MOLECULAR PARTNERS R&D DAY 2019

"Novel Therapeutic Designs Applied"

Thursday, December 12, 2019
Check-in & Breakfast: 7:30-8:00am
Presentations & Q&A: 8:00-10:00am

The Yale Club
50 Vanderbilt Avenue
New York, NY 10017

2019 R&D DAY | *Novel Therapeutic Designs Applied*

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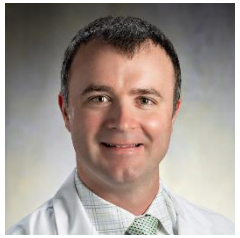
Agenda

Welcome & Introduction	8:00-8:20 Corporate Overview	8:20-8:35 Abicipar - Presentation of Recently Updated 2 Year Data	8:35-8:50 Clinical Pipeline	8:50-9:00 MP0250 Trial in Multiple Myeloma	9:00-9:15 Preclinical Pipeline	9:15-9:30 Novel Therapeutic Designs	9:30-9:35 Summary & Key Takeaways
							9:35-10:00: Q&A
Seth Lewis SVP IR, Comms, & Strategy, Molecular Partners	**Dr. Patrick Amstutz** Chief Executive Officer, Molecular Partners	**Dr. Jeremy Wolfe** Practicing Ophthalmology Specialist	**Dr. Nicolas Leupin** Chief Medical Officer, Molecular Partners	**Dr. Stefan Knop** Department Head Hematology, University of Würzburg, Germany	**Dr. Daniel Steiner** SVP Research, Molecular Partners	**Dr. Jordi Rodon** Associate Professor, Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center	

Corporate Overview

Patrick Amstutz

CEO

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Our Purpose

Transform the lives of people with cancer by delivering truly innovative therapies

Our Vision

Build a leading fully integrated oncology company

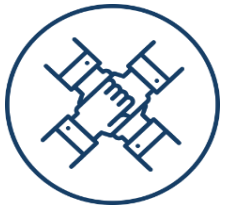
Our Core

A passionate team dedicated to moving the needle of medicine

Our Strategy

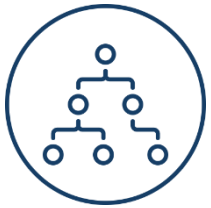
Rapidly innovate using our DARPin® approach to create new therapeutic designs

Our Year in Review



Strengthened Team

- ✓ **Swiss Biotech** – 140 coworkers
- ✓ **Cash** position: **CHF 112m** (end Q3 19)
- ✓ Appointment of medical oncologist **Nicolas Leupin** as **CMO**
- ✓ Senior Vice President of Research **Daniel Steiner** assumed leadership of research activities
- ✓ **Seth Lewis** joined Boston office to head up global IR, communication – Strategy



Burgeoning Oncology Pipeline

- ✓ **MP0250** focused on MM with unique activity in patients that did not benefit from other treatments
- ✓ **MP0310 (AMG 506)**: Collaboration with Amgen to co-develop MP0310 & first patient cohort dosed in Phase 1 trial
- ✓ New development candidate, **MP0317 (FAPxCD40), added to pipeline**
- ✓ Collaboration with Gilead to advance DARPin® candidates binding **peptide-MHC**

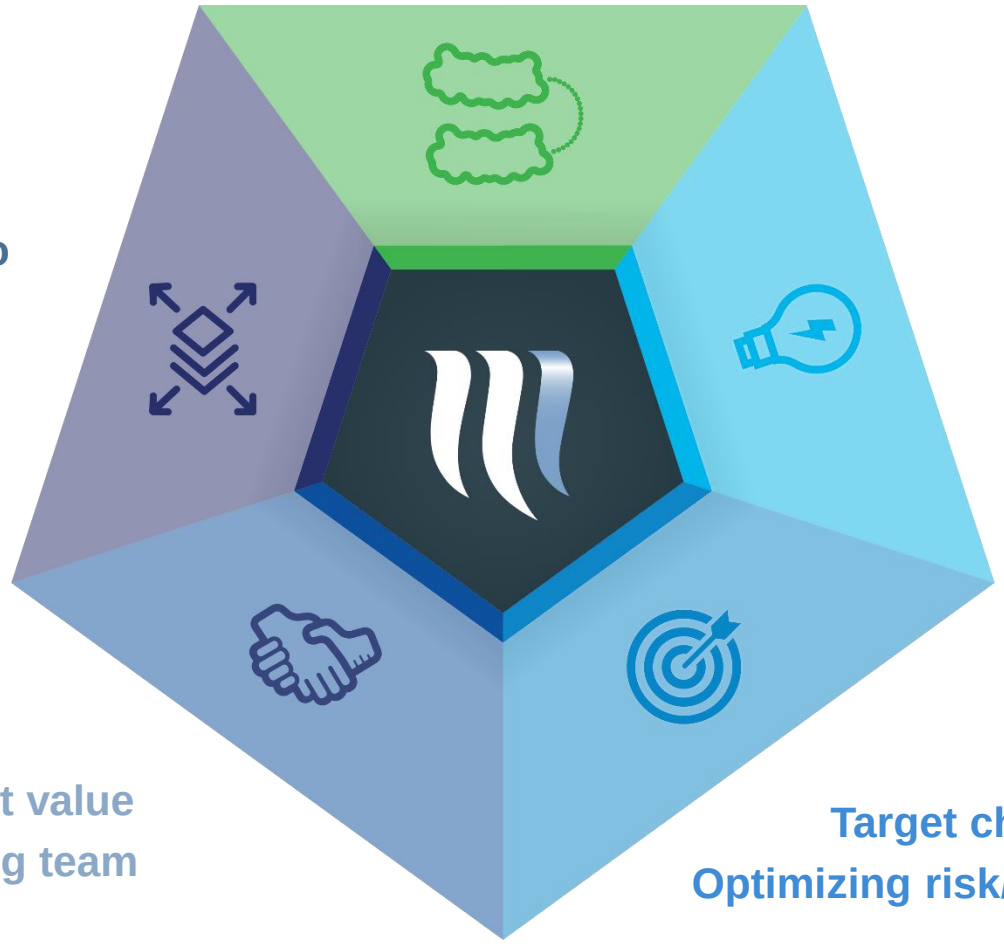
Progress Towards Approval

- ✓ **BLA** of **abicipar accepted** by FDA, MAA of abicipar validated by EMA
- ✓ **90% of patients** show vision gains which were maintained in the 2nd year with **q12 dosing** of abicipar
- ✓ MAPLE data supports optimized manufacturing process for **improved tolerability**

How Molecular Partners Drives Value

Validated source of DARPin® Candidates

Flexible business model to maximize product value



Novel Therapeutic Designs

1. Tumor-local immune agonists
2. pMHC targeting platform
3. Next Gen T-cell engagers

Deliver patient value with our strong team

Target choice: Optimizing risk/reward ratio

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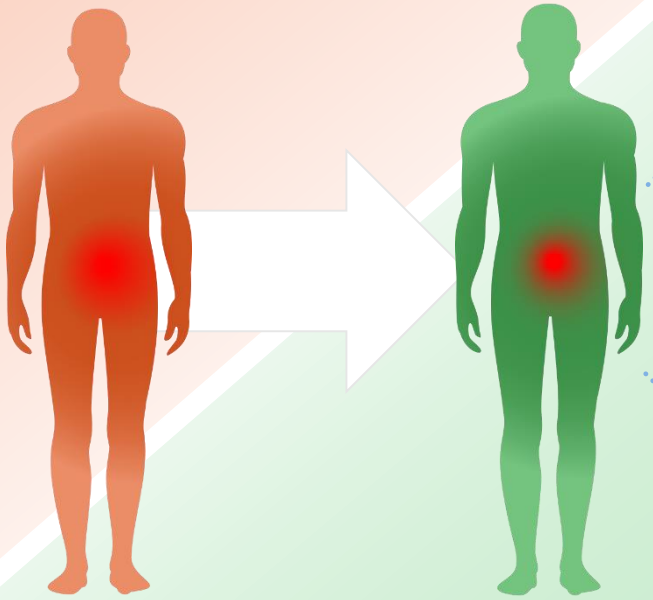
DARPin® Platform: A Validated Source for Drug Candidates

- **Abicipar: Ophthalmic validation**
  - Demonstrated safety and activity in >1,500 patients
  - Manufacturing at commercial scale established
  - Regulatory applications accepted by FDA and EMA
- **MP0250: Systemic validation**
  - Long half-life and low immunogenicity with novel mechanism of action
  - Proof of multi-DARPin® potential to engage with multiple targets simultaneously
  - Validation of DARPin® activity in oncology with unique approach to maximize patient value
- **Novel Therapeutic Designs (NTD) applied**
  - First patients dosed for MP0310 (AMG 506)

Novel Therapeutic Designs Applied – Our Approach

Classical Antibodies & SMEs

- Systemic ctivity
- Dose-limiting toxicities

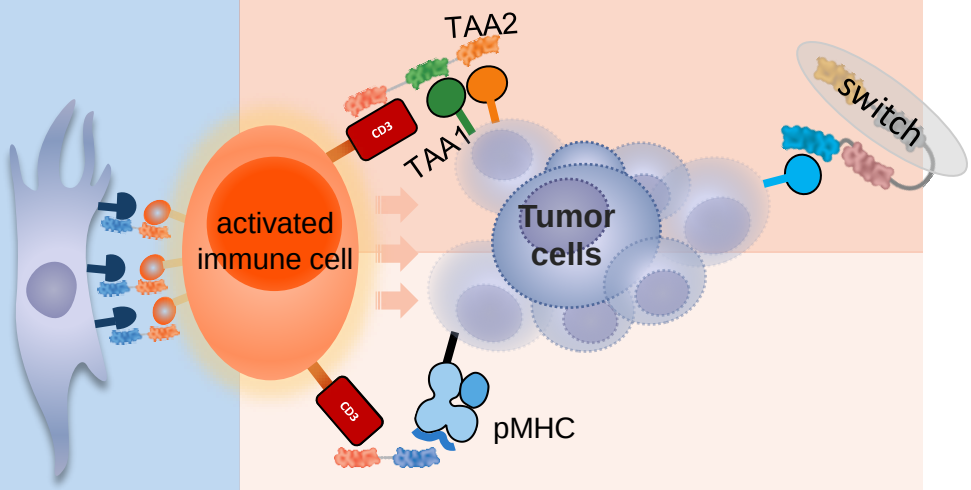


Novel Therapeutic Designs

- Local (super) activity
- Minimal systemic toxicity

Tumor-localized immune cell activation

Next-generation T-cell engagers



Targeting peptide MHC complexes, historically "inaccessible" targets

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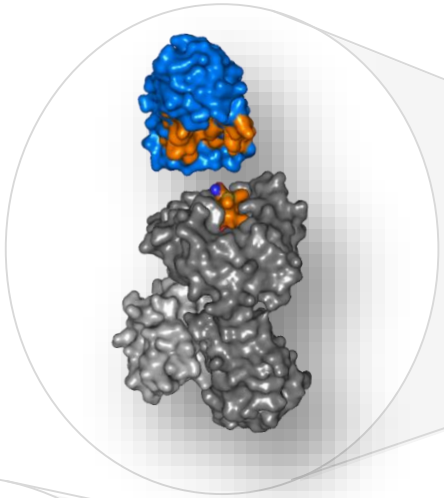
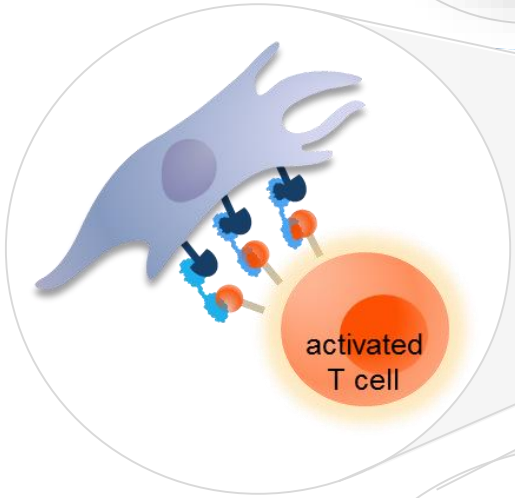
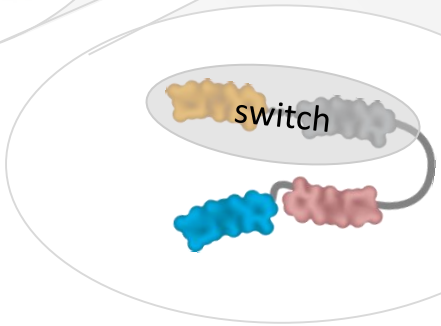
Differentiated Products by Therapeutic Design

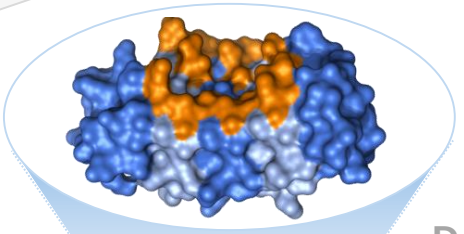






DARPin® Features

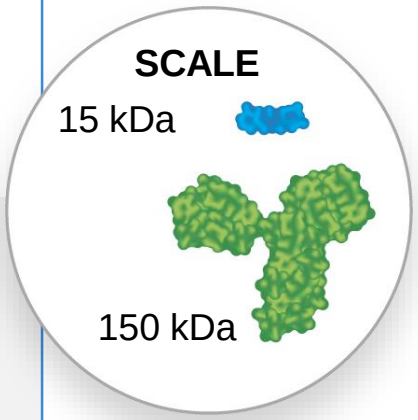
Rigid-body target binding



DARPin® domain

Multi-DARPin® formatting

- Small size: 15 kDa
- Simple repetitive architecture: 1 polypeptide
- High affinity and specificity
- Tunable half-life



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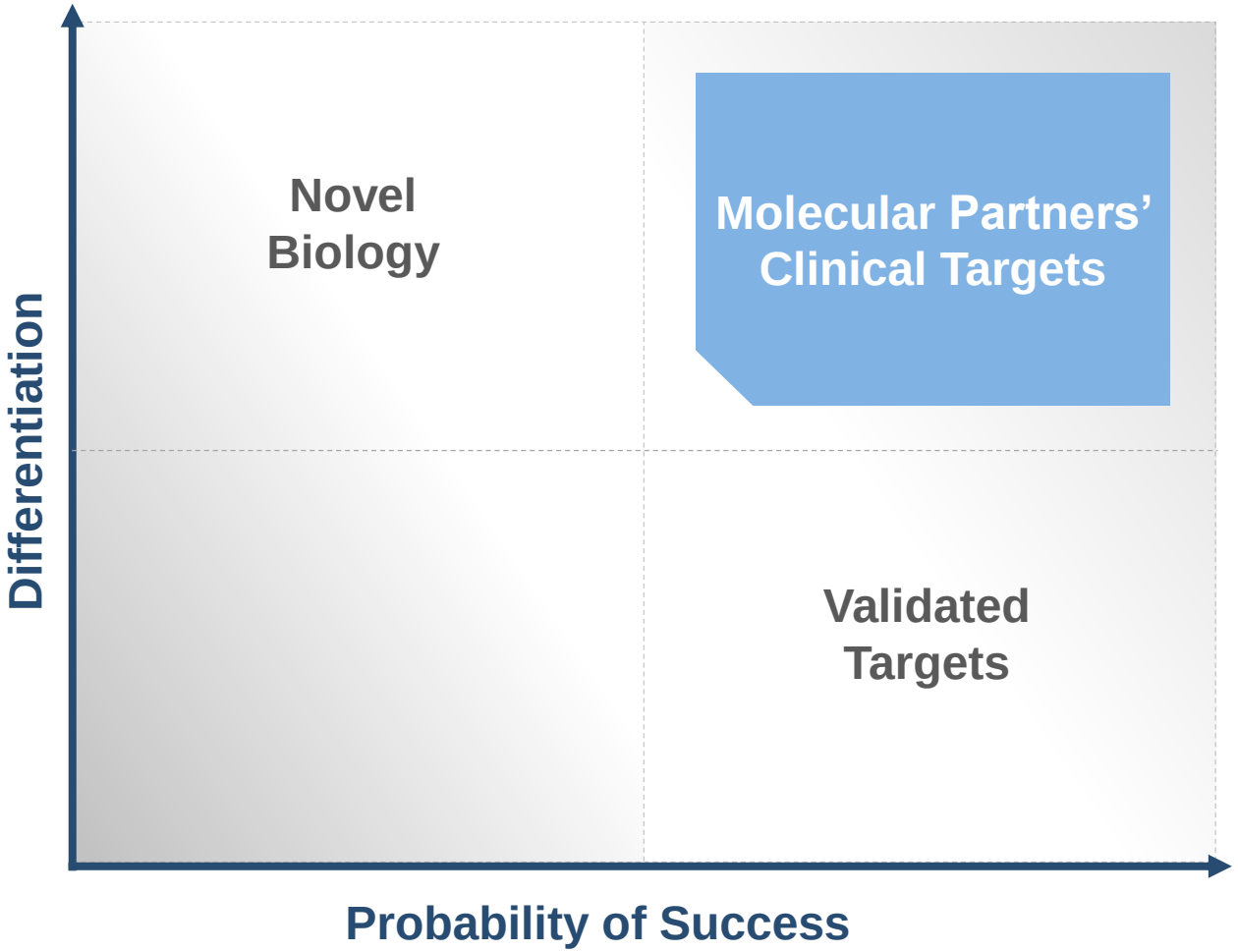
How do we Select Targets for Optimized Risk/Reward



OUR PURPOSE:

Transform the lives of people with cancer by delivering truly innovative therapies

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Right Team, Right Time

Key leadership appointments in 2019

Daniel Steiner

- Protein engineer
- DARPin® expert

Passion for science & building high-performing teams

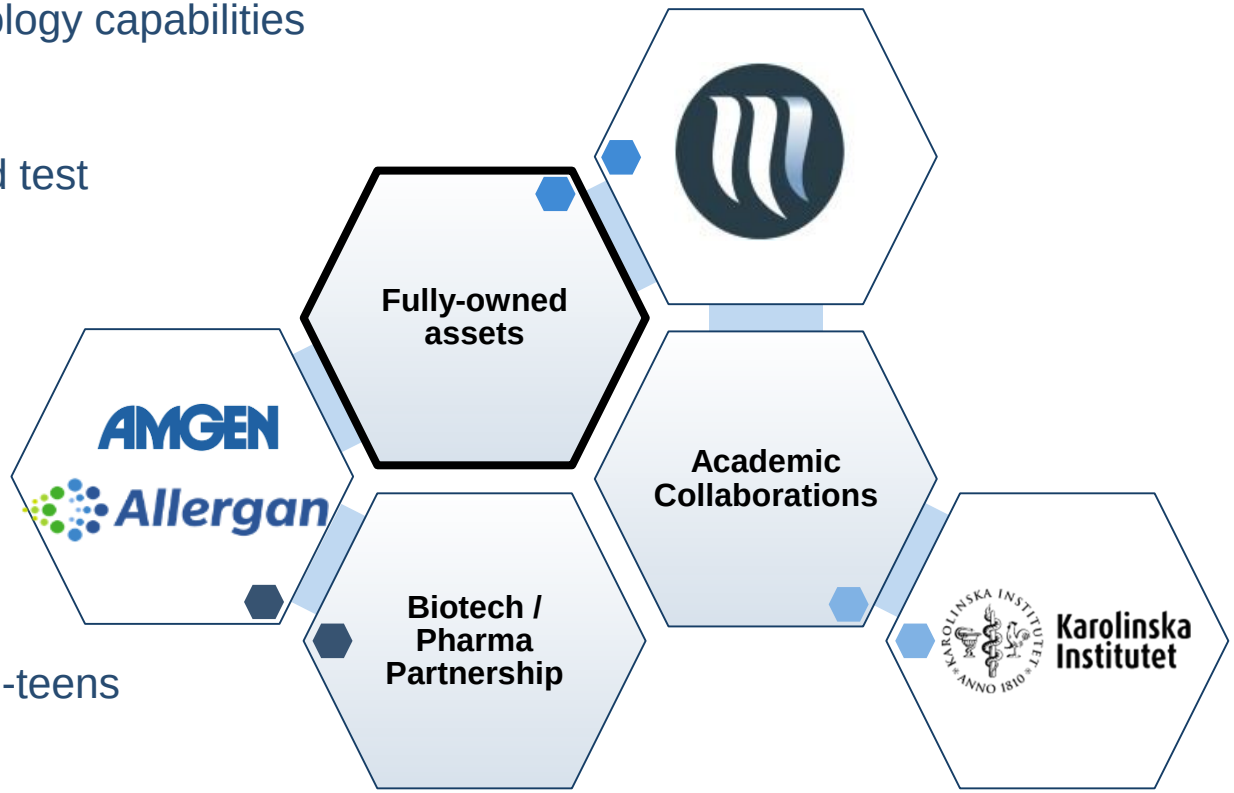
Nicolas Leupin

- Medical oncologist
- Argenx, CMO
- Celgene

Passion for transforming research data into patient value

Flexible Business Model to Maximize Product Value

- Investment in **proprietary pipeline** to bring DARPin® candidates forward
- Engage in **collaborations** to maximize individual product candidate value
  - **Academic and industry collaborations** to access biology capabilities
  - **Allergan** is advancing abicipar in ophthalmology
  - Collaboration with **Amgen** co-developing MP0310 and test of multiple combinations
  - **Explore speed-up and broadening of MP0250** development in collaboration with partner (2020)



- **Cross-funding** of pipeline via partnered assets
  - AGN: USD 360m in potential MS & DD royalties to mid-teens
  - AMG: USD 50m upfront payment, USD 497m in potential MS & DD royalties to high-teens

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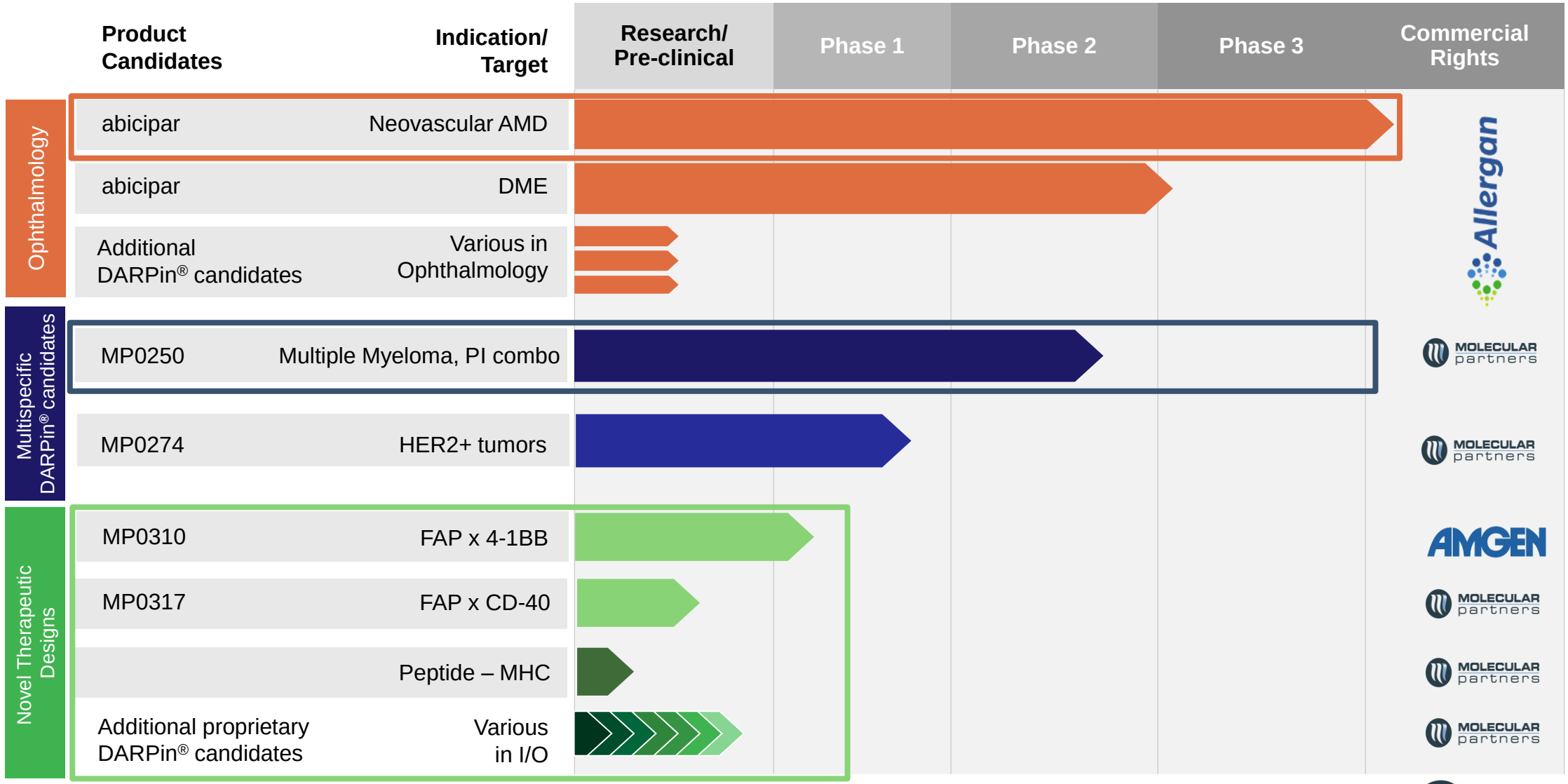
A Balanced and Robust Portfolio



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2011

Phase I MP0112 Wet AMD Study: Results Of A Single Escalating Dose Study With DARPin® MP0112 In Wet AMD

S. Wolf, EH. Souied, M. Mauget-Faysse, F. Devin, M. Patel, UE. Wolf-Schnurrbusch, M. Stumpp for the MP0112 wet AMD Study Group

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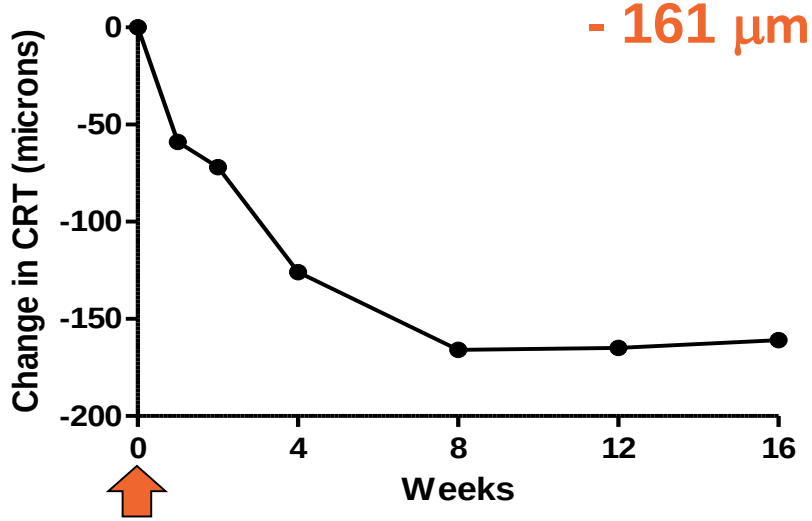
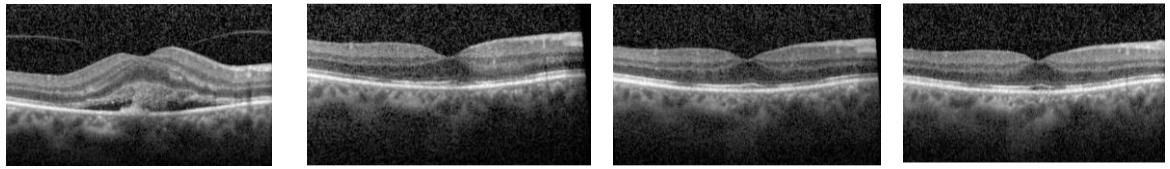
ARVO®
The Association for Research in Vision and Ophthalmology

Universitätsklinik für Augenheilkunde

Most Patients Profit Throughout 16 Weeks from a Single Injection of MP0112*

OCT





Screening Week 8 Week 12 Week 16

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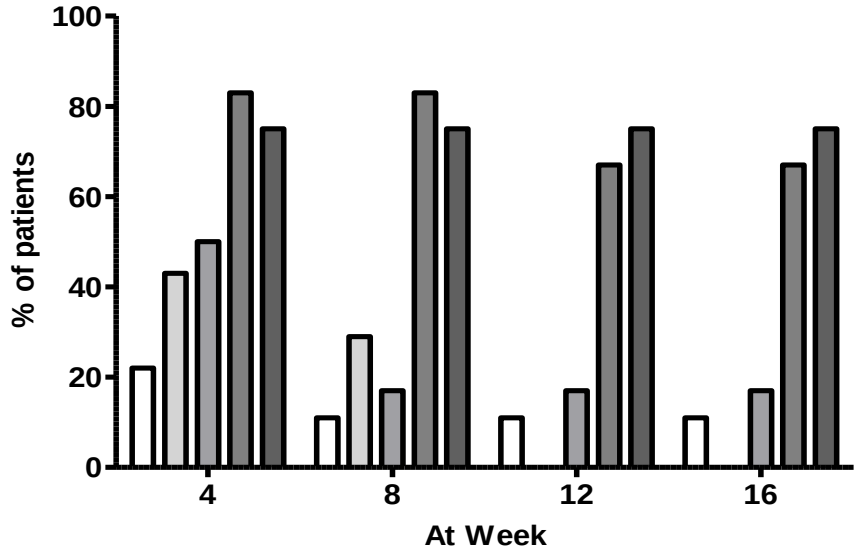
The Association for Research in Vision and Ophthalmology

* 1mg & 2 mg cohort

% of patients with NO rescue therapy



Rescue Criteria

- VA loss of 6 or more letters
- Lesion or leakage increase
- New lesions
- Sub-retinal fluid increase

0.04 mg (N=9)
0.15 mg (N=7)
0.4 mg (N=6)
1.0 mg (N=6)
2.0 mg (N=4)

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Abicipar

Jeremy D. Wolfe, MD, MS

Associated Retinal Consultants
Oakland University William Beaumont School of Medicine
Royal Oak, MI

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Overview

- Rationale for development
- DARPin platform/Abicipar
- Unmet need
- Clinical trial results
  - Year 2 data (CEDAR/SEQUOIA)
- Conclusions

Global Prevalence of AMD

Age-related macular degeneration (AMD) is the **main cause of irreversible moderate or severe visual impairment** or blindness in people **aged 50 years and older**[1]

Accounts for **4.4%** of cases of moderate or severe visual impairment and **5.9%** of cases of blindness in people aged 50 years and older worldwide[1]

The **global prevalence** of advanced AMD is **growing** due to the aging population[2]

It is estimated that by 2020, 11.26 million people will have nAMD, **rising to 18.57 million in 2040**[2]

1. Flaxman SR, et al. *Lancet Glob Health*. 2017;5(12):e1221–e1234.; 2. Wong WL, et al. *Lancet Glob Health* 2014;2:e106-16.

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Rationale for Development of Abicipar

- Anti-VEGF therapy has become preferred treatment for nAMD[1]
- Current anti-VEGF therapies require routine monitoring and frequent intravitreal injections (typically every 4 – 8 weeks) for optimal outcomes[1]
  - When treatment intervals are extended in clinical practice, either through PRN or “Treat & Extend” regimens, visual acuity gains are not as well maintained[2,3]
- Abicipar is a DARPin® therapeutic being investigated as a potential treatment for nAMD with a quarterly injection interval after two monthly loading doses

PRN = pro re nata

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. AAO Preferred Practice Pattern, Age-Related Macular Degeneration. Updated Jan 2015.; 2. CATT Research Group. *Ophthalmology*. 2012;119(7):1388–1398.; 3. Rayess N, et al. *Am J Ophthalmol*. 2015;159:3–8.

