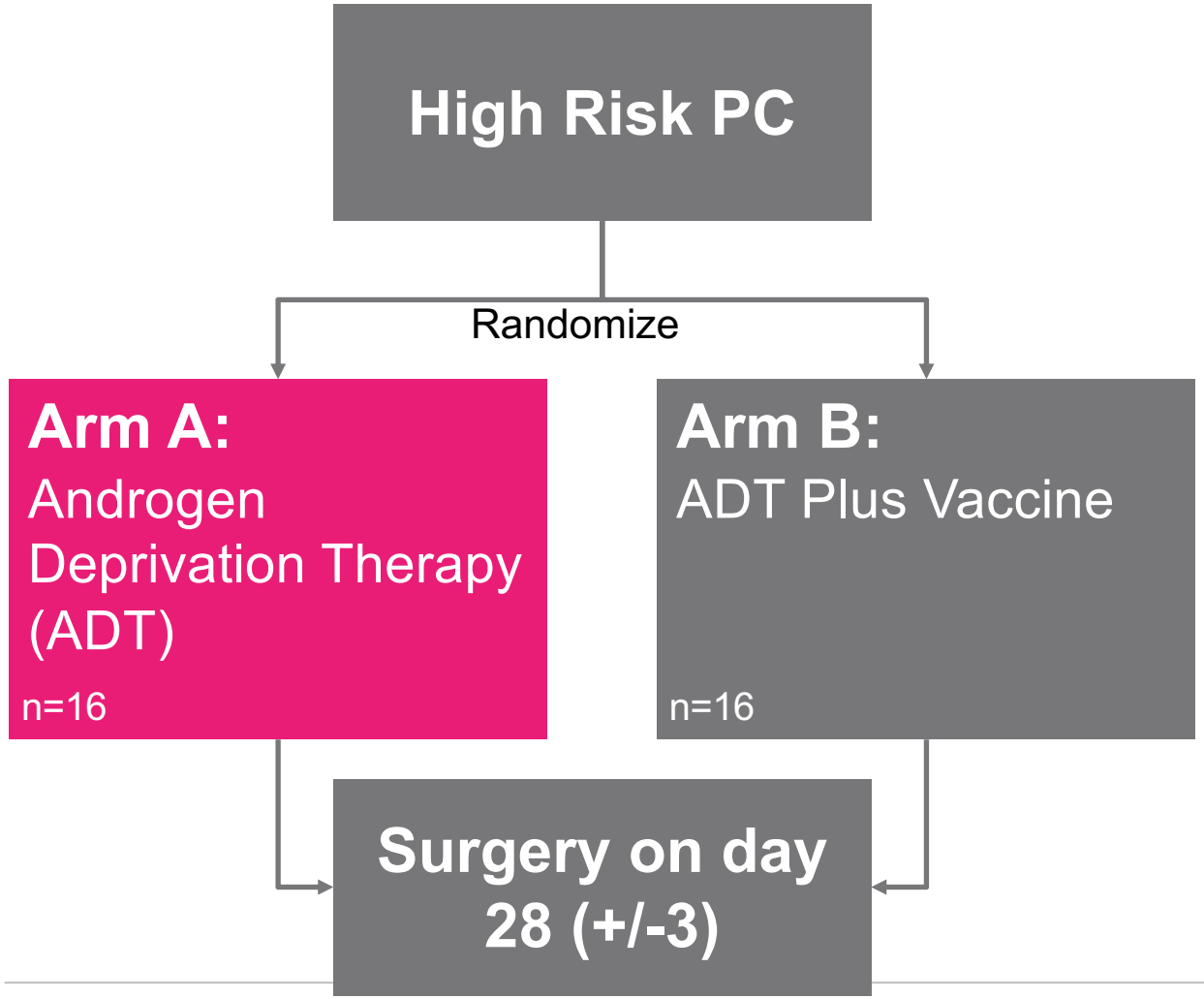
Targeted Treg Depletion Treats Cold Tumors (in mice)



Klages K., et al, *Cancer Research* 2010

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Can a Cancer Vaccine Make A Cold Tumor Hot?
GVAX Vaccine in Prostate Cancer



Endpoints

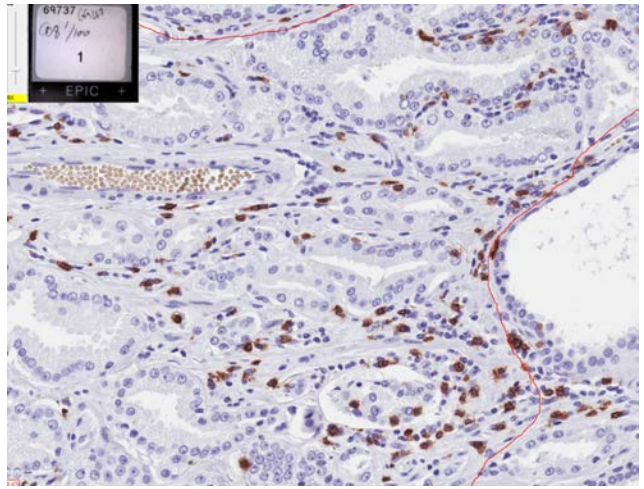
Safety / Tolerability

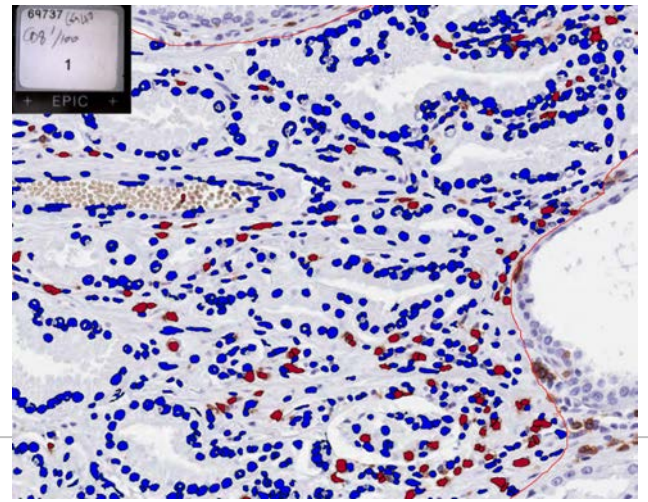
T Cell infiltration of prostate gland

Profile the Tumor Microenvironment Post-Treatment

Charles Drake, Emmanuel Antonarakis, Ashley Ross, Ted Schaeffer, Alan Partin

In Human Prostate Cancer
Increased CD8 Infiltration is Balanced by Treg Influx
Adaptive Treg Resistance



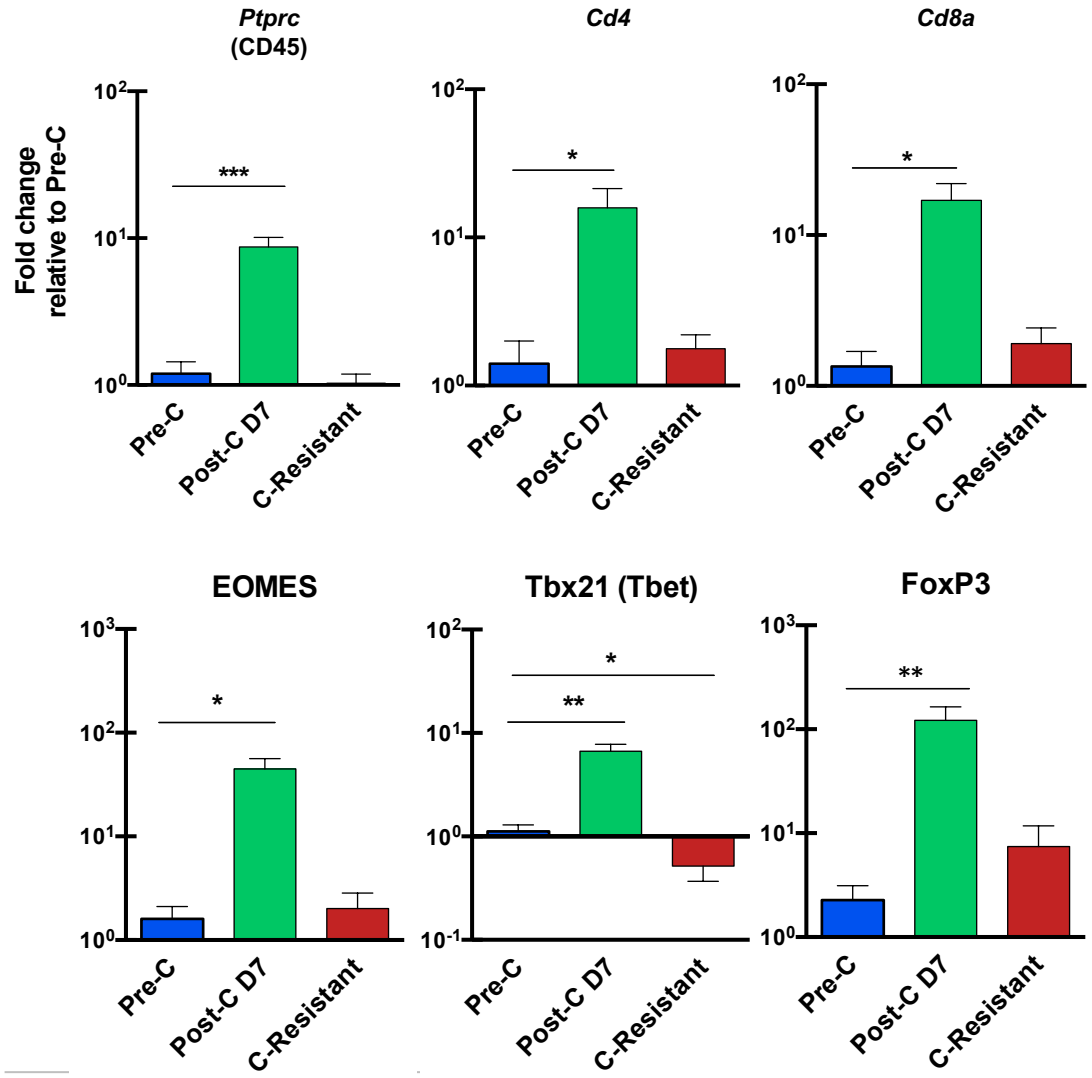


	Untreated Control N = 13	Androgen Deprivation Therapy *N=15*	Androgen Deprivation PLUS Vaccine N=13
CD8+ T cell density (mean, 95%CI)	96 (72–120)	205 (121–289)	263 (129–397)
Treg cell density (mean, 95%CI)	29 (21–36)	59 (34–85)	78 (48–107)
CD8+ / Treg ratio (mean, 95%CI)	3.7 (2.9–4.6%)	4.0 (2.7–5.3%)	3.9 (2.2–5.7%)

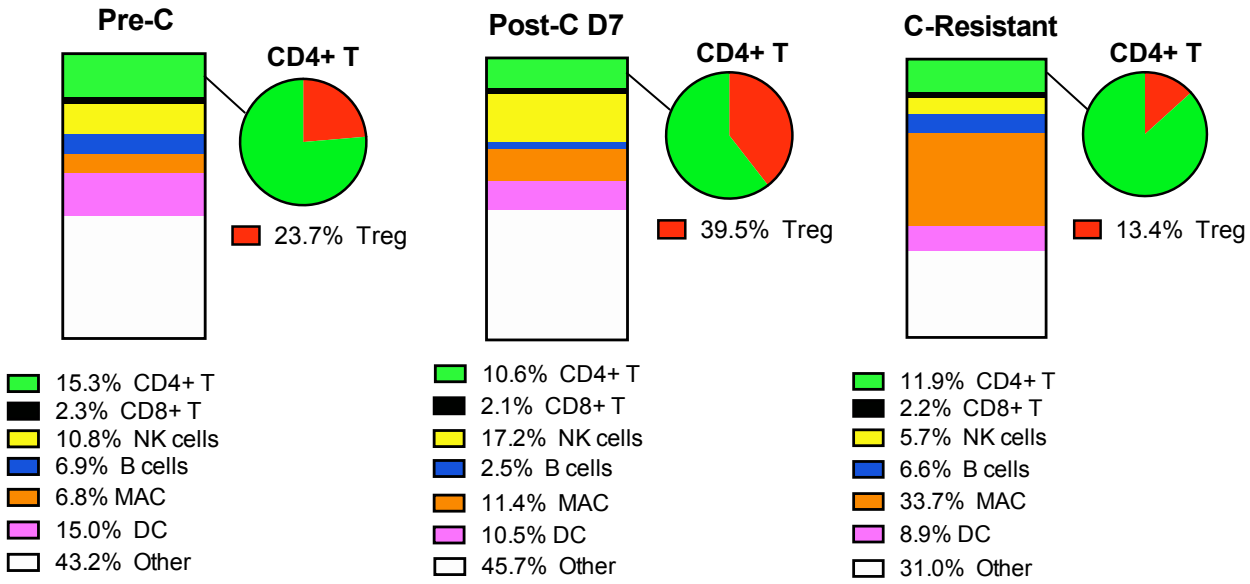
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Obradovic, Dallos, Drake et al in review

