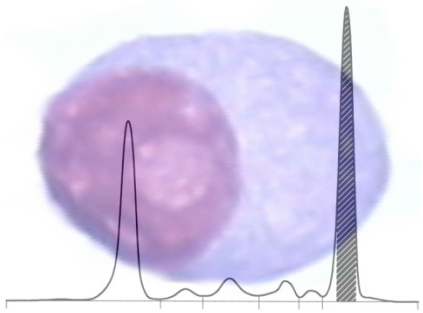
UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Dipartimento
di Scienze Biomediche
e Oncologia Umana

The DARPIN® bispecific molecule

Roberto Ria, MD

Unità per lo Studio e la Terapia
delle Gammopatie Monoclonali



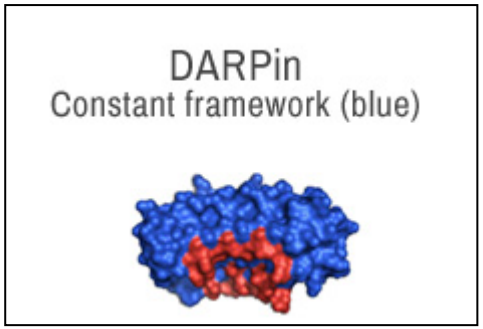
Disclosures for Roberto Ria M.D.

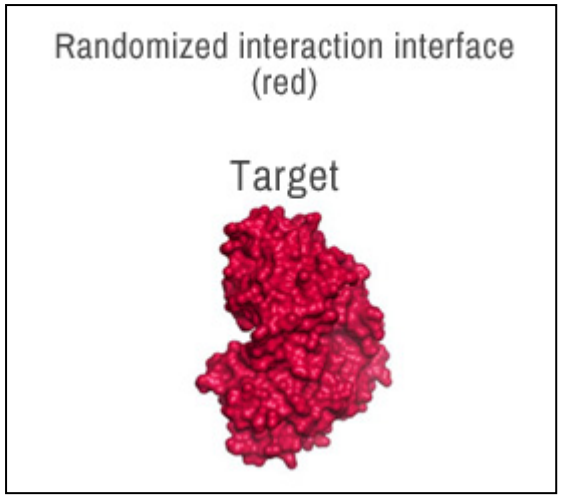
- ✓ Grant/Research Support: no disclosure.
- ✓ Speaker's Bureau: Celgene, Janssen Cilag.
- ✓ Consultant: BMS, Celgene, Janssen Cilag.
- ✓ Major Shareholder: no disclosure.
- ✓ Other: no disclosure.

I will be discussing "off-label" uses of the following medications: none

DARPin® Proteins: A Different Class of Therapeutics

Small protein therapeutic agents derived from natural ankyrin repeat proteins, one of the most common binding proteins in nature and responsible for diverse functions, such as cell signaling and receptor binding.

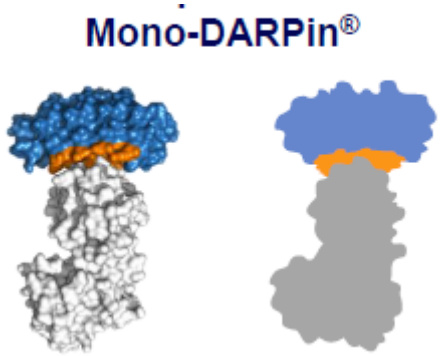




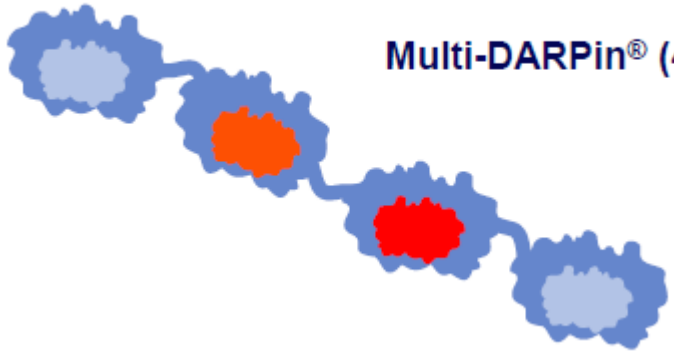
Natural principle: repeat proteins were evolved as binders in multifunctional contexts