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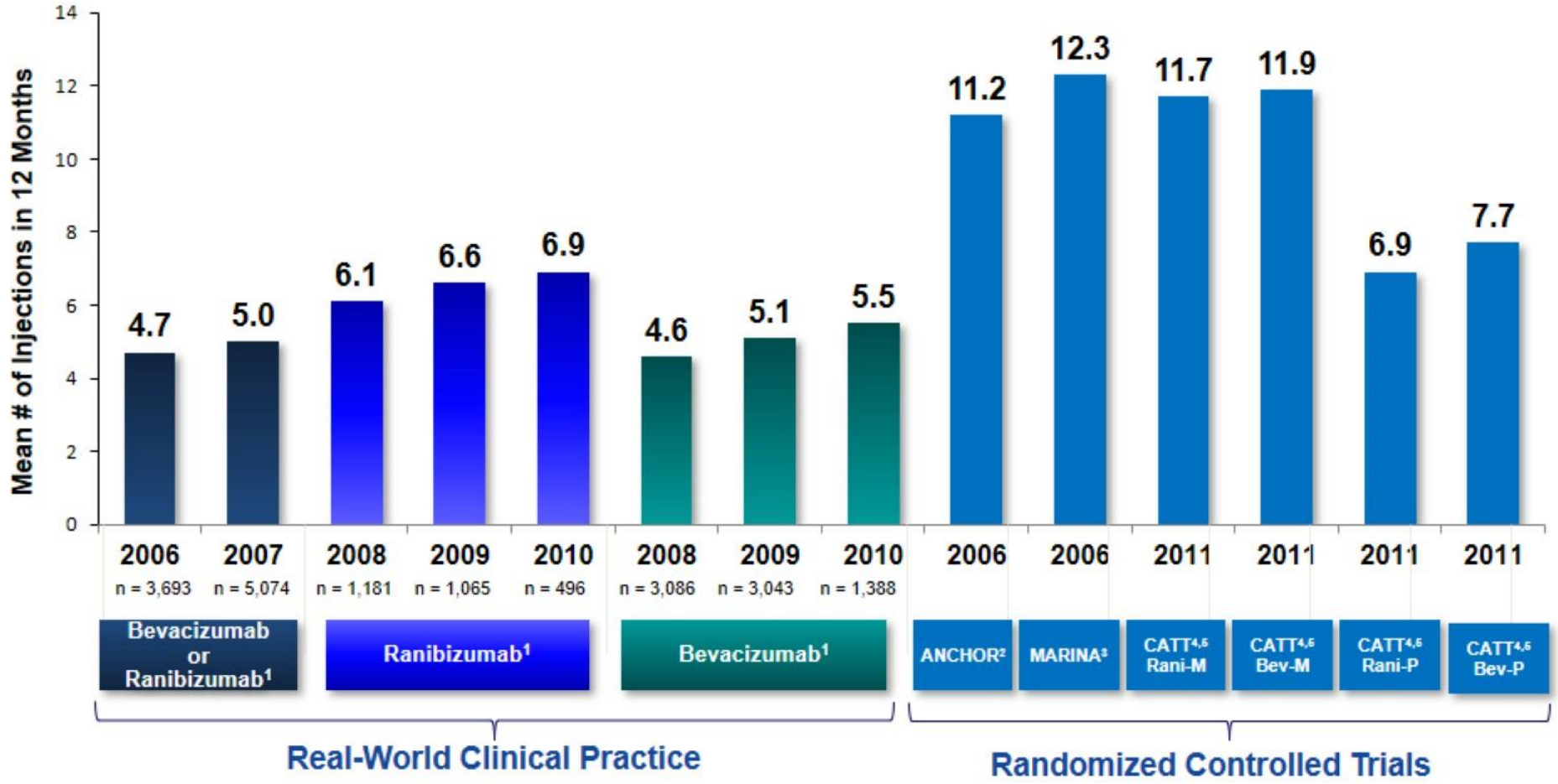
Anti-VEGF Injection Frequency in 12 Months in Clinical Practice vs. Landmark AMD RCTs



The content on this slide is not intended to imply comparisons of clinical efficacy or safety of the studied agents

1. Holekamp NM, et al. *Am J Opthalmol*. 2014;157:825-833.; 2. Brown DM, et al. *N Engl J Med*. 2006;355(14):1432–1444.; 3. Rosenfeld PJ, et al. *N Engl J Med*. 2006;355(14):1419–1431.; 4. CATT Research Group. *N Engl J Med*. 2011;363(20):1897–1908.; 5. CATT Research Group. *Ophthalmology*. 2012;119(7):1388–1398.

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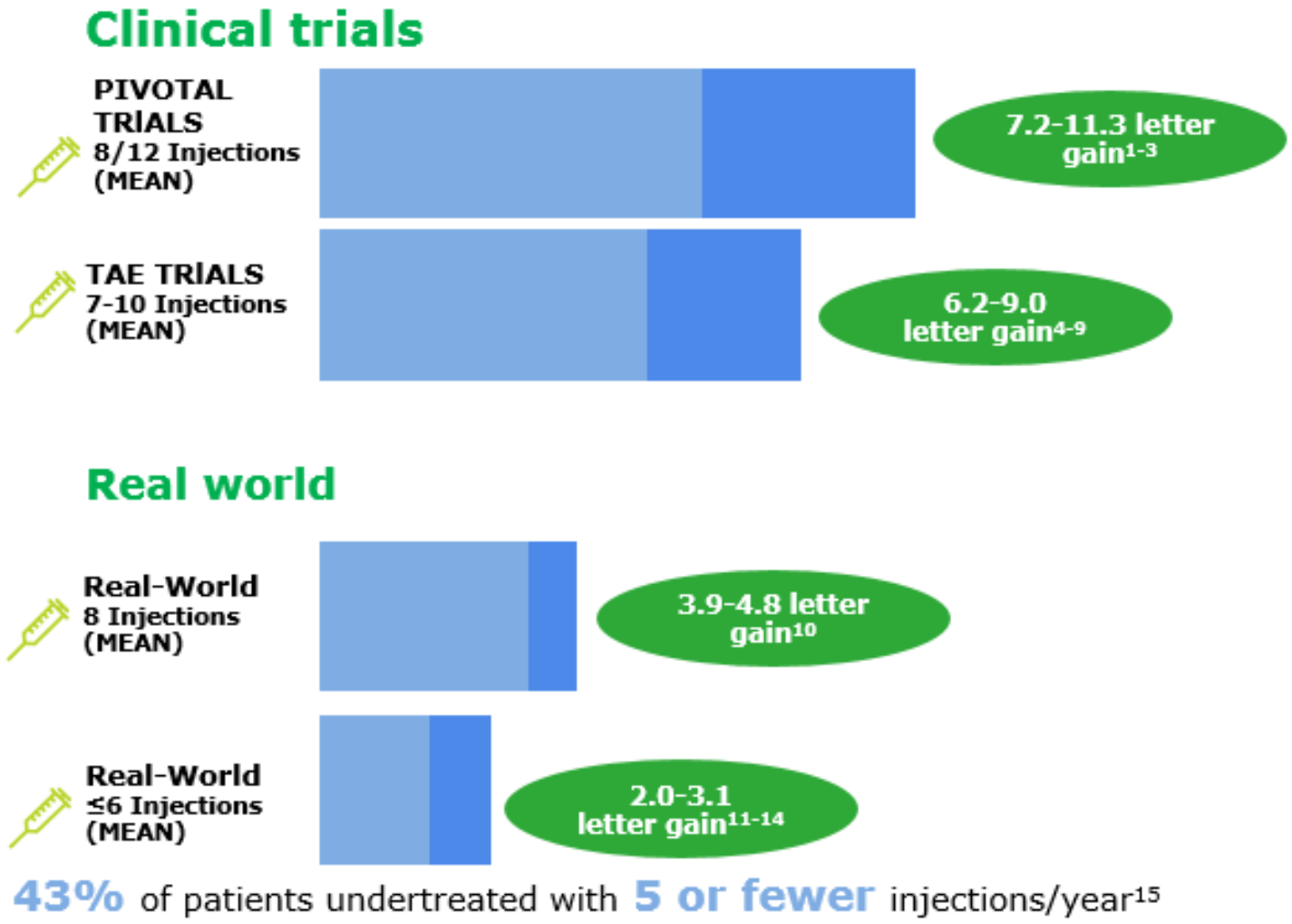
Real-World Evidence Shows Patients Aren't Achieving the Vision Gains Seen in Clinical Trials



- **References: 1.** Brown DM, et al. *Ophthalmology.* 2009;116:57–65. **2.** Rosenfeld PJ, et al. *N Engl J Med.* 2006;355:1419–1431. **3.** Heier JS, et al. *Ophthalmology.* 2012;119:2537–2548. **4.** Wykoff CC, et al. *Ophthalmology.* 2015;122:2514–2522. **5.** Kertes PJ, et al. EURETINA 2017. **6.** Silva R, et al. *Ophthalmology.* 2018;125:57–65. **7.** Berg K, et al. *Ophthalmology.* 2015;122:146-152. **8.** DeCroos FC, et al. *Am J Ophthalmol.* 2017;180:142-150. **9.** Wai et al. *Am J Ophthalmic Clin Trials*. 2018;1:1-6. **10.** Gillies MC, et al. *Ophthalmology.* 2016;123:2545–53. **11.** Holz FG, et al. EURETINA 2017; Oral presentation. **12.** Holz FG, et al. *Br J Ophthalmol.* 2015;99:220–6. **13.** Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. *Ophthalmology.* 2014;121:1092–101. **14.** Kim LN, et al. *Retina.* 2016;36:1418–31. **15.** Treatment patterns & outcomes during 12-months of nAMD Management in Real-World clinical practice, Charles Wykoff **16.** American Society of Retina Specialists Preferences and Trends (PAT) Survey.

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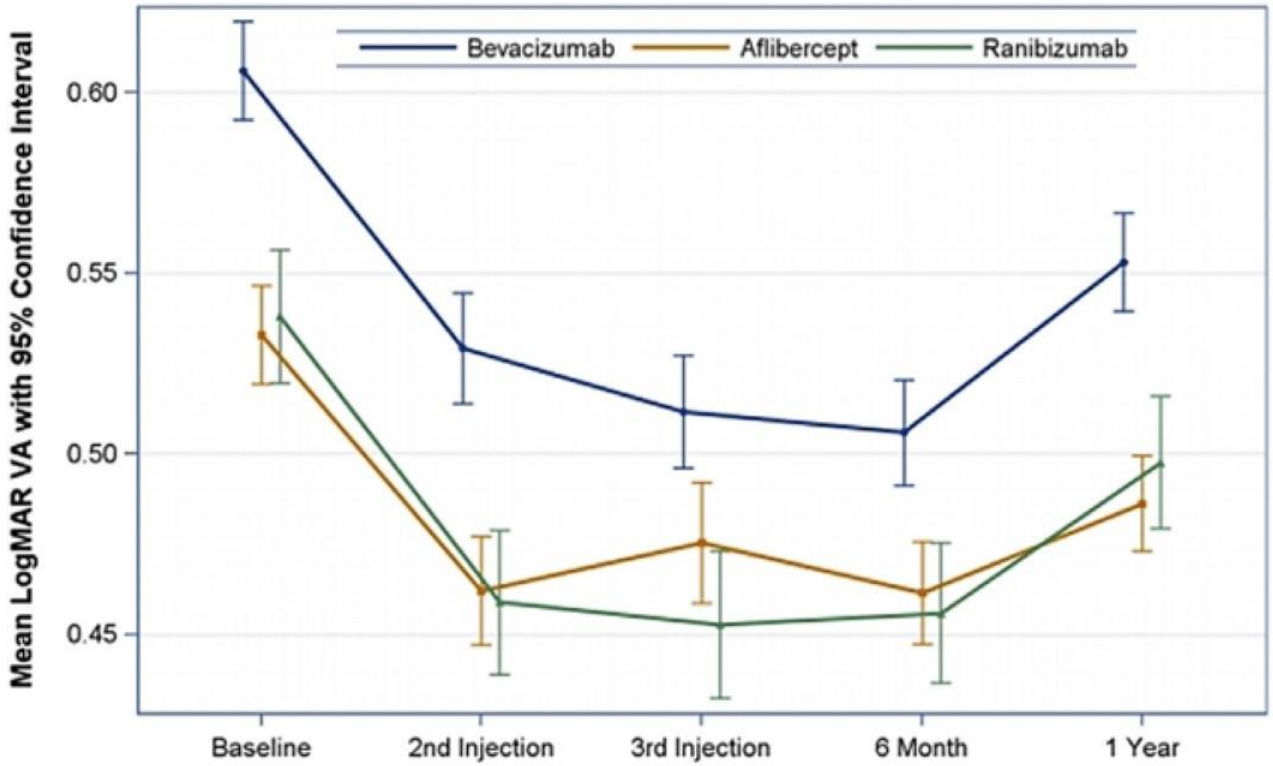
Real-World Vision in AMD Patients Treated with Anti-VEGF Monotherapy

Efficacy Results: Visual Acuity at 1 Year



- 1 year, retrospective, non-randomized study compared real-world visual acuity in nAMD patients treated with anti-VEGF monotherapy
- IRIS Registry participants were divided into 3 groups: bevacizumab (n = 6,723), ranibizumab (n = 2,749), aflibercept (n = 4,387)

- **Mean number of injections at 1 year was 6.4 in the ranibizumab group, 6.2 in the aflibercept group, and 5.9 in the bevacizumab group**
- **Compared with randomized clinical trials, anti-VEGF in the clinical setting was less intensive and resulted in less visual improvement**

1. Rao P, et al. Ophthalmology. 2018;125(4):522-528.

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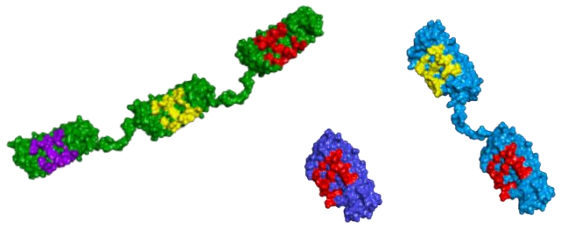
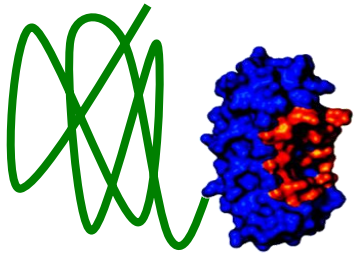
DARPin® Therapeutics and Abicipar Pegol (Abicipar)

The Platform



DARPin® molecules

The Compound



abicipar pegol

Comparison with Ranibizumab

Characteristic	abicipar pegol[a]	ranibizumab
Molecular weight	34 kDa[b,1]	48 kDa
Binding affinity for VEGF-A (Kd)	0.4 pM[2]	42.5 pM
Half-life (t½) in vitreous in animal studies	4–7 days[1]	3 days[3]

[a]Referred to as abicipar in subsequent slides; [b]14 kDa for protein and 20 kDa for PEG portion of the molecule.; VEGF, vascular endothelial growth factor. References: 1. Data on file, Allergan plc; 2. Souied *et al*, *Am J Ophthalmol.* 2014;158:724–732, 2014; 3. Bakri *et al. Ophthalmology.* 2007;114:2179–2182.; VEGF, vascular endothelial growth factor

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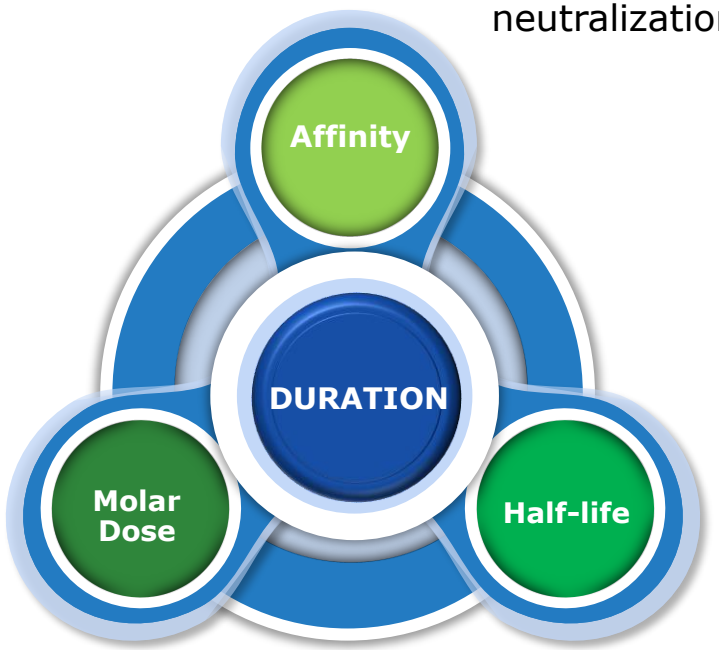
Abicipar Is Designed to Optimize 3 Drivers of Duration

High Affinity[1]
- Abicipar's affinity is designed for potent VEGF neutralization



High Molar Dose[1]
- 2mg of Abicipar provides a high molar dose

Long Half-life[2]
- PEGylation enhances intravitreal half-life

1.Stumpp MT, et al. *Drug Discovery Today* 2008;13:695–701. 2. Molecular Partners. About DARPin® Technology. 2017. Available at: http://www.molecularpartners.com/aboutdarpins/ [Accessed October 2017].

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Abicipar Phase III Clinical Trials: CEDAR & SEQUOIA

Abicipar is under investigation. The safety and efficacy of this product have not been established.

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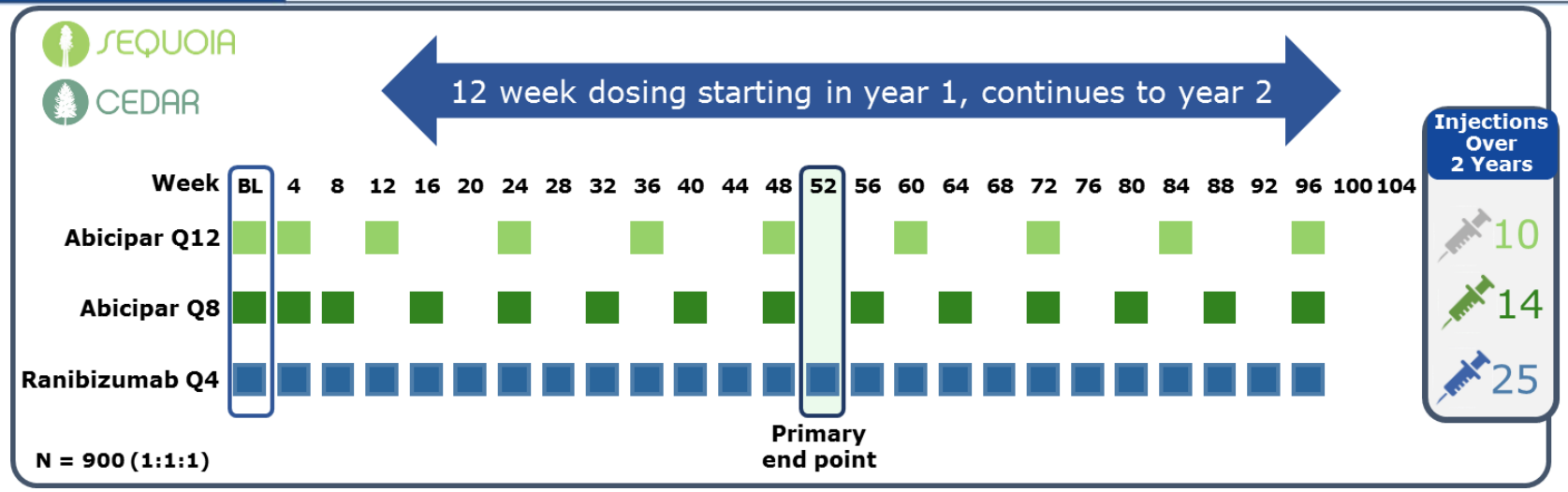
CEDAR SEQUOIA PHASE III STUDY DESIGN

Study Design	Two randomized, double-masked, parallel-group, clinical trials with identical protocols
Objective	To assess safety & efficacy of abicipar compared with ranibizumab in treatment-naïve patients with nAMD
Primary Endpoint	Proportion of patients with stable vision (loss of < 15 ETDRS letters compared with baseline) at Week 52
Key Secondary Endpoints	Mean change from baseline in ETDRS BCVA, mean change from baseline in CRT, and proportion of patients with ≥ 15-letter gain at Week 52



BCVA = best-corrected visual acuity; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; nAMD = neovascular age-related macular degeneration

Abicipar is under investigation and the safety and efficacy of this product have not been established.

ClinicalTrials.gov Identifiers: NCT02462928 and NCT02462486

1. Khurana RN, et al. Presented at AAO 2018 Annual Meeting in Chicago, IL, USA; Oct 27-30, 2018.

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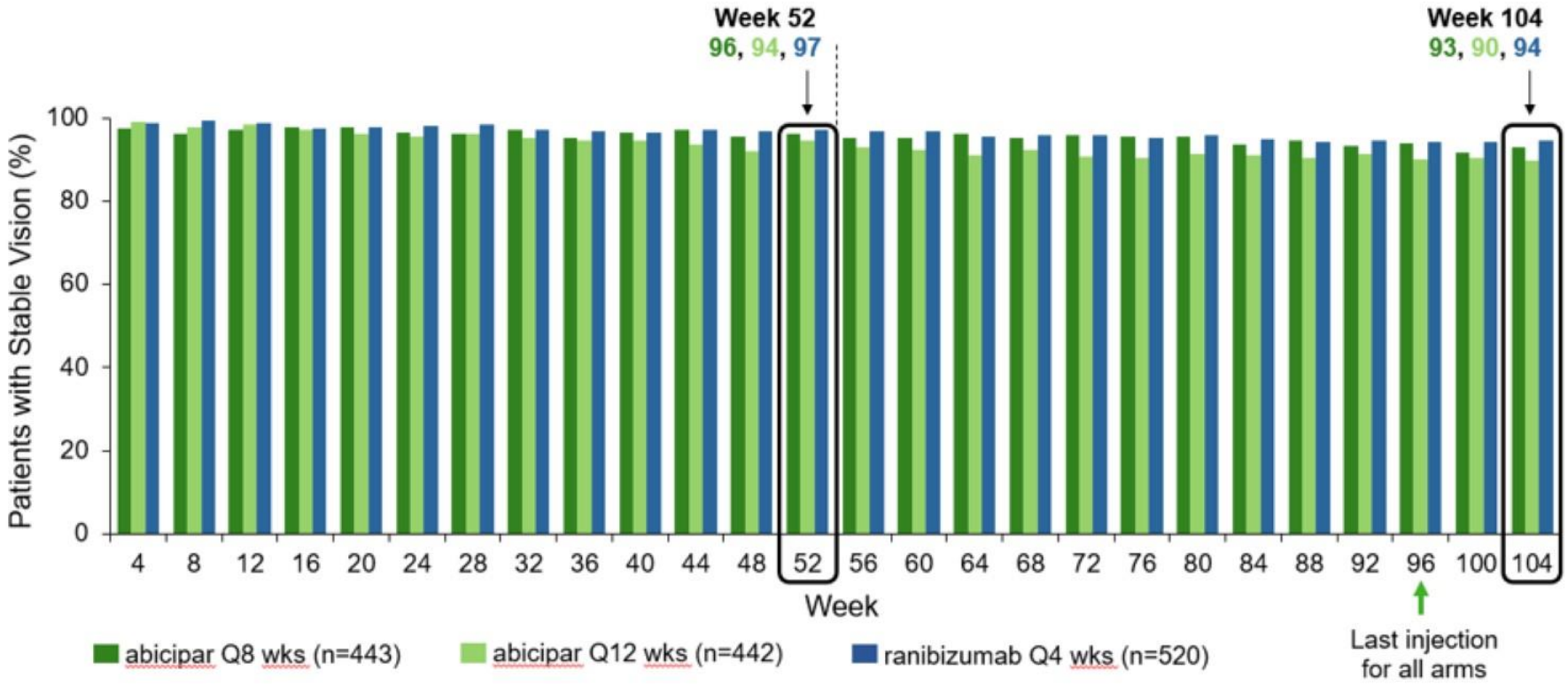
Primary Endpoint: Proportion of Patients With Stable Vision at Weeks 52 and 104

Phase III CEDAR & SEQUOIA



Abicipar treatment effect at Week 52 was maintained in the 2nd year with quarterly injections (10) vs. monthly ranibizumab injections (25)

*Completer population: Patients who completed the study without escaping to standard of care by Week 104

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

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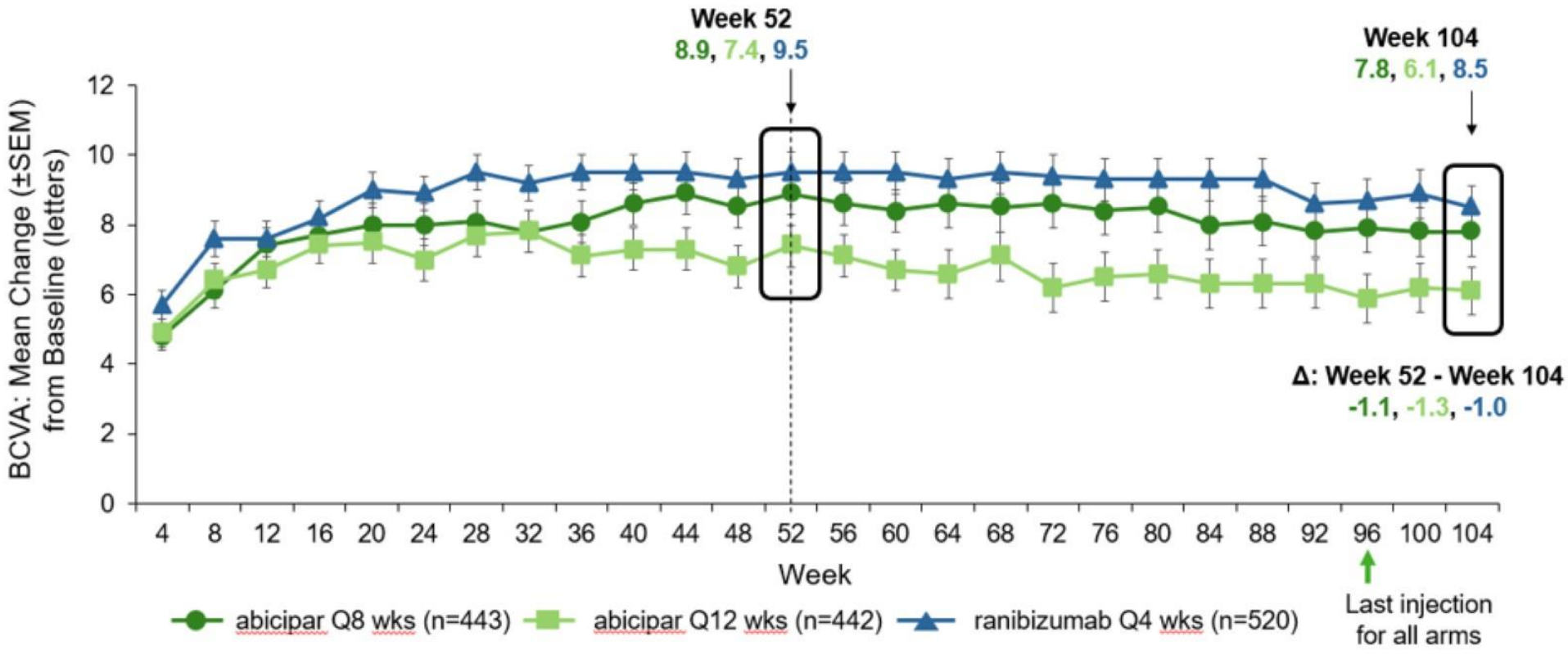
Secondary Endpoint: Mean Change in BCVA From Baseline at Weeks 52 and 104

Phase III CEDAR & SEQUOIA



BCVA improvement after initial doses were maintained to Week 104 with quarterly abicipar injections (10) vs. monthly ranibizumab injections (25)

BCVA = best-corrected visual acuity; SEM = standard error of the mean

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

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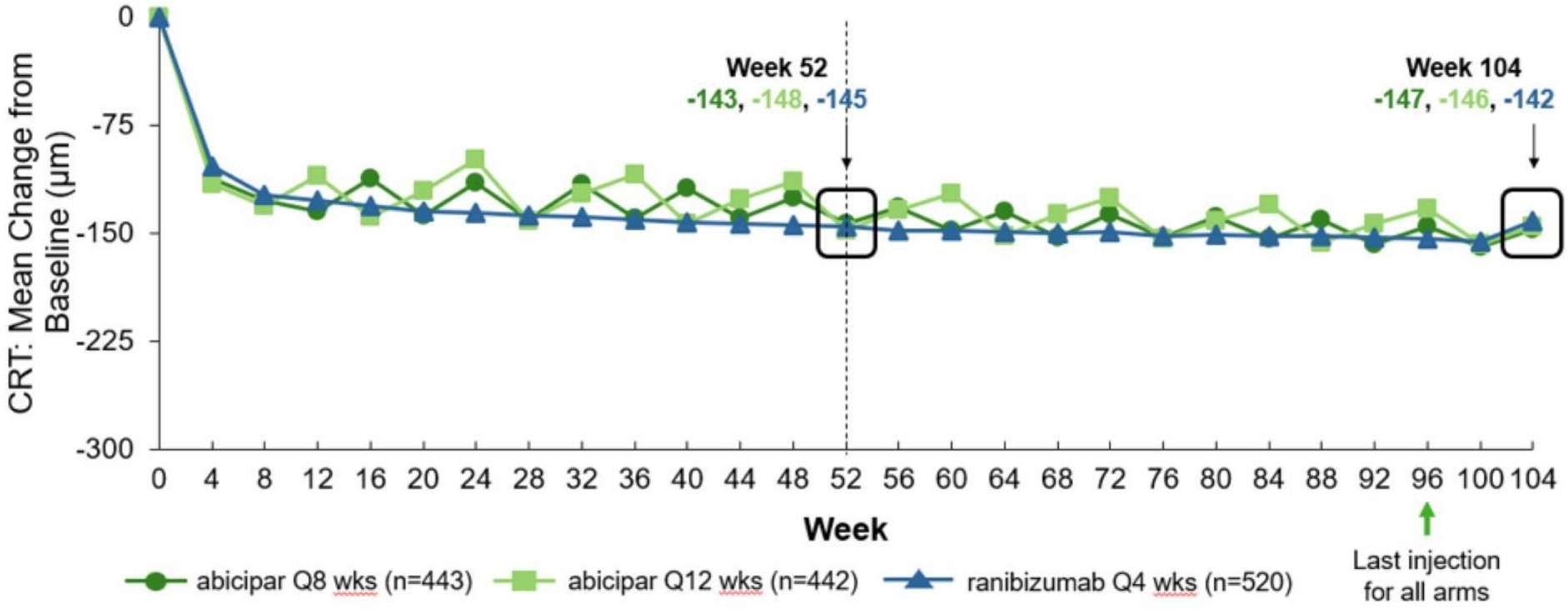
Secondary Endpoint: Mean Change in CRT From Baseline at Weeks 52 and 104

Phase III CEDAR & SEQUOIA



CRT improvement after initial doses were maintained to Week 104 with quarterly abicipar injections (10) vs. monthly ranibizumab injections (25)

CRT = central retinal thickness

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

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Phase III CEDAR & SEQUOIA

Safety: Cumulative Treatment-Emergent Adverse Events (TEAEs) Through Week 104

Adverse event, n (%)	Abicipar 2 mg q8 wks n = 625	Abicipar 2 mg q12 wks n = 626	Ranibizumab 0.5 mg q4 wks n = 625
All TEAEs	548 (87.7)	552 (88.2)	535 (85.6)
Ocular	416 (66.6)	428 (68.4)	388 (62.1)
Nonocular	418 (66.9)	435 (69.5)	465 (74.4)
Treatment-related TEAE	237 (37.9)	257 (41.1)	196 (31.4)
Ocular	232 (37.1)	253 (40.4)	190 (30.4)
Study drug	110 (17.6)	141 (22.5)	40 (6.4)
Study procedure	171 (27.4)	184 (29.4)	177 (28.3)
Serious TEAE	92 (29.5)	102 (32.7)	95 (30.6)

Abicipar is under investigation and the safety and efficacy of this product have not been established.

1. Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019.