In Murine Prostate Cancer Increased CD8 Infiltration is Balanced by Treg Influx



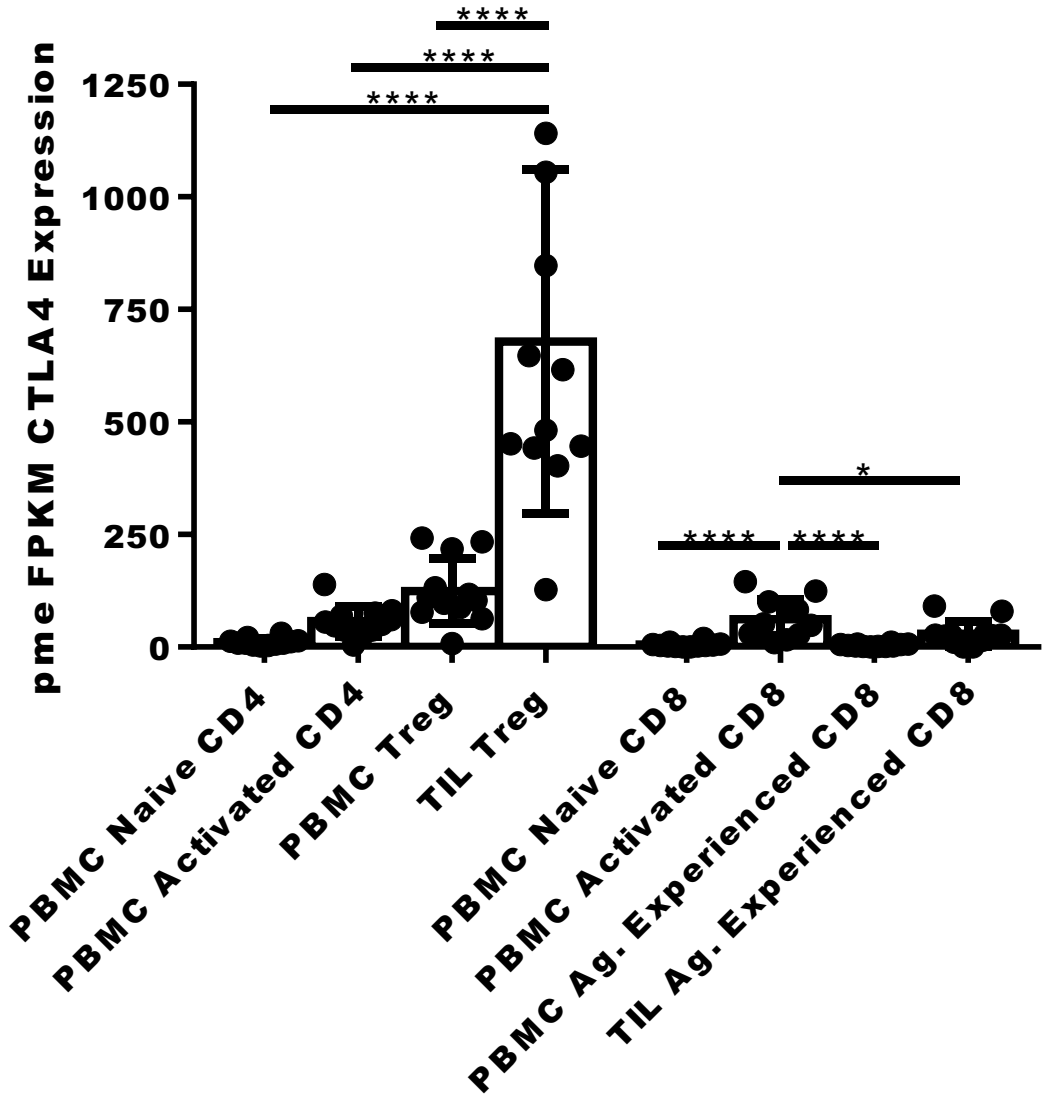
Adaptive Treg Resistance



Shen and Drake *Prostate Cancer Neoplastic Disease* 2017

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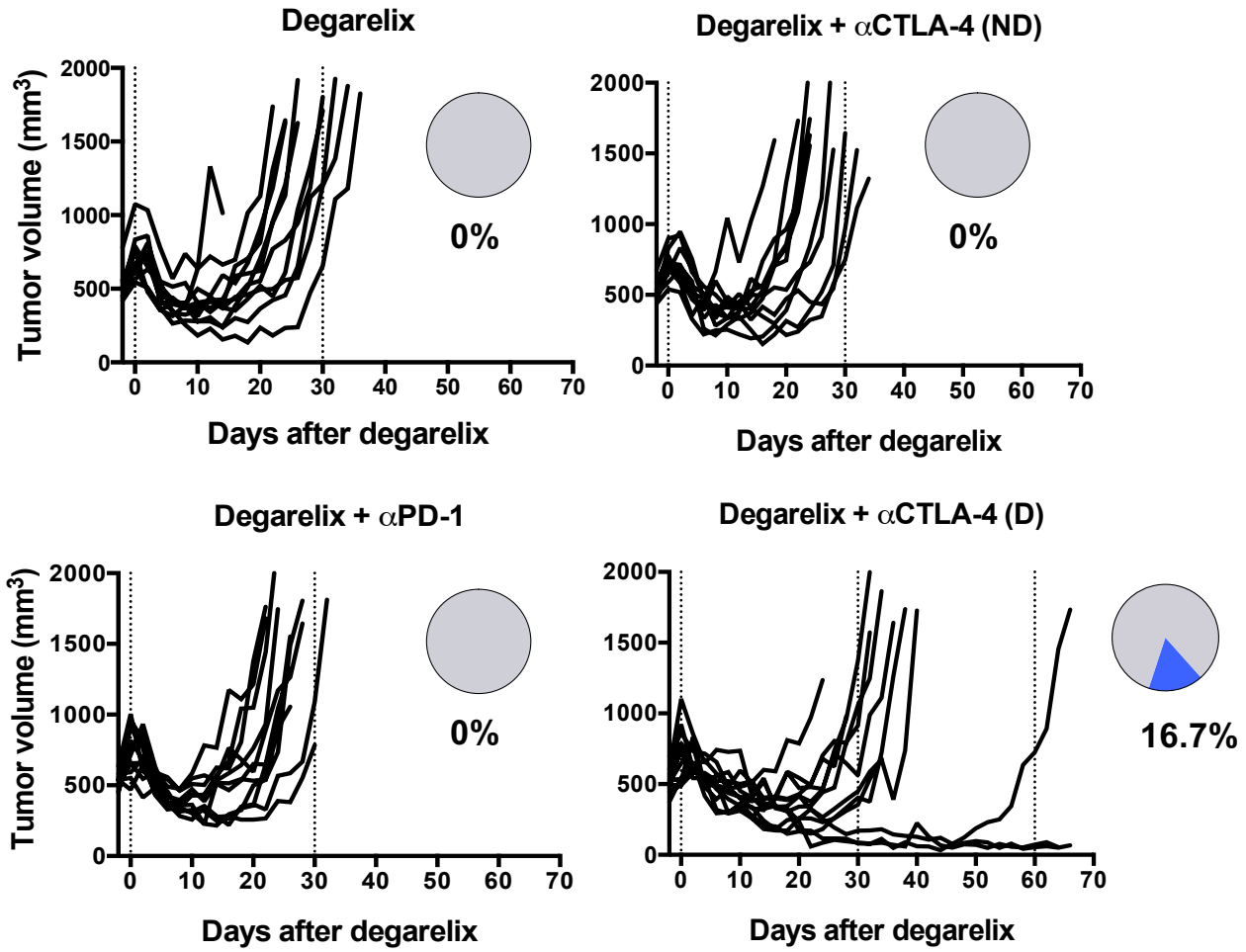
CTLA-4 Is Highly Expressed on The Treg That Infiltrate Cancer



Nirschl T and Drake C
In Preparation

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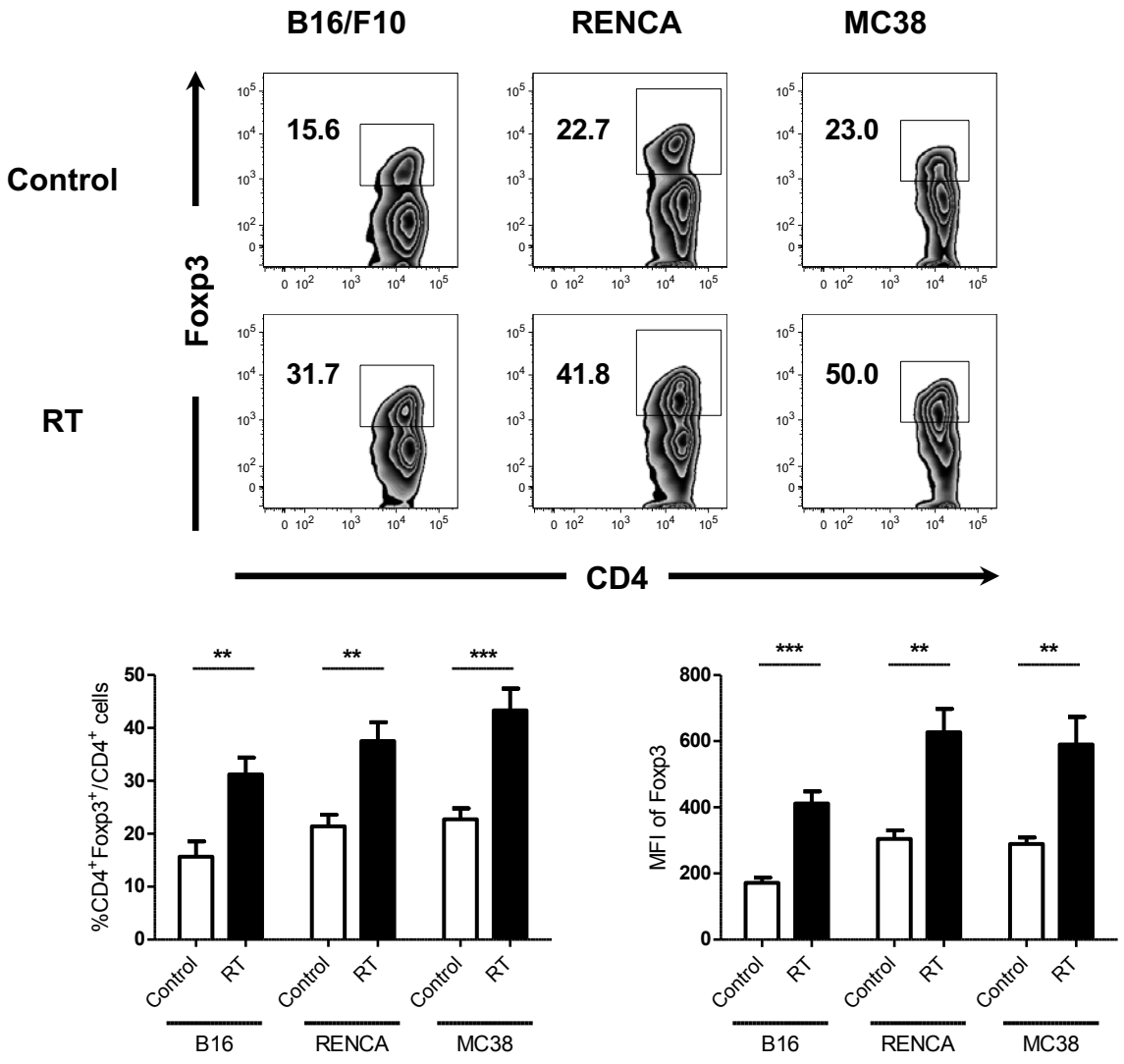
A Depleting Anti-CTLA-4 (IgG2a) Cures a Fraction of Mice with Prostate Cancer



 Shen and Drake *Prostate Cancer Neoplastic Disease* 2017

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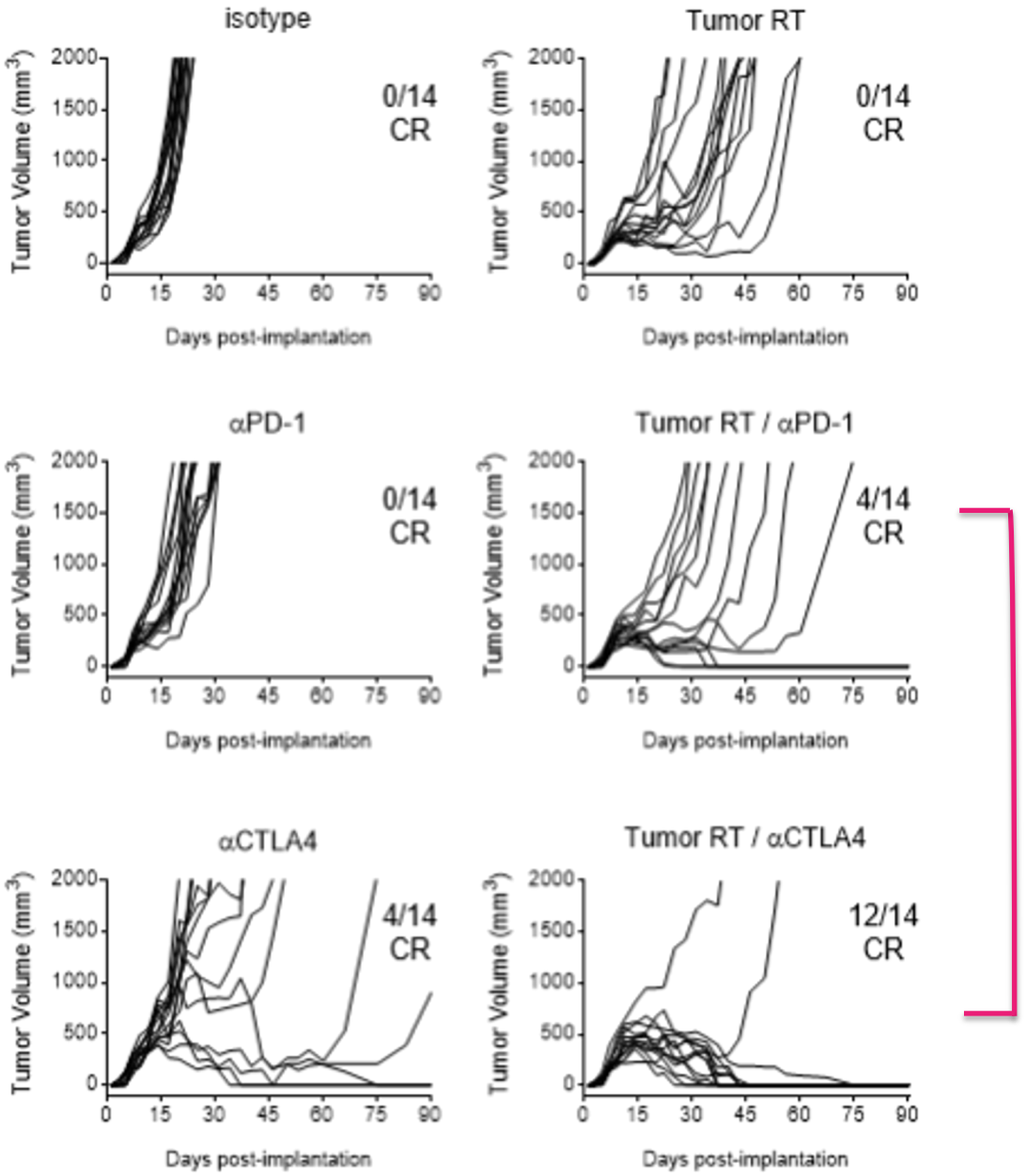
Radiation Therapy Drives Adaptive Treg Resistance



 Muroyama, **Ghasemzadeh**, Drake *Cancer Immunology Research, 2017*

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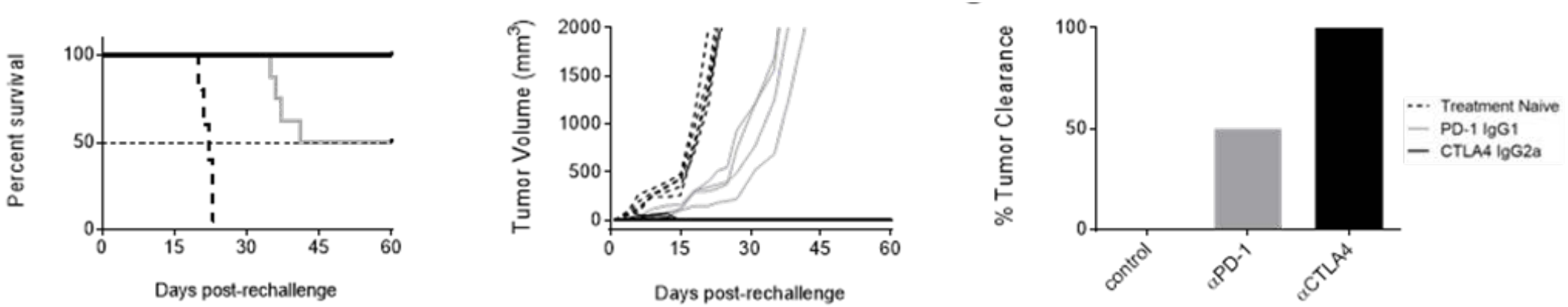
A Depleting αCTLA-4 Plus Radiation Cures The Majority Of Treated Animals