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

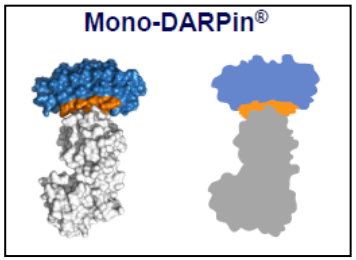
DARPin® Proteins: A Different Class of Therapeutics



Mono-DARPin®: selected to bind a given target with high affinity & specificity (large libraries)

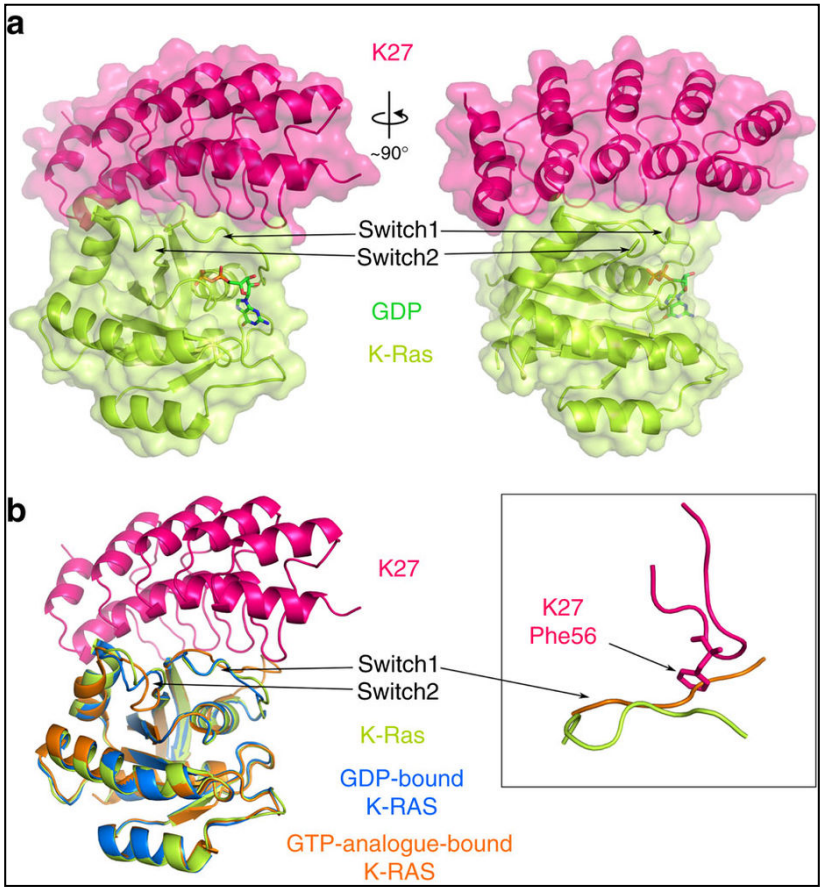


Multi-DARPin®: linked mono-DARPin®(≥ six) & directly used for functional screening