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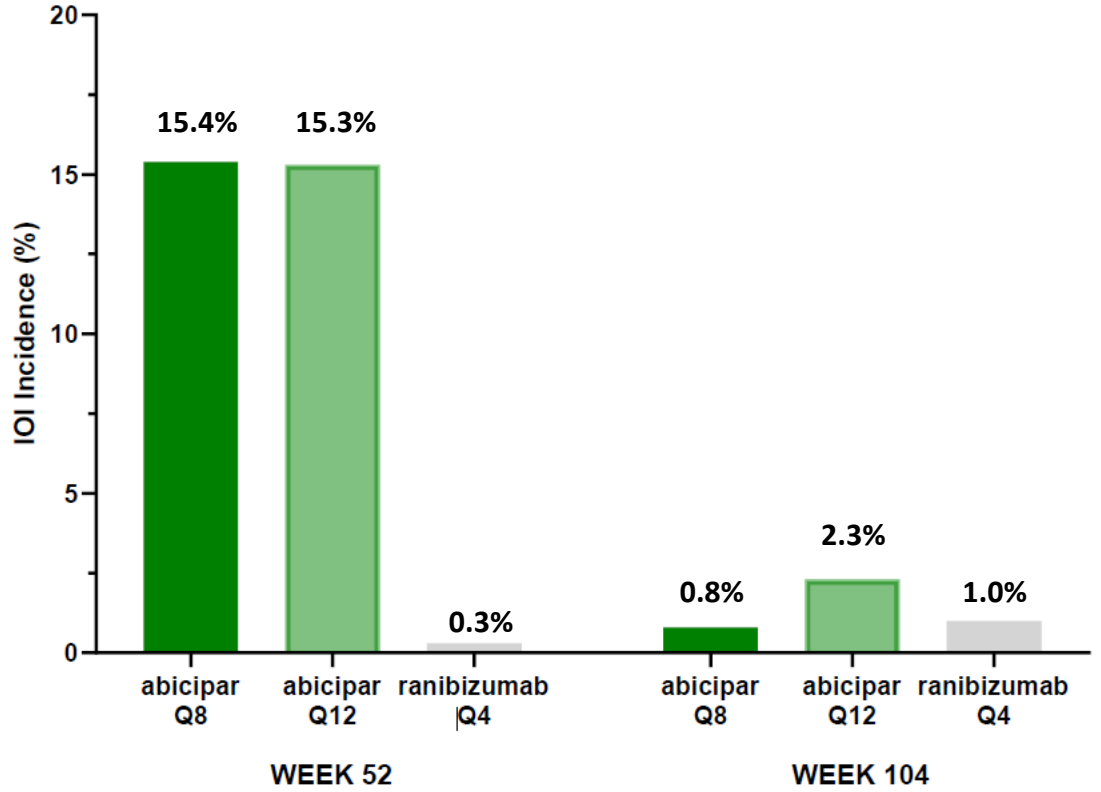
Intraocular Inflammation Through Weeks 52[1] and 104[2] Comparable risk to ranibizumab in Year 2



- Abicipar had comparable risk of IOI to ranibizumab in Year 2
- There were no new cases of retinal vasculitis and endophthalmitis from abicipar groups in Year 2

Abicipar is under investigation and the safety and efficacy of this product have not been established.

Khurana RN, et al. Presented at AAO 2018 Annual Meeting in Chicago, IL, USA; Oct 27-30, 2018
Khurana RN, et al. Presented at AAO 2019 Annual Meeting in San Francisco, CA, USA; Oct 12-15, 2019

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Key Results and Conclusions

- Visual gains achieved by the end of the first treatment year were as effectively maintained with 4 injections of abicipar as with 12 injections of ranibizumab during the second year
- BCVA and CRT improvement after initial doses were maintained to Week 104 and were similar on abicipar Q12 and ranibizumab
- Overall incidence rates of treatment-emergent adverse events at the end of the second year were comparable between treatment groups
- The rate of intraocular inflammation was comparable between treatment groups during the second year

Clinical Pipeline

Nicolas Leupin

CMO

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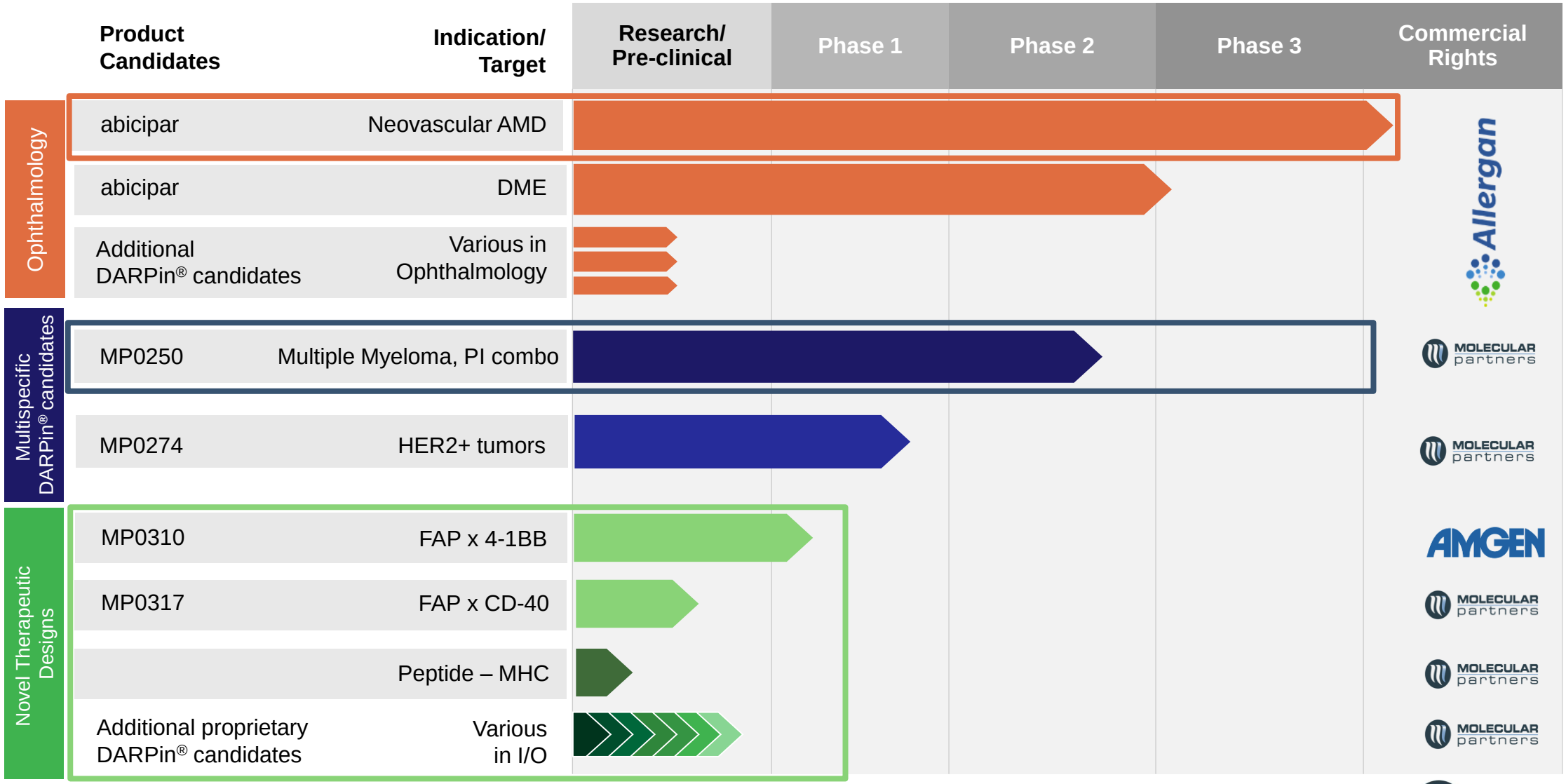

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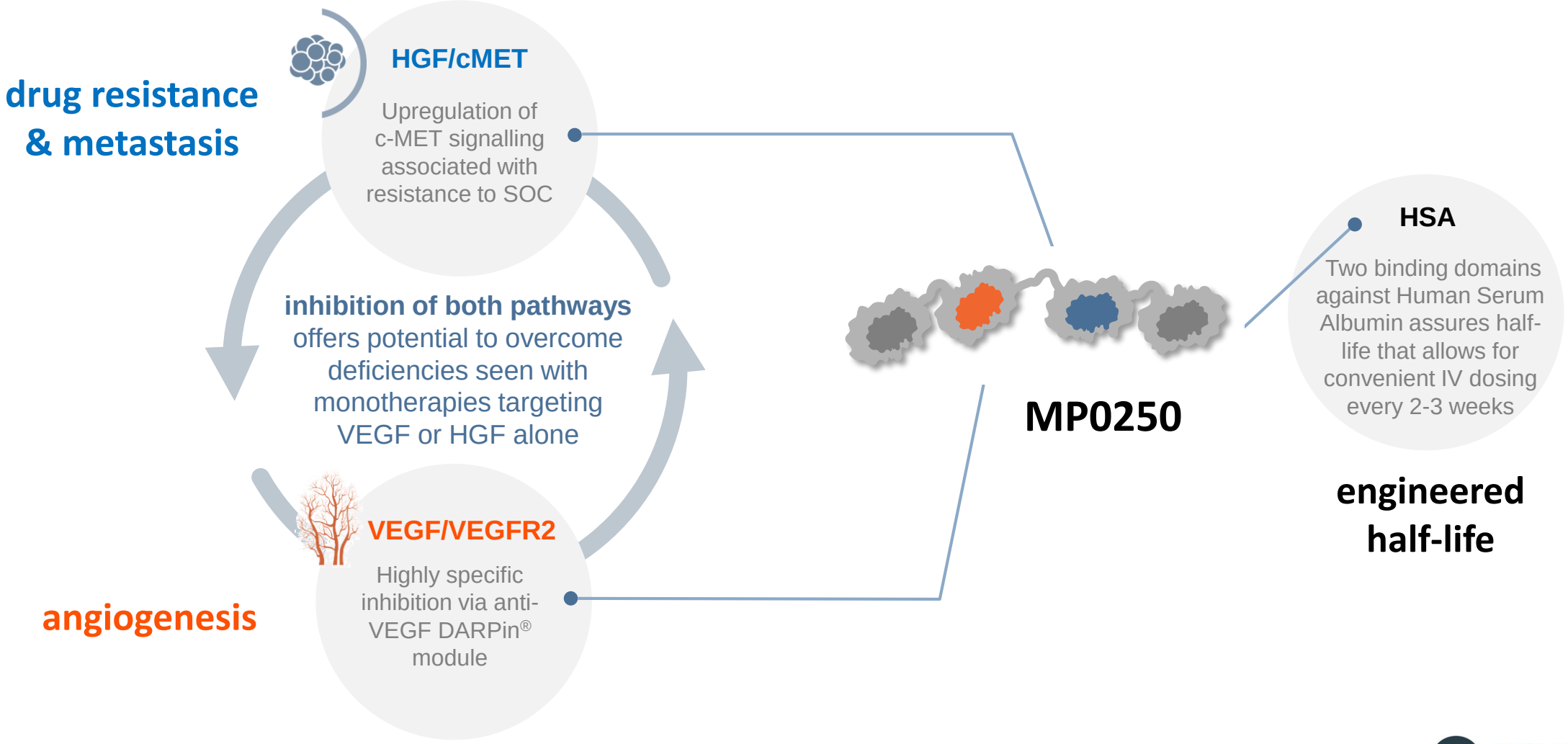
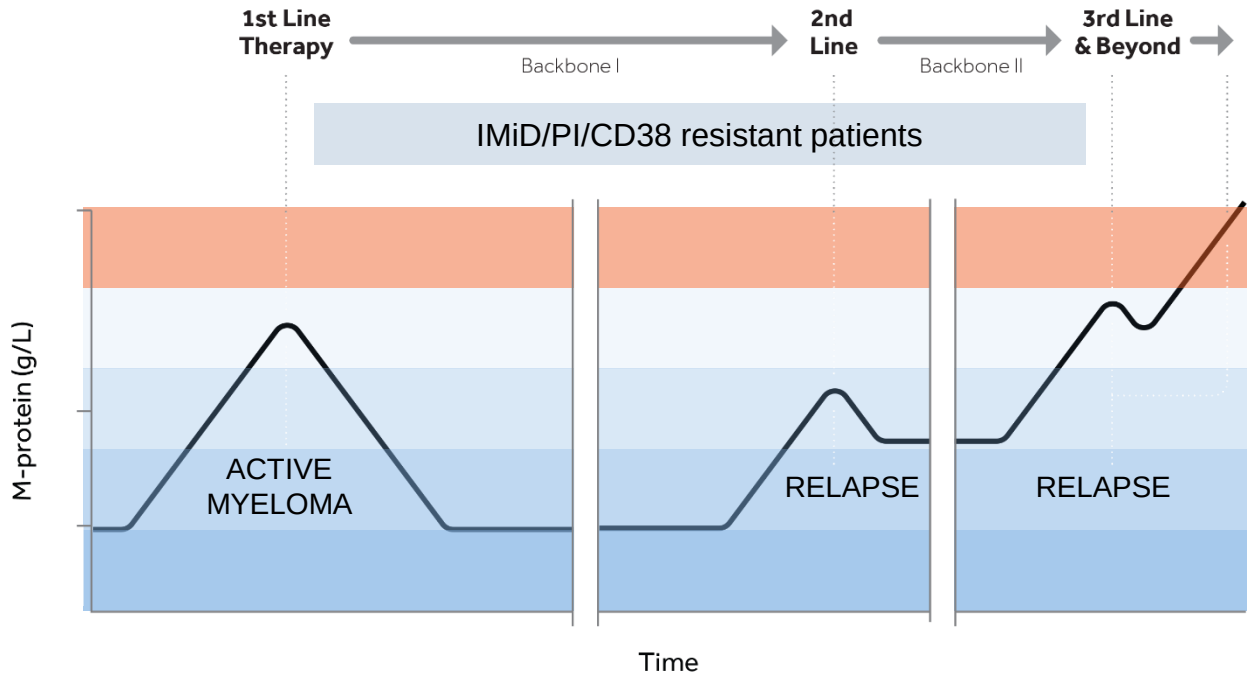
MP0250 Disrupts two Hallmarks of Cancer: Neo-angiogenesis and Resistance to both Immune and Drug Therapies



Paradigm Shift from “Chasing Clones” to Tackling Underlying Disease

Illustrative course of disease of a MM patient*: Current treatment strategy focuses on multi-clonal disease and ignores resistance



MP0250

shows strong clinical activity in combination with Bor/dex and has potential to revert resistance in heavily pre-treated R/R patients

* adapted from: Hajek, R. Strategies for the Treatment of Multiple Myeloma in 2013: Moving Toward the Cure. In “Multiple Myeloma: A Quick Reflection on the Fast Progress” (2013).

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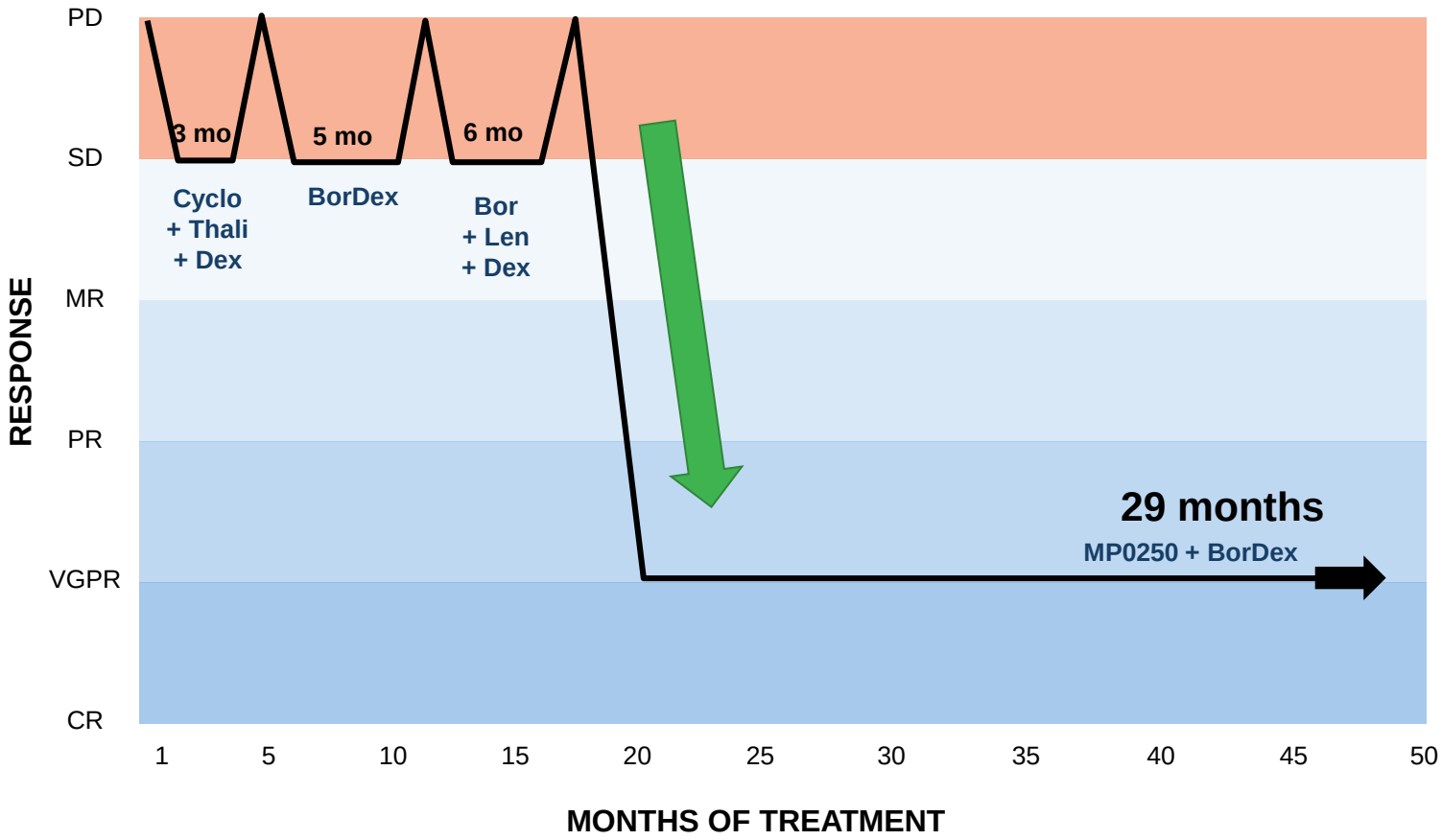
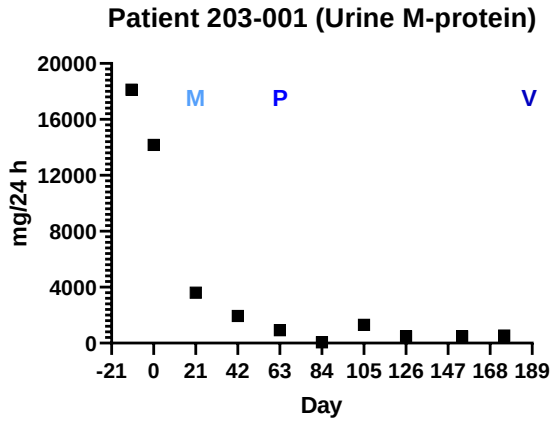
Patient 203-001: IMiD and PI Resistant 64y Female with Ongoing VGPR, on Treatment for more than 29 Months





- **64 year old female**
- 4L patient with prior therapies of Cyclo-Thal-Dex; Bor/Dex; Bor/Len/Dex, but only with limited disease control (SD at best)
- Disease characteristics: IgG kappa, t(11;14)(q13;q32)

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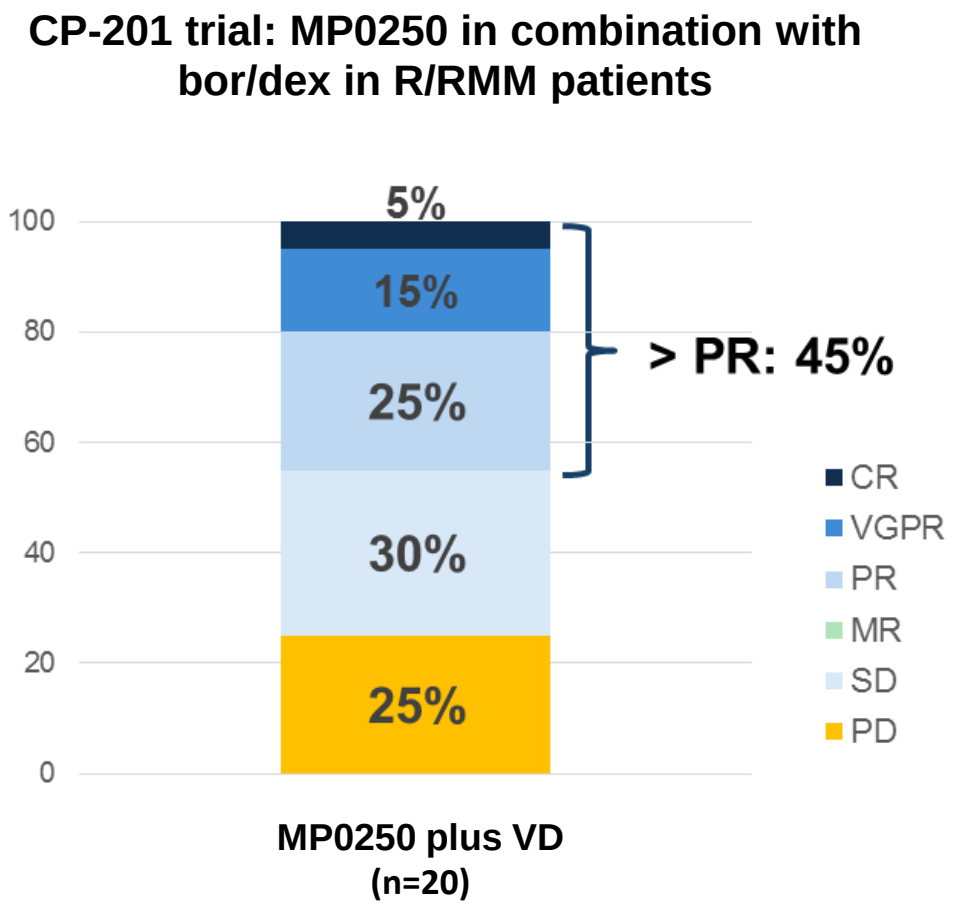
Rapid & Durable Deepening of Response in Diverse MM Phenotypes



- Updated **ASH 2019**
- **Responses** in patients who have **never responded**
- **Heavily pretreated patients**, representative of typical RRMM population; median of 4 prior lines (n=20)
- 4/6 patients coming **directly from Dara** had clinical benefit (incl. 4/5 Dara-refractory patients)
- 3/7 **patients with 1q** gain (poor outcome cytogenetics) had clinical benefit, 2 responded well
- Patients with **17p deletion** progressed quickly

MP assessment based on IMWG criteria data cut-off Sep 2019

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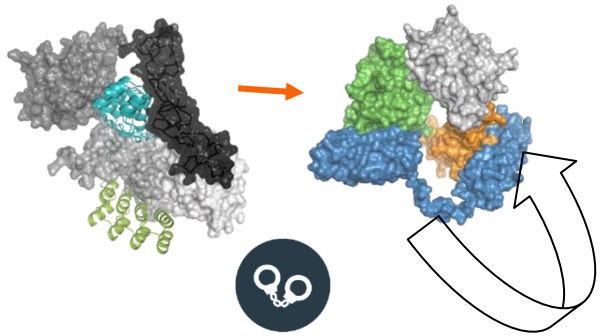
MP0274 Study Design



MP0274 Bi-paratopic DARPin®

- MP0274 **locks** HER2 in a fully inactive conformation and acts as broad allosteric inhibitor

Dose Escalation
3 by 3 Design

Leads to

Establish Dose

Dose Expansion
Up to 11 patients

Leads to

Efficacy signal

Interim evaluation

Dose Expansion
Up to 15 patients

Leads to

Efficacy signal confirmation

Establish dose and define path forward in 2020

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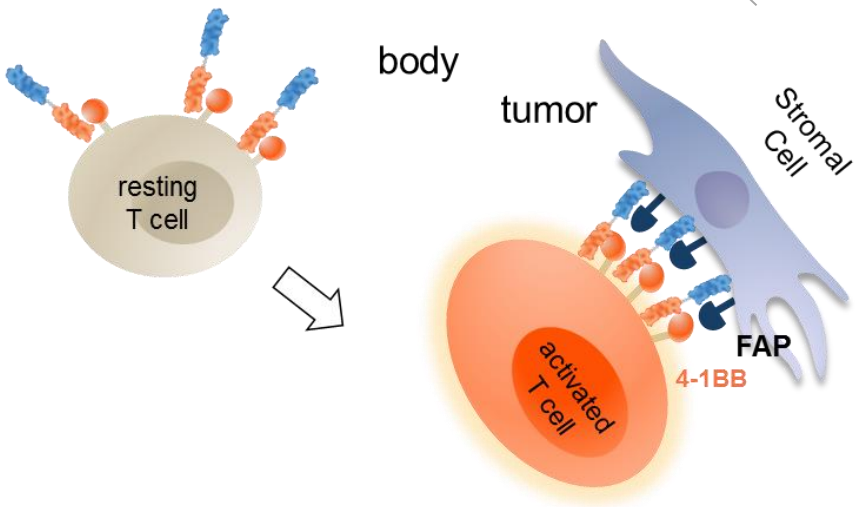
MP0310 (AMG 506; FAP x 4-1BB): Activating T cells in the Tumor

MP0310 (AMG 506)
DARPin® modules

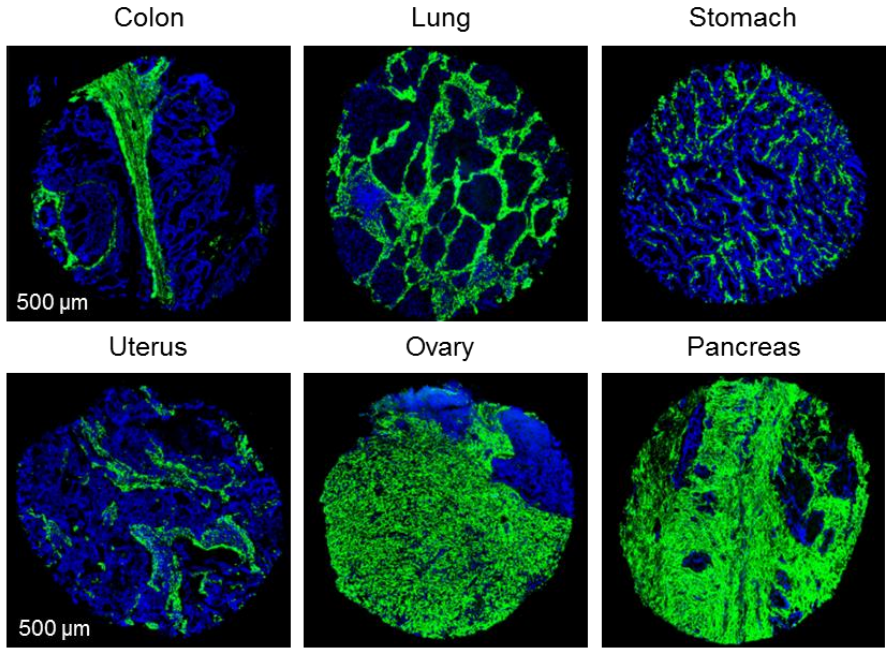
Immune modulator | Localizer | Half-life extender

4-1BB + FAP + HSA

Illustrative graphic



FAP expression in human tumor sections



Human FAP, DAPI

HSA, human serum albumin.

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MP0310 (AMG 506) Study Design

Part I
Single-Agent Dose Escalation
- ≥ 21 pts
- Single agent safety & PK/PD

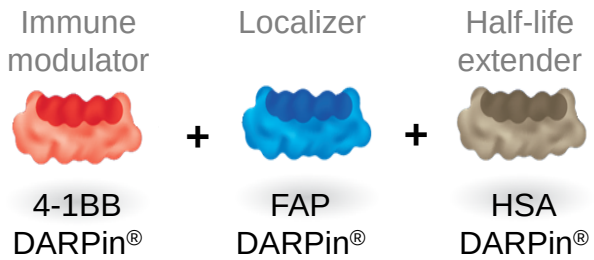
Leads to

Dose Monotherapy, Selection of Part II dose

Subsequent Parts:
Combo Dose Escalation

Leads to

- Safety, PK/PD & efficacy review
- Selection of P2 dose
- Selection of tumor types



Reaching relevant doses and expected to start MP0310 (AMG 506) combination trials in 2020

* conceptual

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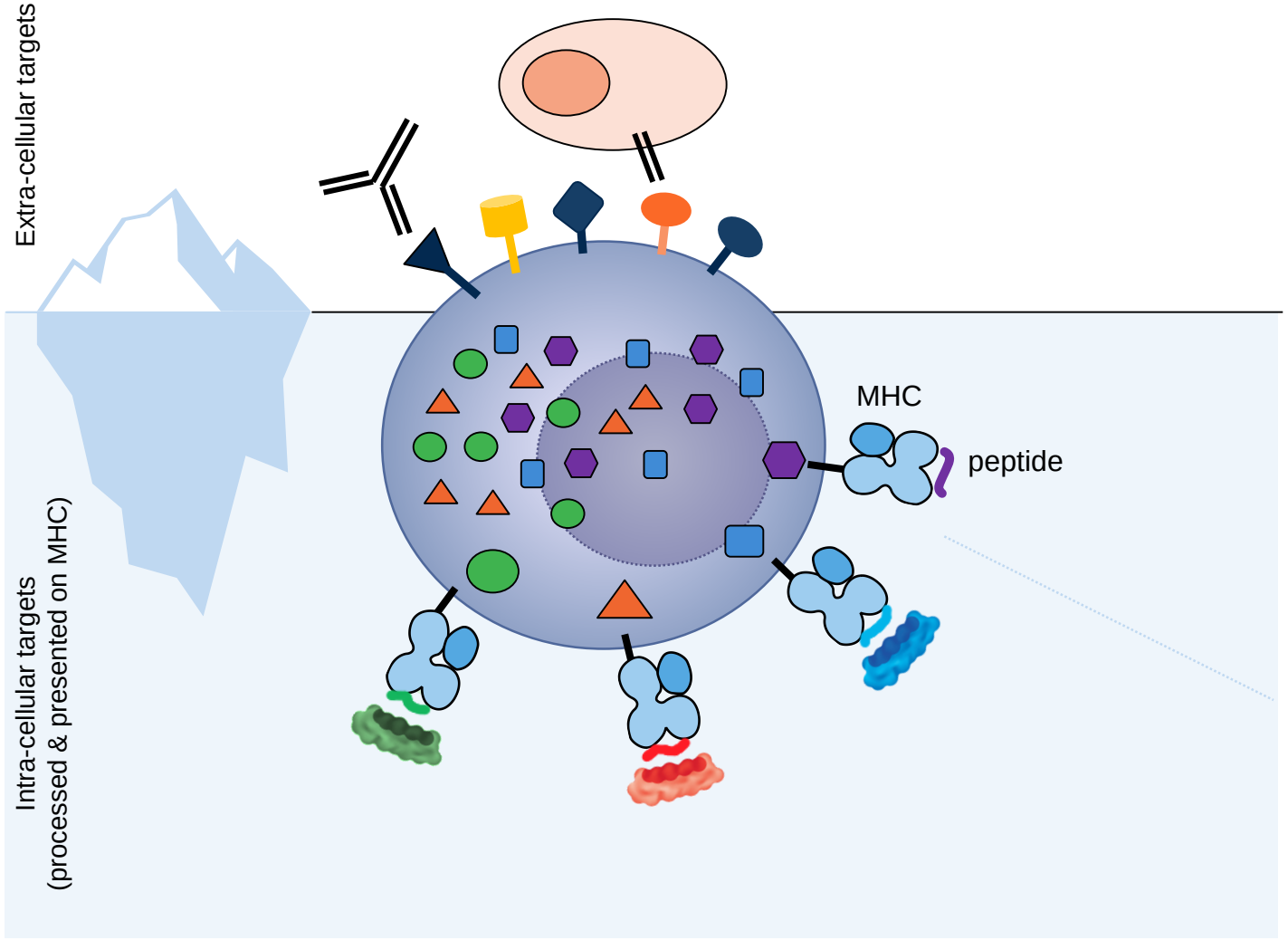
pMHC: Approach for “Inaccessible” Highly Selective Targets



Challenging to generate antibodies and enhanced T-cell receptors which bind to peptide-MHC with both high selectivity and high affinity

Opens substantial target space in Oncology, Virology and Autoimmunity

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Clinical Conclusions

- DARPin® **platform on track** to lead to **first approved** clinical candidate (abicipar)
- MP0250 shows **encouraging clinical activity in MM** patients who never responded
- **MP0274 & MP0310 are in dose-escalation** in solid tumor patients
- **Actively pushing** earlier molecules to enter clinical stage.