Marisciano, Drake et al *Clinical Cancer Res* 2018

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100% of RT + αCTLA-4 Cured Mice Show Long-Term Protection



Not the Case for RT + αPD-1

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Selected αCTLA-4 Agents in the Clinic

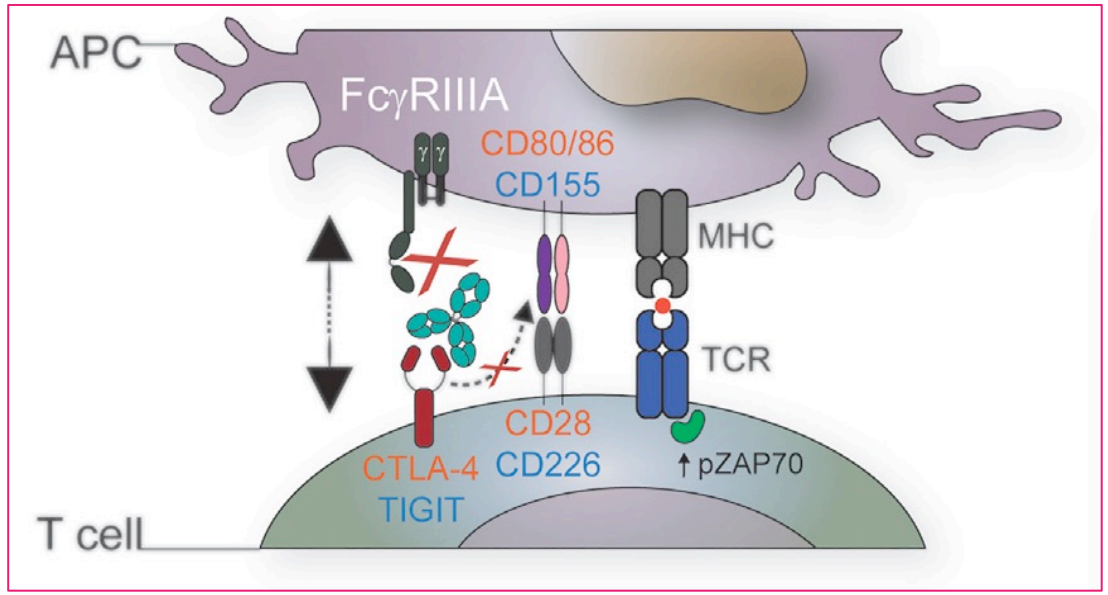
	Ipilimumab	Tremilimumab	BMS 928218	MK 1308
IgG Isotype	IgG1	IgG2	Afucosylated IgG1	Not Reported
Treg Depletion	+/-	No	Not Reported	Not Reported
Grade III / IV IRAE	≈25%	≈15%	Not Reported	Not Reported

Optimized αCTLA-4 Product Profile

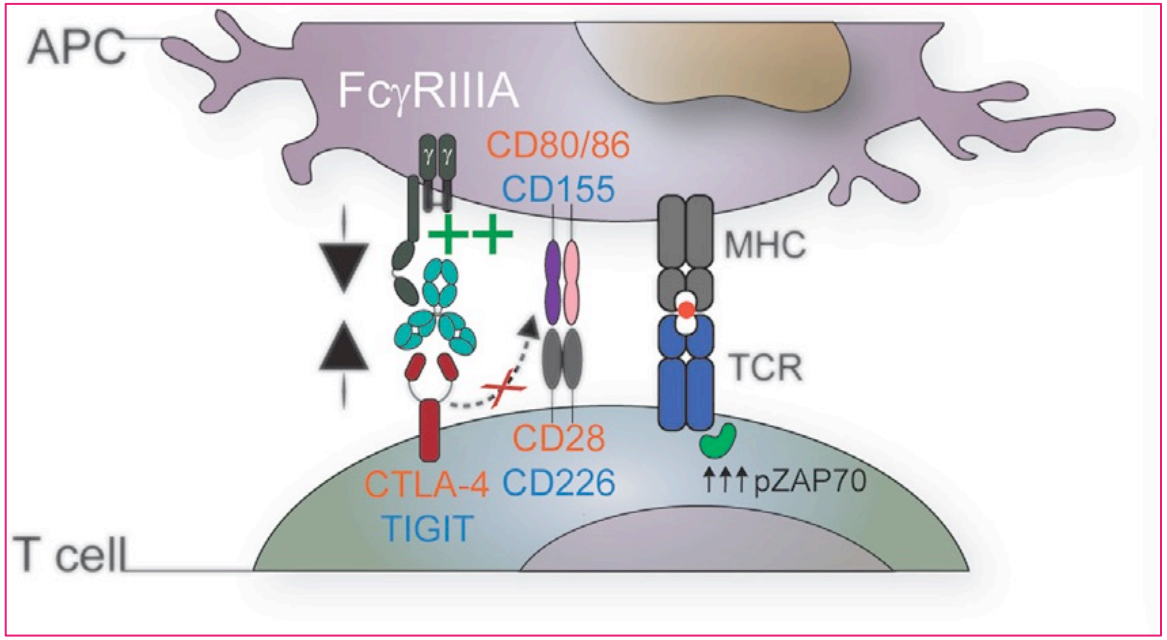
- High Affinity for CTLA-4
- Fc Optimized to Enhance Depletion
- Enhanced T Cell Activation
- Promote T Cell Memory
- Reasonable Tolerability

The Fc Engineered "DLE" Scaffold
1. Enhances Binding to Human FcγRIIIa
2. Bind to both the f/f and v/v FcγRIIIa Variants

IgG1 αCTLA-4

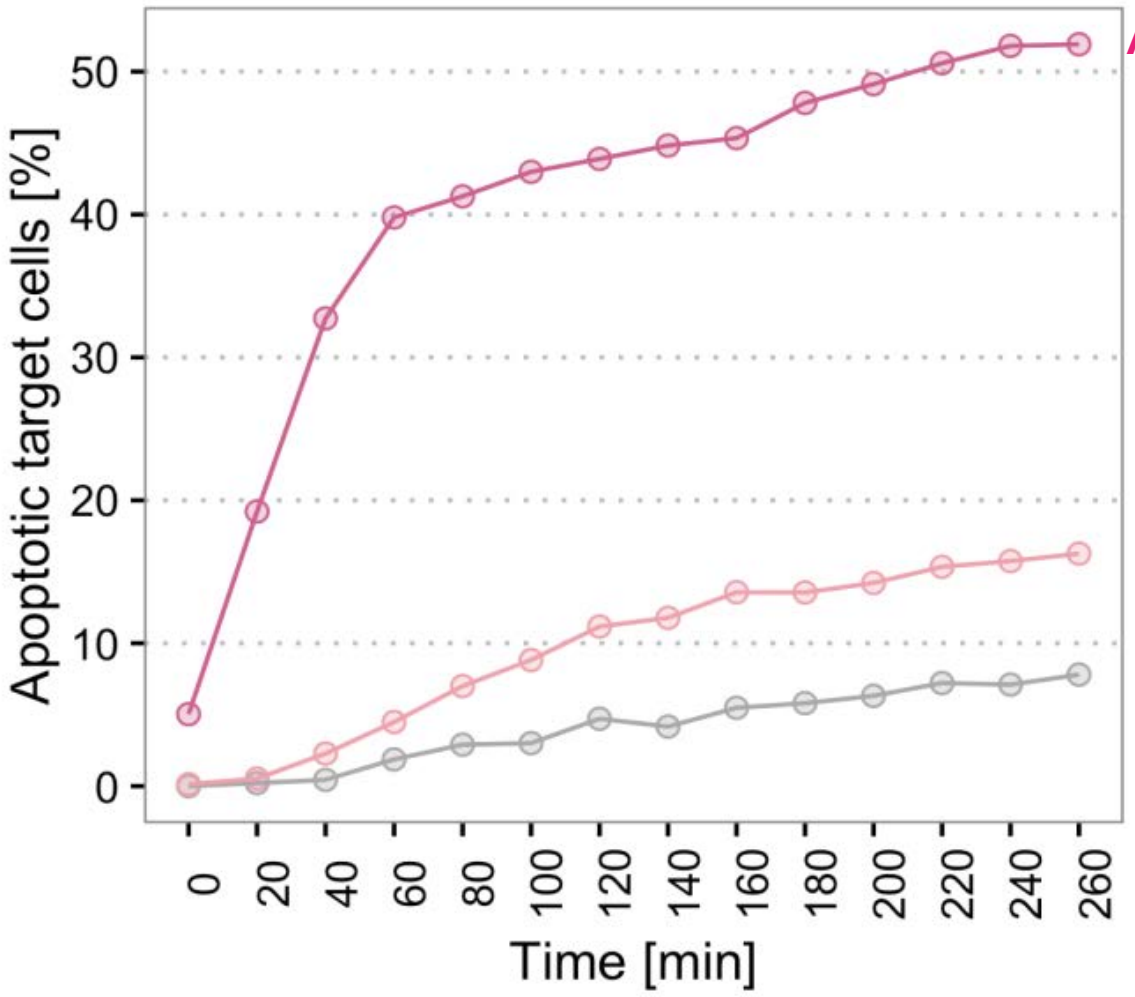


Fc Engineered αCTLA-4



Waight, JD et al, *Cancer Cell* 2018

Enhanced Treg Depletion with AGEN1181



AGEN1181

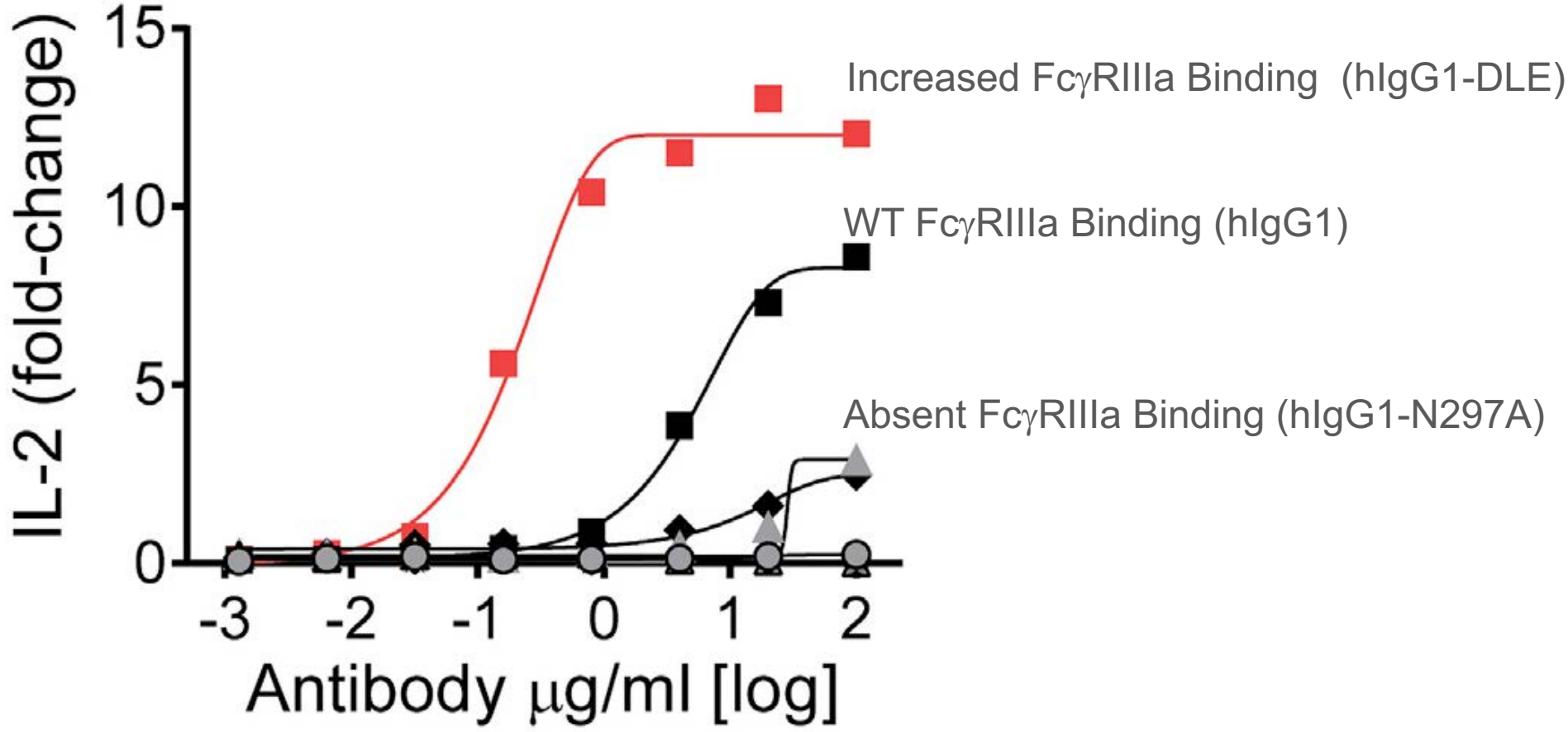
Parental IgG1

Isotype Control

Source: Agenus Data

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Enhanced T Cell Activation with AGEN1181