	Product Candidates	Indication/ Target
Ophthalmology	abicipar	Neovascular AMD
	abicipar	DME
	Additional DARPin® candidates	Various in Ophthalmology
Multispecific DARPin® candidates	MP0250	Multiple Myeloma, PI combo
	MP0274	HER2 positive
Novel Therapeutic Designs	MP0310	FAP x 4-1BB
	MP0317	FAP x CD-40
		Peptide – MHC
	Additional proprietary DARPin® candidates	Various in I/O

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Molecular Partners R&D Day

Multiple Myeloma –
Current Treatment Strategies and Results

Stefan Knop

Würzburg University Medical Center *and*

Wilhelm Sander Myeloma Research Unit

Würzburg, Germany

New York City, NY, December 12, 2019

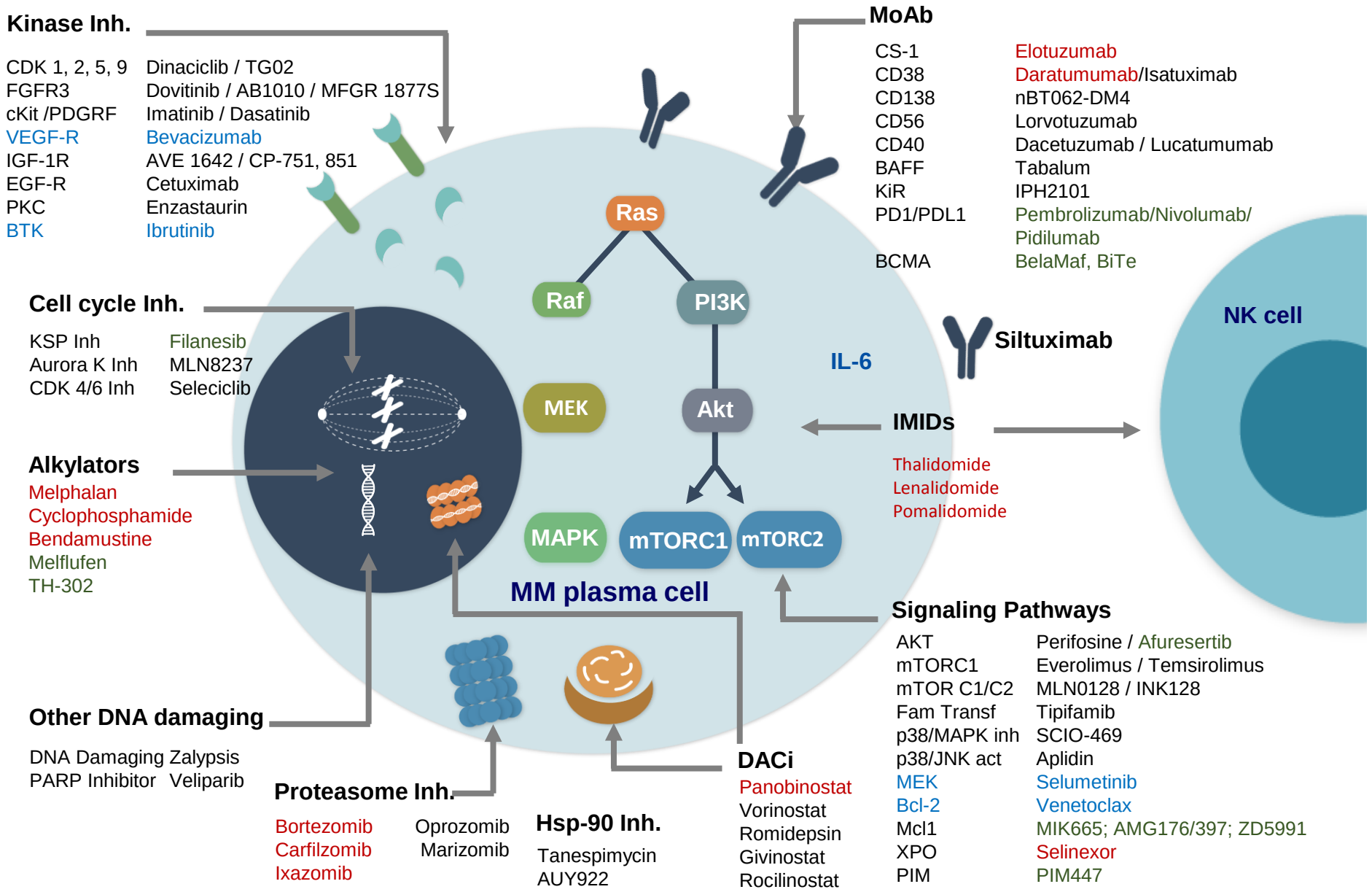
deutsche studiengruppe
multiples myelom

dsmm

doing studies on multiple myeloma

MEDIZINISCHE KLINIK
UND POLIKLINIK II

Drugs and Mechanisms of Action in MM today



New Kids on the Block: Therapeutic Armamentarium in 2019

Cytotoxic chemotherapy
- PACE, Dexa-BEAM, Bendamustin, etc.

High dose chemotherapy
- Single ASCT
- Tandem ASCT

Allogeneic SCT
- RIC

Proteasome inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

Immunmodulatory drugs(IMiDs)
- Thalidomide
- Lenalidomide
- Pomalidomide
- Iberdomide

Monoclonal antibodies
- Anti-SLAMF7 (Elotuzumab)
- Anti-CD 38 (Daratumumab, isatuximab)
- Anti-BCMA (Belantamab mafodotin)

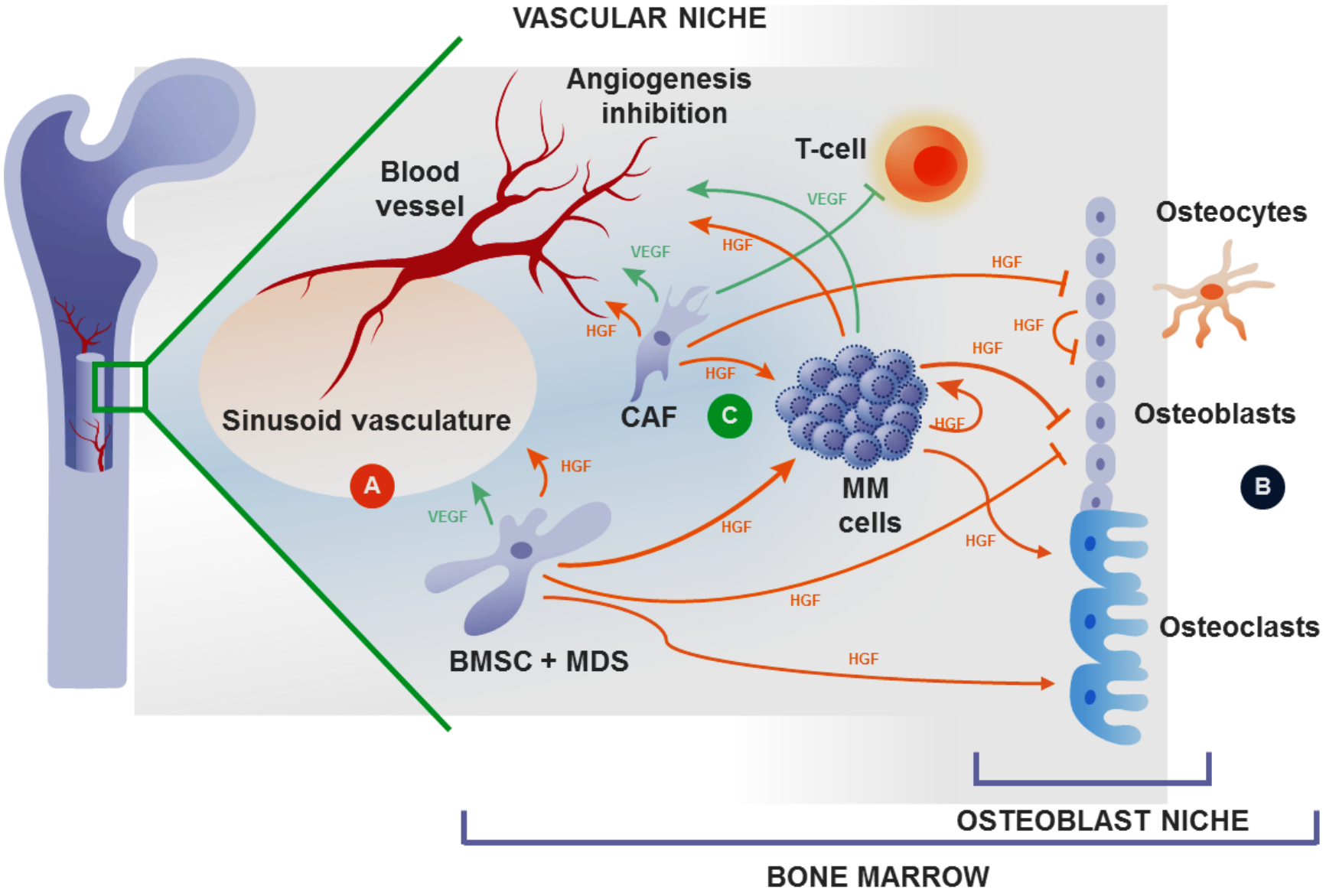
Small molecules
- HDAC inhibitor (Panobinostat)
- Bcl-2 inhibitor (Venetoclax)
- Sel. XPO1 inhibitor (Selinexor)

DARPin proteins
- HGF/VEGF inhibitor (MP0250)

BRAF inhibitors
- Vemurafenib

Adoptive T cell transfer
- Anti-BCMA CAR T cell constructs
- CTL019 CAR T cells

Novel and Unique Mechanism of Action of MP0250

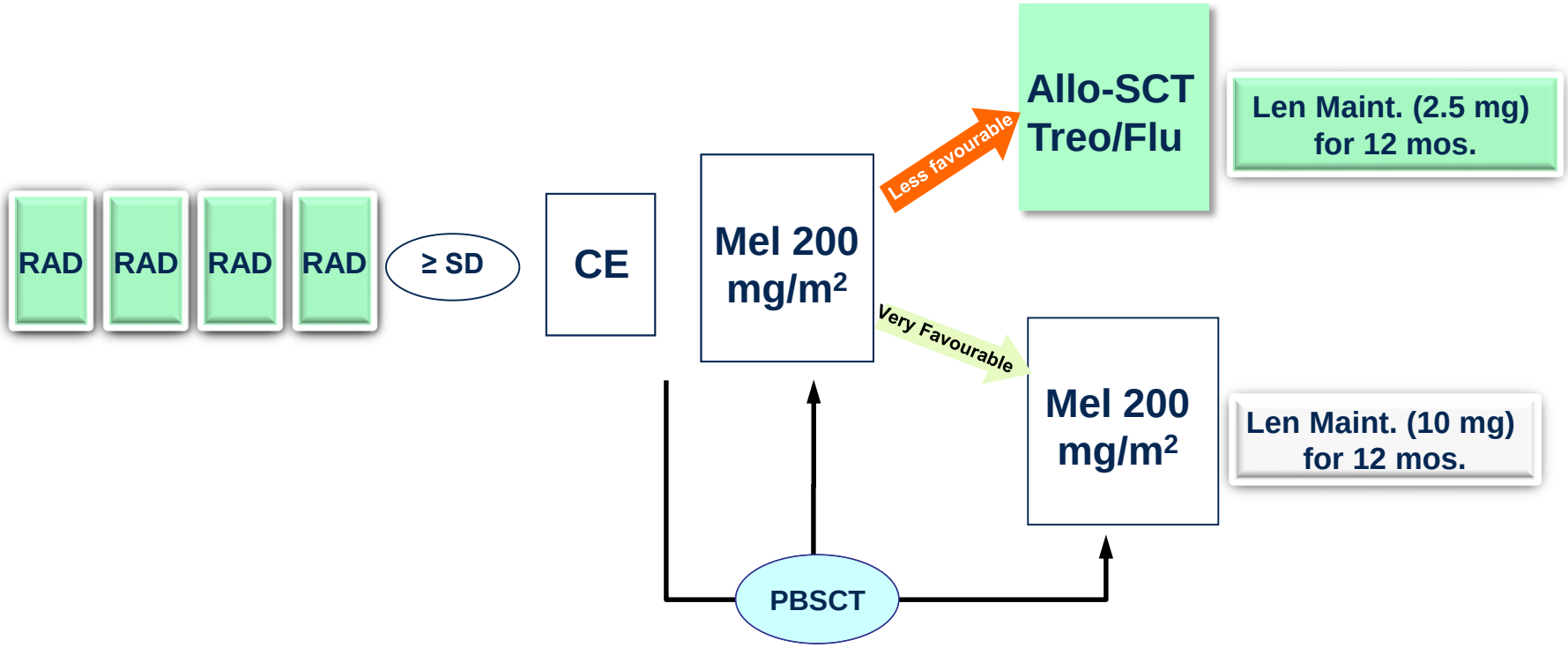


Case Presentation (I)

- 66-year old male patient; diagnosed with lambda light-chain myeloma when aged 58 in April 2011
  - ISS stage II
  - molecular cytogenetics: del13q14
  - Bence Jones proteinuria: 8.600 mg/24 h
  - MDRD 75 ml/min
  - serum free lambda light chains: 2.100 mg/l
  - diffuse lytic lesions in thoracic spine, sternum, right humerus
- Initially managed with dexamethasone pulse
- Enrolled onto a phase 2 clinical trial of the German DSMM myeloma study group in May 2011, „DSMM XII“ study

Phase II Study: 4 x RAD →Tandem SCT → 1 year fixed duration Len

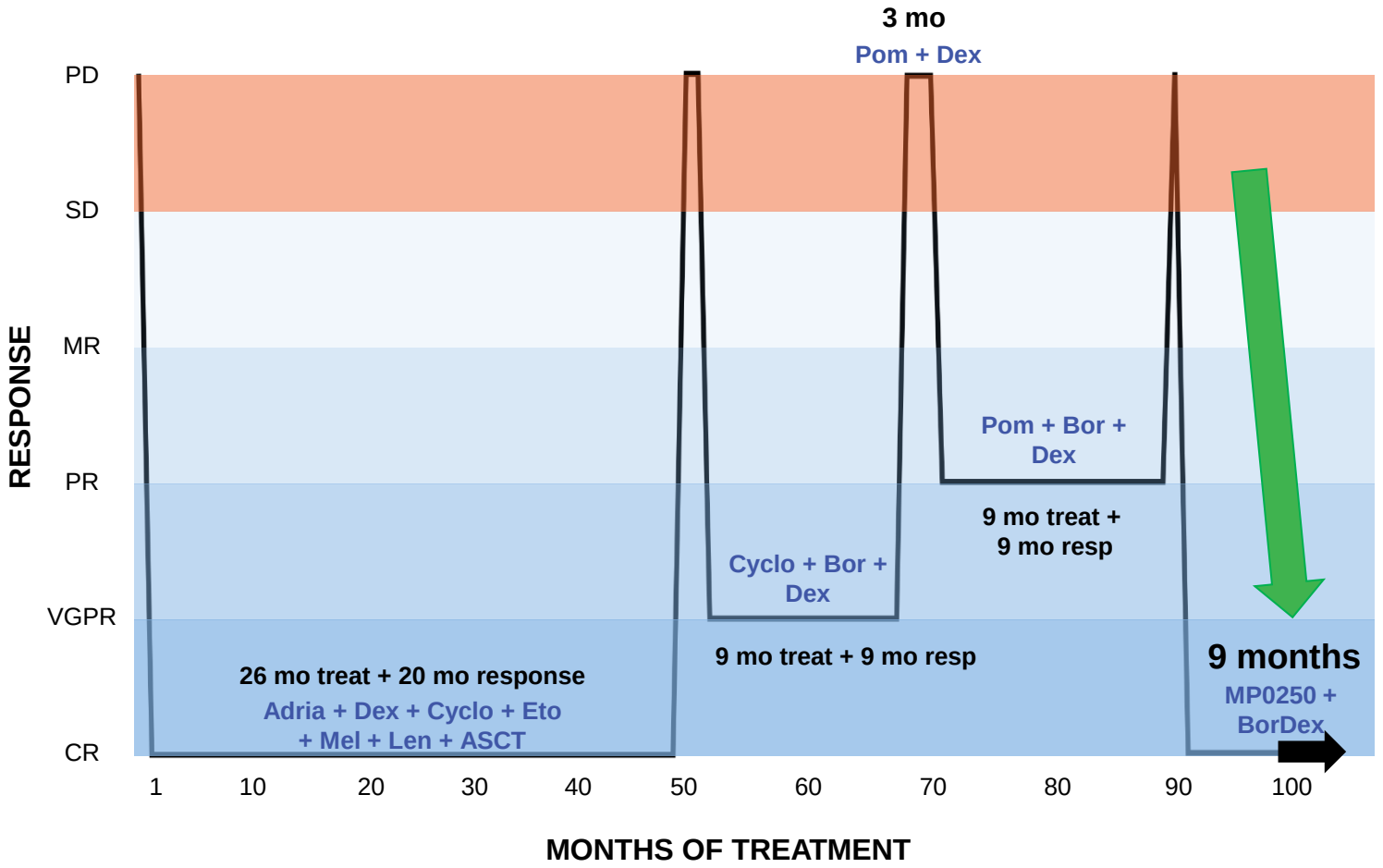
DSMM XII Phase-II-Trial; *n* = *190*

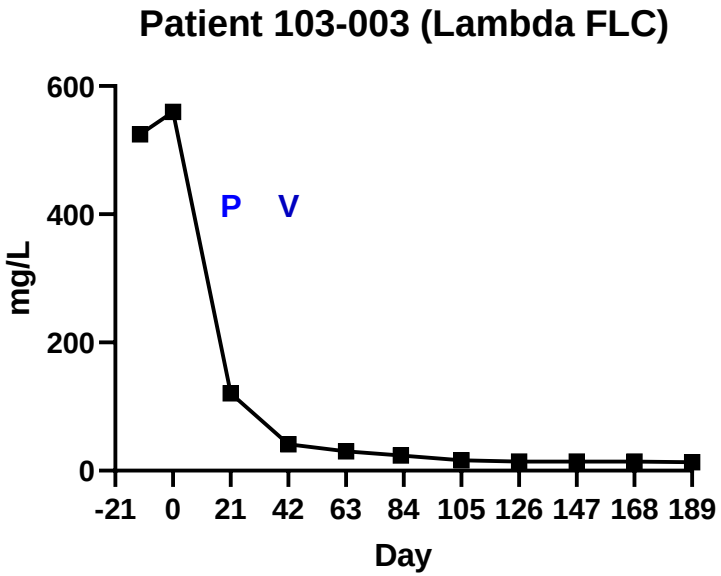


Patient was recommended to undergo auto/allo SCT due to „less favourable“ risk

Clinicaltrials.gov, #NCT01685814
Knop *et al.*, Leukemia 2017

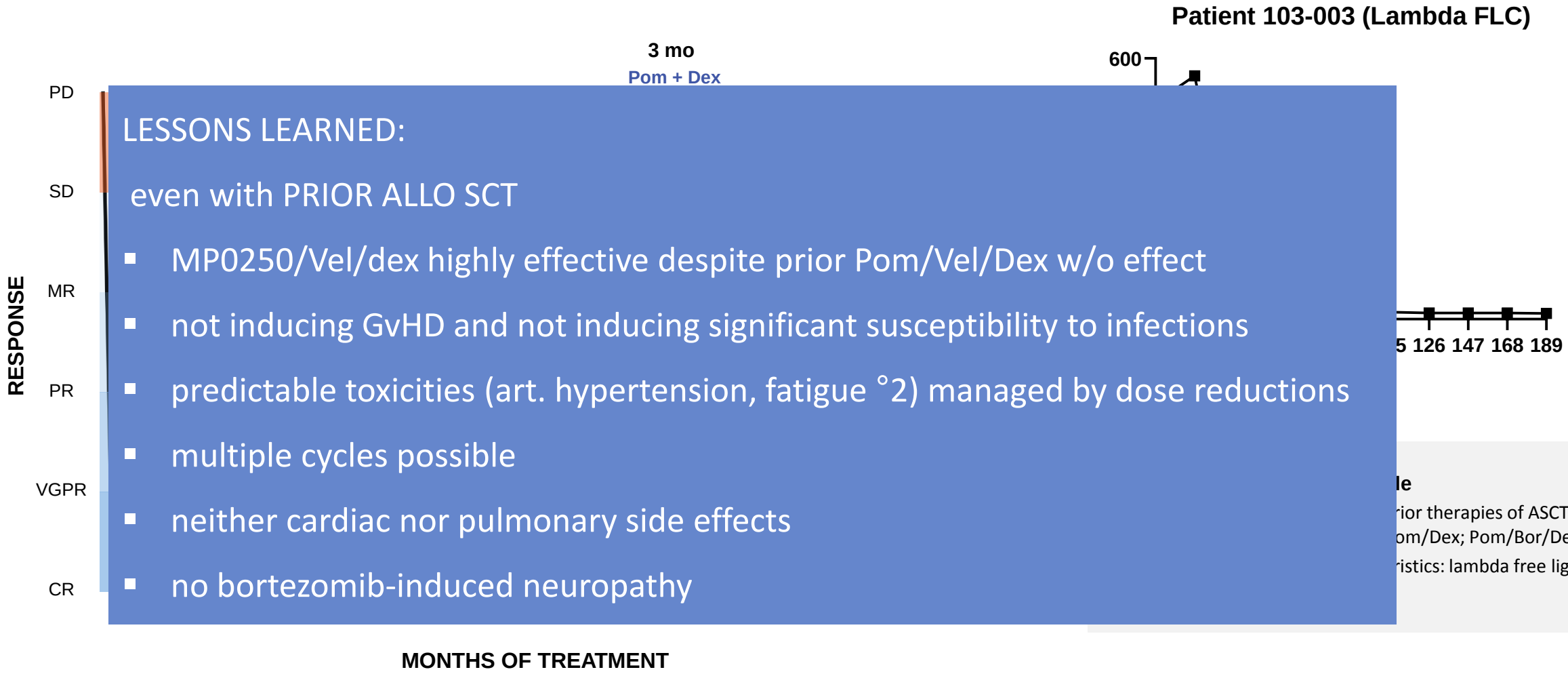
Patient 103-003: 66y male in CR after increasing resistance following 1st line therapy (including ASCT)





- **66 year old male**
- 5L patient with prior therapies of ASCT+, Cyclo/Bor/Dex; Pom/Dex; Pom/Bor/Dex
- Disease characteristics: lambda free light chain, 1q gain

Patient 103-003: 66y male in CR after increasing resistance following 1st line therapy (including ASCT)



LESSONS LEARNED:

even with PRIOR ALLO SCT

- MP0250/Vel/dex highly effective despite prior Pom/Vel/Dex w/o effect
- not inducing GvHD and not inducing significant susceptibility to infections
- predictable toxicities (art. hypertension, fatigue °2) managed by dose reductions
- multiple cycles possible
- neither cardiac nor pulmonary side effects
- no bortezomib-induced neuropathy

le

rior therapies of ASCT+,
om/Dex; Pom/Bor/Dex
ristics: lambda free light

New protocol reflects findings from patient case

MP0250-CP201: Key eligibility criteria (Protocol V3.0)

- **Inclusion:**
  - **≥2 lines of prior therapy** (including a proteasome inhibitor* and an IMiD**);
  - Unresponsive or refractory to a bortezomib or carfilzomib-based regimen **as last prior line of Rx**;
  - Measurable disease;
  - ECOG PS 0–1;
  - Adequate liver (AST/ALT <3x ULN, bilirubin <2x ULN), bone marrow and kidney (CrCL ≥45 mL/min) function.
- **Exclusion:**
  - Non-/oligosecretory myeloma, plasma cell leukemia;
  - Peripheral neuropathy Grade ≥ 2 at baseline *or* history of Grade ≥3 or Grade 2 with pain;
  - Uncontrolled hypertension;
  - CHF, symptomatic myocardial ischemia or MI within 6 mos of screening;
  - Stroke, TIA or other symptomatic peripheral vascular disease.

Conclusions

- MM: highly active and competitive therapeutic field
- MP0250 holds promise based on preclinical rationale
- Substantial, long-lasting remissions possible
- Vel/Dex: active, well-tolerated and well-known backbone for MP0250
- Predictable, non-overlapping and manageable toxicity
- Combination of molecularly-targeted approaches against MM plasma cell (Anti-CD38 MoAb) and microenvironment (MP0250) desirable

knop_s@ukw.de

Preclinical Pipeline

Daniel Steiner

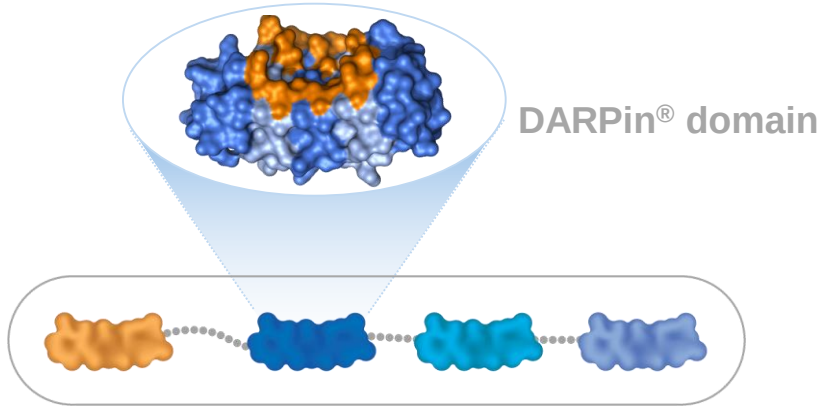
SVP Research

MOLECULAR partners

DARPin® Proteins Offer Features Beyond Antibodies

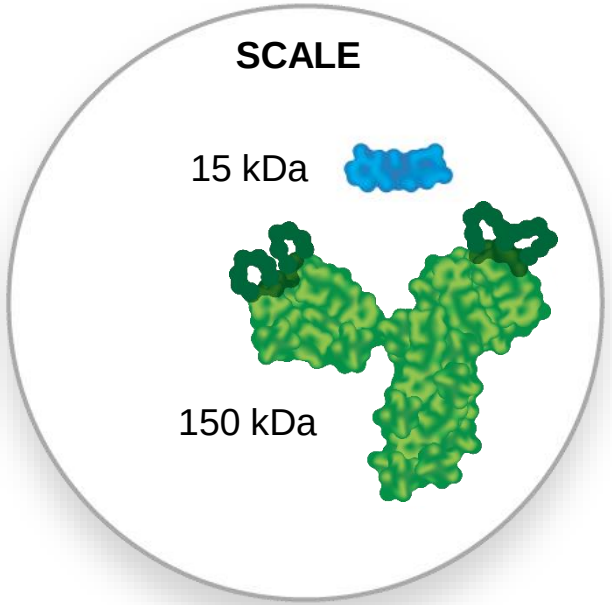
DARPin® Features

Rigid-body Target Binding



Multi-DARPin® Formatting

- Small size
- Simple repetitive architecture: 1 polypeptide
- Highly favorable biophysical properties
- Tunable half-life…



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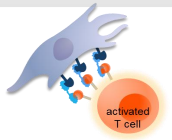
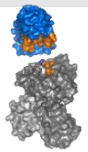
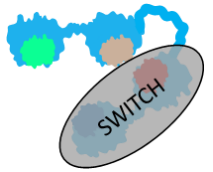
Innovating with Novel Therapeutic Designs

DARPin® Features







Novel Therapeutic DARPin® Designs	Local clustering-induced activation	Highly selective binding of “inaccessible” targets	Prodrug concepts
Application / Project	MP0310 / FAP x 4-1BB MP0317 / FAP x CD40	Peptide MHC	Masked CD3
Benefit	**Tumor-localized activation of immune cells**	**Highly tumor selective delivery of potent effector functions**	**Tumor-local activation of highly potent effector molecules**

PATIENT VALUE by DIFFERENTIATED PRODUCT

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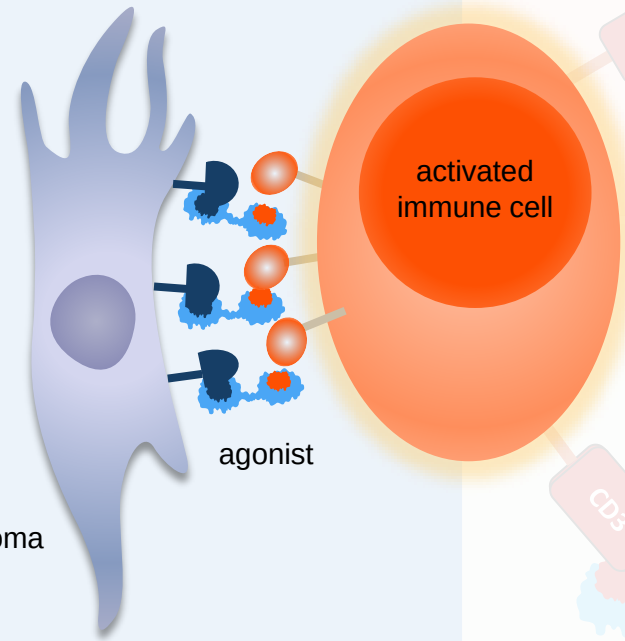
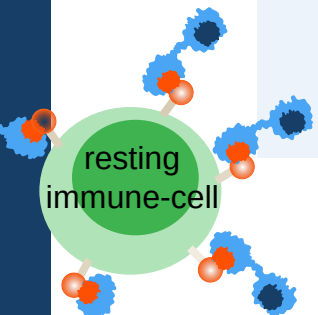
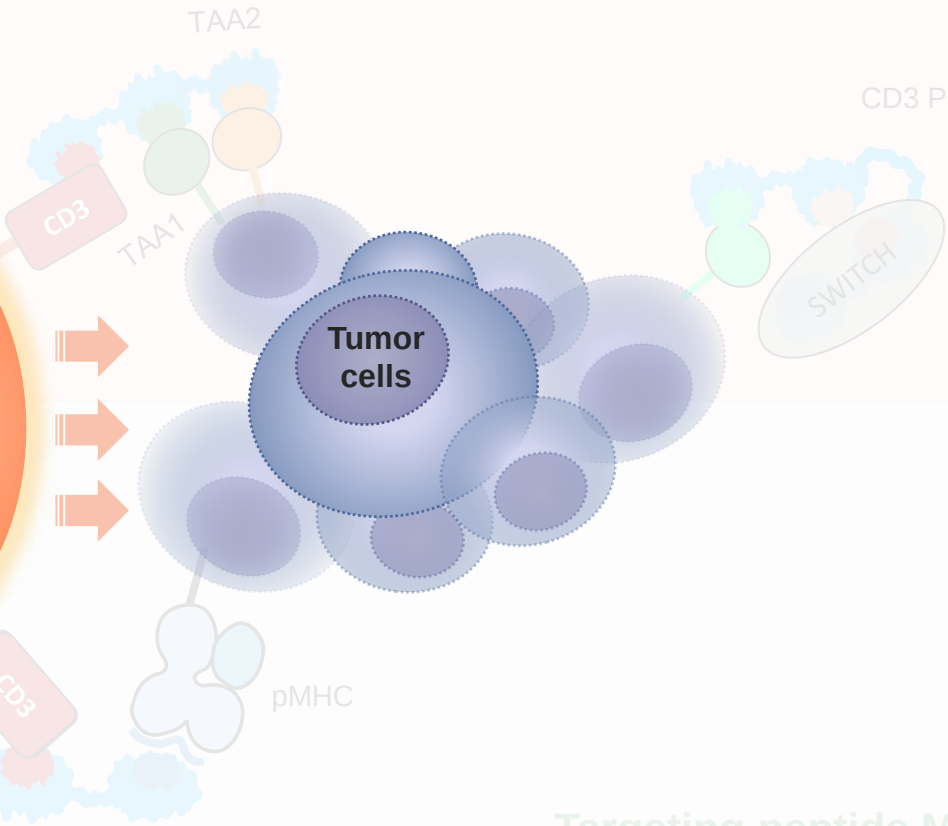
Focus 1: Tumor-Localized Immune Cell Activation