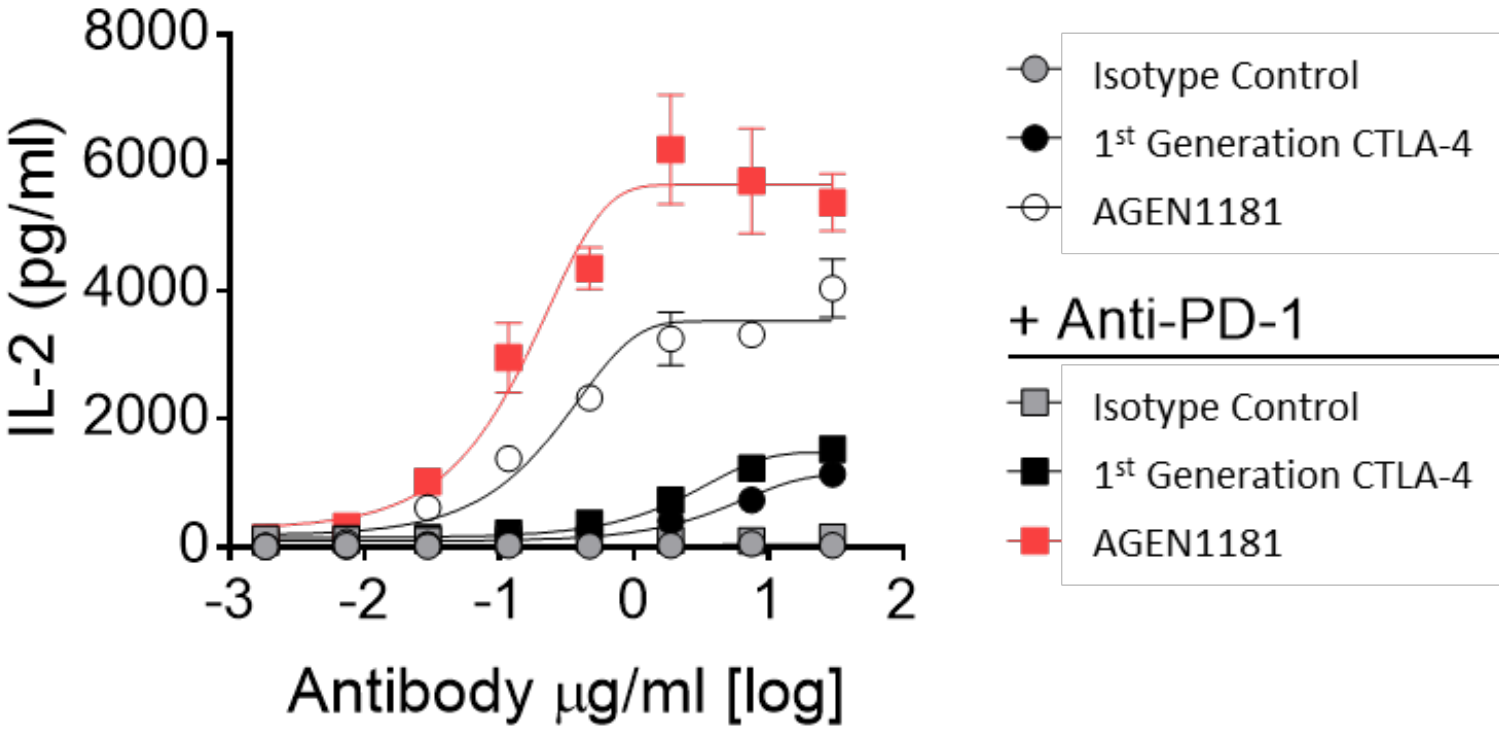
Waight, JD et al, *Cancer Cell* 2018

Source: Agenus Data

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Superior Combination Activity with PD-1 Blockade

In comparison to first-generation anti-CTLA-4



Source: Agenus data

Waight *et al.*, Cancer Cell 2018

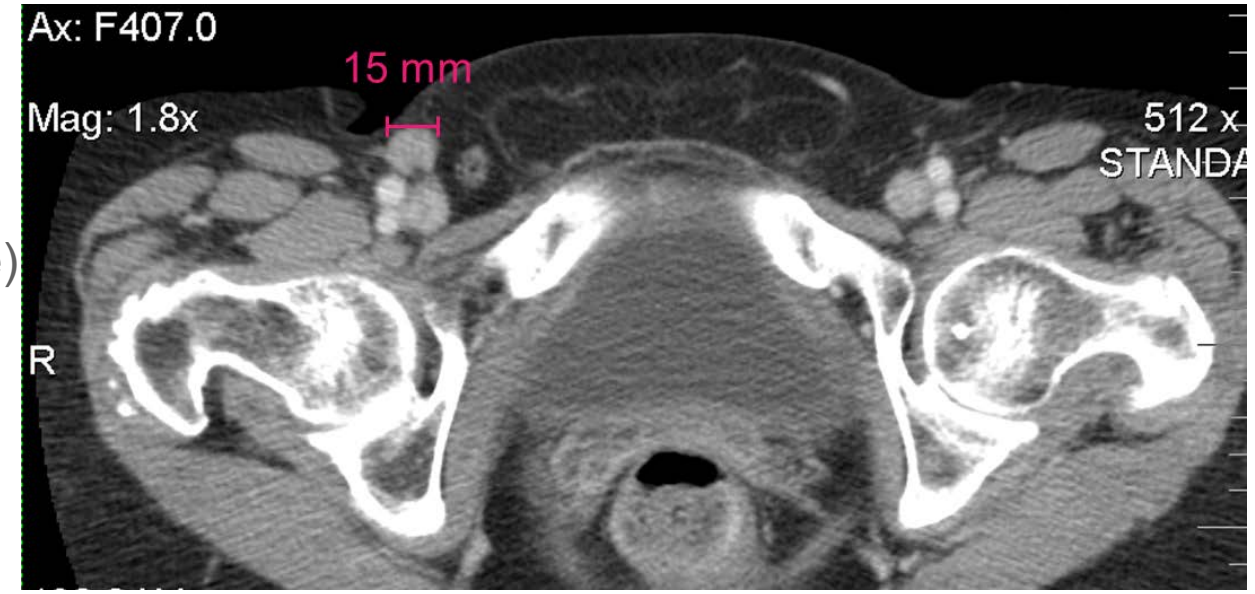
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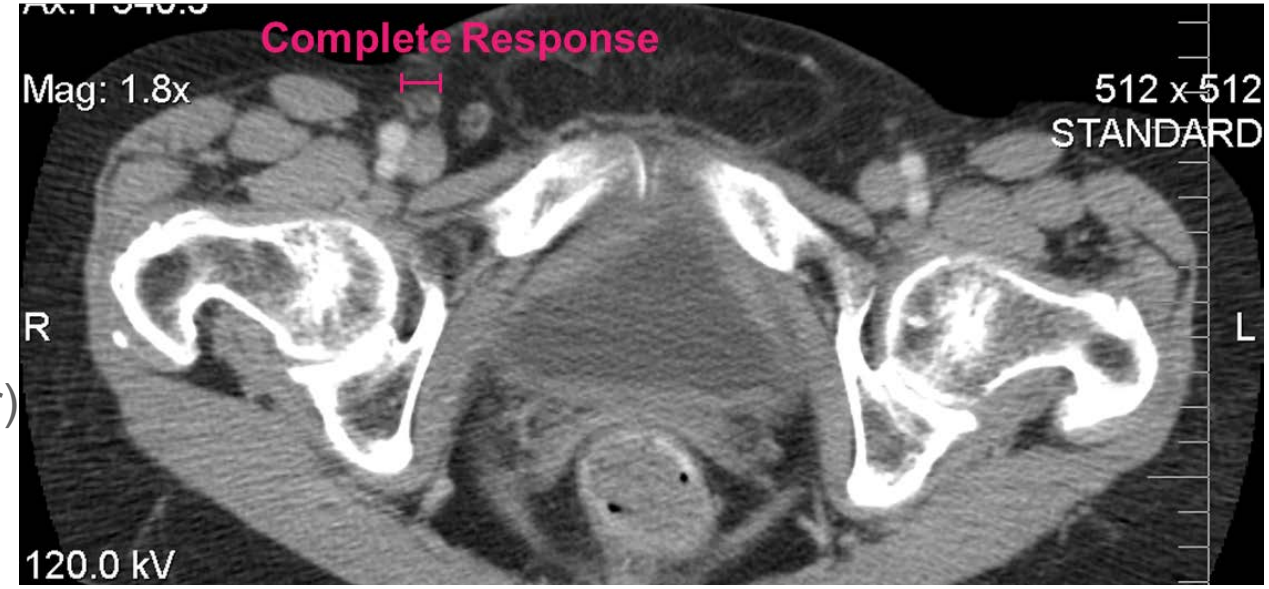
Early Clinical Activity with AGEN1181

- Ongoing Dose-Escalation Trial
- Combination with Agenus' αPD-1, balstilimab, initiated in Dec 2019
- **20 patients treated to date on monotherapy and in combination with balstilimab**
- **1 CR and disease stabilization in majority of response evaluable patients**
- Based on AGEN1181's MOA, **expect to target 3 times the population who benefit from Ipilimumab (Yervoy®)**

Metastatic Endometrial Cancer: Confirmed Complete Response

- 73 y/o Female with Endometrial Carcinoma (Uterine)
  - Initial Diagnosis 04-Nov-2015: Stage II
  - Prior treatment
    - TABHSO with Lymphadenectomy,
    - Carboplatin, Taxol, HDR Vaginal Cuff Radiation
    - Pembrolizumab
    - Incyte 107 (PI3K Inhibitor),
    - 5FU, Cisplatin, Palliative Radiation
- Metastatic progression: lymph node + sigmoid colon
- AGEN1181 Treatment
  - After Dose 2 – symptom resolved (per investigator)
  - After Dose 4 – CONFIRMED CR





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A complete response to CTLA-4 monotherapy (AGEN1181) is noteworthy in solid tumors

1 CR (1mg/kg) & 2 SD durable (0.1 and 1mg/kg) seen with AGEN1181

Ipilimumab Monotherapy

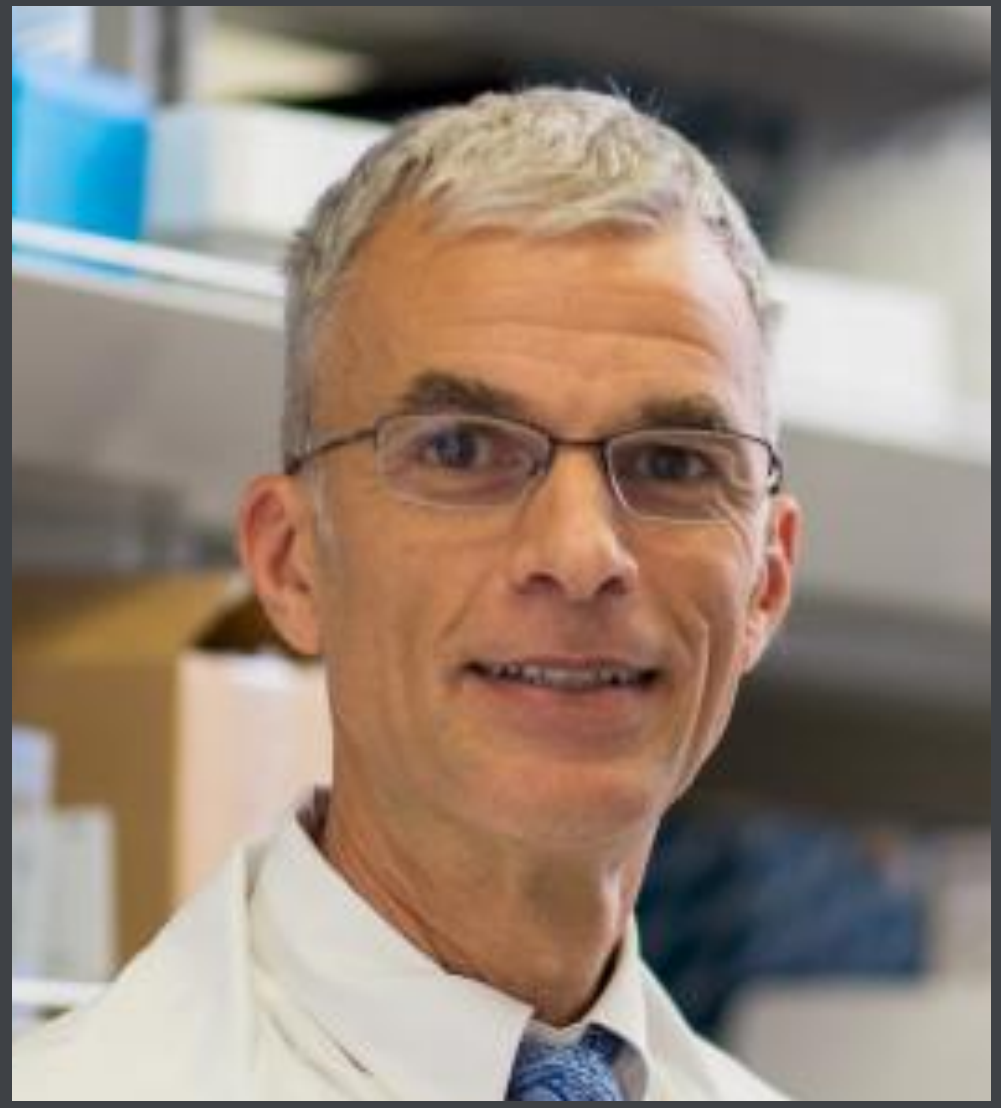
- Most CRs in solid tumors are in melanoma
- All CRs in solid tumors were at dosed at **3 or 10 mg/kg**
- **With >1000 patients, 4 CRs reported across all** solid tumors outside of melanoma

AGEN1181 Monotherapy

- Stable disease in solid tumors outside of melanoma (endometrial, ampullary, ovarian)
- CR/SD were at low doses: **1 mg/kg** or less
- **2** out of first **3** patients treated with1mg/kg dose demonstrate clinical benefit (1 CR, 1 SD)
- **AGEN1181 shows surprising early activity for an αCTLA-4 antibody**

Summary / Forward Looking

- AGEN1181 is an Fc Enhanced Anti-CTLA-4
- Well-documented enhanced *in vitro* activity (Waight et al)
- Potential for Enhanced Clinical Activity vs IgG1 (Ipilimumab)
  - In combination with anti-PD-1
  - In combination with Radiation Therapy
  - In combination with other Anti-Cancer Therapies



Dr. Tyler Curiel

MD, MPH, FACP

- Daisy M. Skinner President's Chair in Cancer Immunology Research
- Professor of Medicine and Microbiology, Immunology & Medical Genetics
- University of Texas Health, San Antonio, TX

A Deeper Look

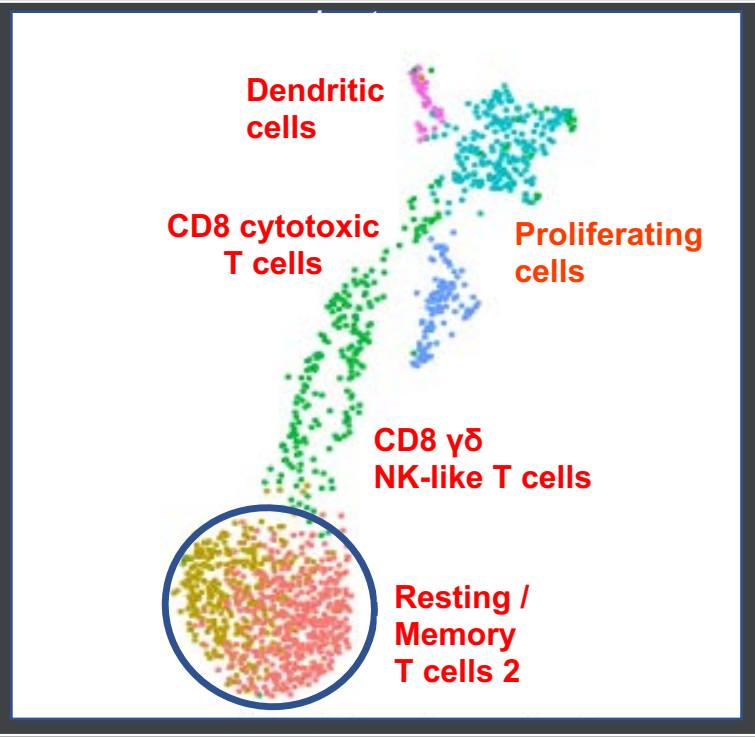
Endometrial Cancer Patient Complete Response