Tumor-localized immune cell activation





Next-generation T-cell engagers



Targeting peptide MHC complexes, historically “inaccessible” targets

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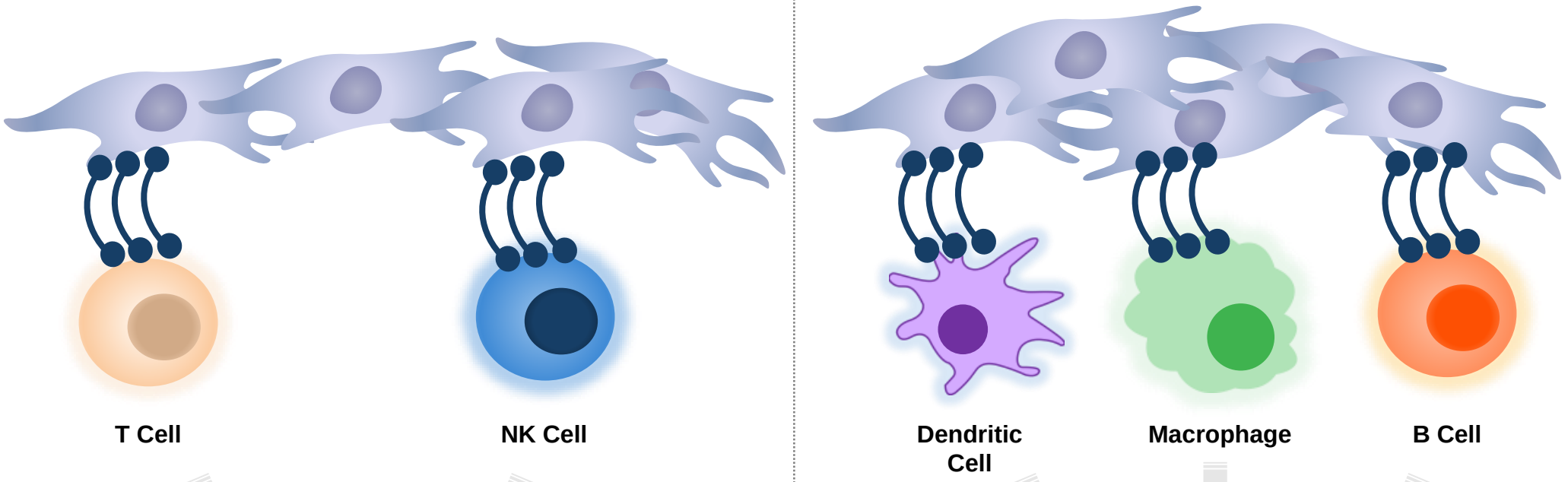
Tumor-Localized Immune Modulation of the Innate and Adaptive Arms of the Immune System

FAP x 4-1BB
(MP0310 / AMG 506)

4-1BB + FAP + HSA

FAP x CD40
(MP0317)

CD40 + FAP + HSA



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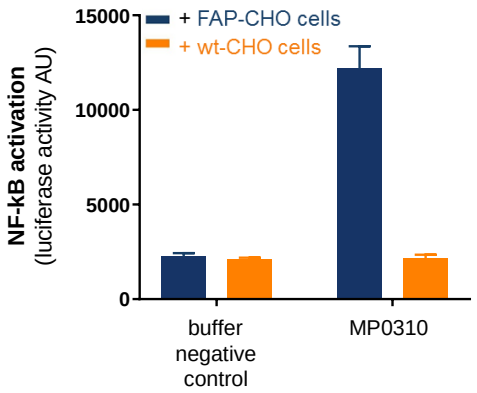
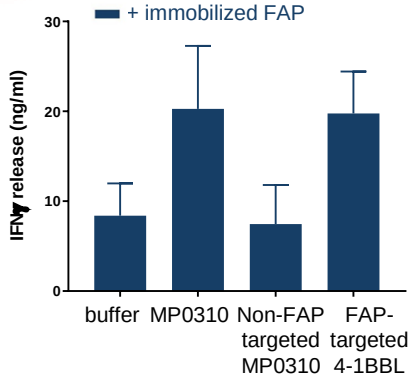
FAP-Dependent Activation of Respective Class of Immune Cells

FAP x 4-1BB (MP0310 / AMG 506)

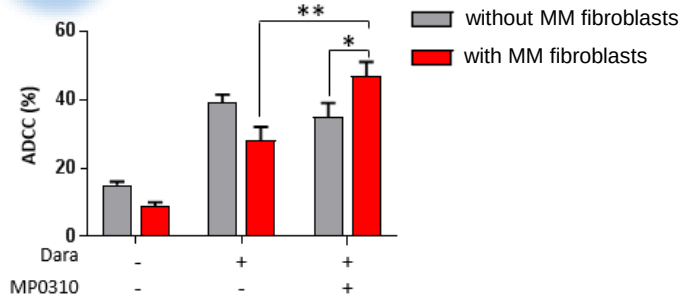
Reporter cell assay



T cell assay

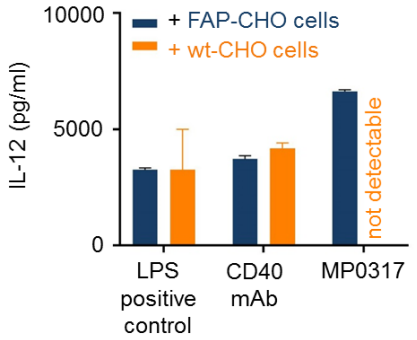


NK cell assay

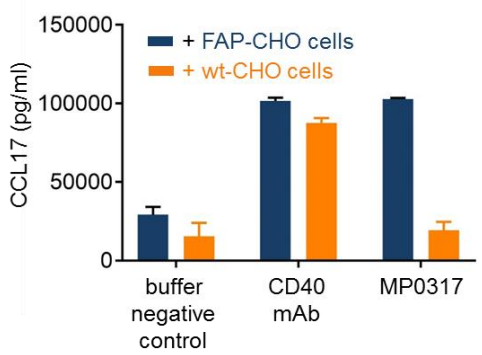


FAP x CD40 (MP0317)

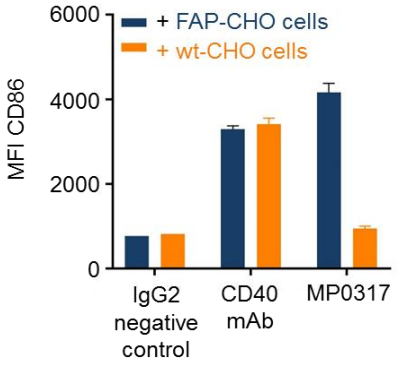
Dendritic cell assay



Macrophage assay



B cell assay



Data lab Angelo Vacca, Bari, Italy – Poster shown at SIMI conference 10/2019

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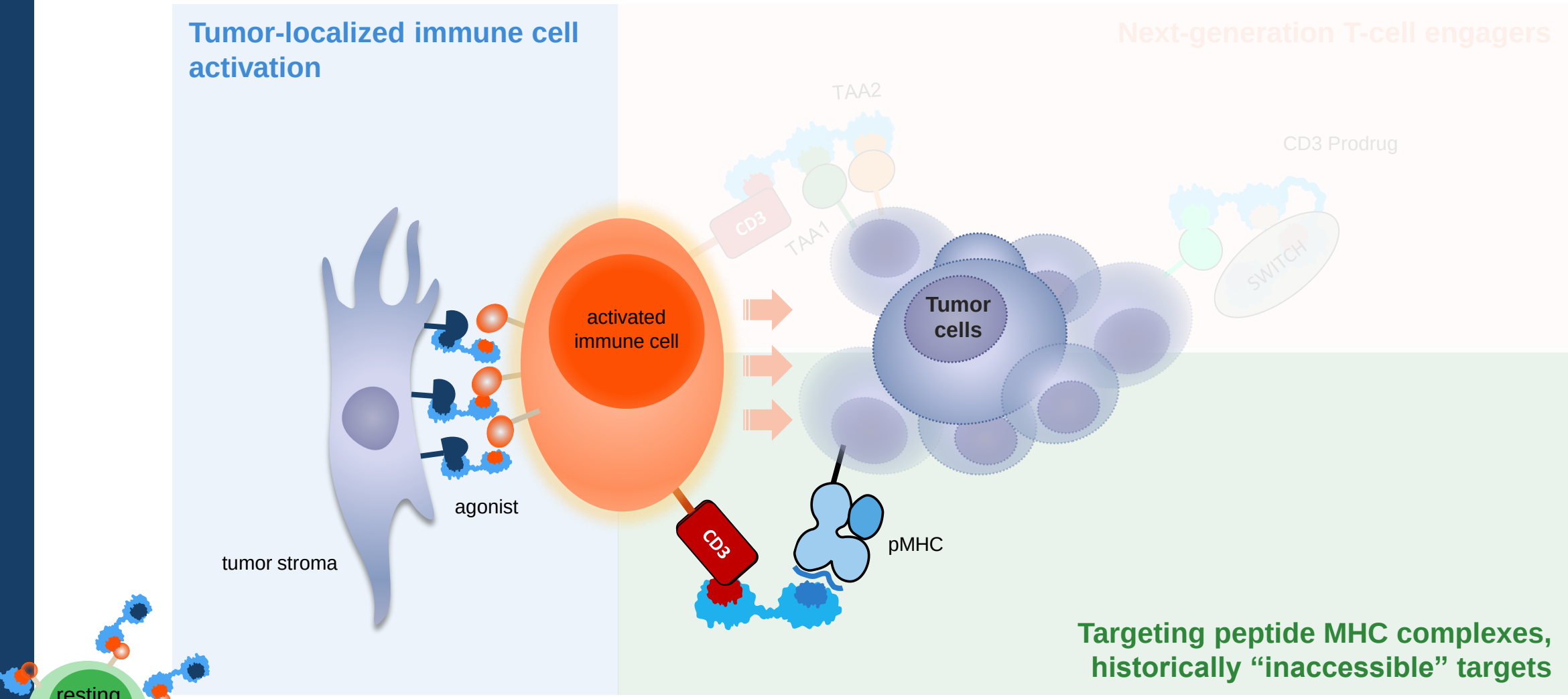
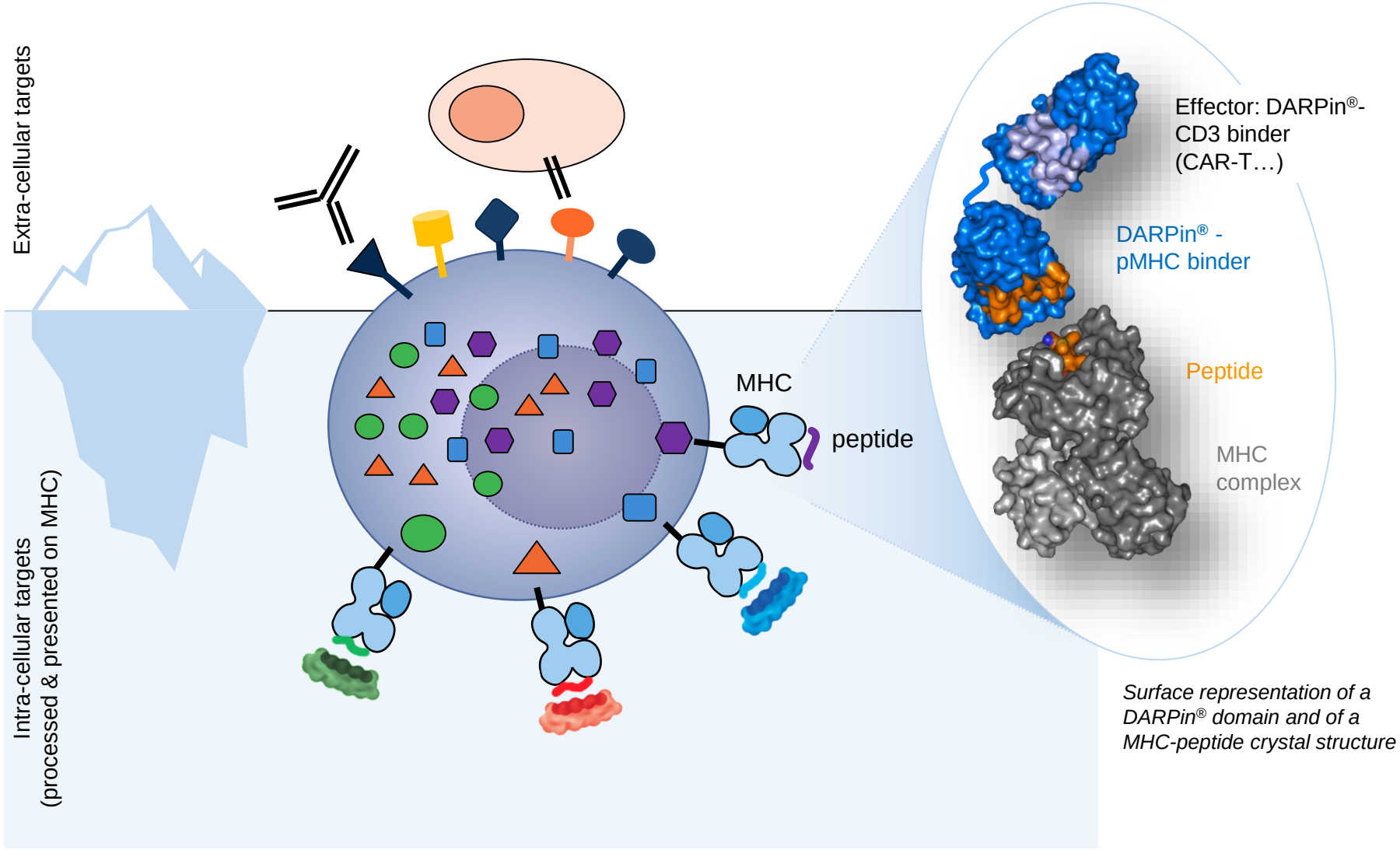
Focus 2: Targeting Peptide MHC Complexes



MOLECULAR partners

pMHC: Approach for “Inaccessible” Highly Selective Targets



Surface representation of a DARPin® domain and of a MHC-peptide crystal structure

Challenging to generate antibodies and enhanced T-cell receptors which bind to peptide-MHC with both high selectivity and high affinity

Opens substantial target space in Oncology, Virology and Autoimmunity

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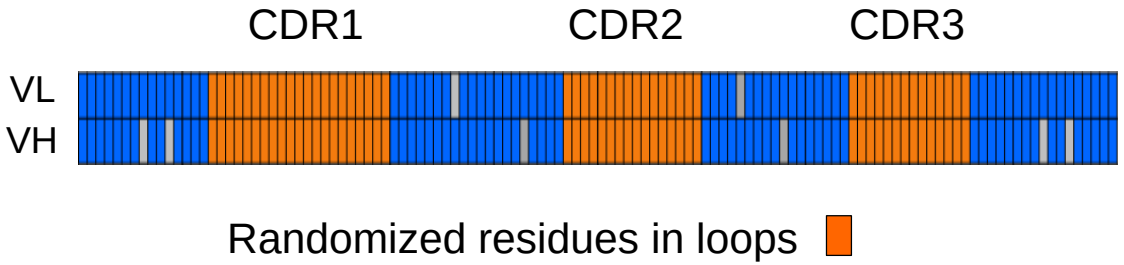
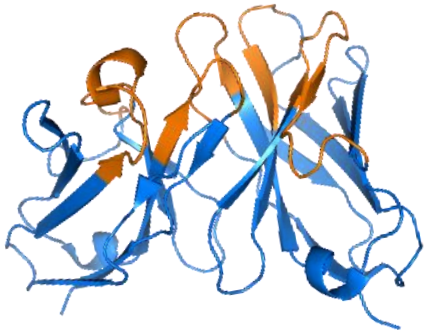
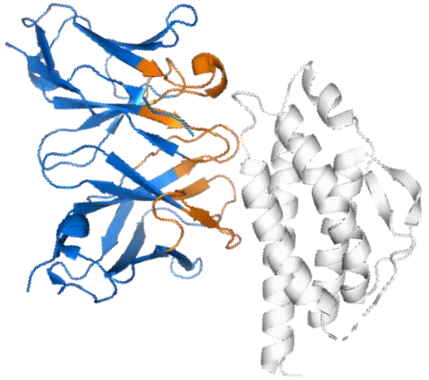
Leveraging DARPin® Features for pMHC

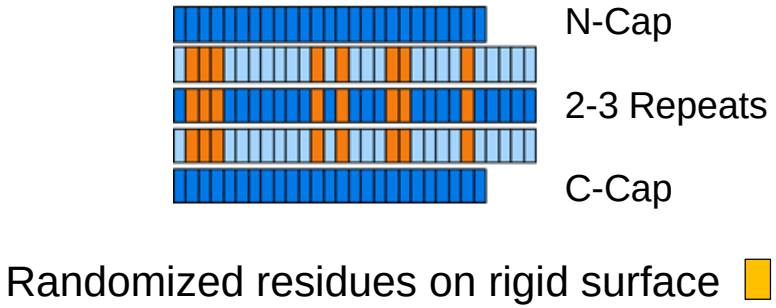
Antibody (Ig-) Domain: binding via flexible loops

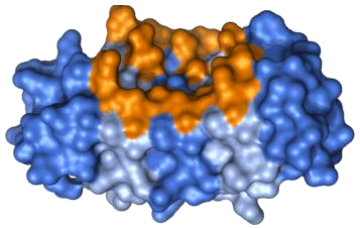


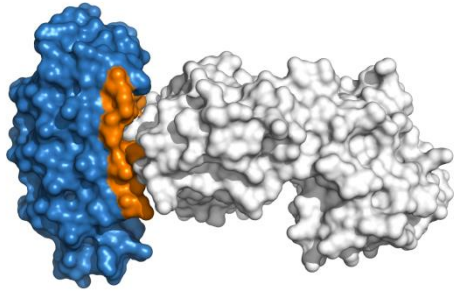




DARPin® Domain: binding via rigid surface



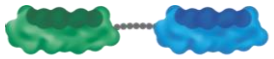




MOLECULAR partners

pMHC: Rapid and Straightforward Selection of Diverse DARPin® pMHC Binders with High Selectivity

DARPin®

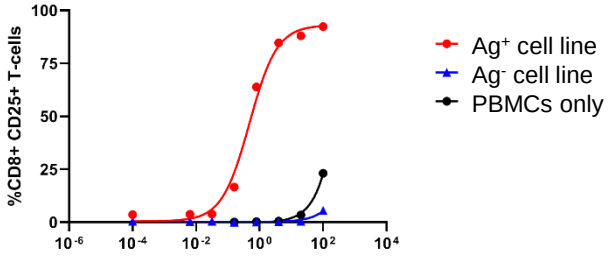


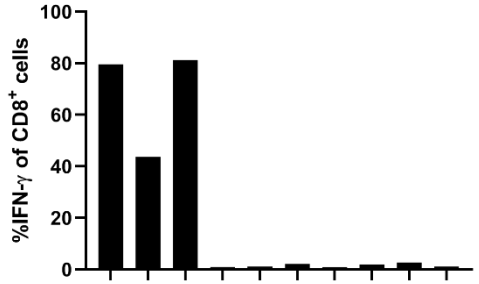
anti-pMHC anti-CD3

Activity & Selectivity
(T cell activation assay)

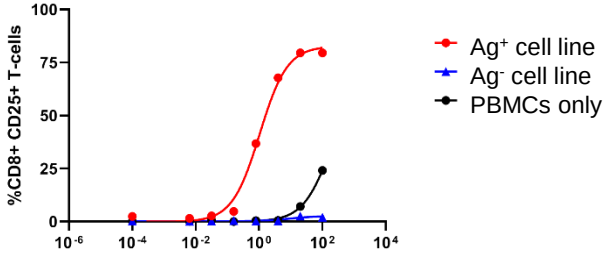
Selectivity
(binding pattern by Alanine scanning)

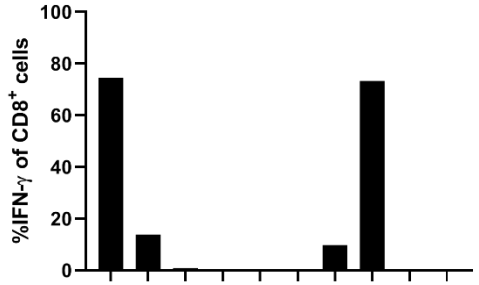
pMHC-A x CD3



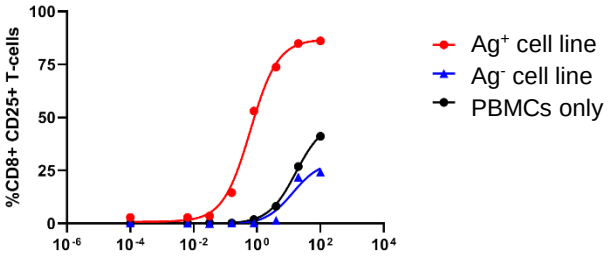


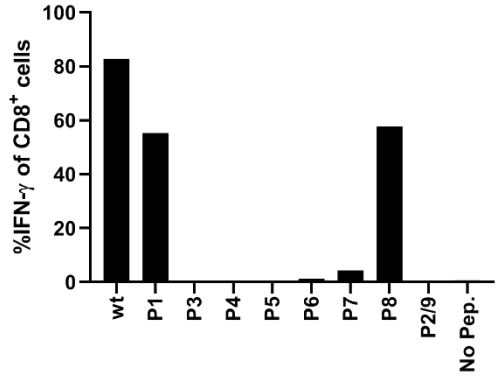
pMHC-B x CD3





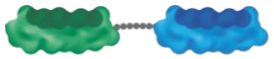
pMHC-C x CD3





pMHC: Rapid and Straightforward Selection of Diverse DARPin® pMHC Binders with High Selectivity

DARPin®



anti-pMHC anti-CD3

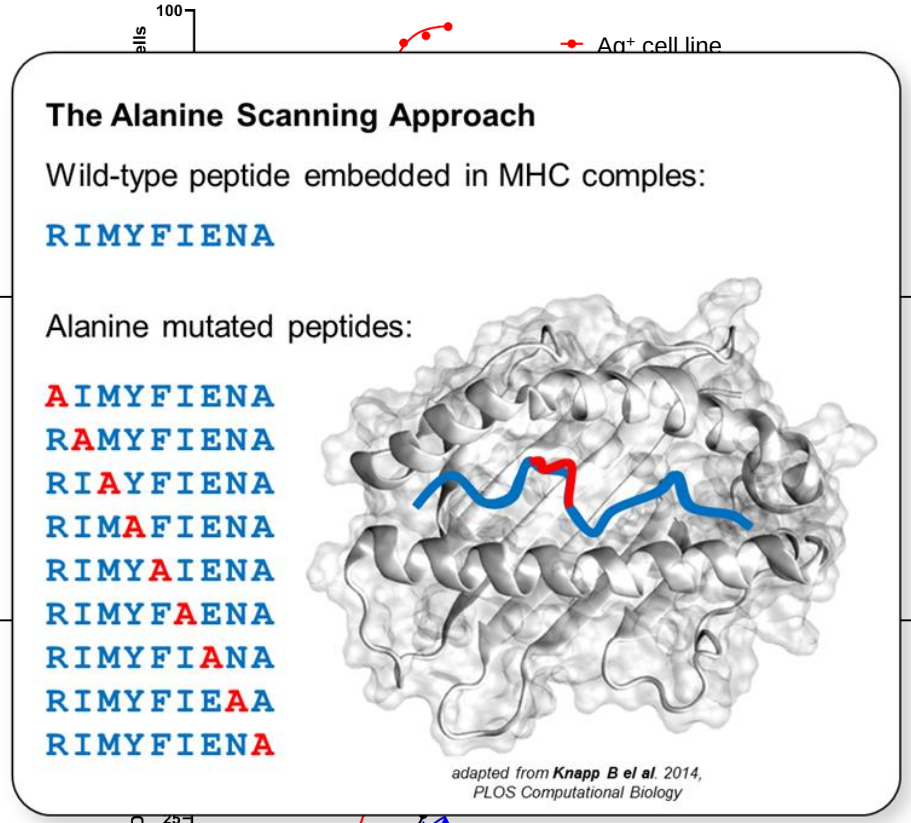
Activity & Selectivity
(T cell activation assay)

Selectivity
(binding pattern by Alanine scanning)

pMHC-A x CD3

pMHC-B x CD3

pMHC-C x CD3



The Alanine Scanning Approach

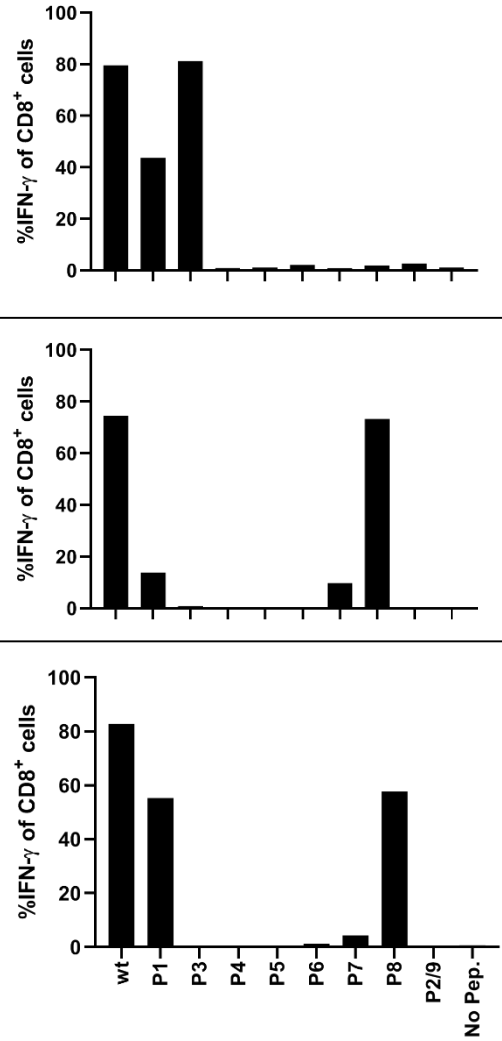
Wild-type peptide embedded in MHC comples:

RIMYFIENA

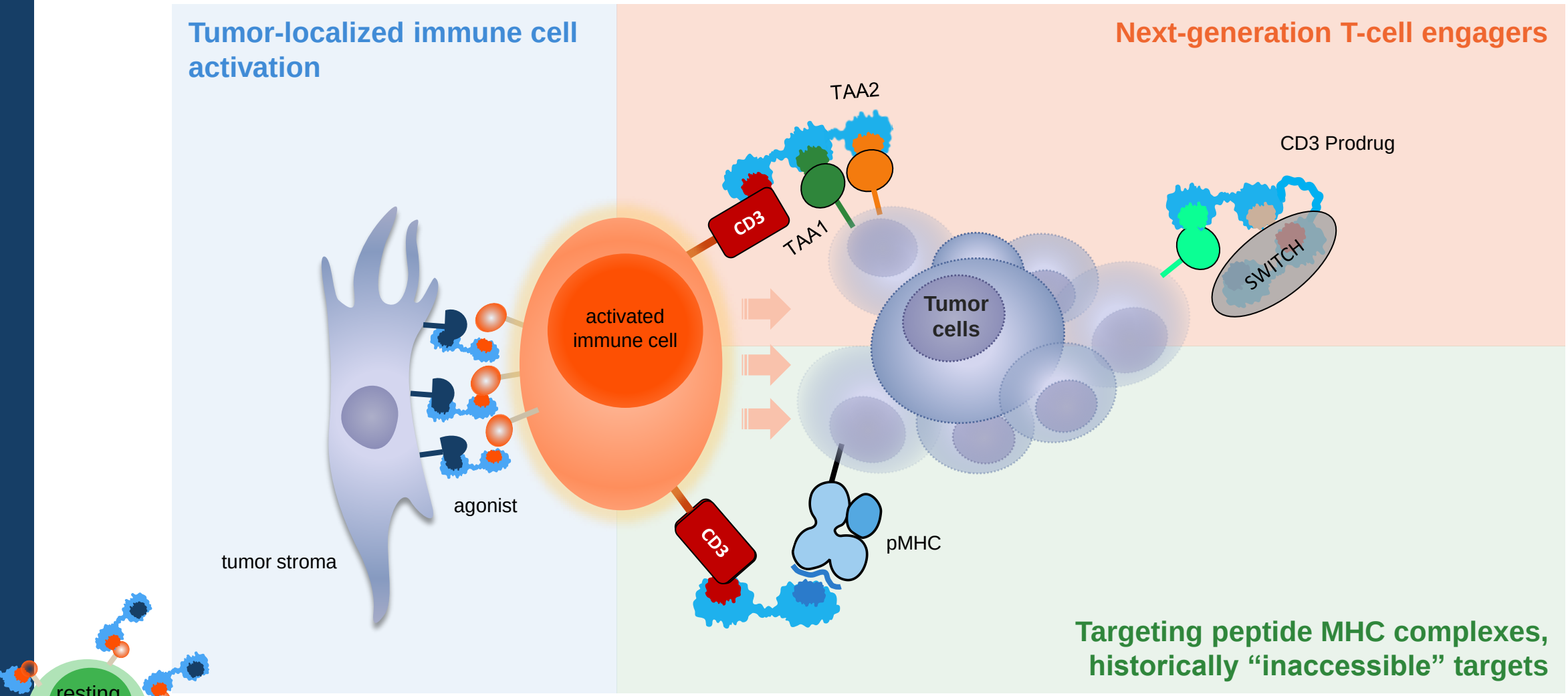
Alanine mutated peptides:

AIMYFIENA
RAMYFIENA
RIAYFIENA
RIMAFIENA
RIMYAIENA
RIMYFAENA
RIMYFIANA
RIMYFIEAA
RIMYFIENA

*adapted from **Knapp B et al**. 2014, PLOS Computational Biology*



Focus 3: Next-Generation T-cell Engagers



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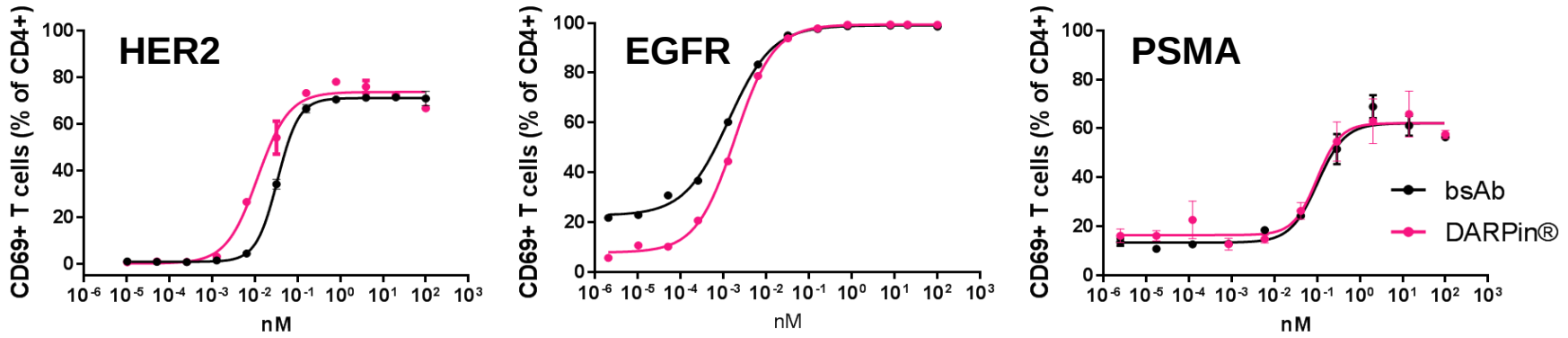
Fully DARPin®-Based T-Cell Engager Platform Established



- Potency at level of respective benchmark molecules
- All relevant cellular events for anti tumor immunity triggered
- Highly favorable biophysical properties and high format flexibility
- Multispecific T-Cell engagers for higher selectivity and increased efficacy
- Tunable half-life

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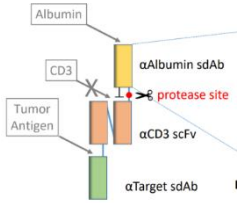
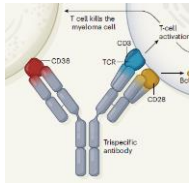
Building Next Generation of DARPin® T-Cell Engagers

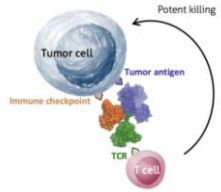
T-cell engager field is progressing to the next level to address key limitations



Tumor Activate T-Cell Engager
(e.g. Prodrug by Harpoon)

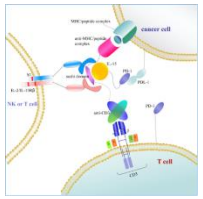
Co-stimulate T Cell Receptor
(e.g. CD28 by Sanofi)





Block Checkpoint in Synapse
(e.g. LocATE by CDR-life)

Integrate Stimulating Features
(e.g. TriTE by TIMMUNE: IL-15 fusion)



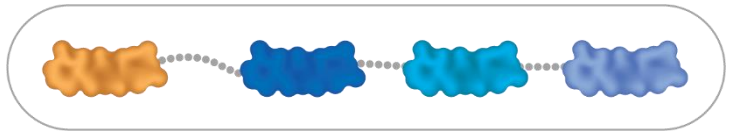
Improving Safety

Boosting Activity

Removing Brake

Sustained Activity

Multi-DARPin® T-Cell Engagers for better safety and increased efficacy



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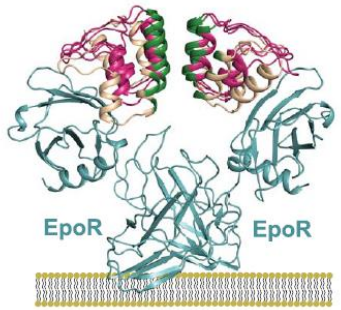
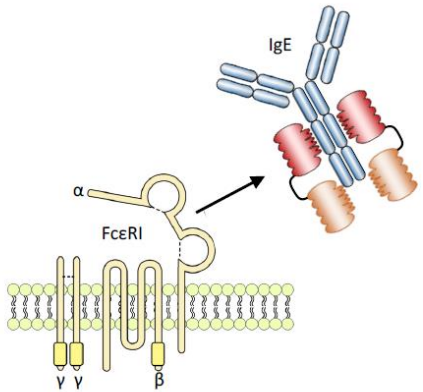
DARPin® Features Inspire People to Develop Novel Designs



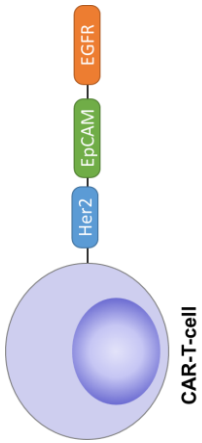
EPO mimetics
(Mohan et al., Science, 2019)

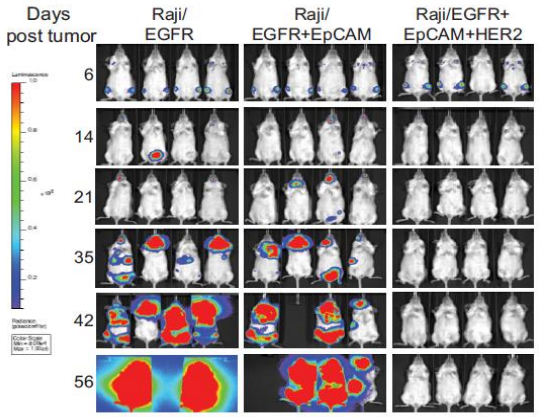
Science JOURNALS AAAS



DARPin® IgE remover/blocker
(Eggel et al., Nature, 2012)

nature
International journal of science





Trispecific CAR-T cells with DARPin®
(Balakrishnan et al., Clin Canc Res, 2019)

Clinical Cancer Research

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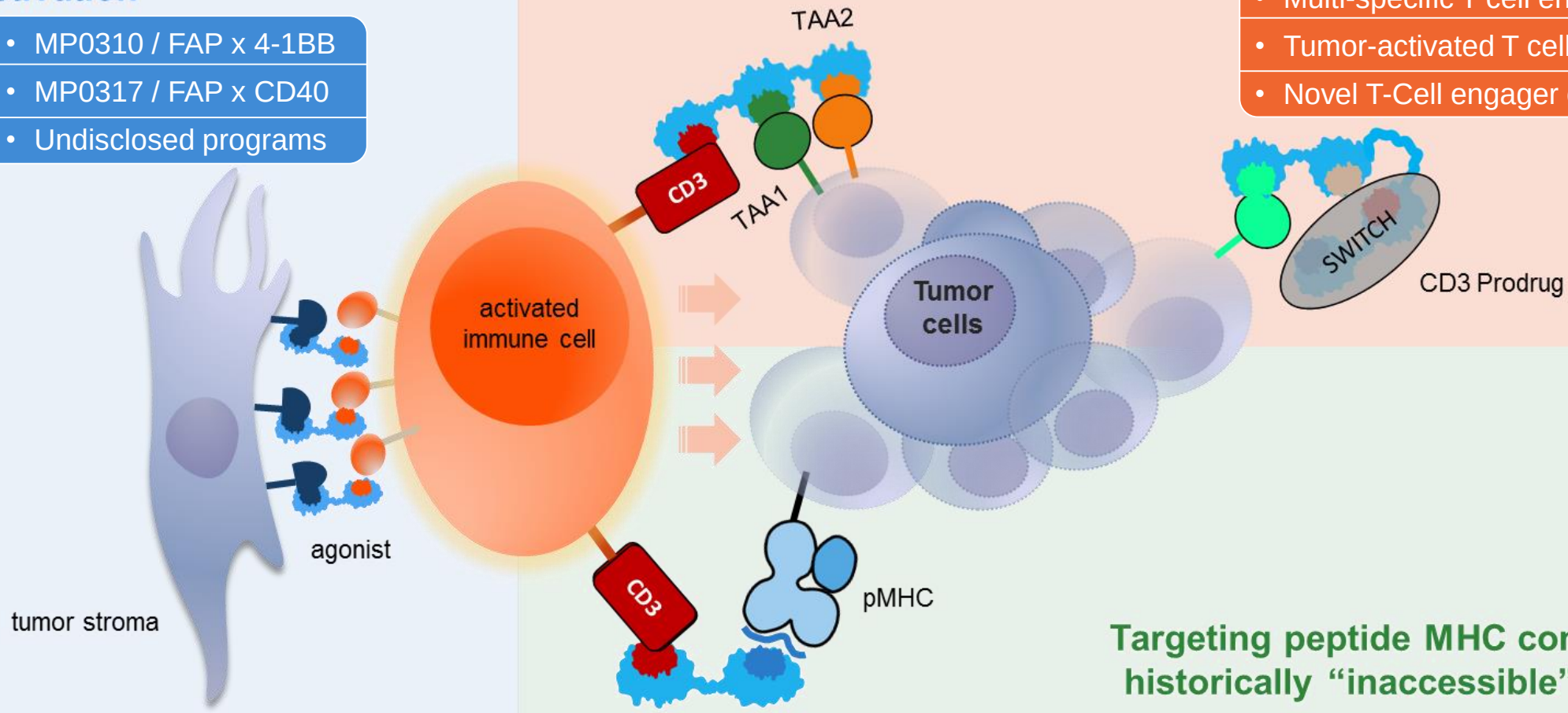
Applying our Therapeutic DARPin® Designs for Tumor-localized Activity

Tumor-localized immune cell activation

- MP0310 / FAP x 4-1BB
- MP0317 / FAP x CD40
- Undisclosed programs

Next-generation T-cell engagers

- Multi-specific T cell engagers
- Tumor-activated T cell engagers
- Novel T-Cell engager concepts



Targeting peptide MHC complexes, historically "inaccessible" targets

- Several undisclosed programs

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Novel Therapeutics: Lessons learned from IO Combos in the Clinic

Jordi Rodon, MD PhD

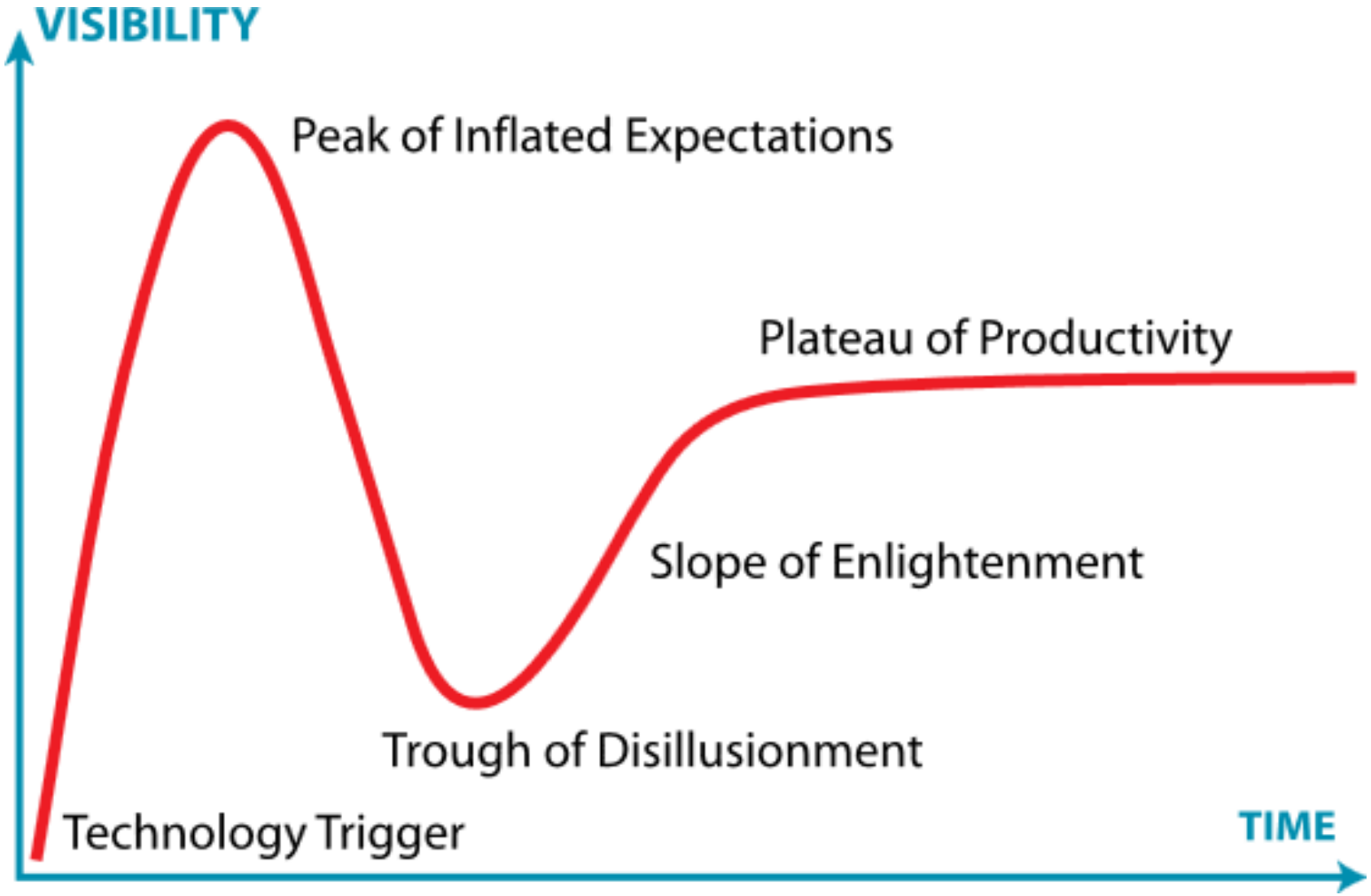
Associate Professor, Investigational Cancer Therapeutics
Khalifa Institute for Personalized Cancer Therapy

Molecular Partners R&D Day, NEW YORK
December 2019

The innovation cycle (aka Gartner's Hype Cycle)

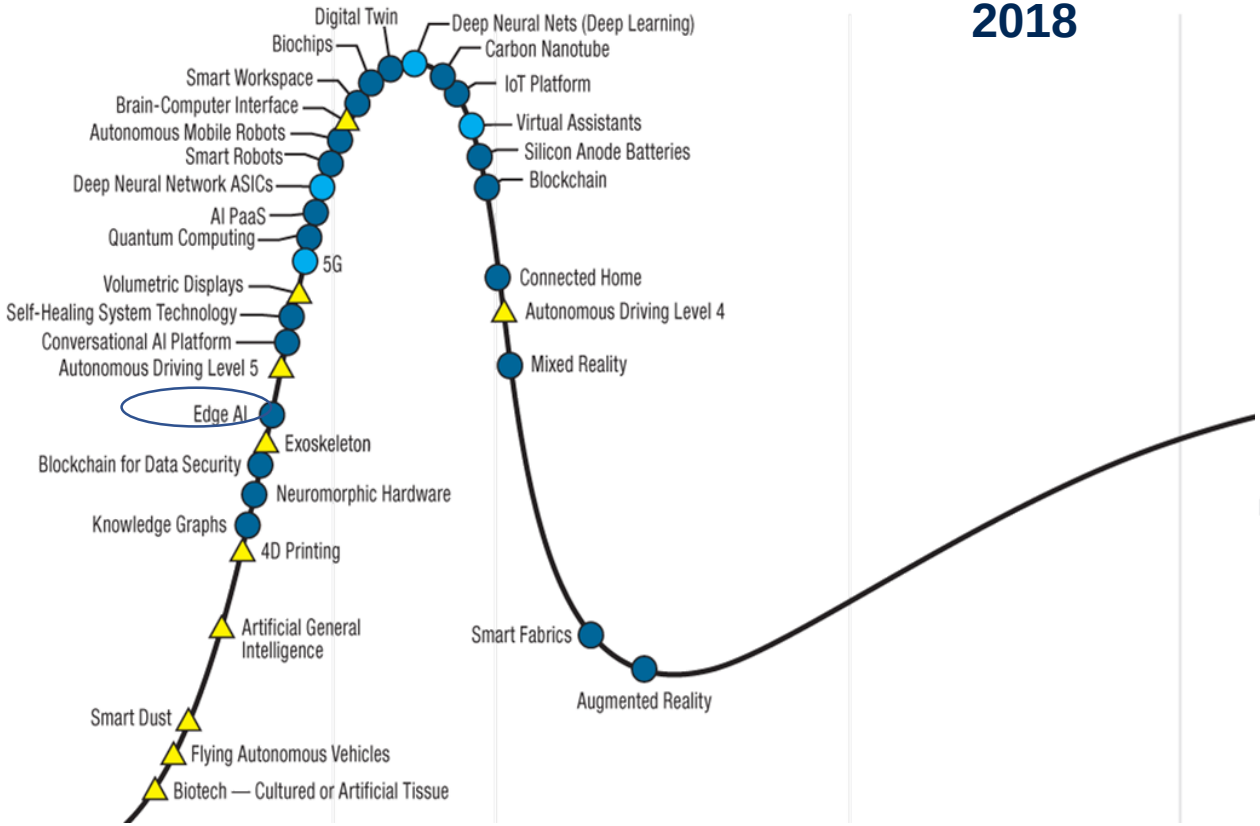
- Graphical representation of the maturity, adoption and social application of specific technologies

- **Five key phases of a technology's life cycle**
  1. Technology Trigger
  2. Peak of Inflated Expectations (hype)
  3. Trough of Disillusionment
  4. Slope of Enlightenment
  5. Plateau of Productivity

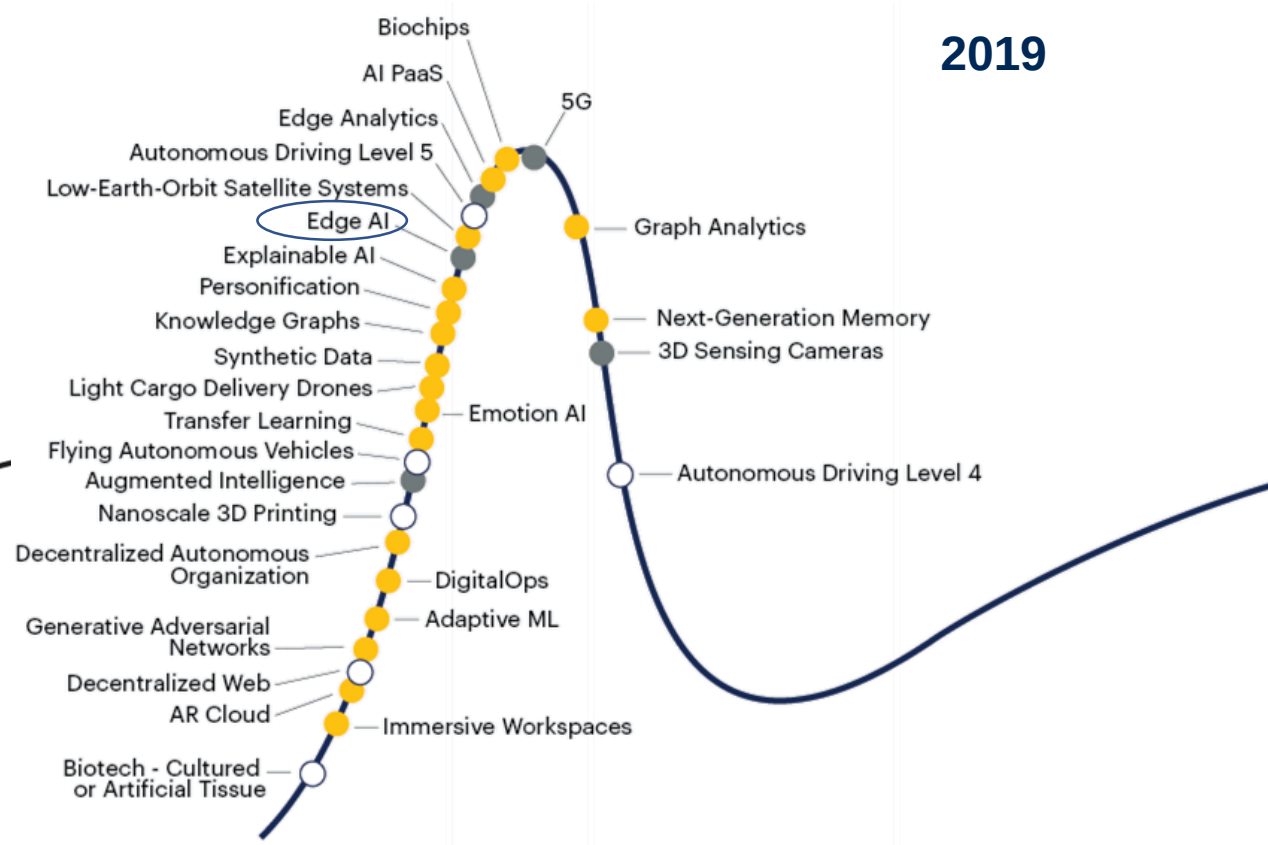


Gartner Hype Cycle for Emerging Technologies

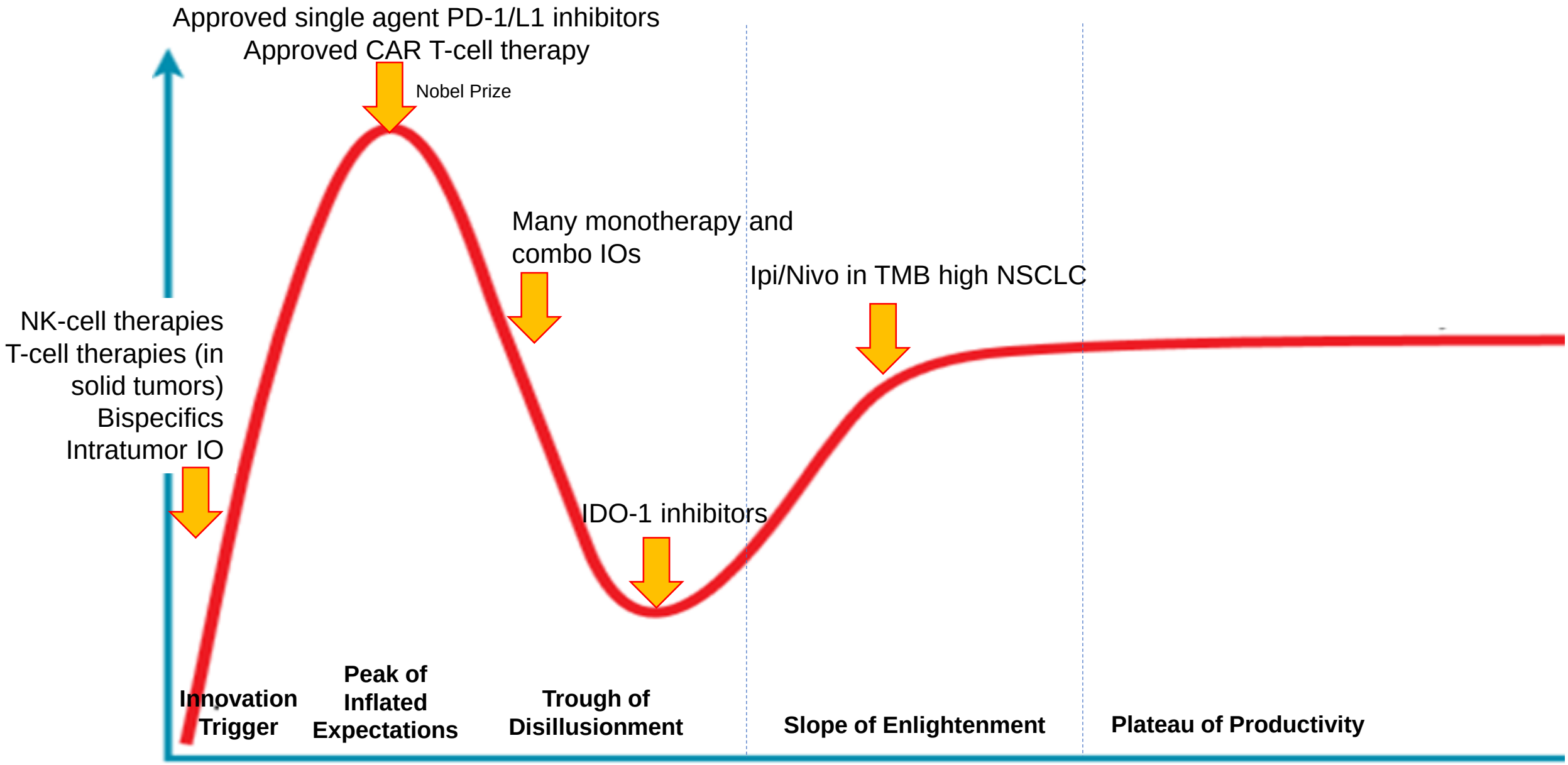
2018



2019

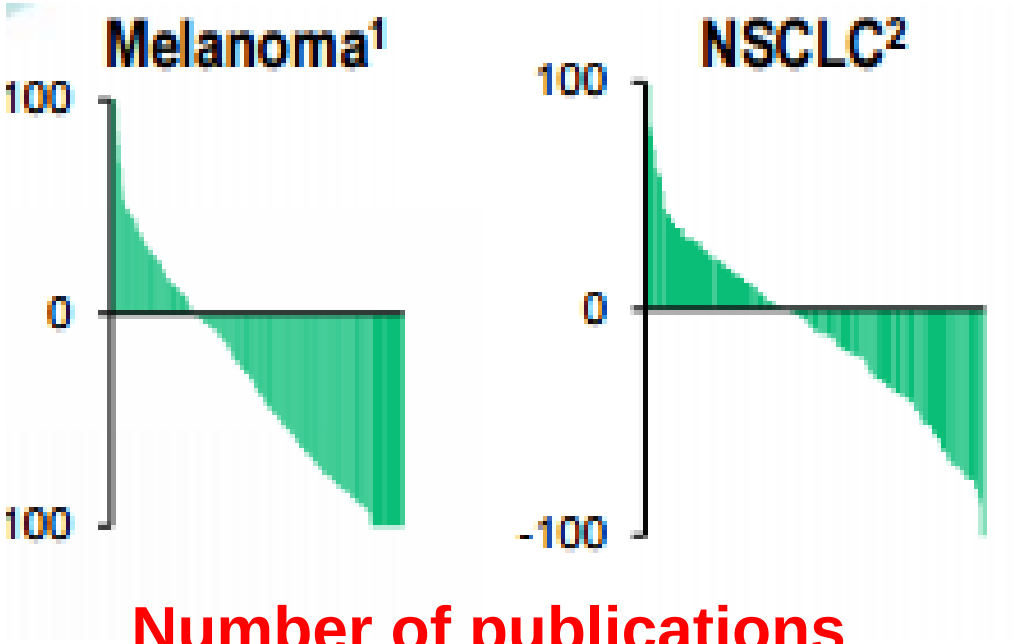


The innovation cycle for immunotherapy

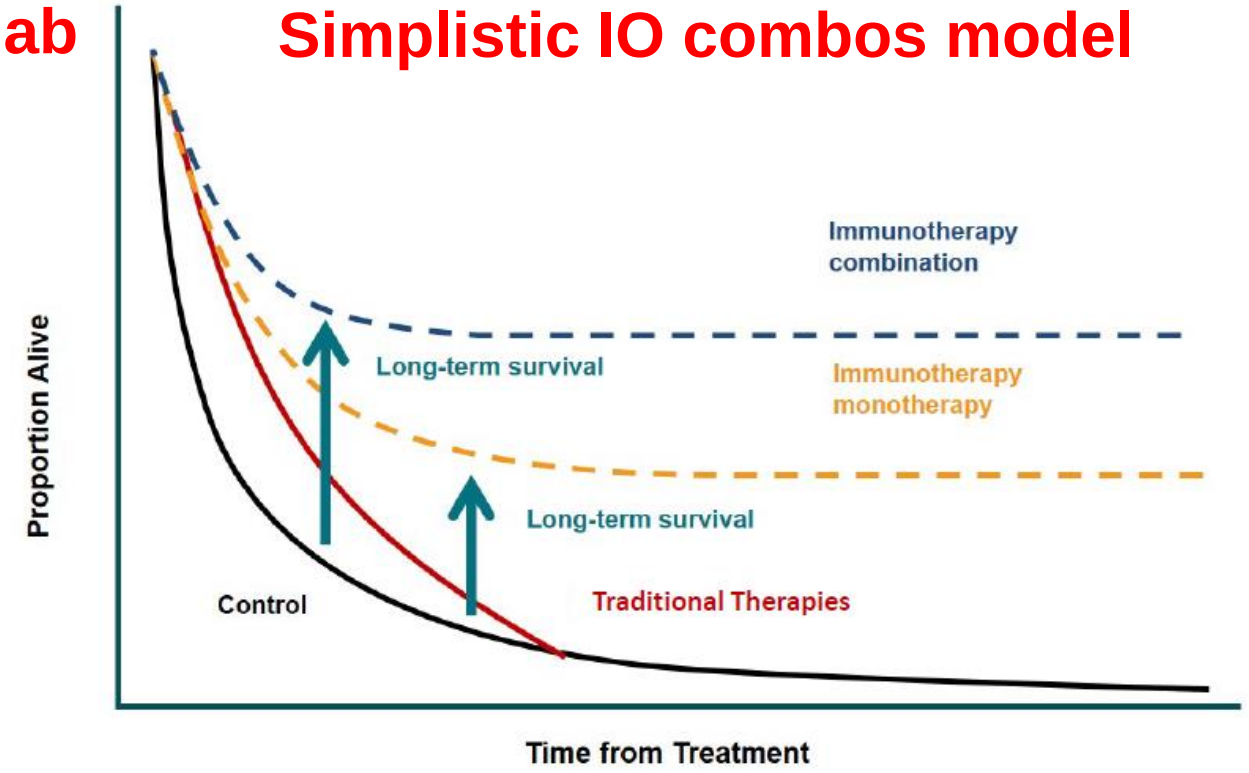


Lessons learnt from a **hyped** research field

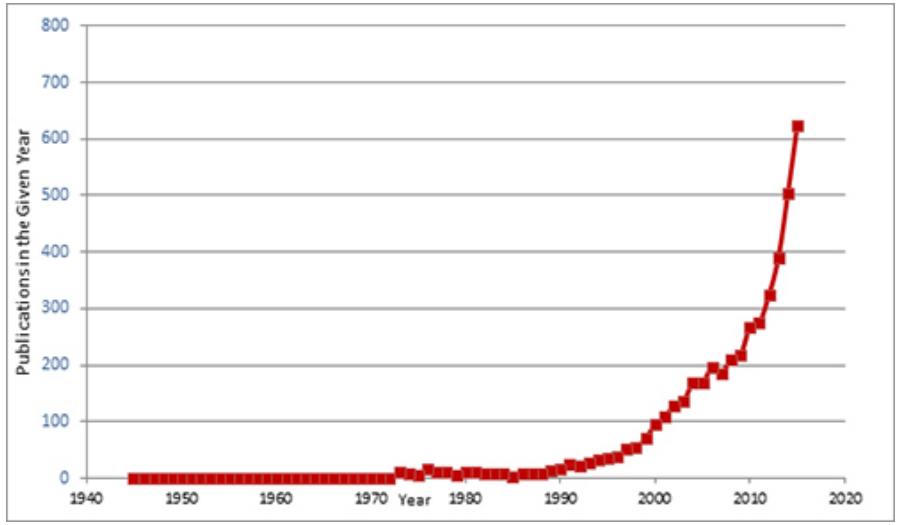
Initial antitumor activity of Pembrolizumab



Simplistic IO combos model

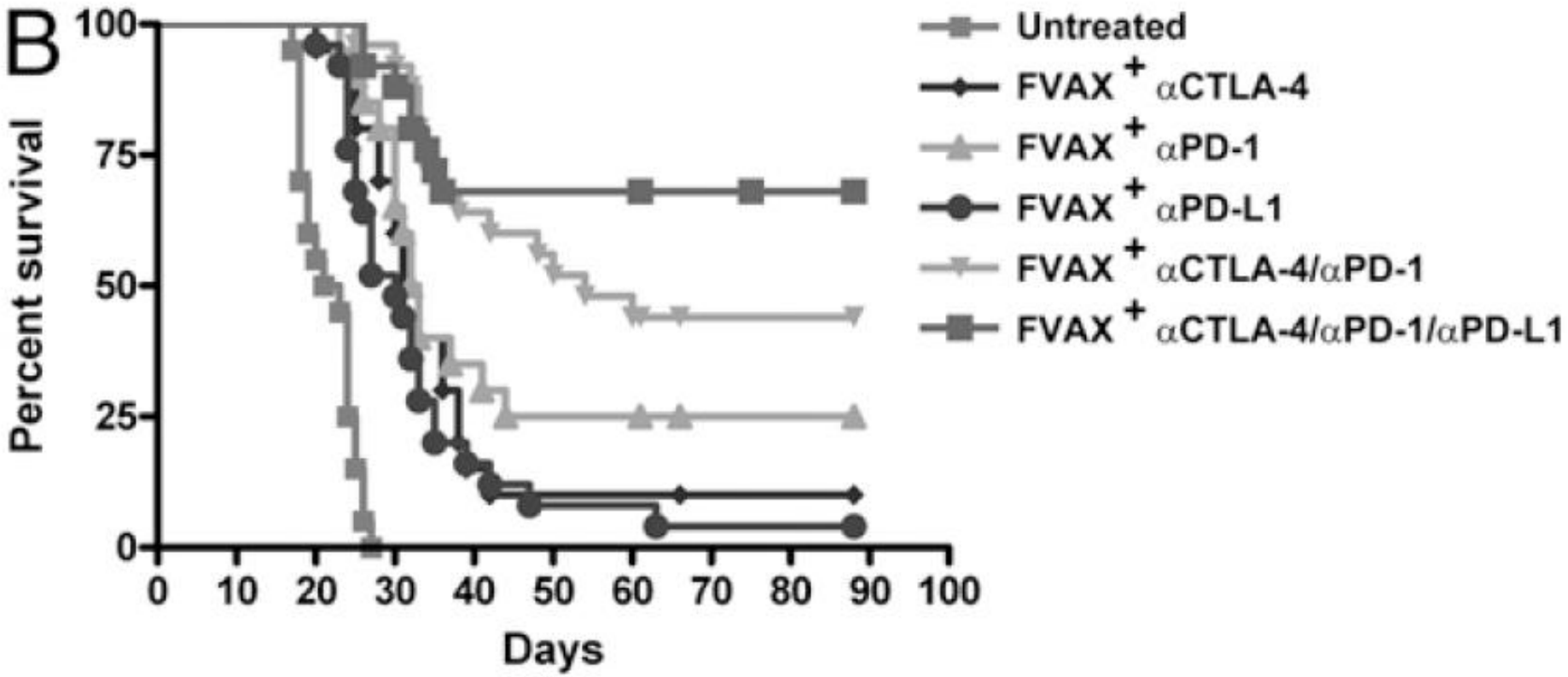


Number of publications



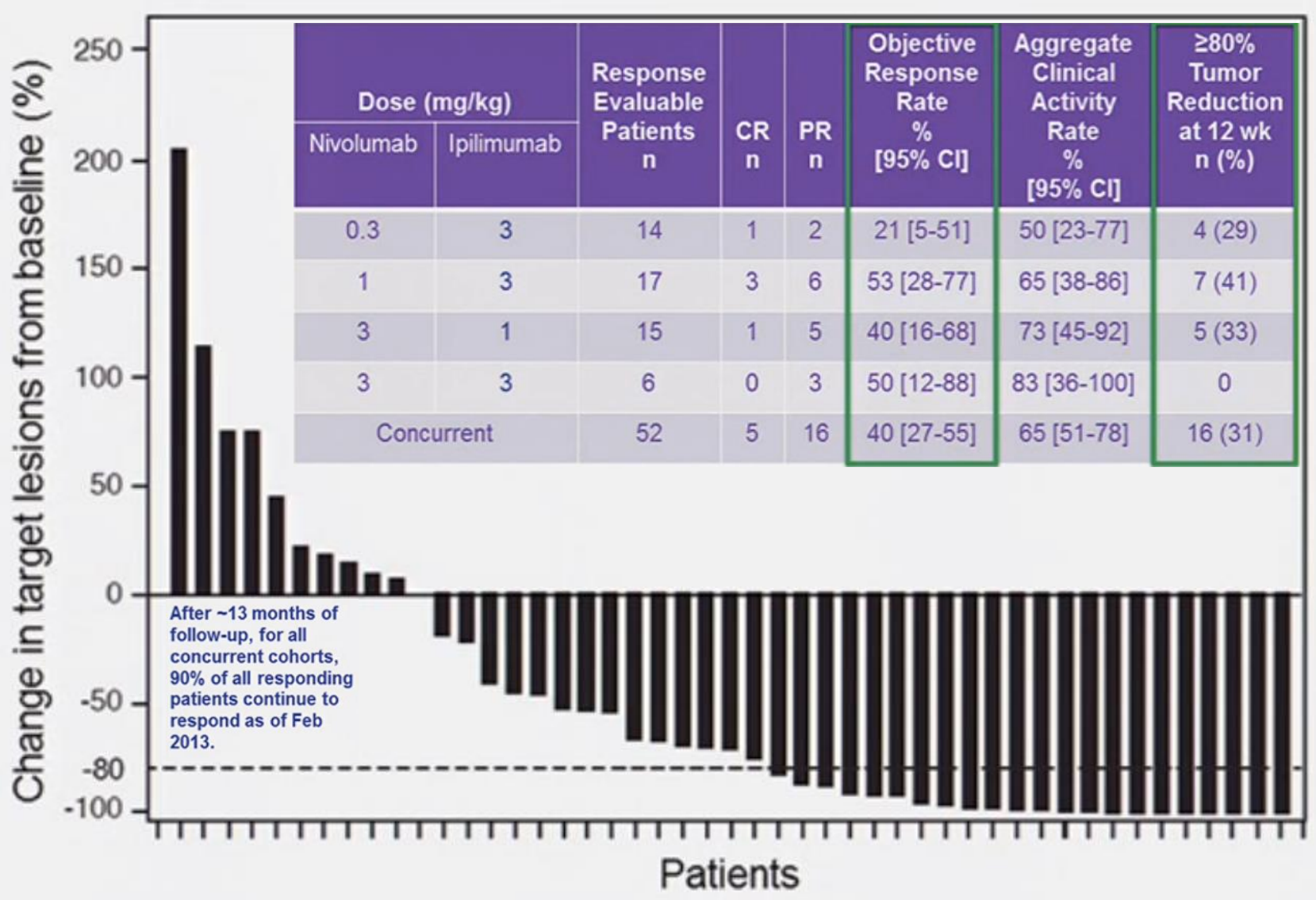
Rapid increase of new anti-PD-1/L1combo trials