- **BRCA (-)**
- **MSI stable**
- **PD-L1 (-)**
- **FcγRIIIA FF phenotype**

PATIENT UNLIKELY TO RESPOND TO IMMUNE THERAPY

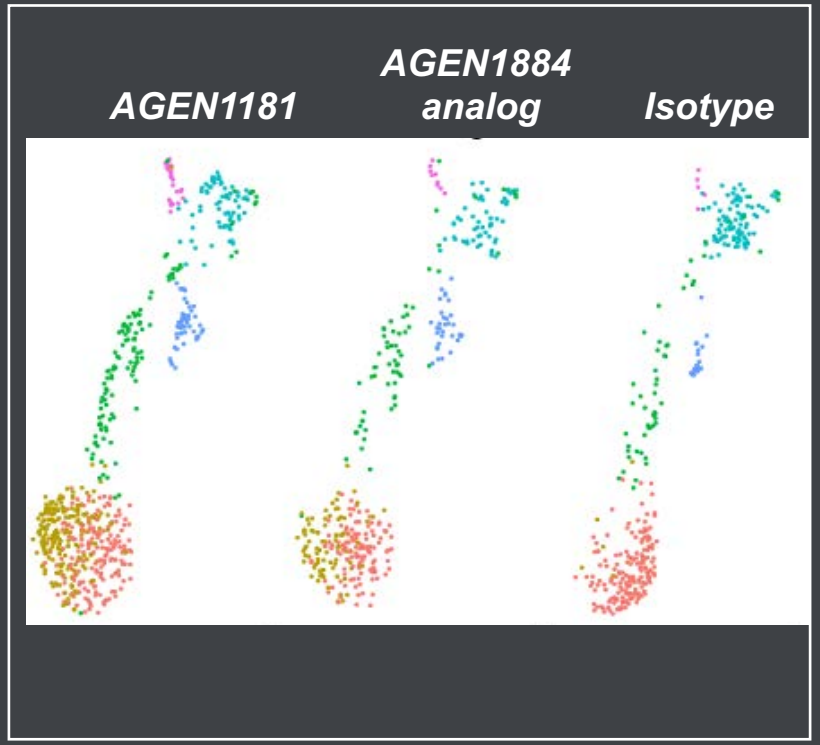
AGEN1181 Selectively Expands an IFN-Responsive Memory CD8+ T Cell Population *in vitro*

1. K-means clustering & UMAP visualization
Combined AGEN1181, AGEN1884 analog



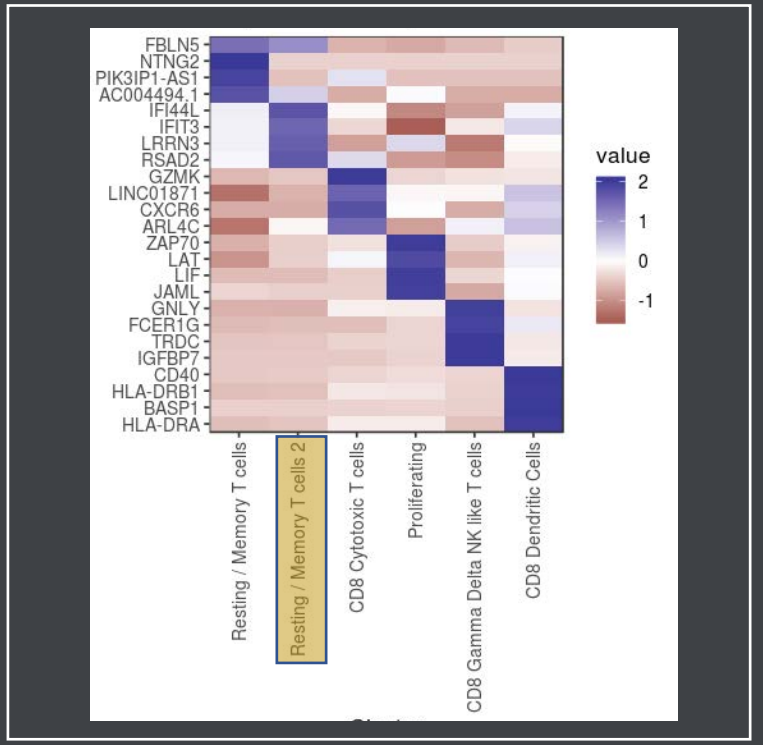
Resting / memory T cells identified

2. Conditional cell type differences



Changes in CD8+ memory T cells

3. Key insight: AGEN1181 selectively expands an IFN type 1 responding memory T cell



Enriched for AGEN1181

Source: Agenus data

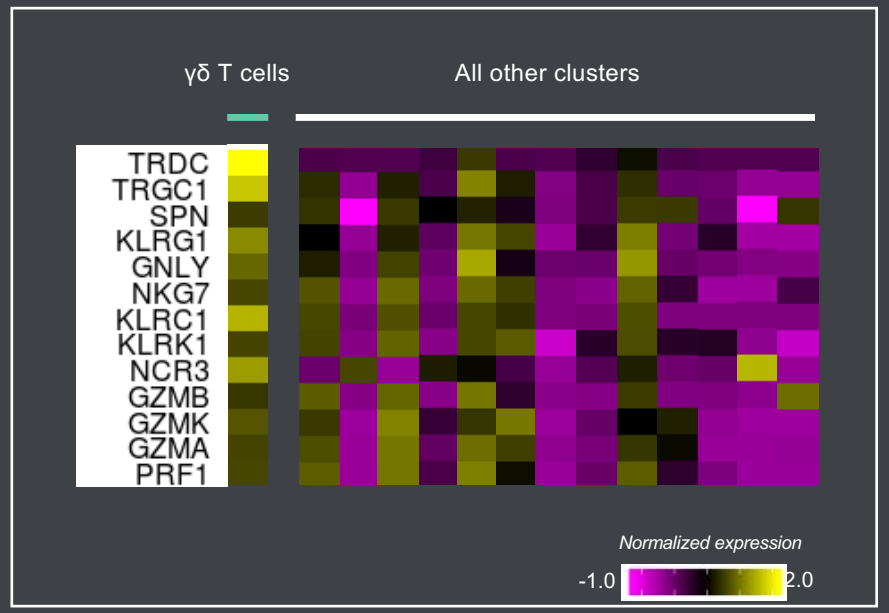
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AGEN Discovery: Response to ipilimumab + nivolumab correlates with expansion of gamma delta (γδ) T cells in melanoma patients

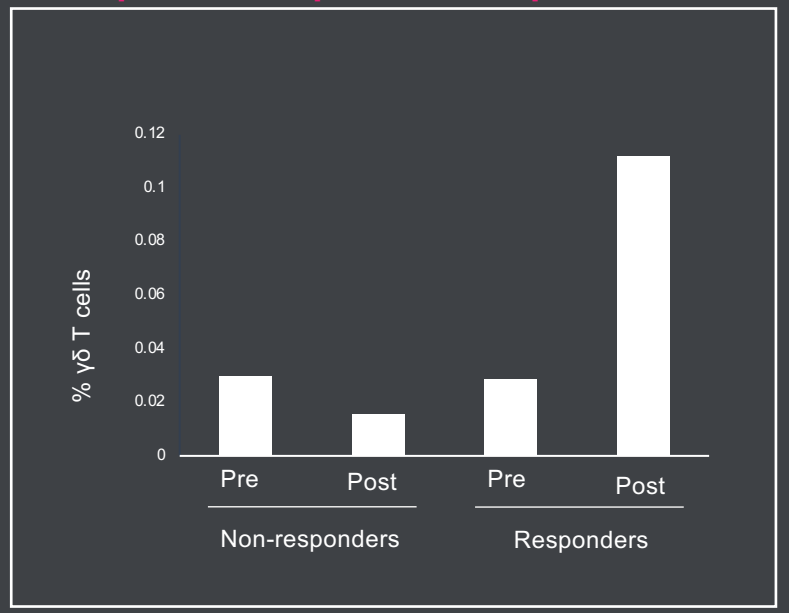
- Intratumoral CD45+ cells isolated from melanoma patients receiving ipilimumab + nivolumab
- Single cells were sequenced using Smart-seq2
- AGEN analysis drives new mechanistic insight:

Identify γδ T cell population

Co-express γδ TCRs, NK receptors & cytolytic markers



Key insight: γδ T cell population is expanded in ipi + nivo responders

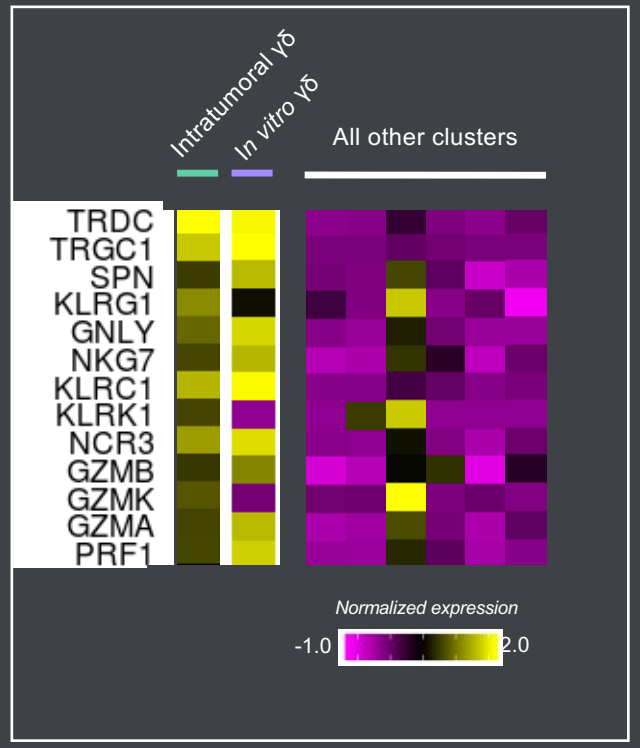


Data source: Sade-Feldman et al., Cell 2018
Data analysis: Agenus

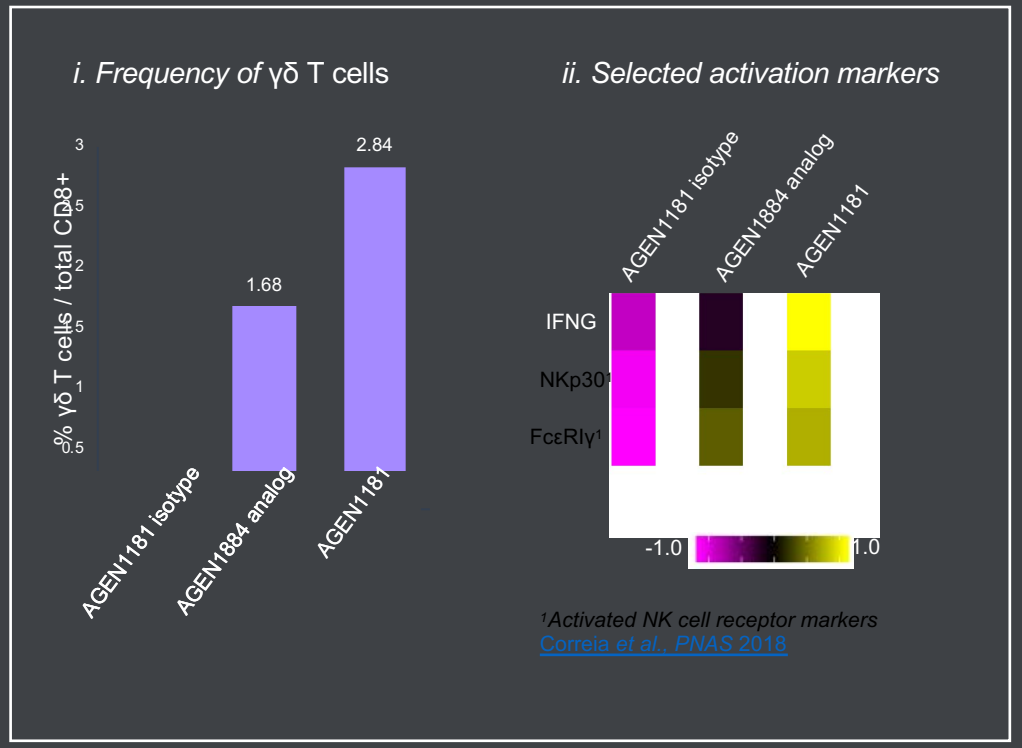
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Next-Generation Benefit: AGEN1181 enhances the γδ T cell response *in vitro* relative to 1st generation CTLA-4

Identify γδ T cell population
Comparable to intratumoral population



Key insight: AGEN1181 (i) selectively expands and (ii) may increase cytotoxic potential of γδ T cells *in vitro*



Source: Agenus data

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Conclusions

- **Uncovered potential cellular mechanisms underlying enhanced T cell responses to next generation CTLA-4 in pre-clinical studies**
  - *Next generation CTLA-4 benefit on memory-like T cell subset*
  - *Next generation CTLA-4 benefit on γδ T cell subset*

- **Next experiments will expand observations to patients on AGEN1181**

Next Steps

1. **Make better killers**
   - **AGEN1181 (conventional T cells, gamma delta T cells)**
   - **CAR iNKT**
   - **Epitope prediction**

2. **Soften the battlefield**
   - **AGEN1181 (reduce regulatory T cells)**
   - **Bi-specific molecules (*e.g.,* reduce myeloid cell effects, soluble factors or direct signals)**

OUR NEXT WAVE OF INNOVATION

Dhan Chand, PhD
Head of Drug Discovery

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CD73-adenosine and TGFβ are Major Contributors to Therapeutic Resistance

AGEN Solution: A Bi-functional Tumor Conditioning Agent



GS-1423* is potentially a first-in-class bi-functional antibody

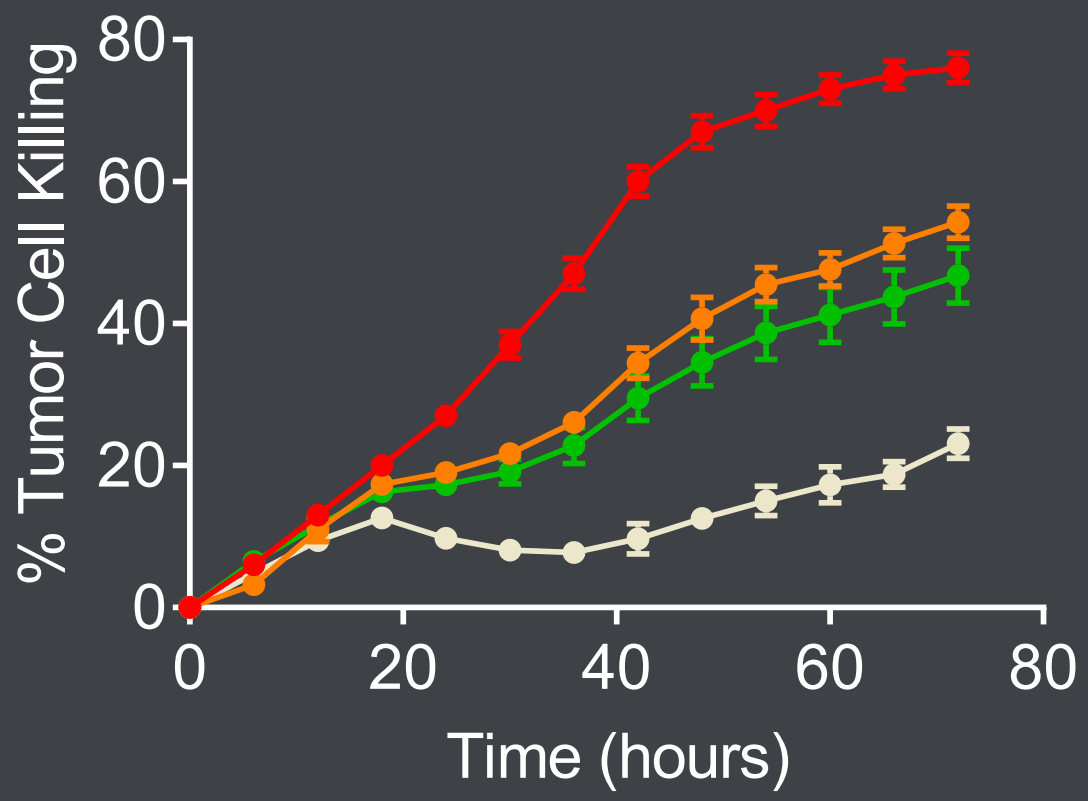
Phase I initiated

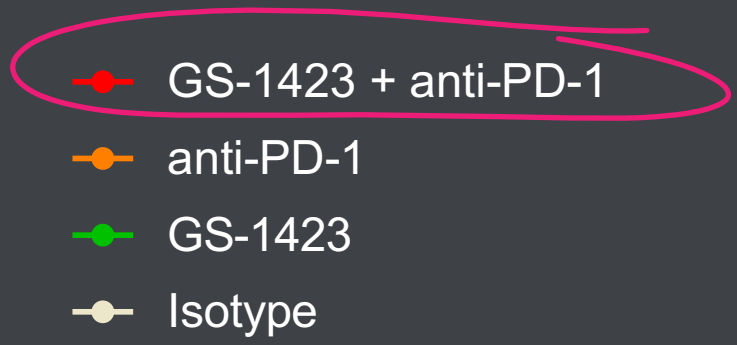
Q2 2019

*(*licensed to Gilead)*

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GS-1423* Enhances Tumor Cell Killing Alone and in Combination with anti-PD-1 in **a Suppressive Tumor Microenvironment**





Phase I initiated

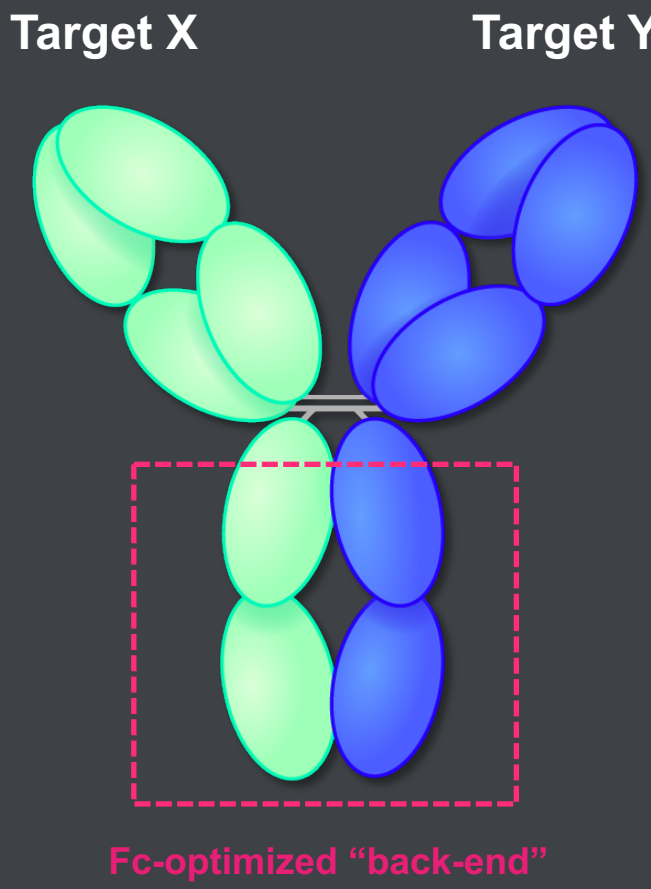
Q2 2019

*GS-1423 is licensed to Gilead by Agenus

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Regulatory T Cells are a Potent Suppressive Barrier to Effective Anti-tumor Immune Responses

AGEN Solution: Bispecific Antibody Designed for Selective Intratumoral Treg Depletion and T Cell Co-stimulation



AGEN1223 – first-in-class bispecific to:

- Selectively deplete intratumoral Tregs
- Enhance T cell effector function
- Improve safety

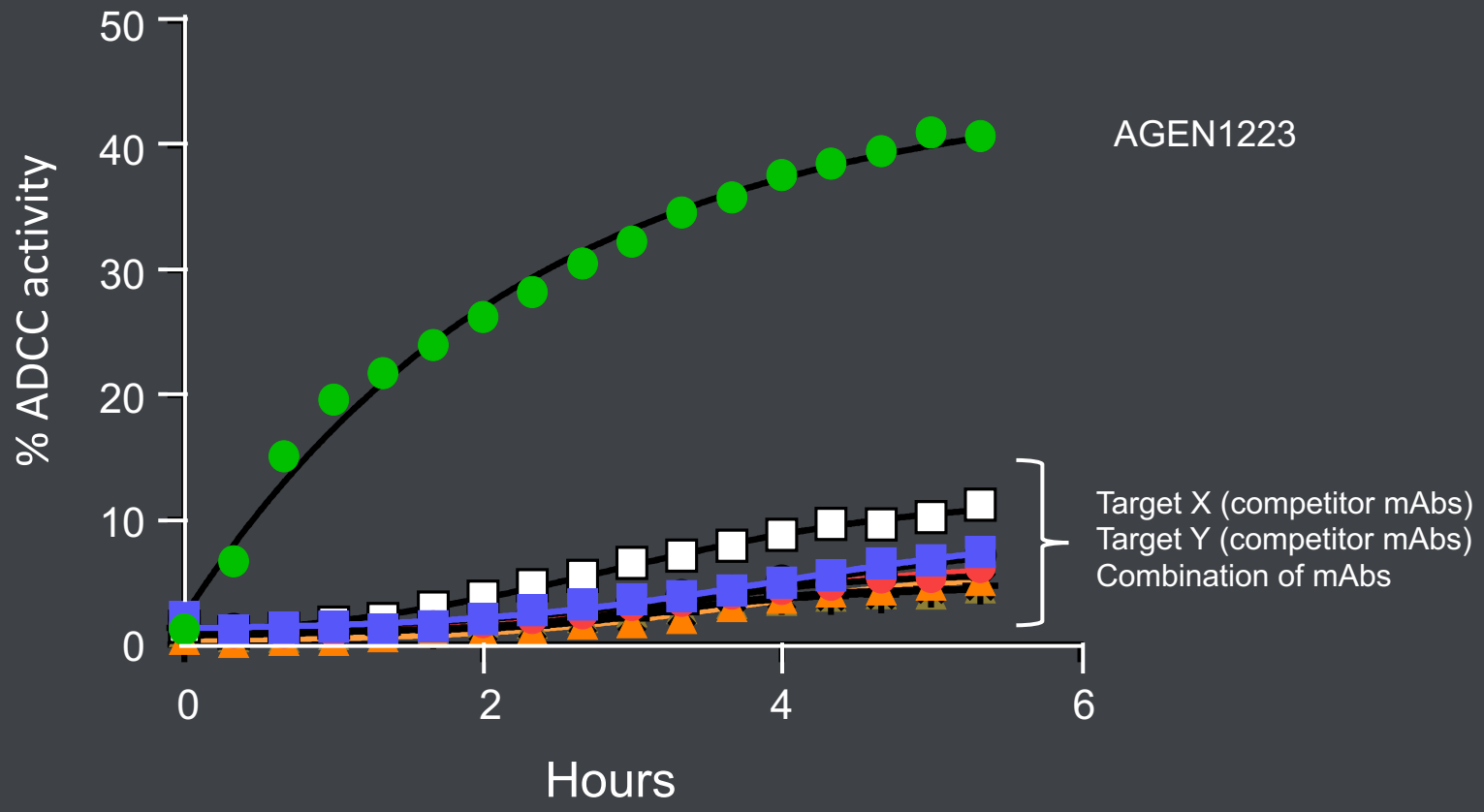
Phase I initiated

December 2019

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AGEN1223 Offers Dual Mechanism of TME Conditioning and Effector T Cell Stimulation

Enhanced Treg depletion compared to mAbs or combination of mAbs

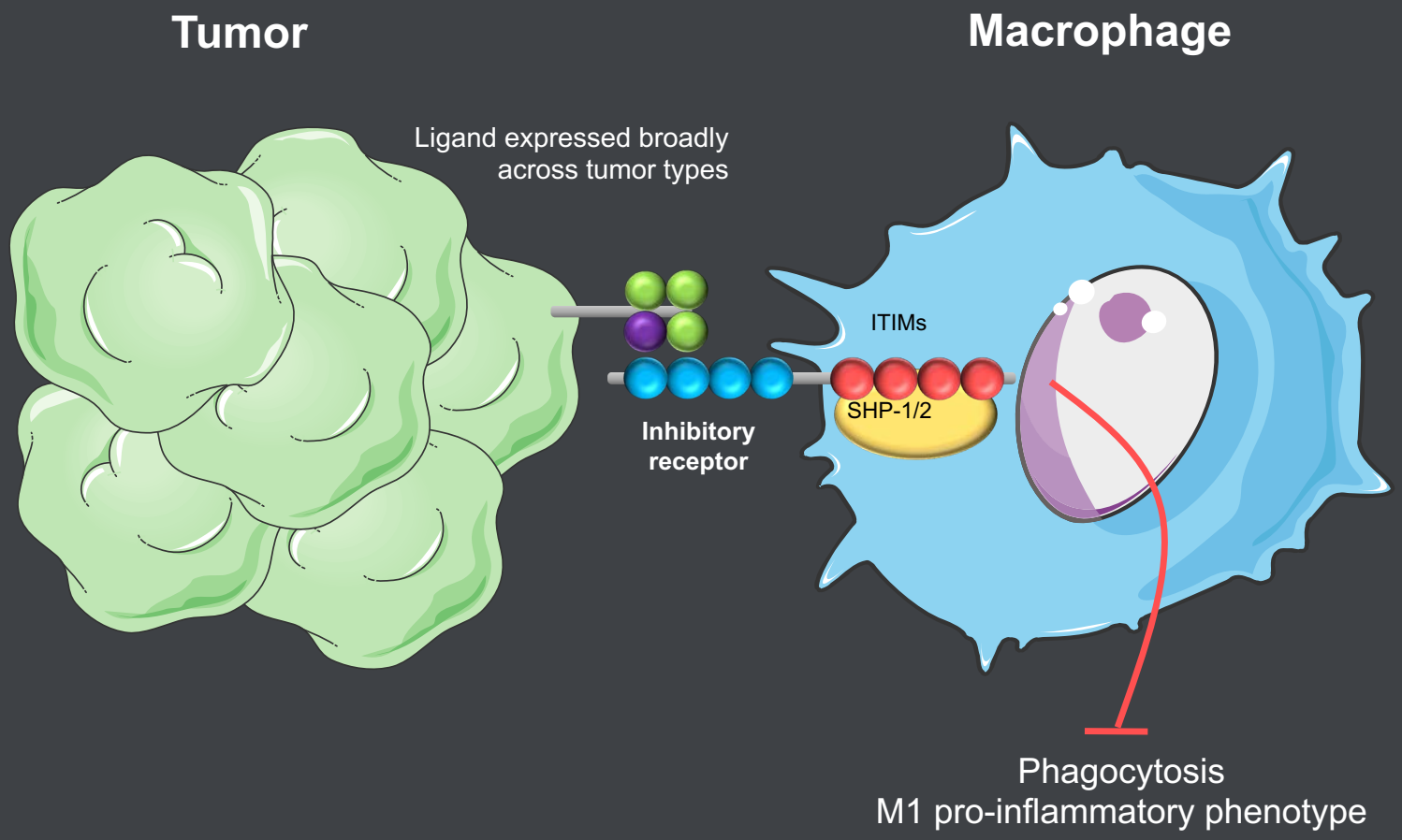


Phase I initiated

December 2019

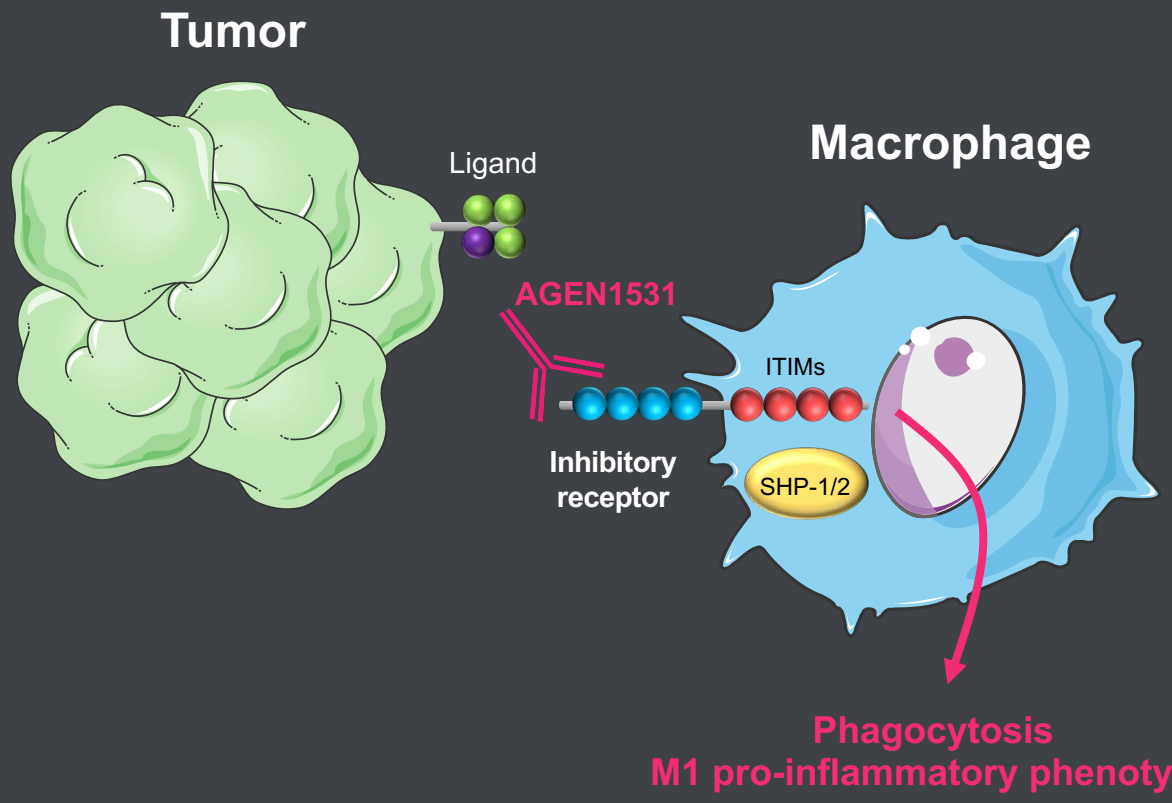
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Tumor-associated Macrophages Adopt a Suppressive Phenotype and Attenuate Antitumor Immunity