PD-1 blockade synergizes with CTLA-4 inhibition



Curran,… Allison, PNAS 2010

Immunotherapy in melanoma: Ipilimumab + Nivolumab



Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

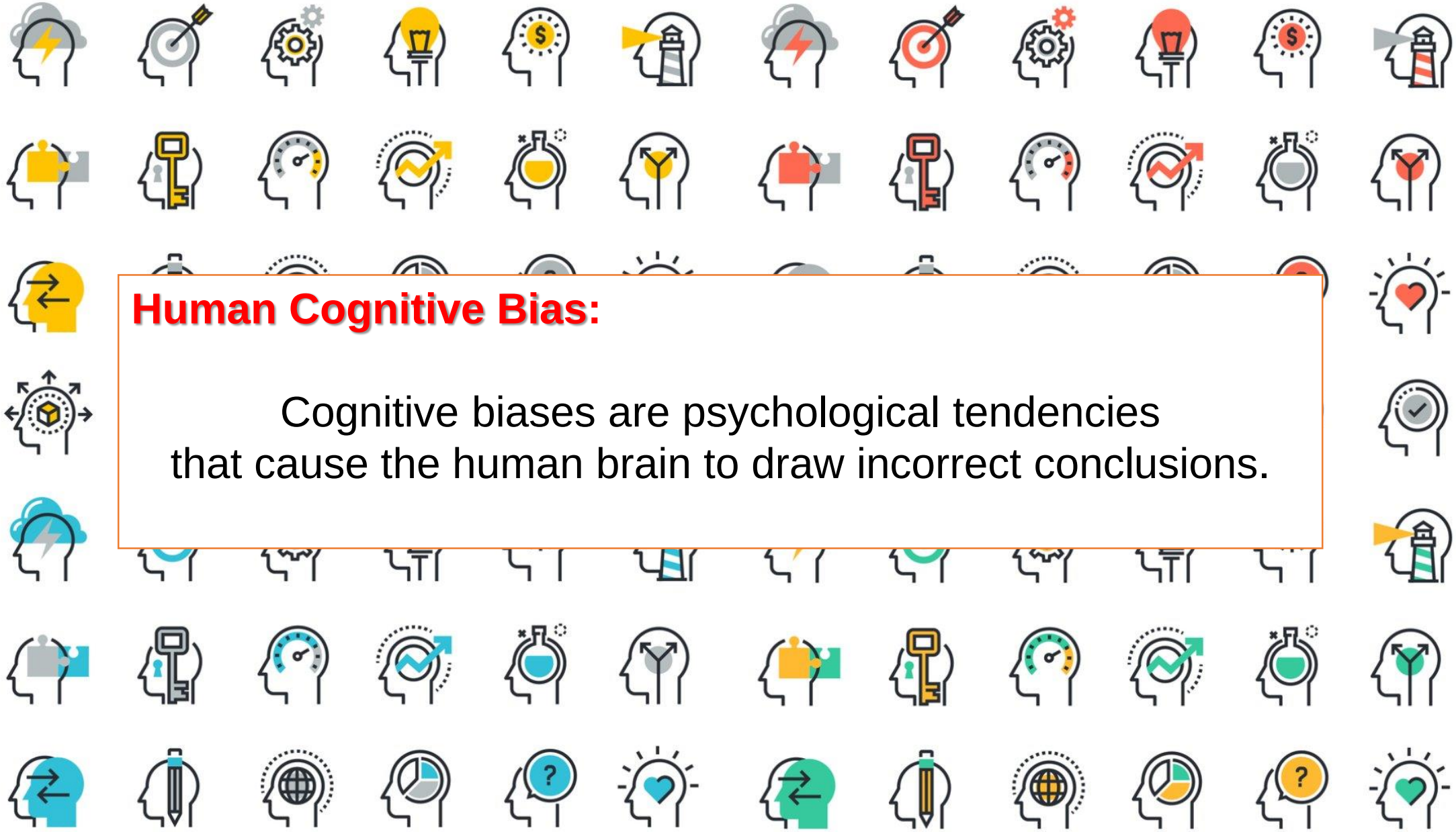
Wolchok et al. ASCO 2013 # 9012

Nobel prize for discovery of cancer therapy by inhibition of negative immune regulation

Jim Allison **Tasuku Honjo**

Why did things spiral out of control?

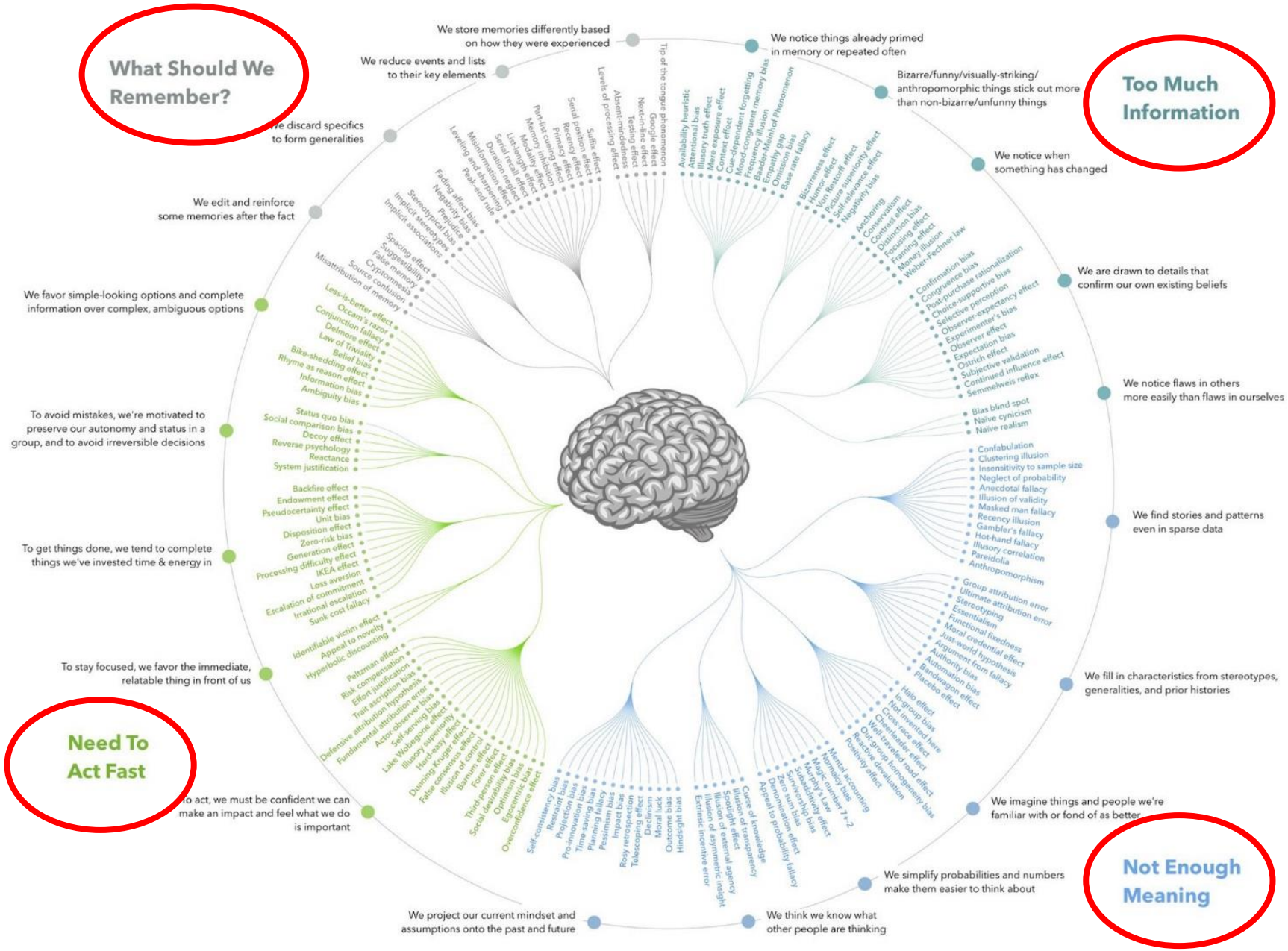
Hypothesis: We are all victims of **cognitive bias**



Human Cognitive Bias:

Cognitive biases are psychological tendencies
that cause the human brain to draw incorrect conclusions.

COGNITIVE BIAS CODEX, 2016



ALGORITHMIC LAYOUT + DESIGN BY JM3 · JOHN MANOOGIAN III // CONCEPT + METICULOUS CATEGORIZATION BY BUSTER BENSON // DEEP RESEARCH BY WIKIPEDIANS FAR + WIDE

Lesson 1: The Cheerleader effect

SCIENTIFIC AMERICAN

The Cheerleader Effect

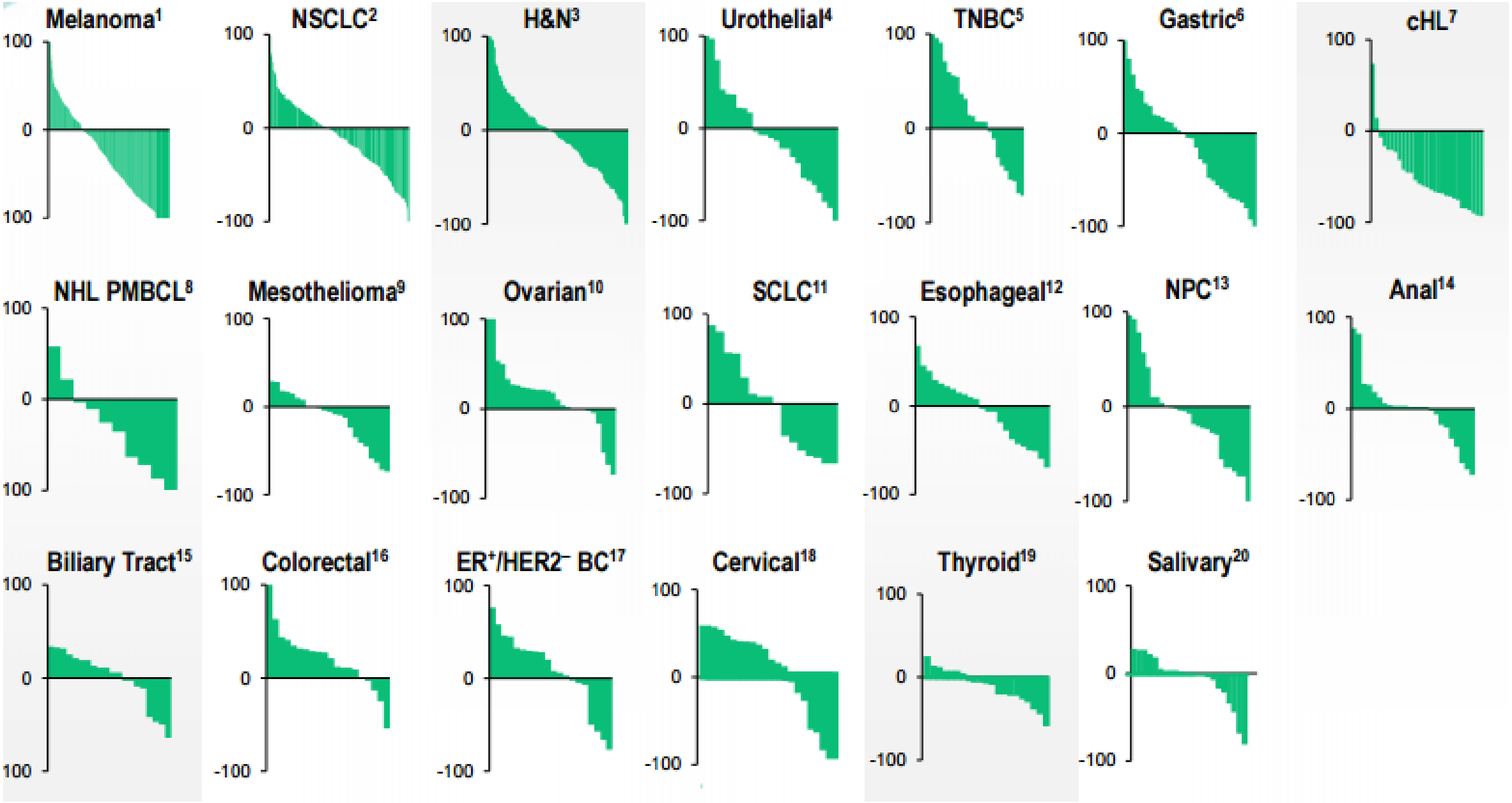
Seeing faces in groups makes them appear more attractive

By Cindi May on December 3, 2013 12

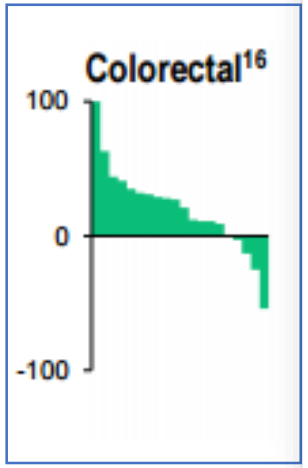
The tendency for people or things to appear more attractive in a group than in isolation

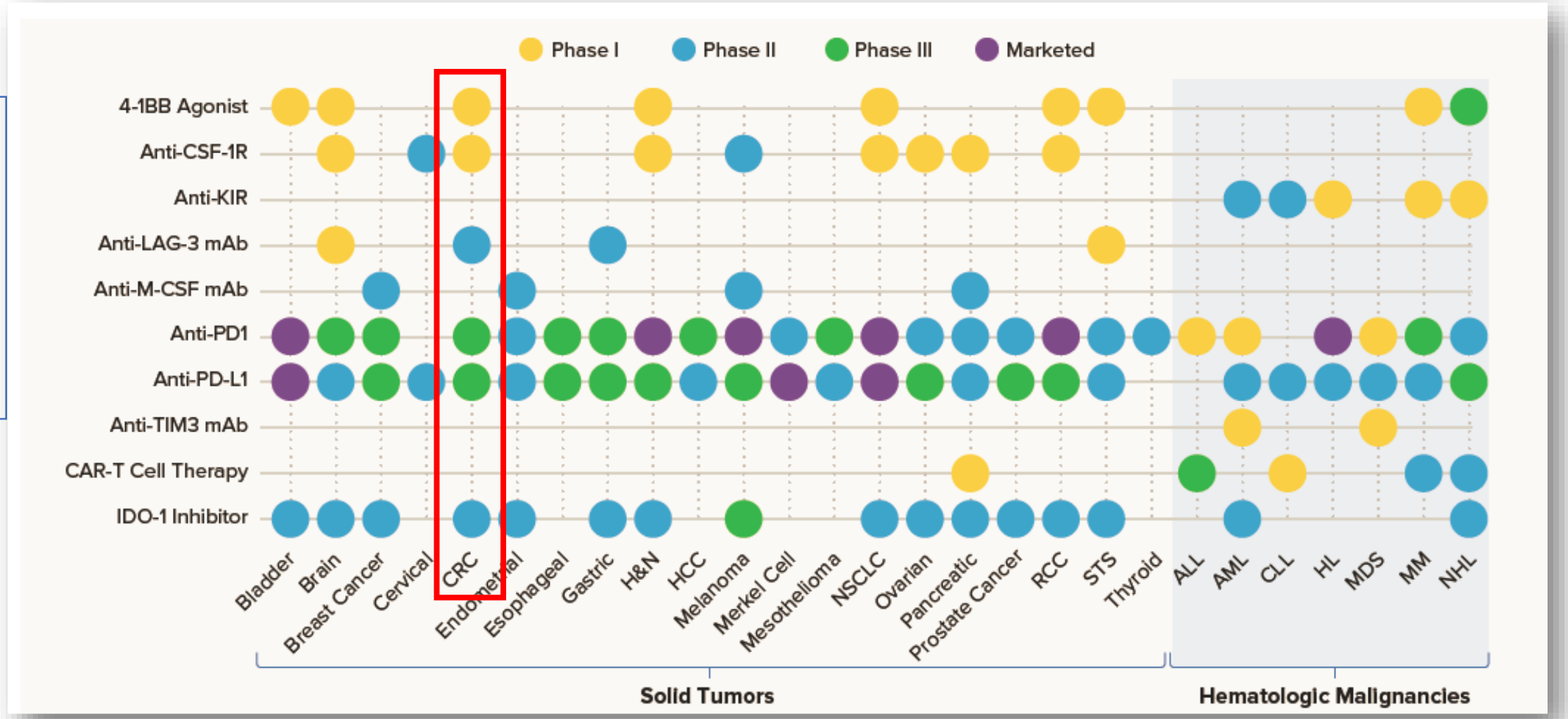
Drew Walker and Edward Vul, Psychological Science, 2014

"Pembro monotherapy has shown activity in 20 tumors"

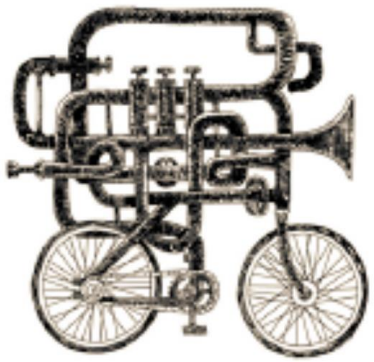


Lesson 1: The Cheerleader effect





Lesson 2: The Bandwagon effect

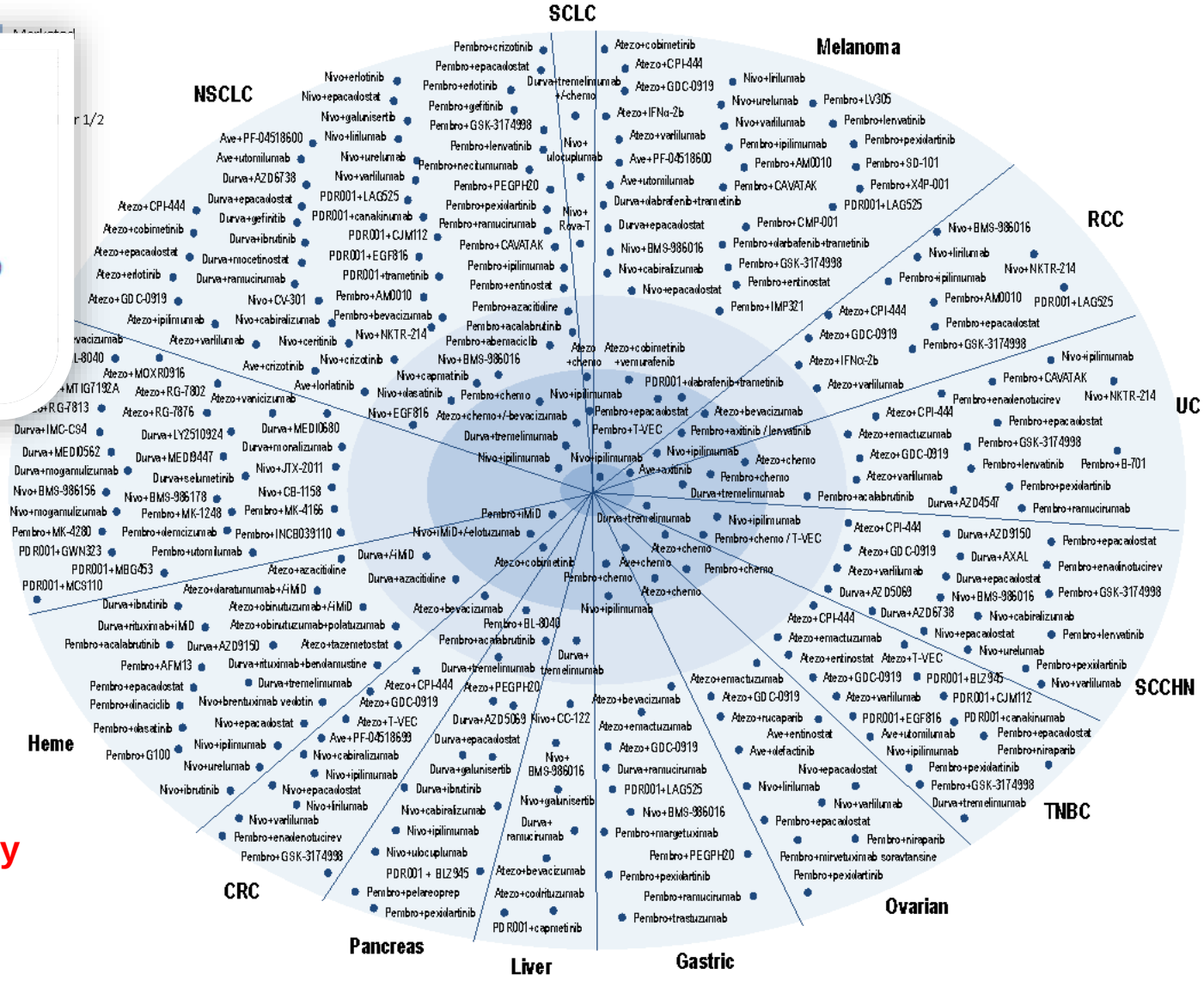


Bandwagon effect

The tendency to do (or believe) things because many other people do (or believe) the same. Related to groupthink and herd behaviour.

PD-1/L1 inhibitors are like the chocolate of oncology

Chocolate makes everything better

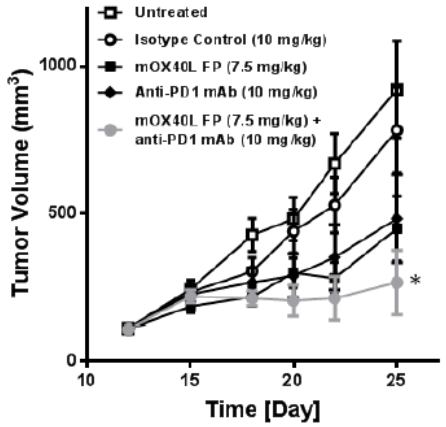


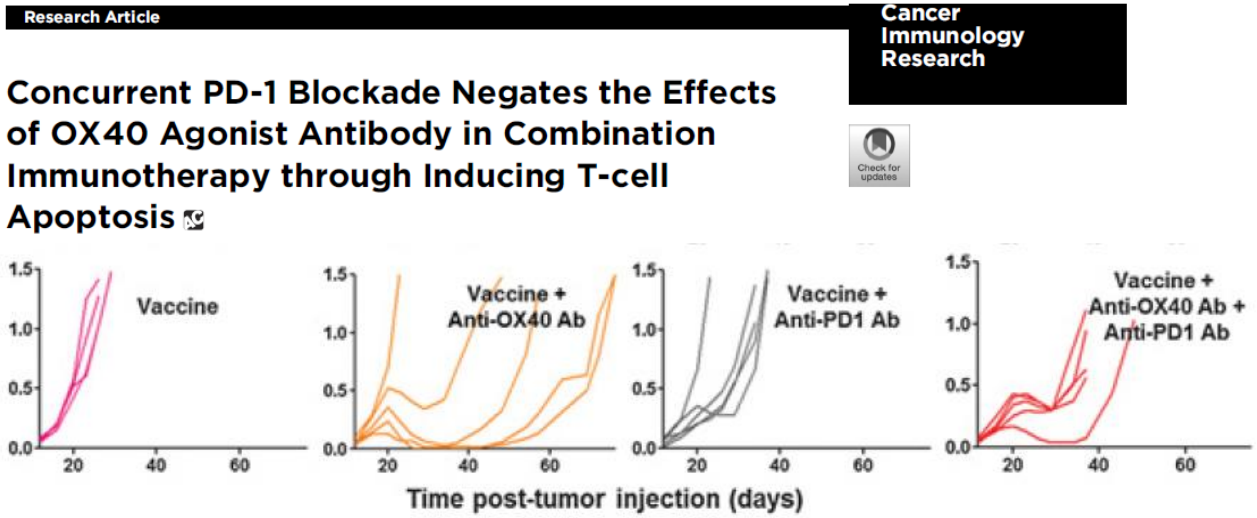
In March 2017, there were ***1,122*** cancer immunotherapy combination trials...

…then I stopped counting…

Combo scheduling matters

OX40 agonist + PD-1/L1 inhibitor combination





Shrimali et al. Cancer Immunol Res 2017

Cohort	Q2w	Q4w	Subjects
A1	X1	Y1	3-6
A2	X2	Y2	3-6
A3	X3	Y3	3-6
A4	X4	Y4	3-6
A5	X5	Y5	3-6
A6	X6	Y6	3-6

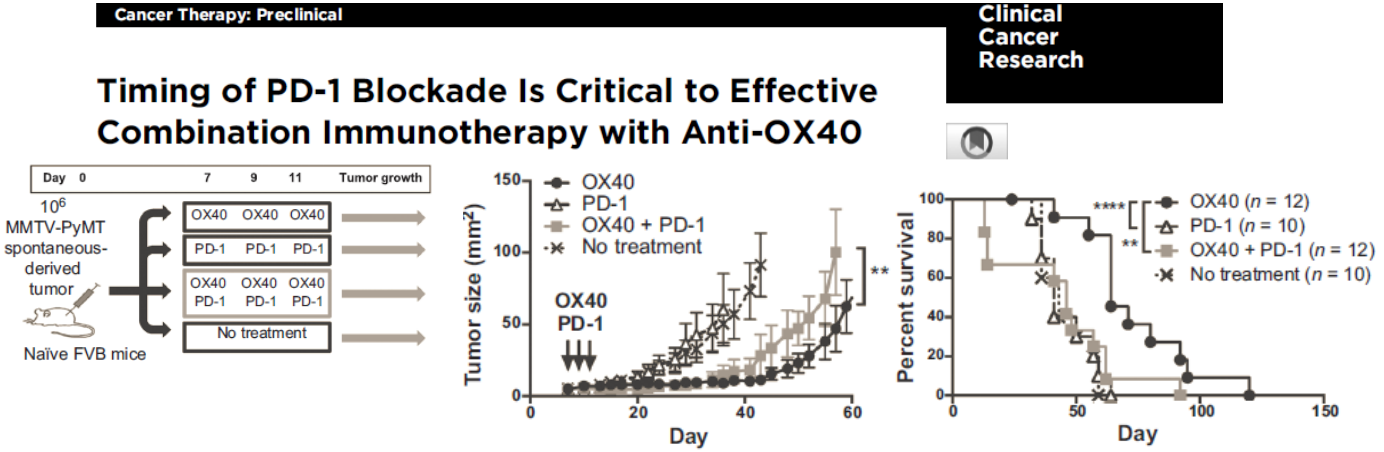
Dose escalation

MTD

Dose Expansion

N= 258-276

Cohort	Q2w	Q4w	Subjects
MSS CRC	X1	Y1	40
Io naïve NSCLC	X2	Y2	40
Io-R NSCLC	X3	Y3	40
Io-Ref	X4	Y4	40
SCCHN	X5	Y5	40
UC	X6	Y6	40

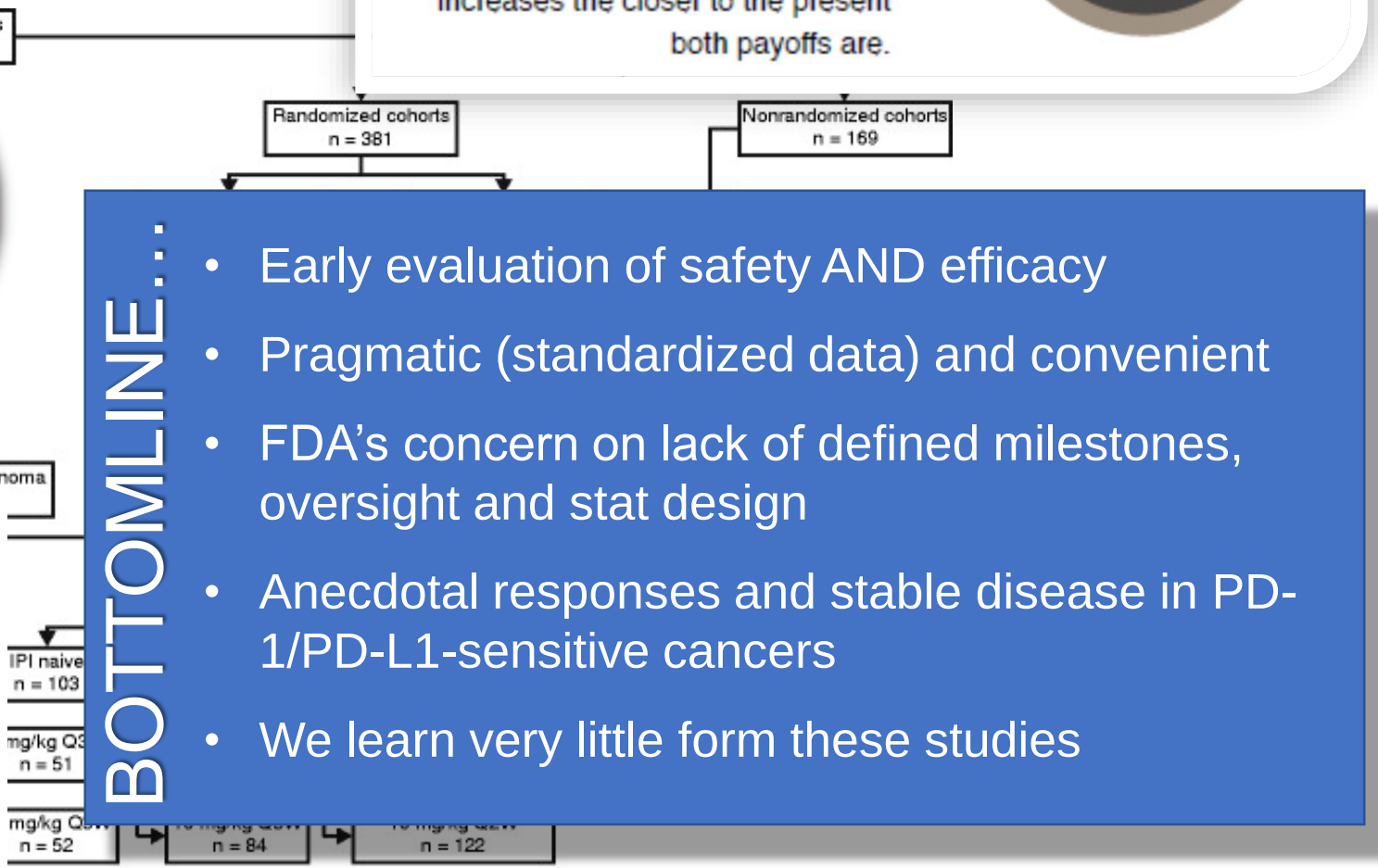


Messenheimer et al, Clin Cancer Res 2017

mAb OX40	Pfizer	PF-04518600	Phase 2
	AstraZeneca	MEDI0562	Phase 1
	GSK	GSK3174998	Phase 1
	BMS	BMS-986178	Phase 1
	Incyte	INCAGN01949	Phase 1

Lesson 2: Hyperbolic discounting:
Seamless supersized Phase I trials

KEYNOTE-001 (n=1235)



Hyperbolic discounting

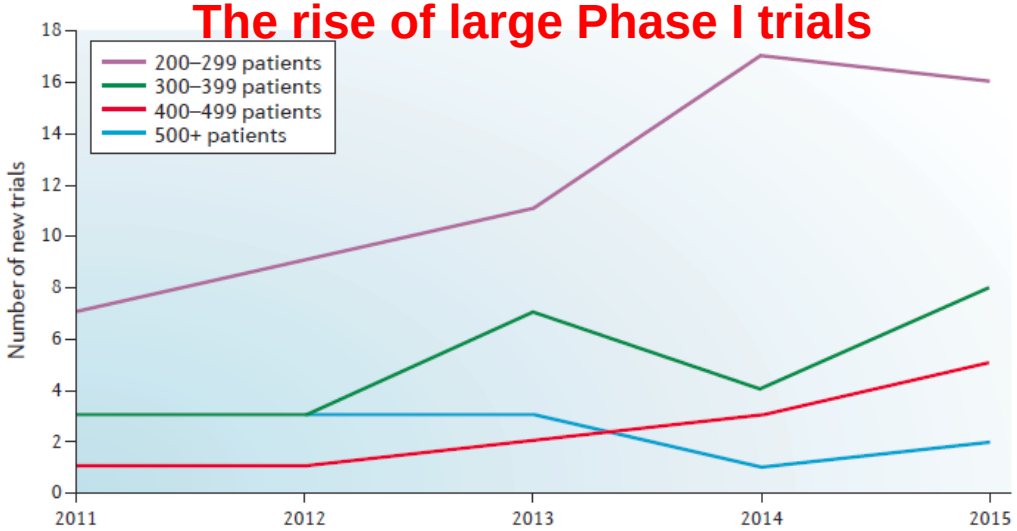
The tendency for people to have a stronger preference for more immediate payoffs relative to later payoffs, where the tendency increases the closer to the present both payoffs are.