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AGEN Solution: Ligand-blocking Antagonist Antibody Designed to Repolarize and Enhance Function of Tams



AGEN1531 is a potential first-in-class antagonist antibody designed to:

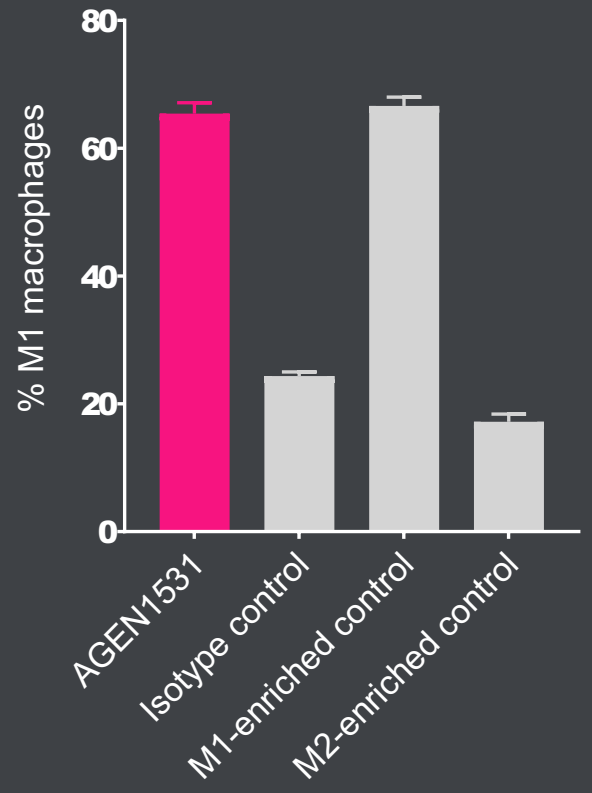
- Repolarize tumor-associated macrophages towards an M1 pro-inflammatory state
- Restore effector functions of intratumoral T & NK cells
- Overcome dendritic cell tolerogenicity

IND Projected 2020

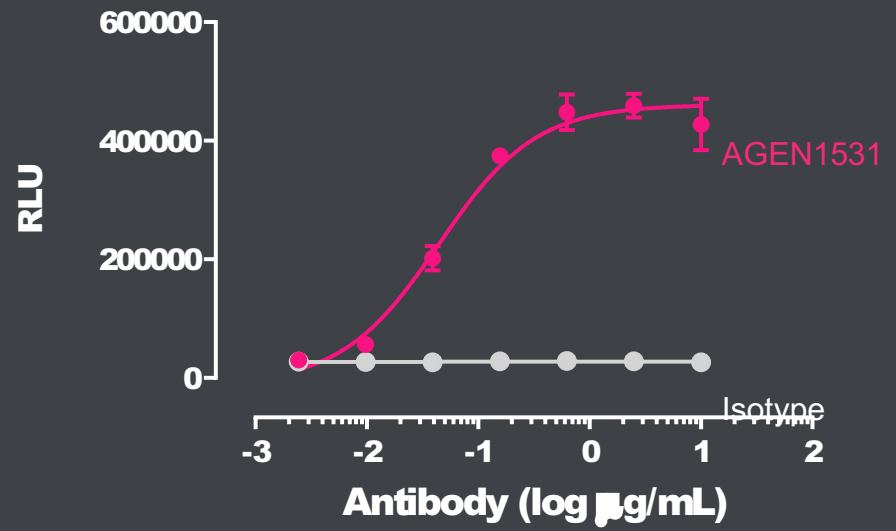
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AGEN1531 Antagonizes a Key Immunosuppressive Interface

AGEN1531 converts macrophages from immune suppressing to tumor fighting



AGEN1531 relieves target-mediated inhibition of FcγR signalling

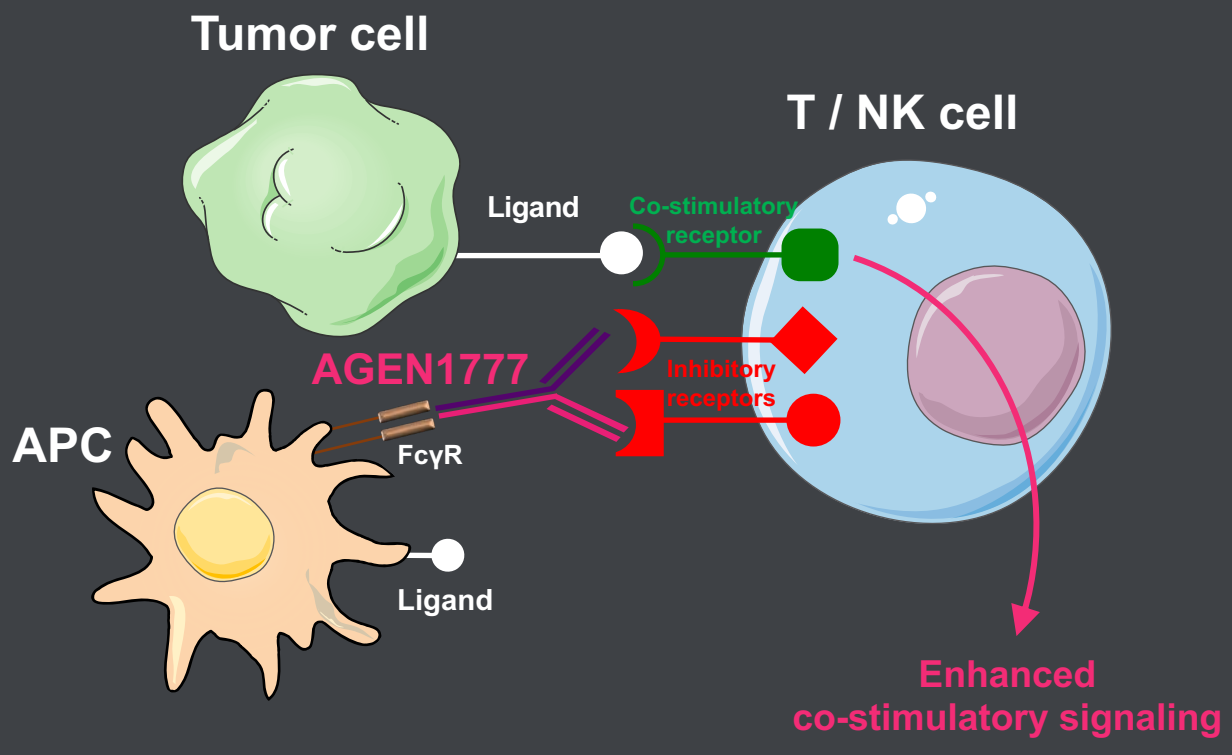


IND Projected 2020

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Patient Progression on Anti-PD-1 Driven by Secondary Immune Checkpoints

AGEN Solution: Dual Functioning Bispecific that Biases a Major T & NK Cell Immunoregulatory Interaction Towards Activation

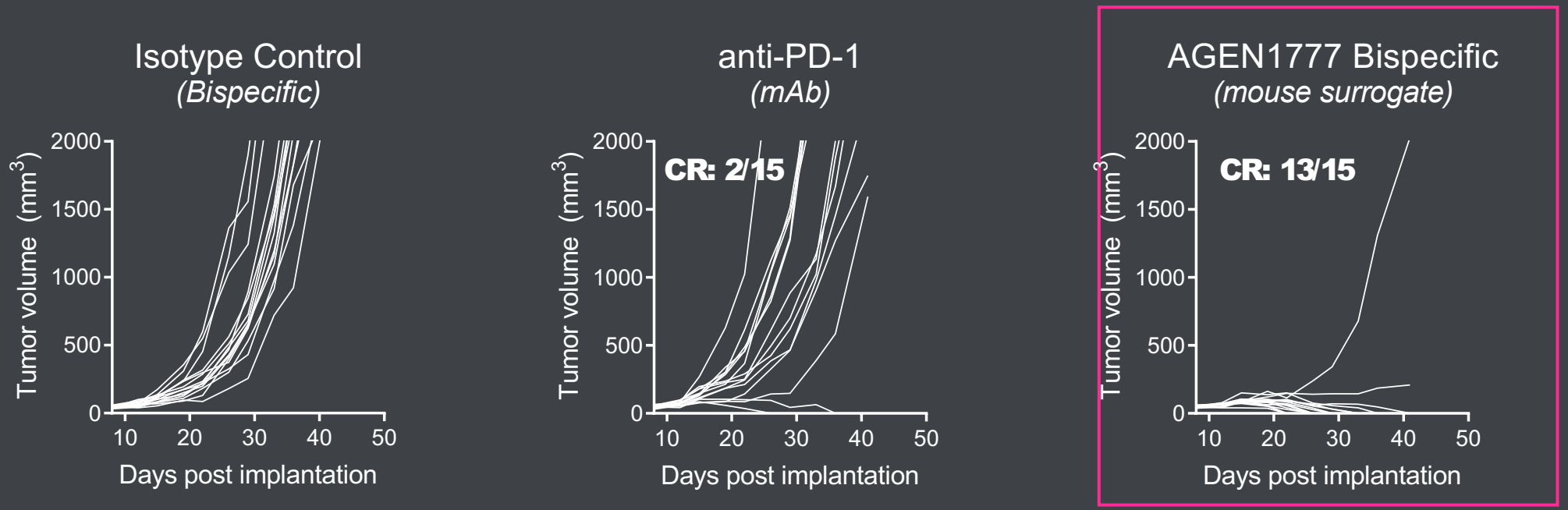


AGEN1777 is a potential first-in-class dual antagonist bispecific

IND Projected 2020

agenus

AGEN1777 Controls Tumors in a Mouse Colon Tumor Model



IND Projected 2020

Source: Agenus data

agenus

Novel Combinations Address Therapeutic Resistance

Data Accepted for Presentation at AACR 2020

(Abstract #922)

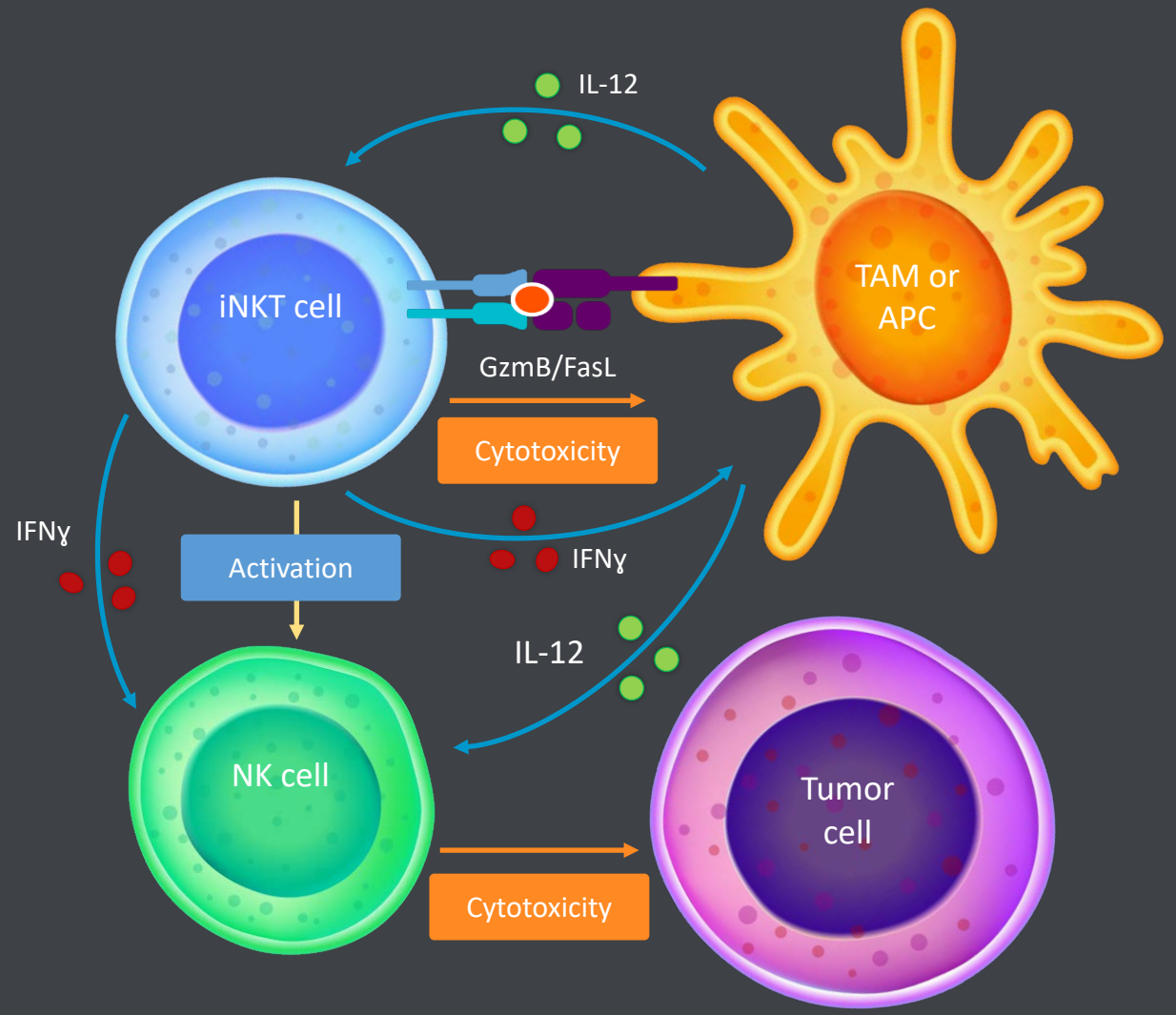
Our next disruptors exemplify **innovation** and **smart design**



Dr. Mark Exley
PhD

- Affiliate, Harvard Medical School
- Professorship, University of Manchester
- Founder of NKT Therapeutics

INVARIANT NKT CELLS BOOST IMMUNE RESPONSE NATURALLY

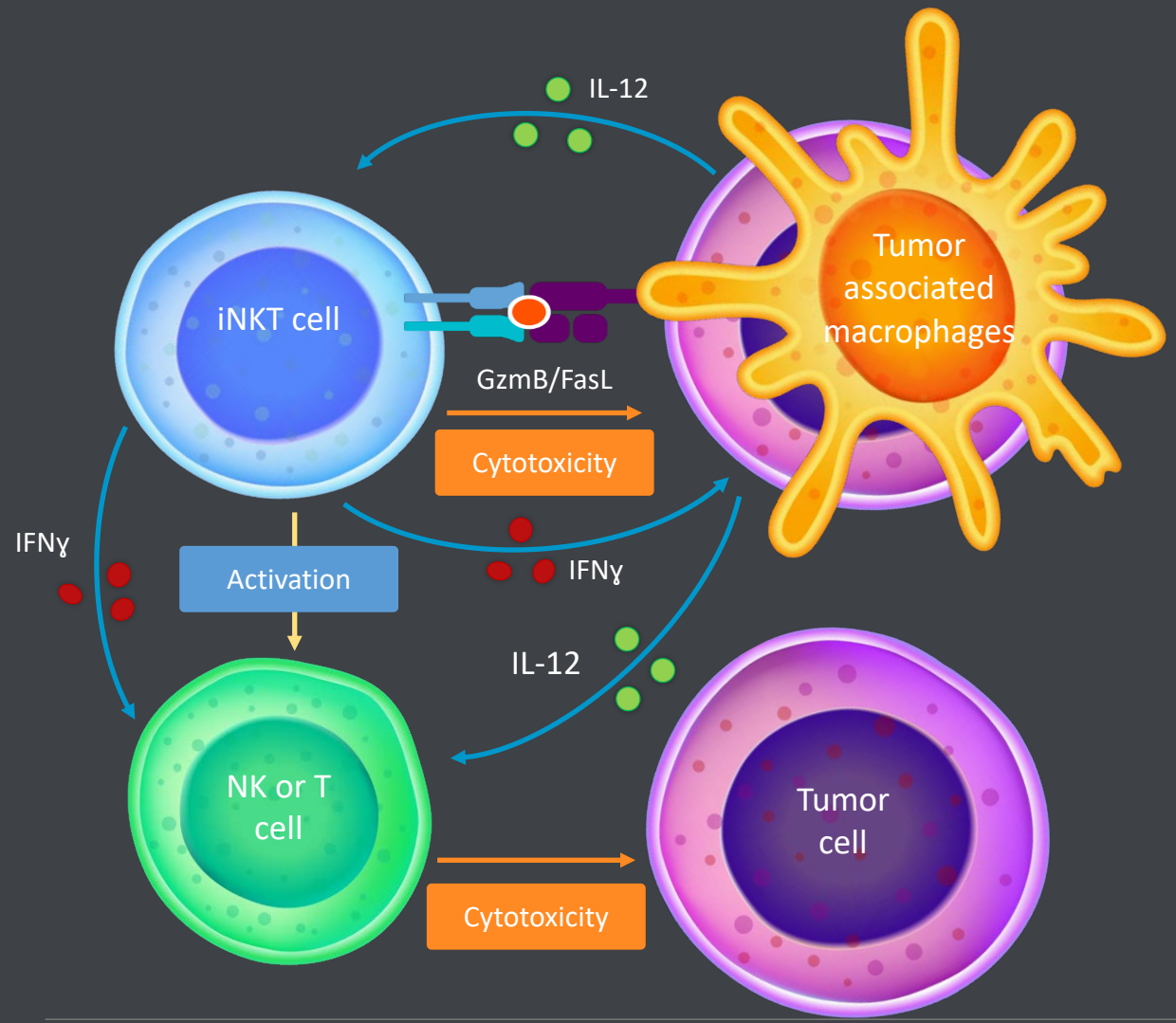


Mark Exley, PhD
Principal

agenus

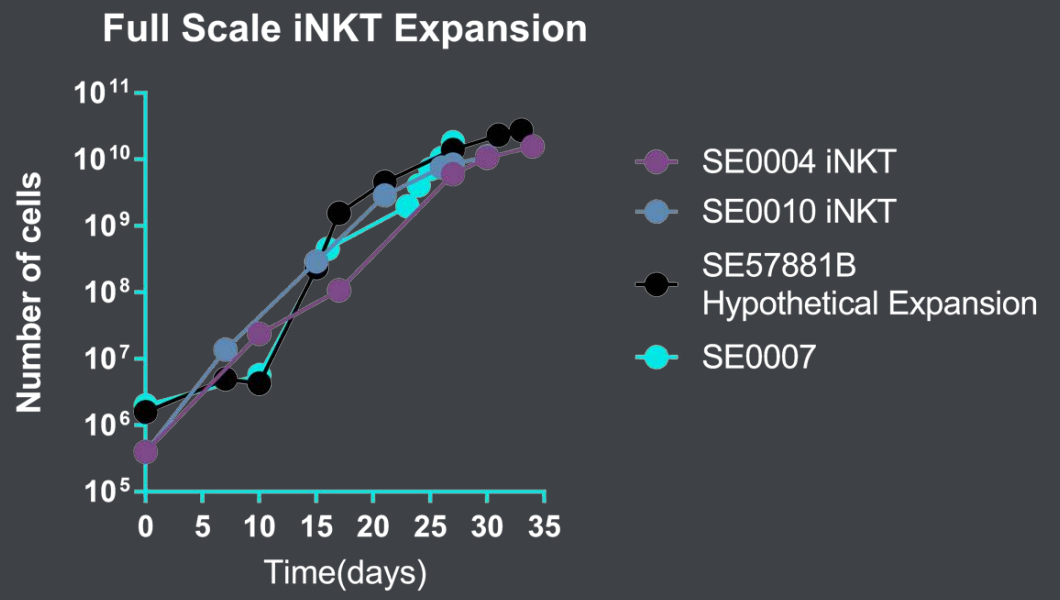
Invariant Natural Killer T (iNKT) Cells

Orchestrators of the immune system



iNKTs:

- Suppress GvHD (no gene editing)
- Home to tumor site
- Massive expansion capacity >40,000 fold (1 healthy donor ~ 1000 doses)



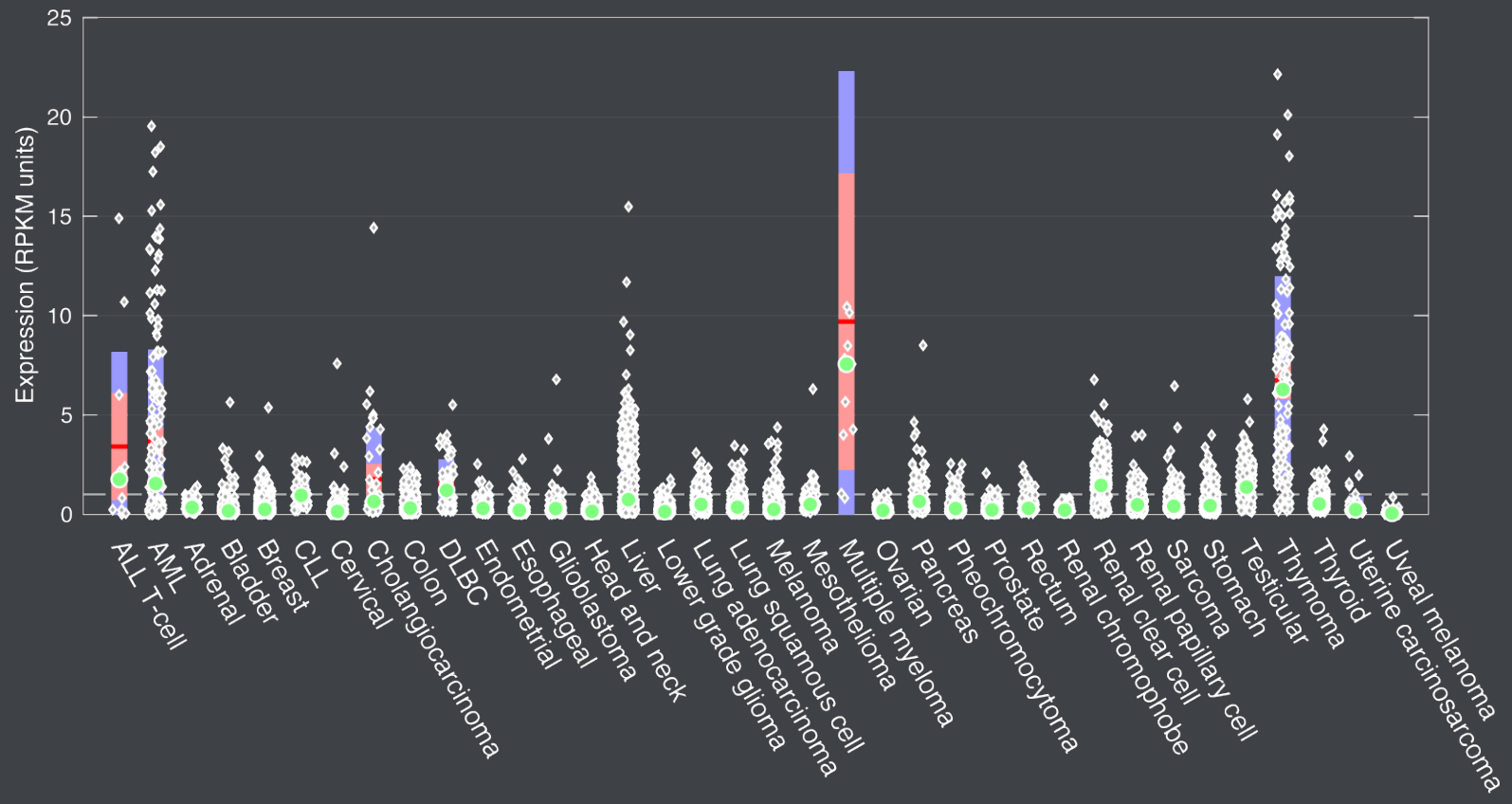
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iNKTs May be Effective in Solid and Hematologic Tumors

Allogeneic iNKTs expected to enter clinic as mono and CPI combinations in 2020

- **1H2020**: Safety with iNKT in Multiple Myeloma, CLL/SLL, iNHL (FL, MZL), and DLBCL
- **2H2020: S**afety and efficacy of iNKT and CPIs (i.e. AGEN1181, AGEN2034) in solid tumors

Some cancers over-express CD1d



agenus

SMART COLLABORATIONS

Julie DeSander
Head of Business Development

agenus

Agenus Notable Strategic Partnerships

~$2.5B *in potential milestones & royalties;* $525M *already received*

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

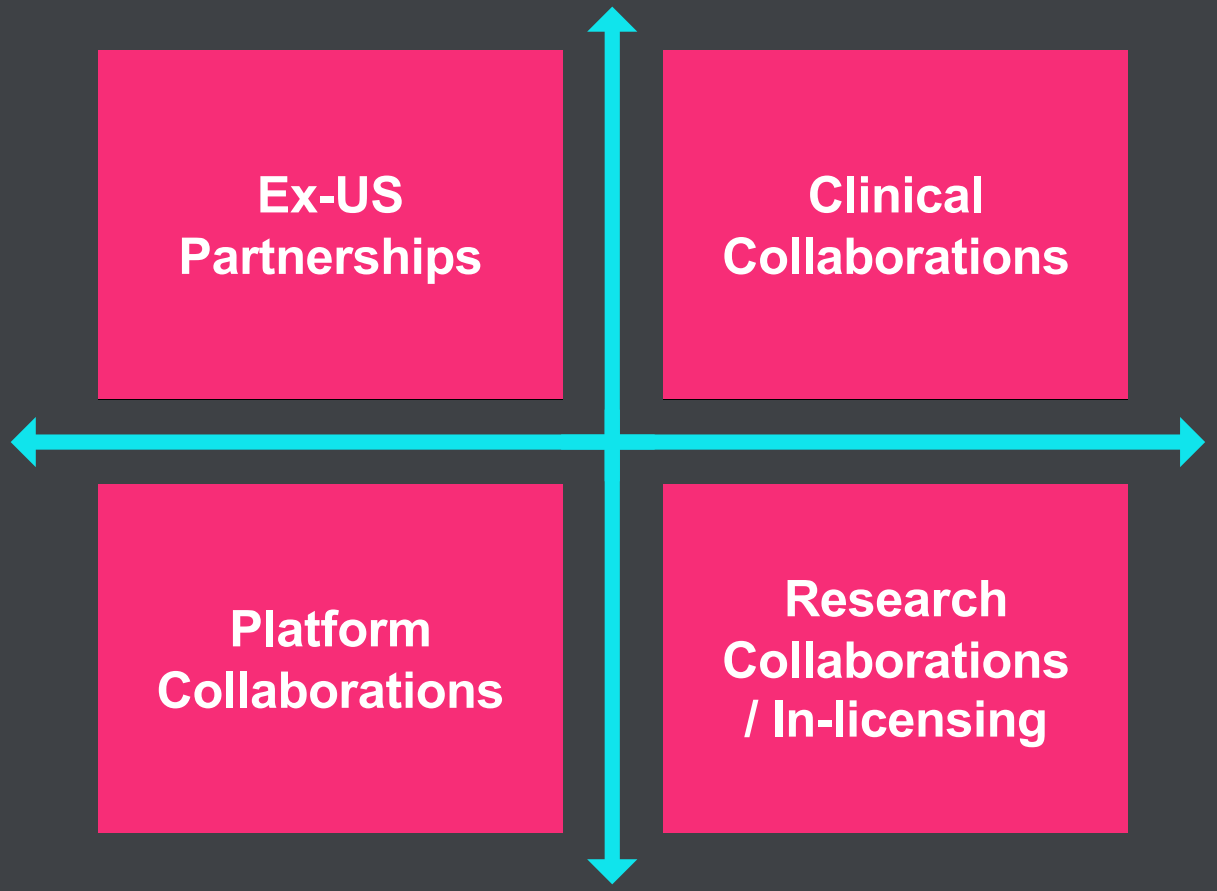
More detailed information available in Agenus SEC and 10k filings

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

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

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

2020 Partnering Strategy



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Q&A

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