BOTTOMLINE…

- Early evaluation of safety AND efficacy
- Pragmatic (standardized data) and convenient
- FDA's concern on lack of defined milestones, oversight and stat design
- Anecdotal responses and stable disease in PD-1/PD-L1-sensitive cancers
- We learn very little form these studies

Theoret, FDA. The Drug Development Paradigm in Oncology 2016

The rise of large Phase I trials



Mullard et al, Nature Reviews Drug Discovery 2016

Lesson 3: The Bandwagon effect

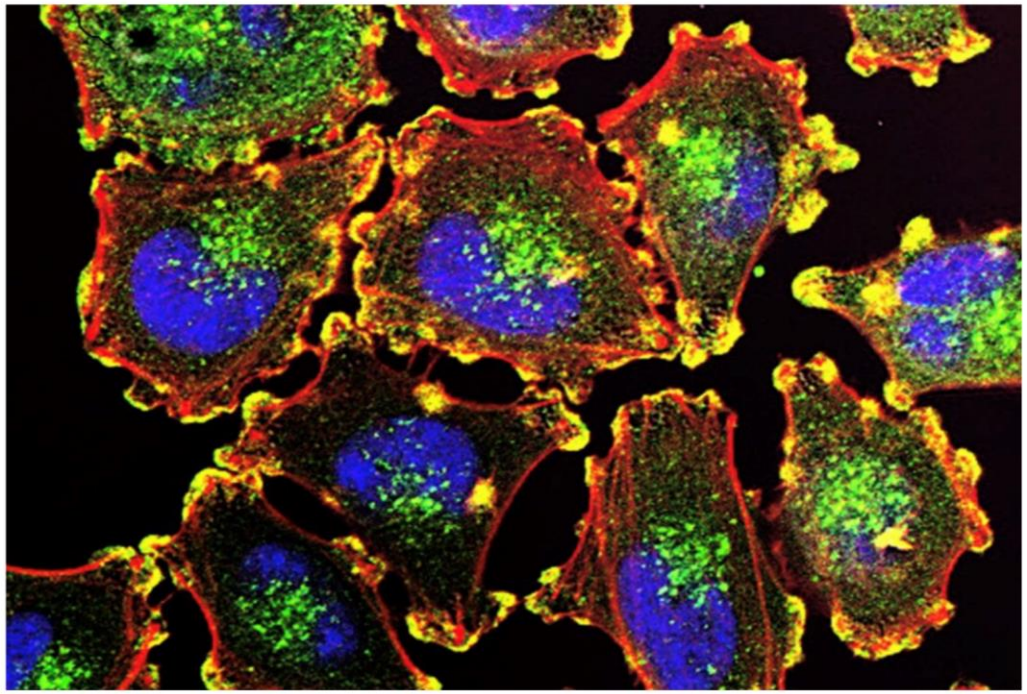
Effect of epacadostat plus pembro failing

Clinical programs scaled back after ECHO-301 setback

Combination	Cancer type	Trial name	Status
Epacadostat + Keytruda	Melanoma	ECHO-301	Failed, study stopped
Epacadostat + Keytruda	Renal cancer	ECHO-302	Enrollment to be discontinued
Epacadostat + Keytruda	Bladder cancer	ECHO-303 & -307	Enrollment to be discontinued
Epacadostat + Keytruda	Head & neck cancer	ECHO-304	Enrollment to be discontinued
Epacadostat + Keytruda	NSCLC	ECHO-305 & -306	Converted into Phase 2 studies
Epacadostat + Opdivo	NSCLC	ECHO-309	Enrollment to be discontinued
Epacaodstat + Opdivo	Head & neck cancer	ECHO-310	Enrollment to be discontinued
Epacadostat + Imfinzi	NSCLC	Pacific-3	Will not be initiated

SOURCE: Incyte Corp.

Bristol-Myers Latest to Drop IDO Studies in Wake of Incyte Failure



Frank Vinluan
April 30th, 2018

@frankvinluan @xconomy Like Us

Xconomy New York — [*Updated 5/1/18, 12:34 p.m. See below.*] Drug giant Bristol-Myers Squibb is the latest to feel the shockwave caused by the failure of a widely watched cancer immunotherapy nearly a month ago.

Xconomy has learned that Bristol (NYSE: **BMY**) is curtailing work on three late-stage studies **testing an experimental cancer drug that it bought for $800 million three years**

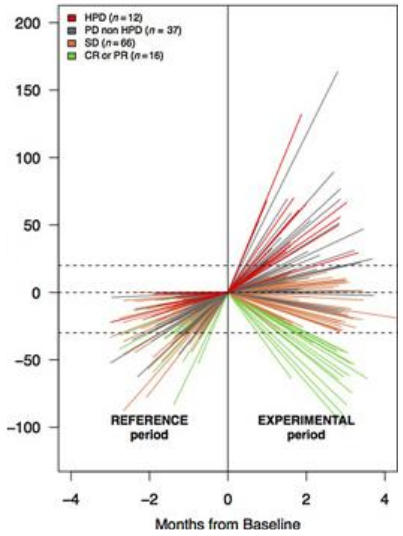
Lesson 4: Attentional bias:
Neglecting hyperprogression and safety issues

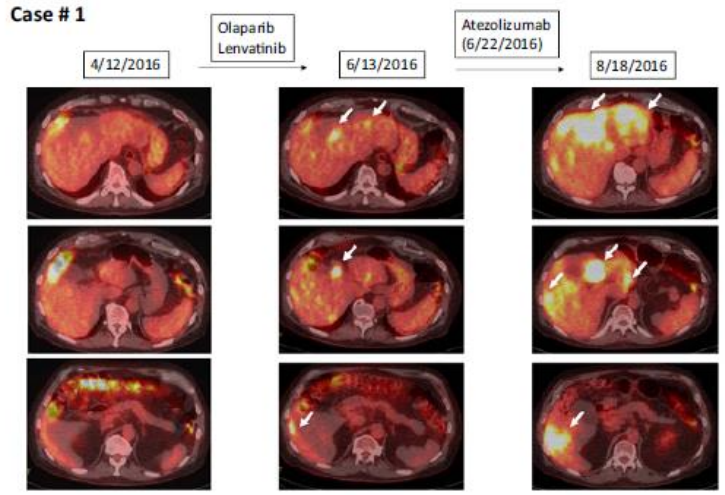
Attentional bias

The tendency to neglect relevant data when making judgments of a correlation or association.

In NSCLC…

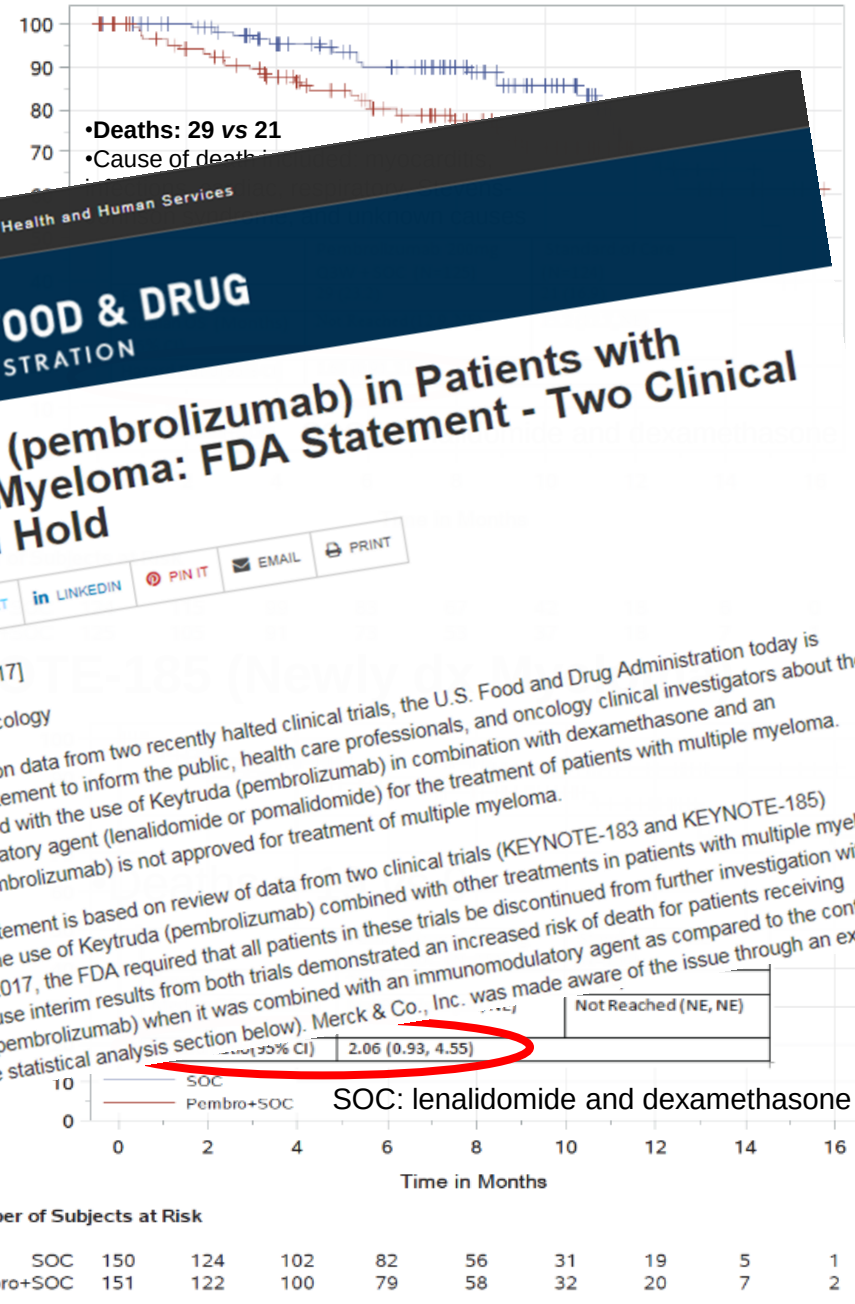
- 10% of patients could be experiencing Pseudo-progression
- 10% of patients could be experiencing Hyper-progression



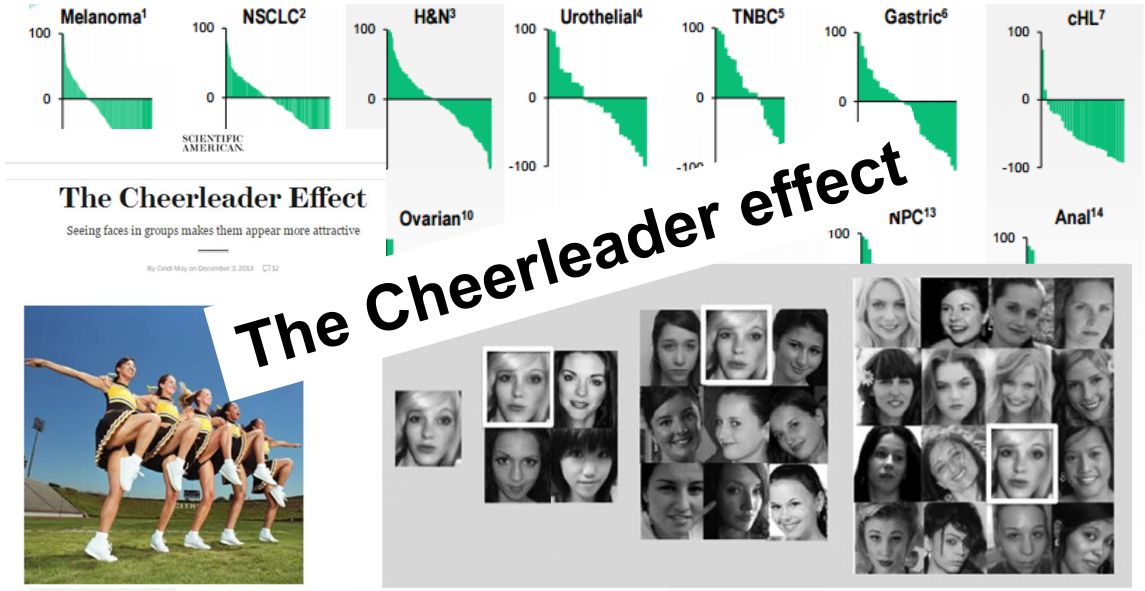


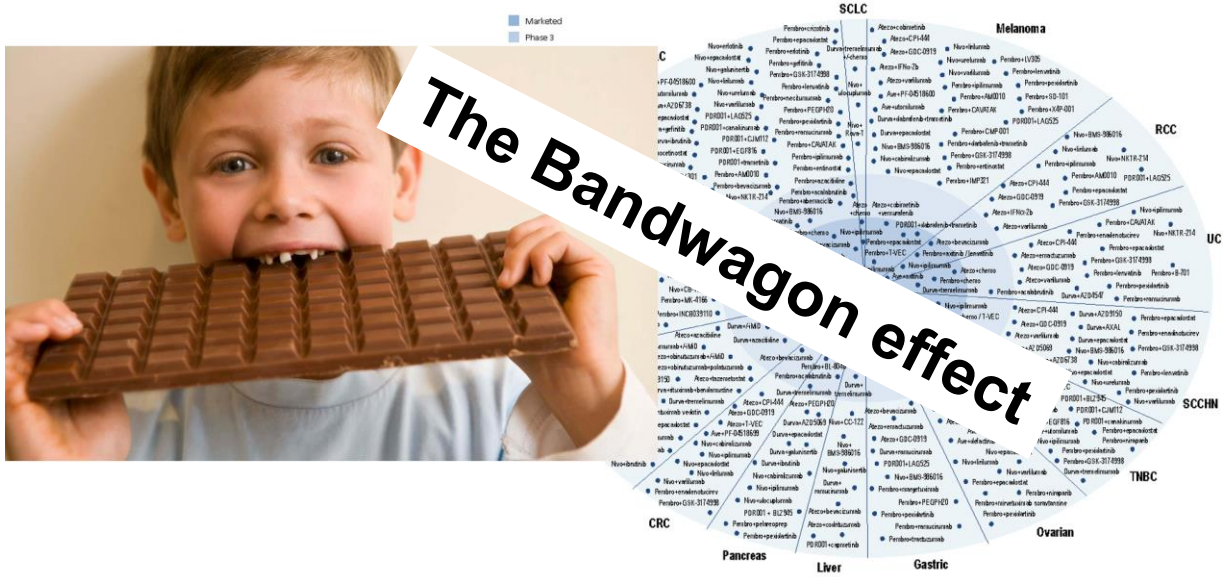
Kato S, et al Clin Cancer Res, 2017
Champiat S et al. Clin Cancer Res, 2017

KEYNOTE-183 (Relapsed Myeloma)

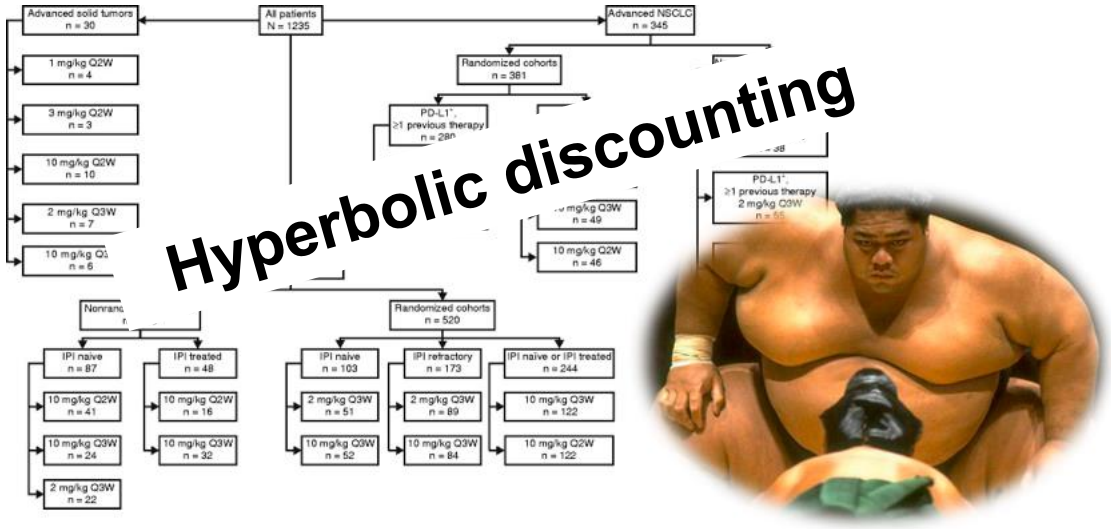


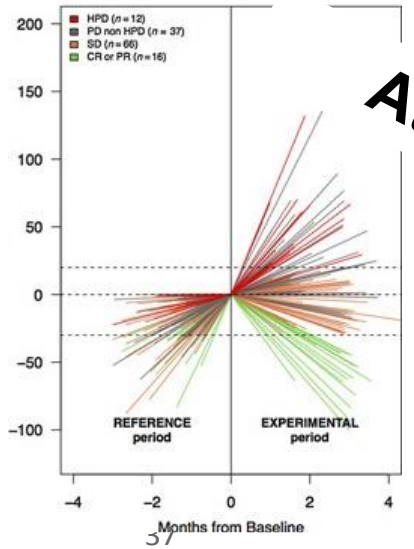
SOC: lenalidomide and dexamethasone

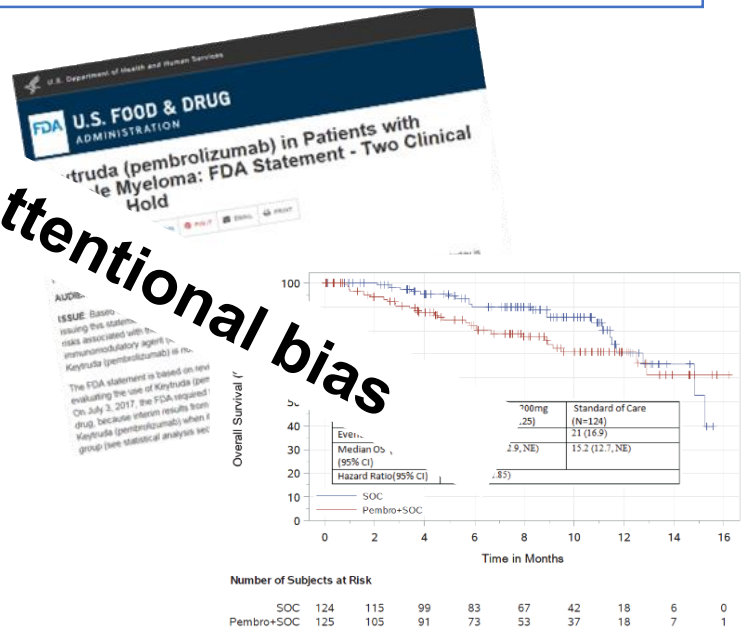




Cognitive biases that have influenced IO combo drug development







Developing therapeutics in the Slope of Enlightenment

- Need to stop serendipitous development of immunotherapeutics
- Biology should be driving development

IO combination checklist

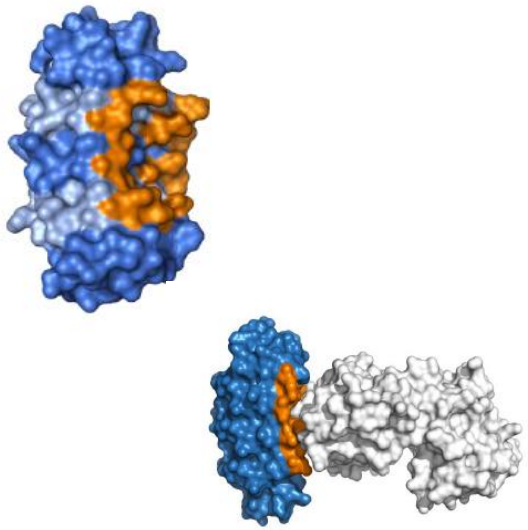
- Single agent efficacy ☑
- Biology-driven rationale ☑
- No overlapping toxicities ☑
- Biomarker-based pt selection ☑

- Large amount of clinical data from other compounds, and a huge body of translational research will be available
- Optimized compounds adaptable to the needs of the biology

DARPins and Molecular Partners

DARPins

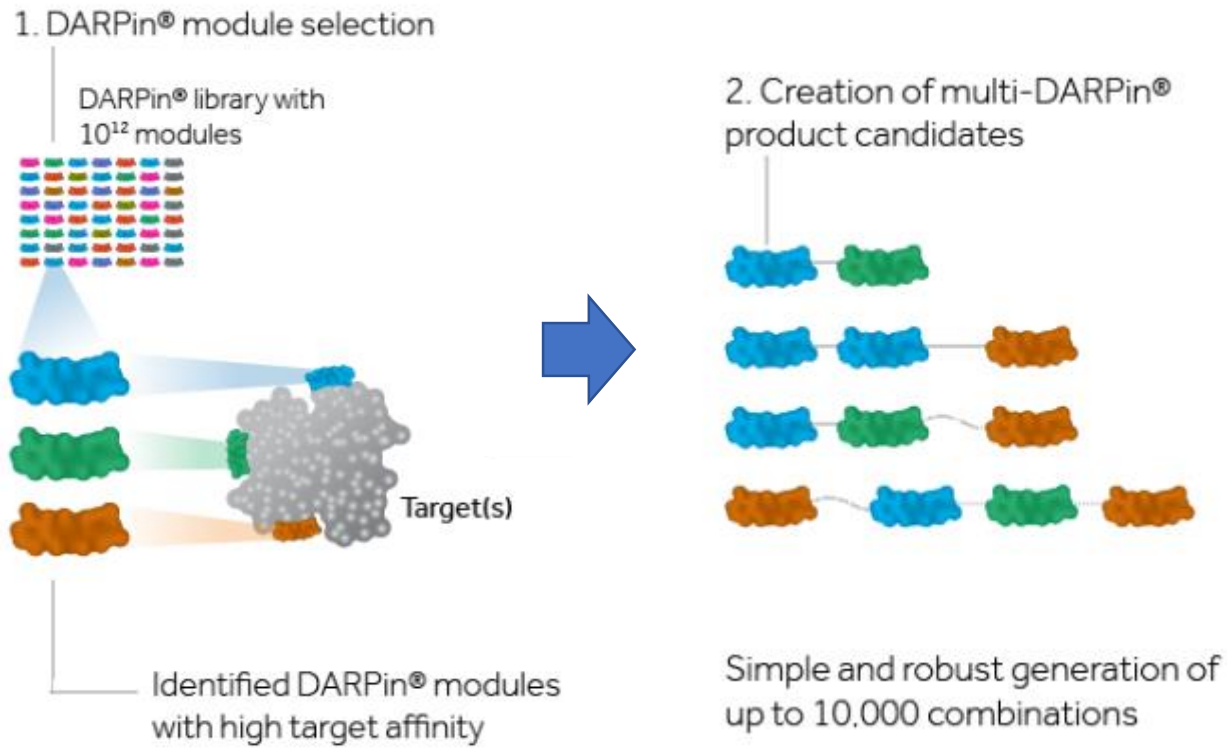
- Although antibodies are, and will continue to be the dominant therapeutic option, there are numerous **disadvantages** including their relatively bulky size, complexity in creation and manufacturing, difficulties in formatting (making drug conjugates, bispecifics etc) and a high cost of production.
- **Antibody-mimetics:** lipocalins (Pieris Pharmaceuticals), affimers (Avacta), bicycle (Bicycle Therapeutics), DARPins (Molecular Partners).
- **DAPRins seem to have ideal properties:**
  - Mono-& multi-DARPin are soluble, stable, small size, high potency, high stability, high affinity.
  - High-yield production and high developability



Small size	14 – 18 kD	a increased tissue penetration
High potency	< 5 – 100 pM	active at low concentration
High stability and solubility	soluble at > 100 g/L	ideal drug properties
Cost efficient bacterial production	7 – 15 g/L	rapid and low-cost
Tunable PK properties	PK toolbox (min – weeks)	adjust to patient need
High developability	robust class behavior	standard processes

Versatility

- Tunable
  - Half life
  - Pro-Drugs
  - Modularity and multiple formats



- DARPin technology can be used for:
  - Monospecifics
  - Bispecifics
  - Conjugated to non-DARPin elements (toxins, XRT)
  - Targeting MHC-peptides
  - Chimeric antigen receptors for T Cells.

- Clinical proof of concept with 3 compounds

Key Takeaways & Outlook

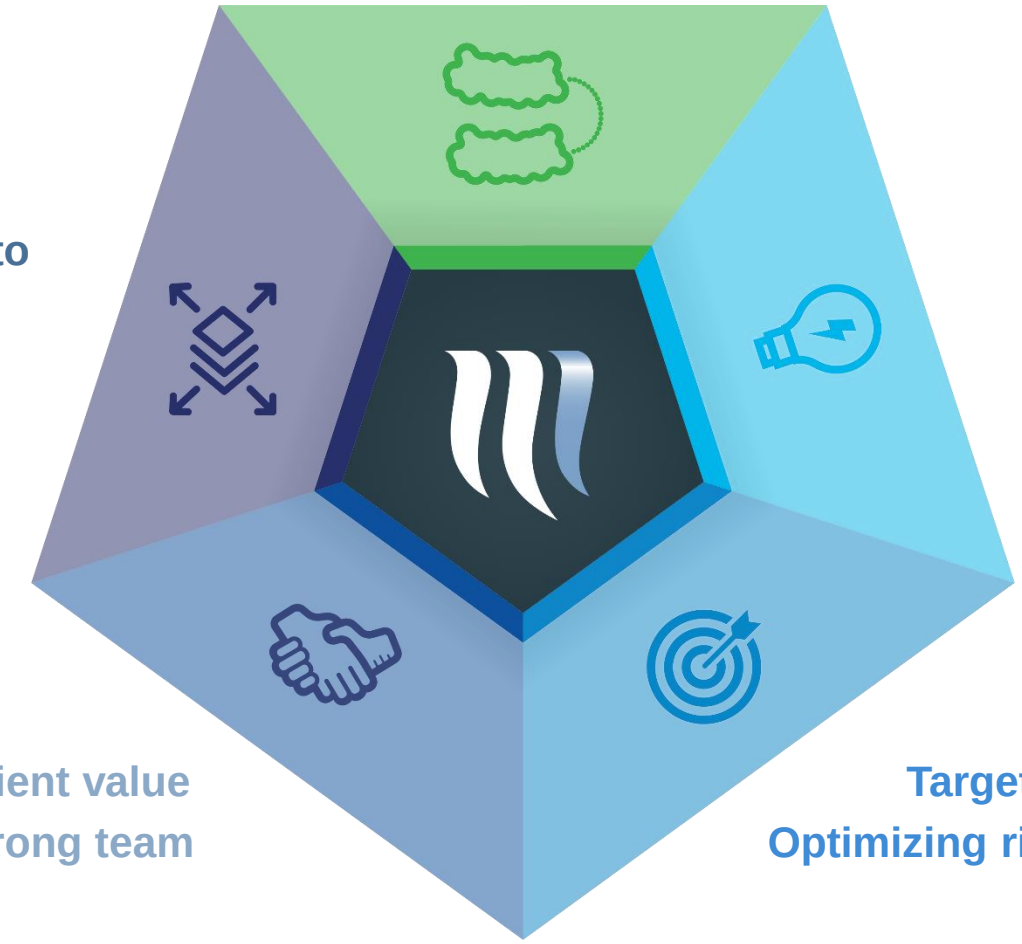
Patrick Amstutz
CEO

MOLECULAR partners

Key takeaways R&D Day 2019

Validated source of DARPin® Candidates

Flexible business model to maximize product value



Novel Therapeutic Designs

1. Tumor-local immune agonists
2. pMHC targeting platform
3. Next Gen T-cell engagers

Deliver patient value with our strong team

Target choice: Optimizing risk/reward ratio

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Review of 2019 and expected 2020 Catalysts

	2019	2020
Abicipar	✓ BLA & MMA accepted for review ✓ MAPLE: improved safety	▪ Approval and launch in nAMD ▪ DME: P3 start (AGN guidance)
MP0250	✓ P2 MM trial: Positive data at ASH ▪ Decision to accelerate MP0250 development through partnership ▪ P2 NSCLC trial stopped	▪ Interim P2 data: PI-combo trial ▪ Continued development of MP0250 in partnership
MP0274	▪ P1 Dose escalation progressing	▪ Establish dose and define path forward
MP0310	✓ FIH with MP0310 (monotherapy)	▪ MP0310 reaching relevant doses ▪ Start MP0310 combination trials
Research	✓ Novel Therapeutic Designs Applied ✓ MP0317 candidate defined ✓ pMHC platform established	▪ Prepare for MP0317 IND submission ▪ Selection of 1st pMHC candidate ▪ Multiple updates at AACR & other international conferences

Funding into H2 2021 (excl. any future proceeds related to Abicipar and partnerships; Cash Q3 19: CHF112mn)

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Questions?

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Thank you!

MOLECULAR partners

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IR Agenda

February 6, 2020	Publication of Full-year Results 2019 (unaudited)
April 29, 2020	Annual General Meeting