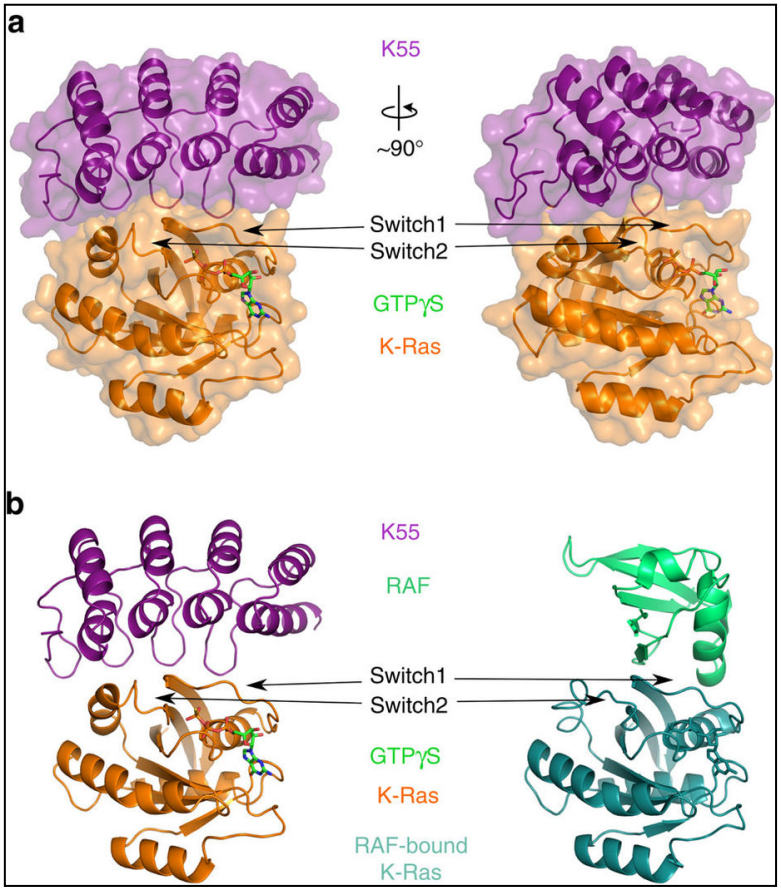


DARPin® Proteins: A Different Class of Therapeutics

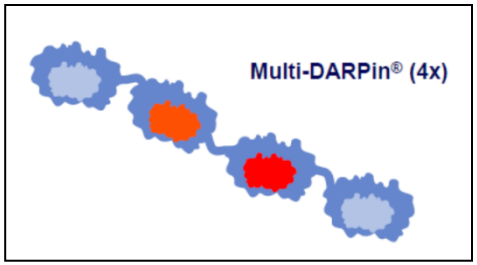
DARPin K27 inhibits nucleotide exchange



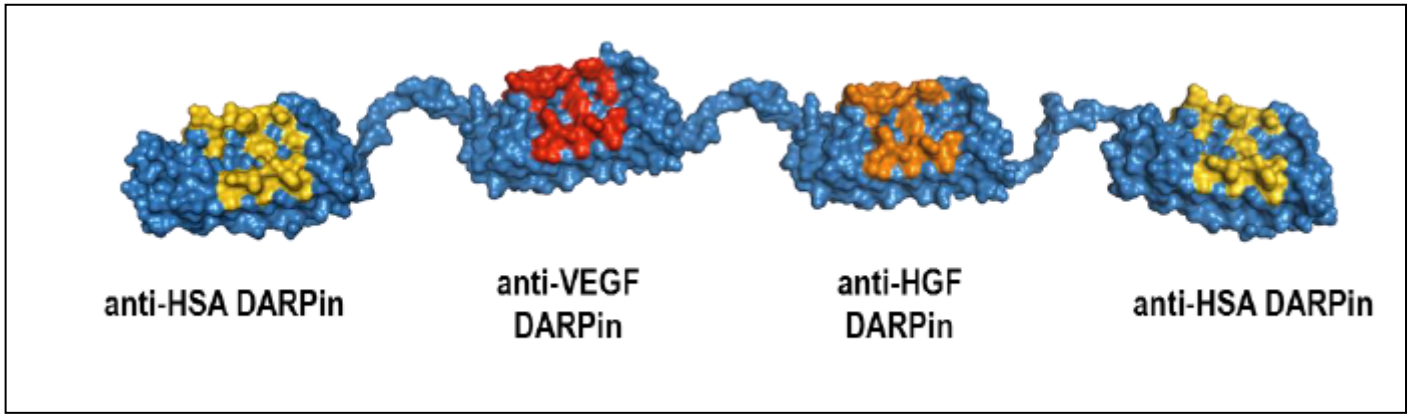
DARPin K55 inhibits the Ras/Raf interaction



Guillard S, et al. Nature Commun 2017

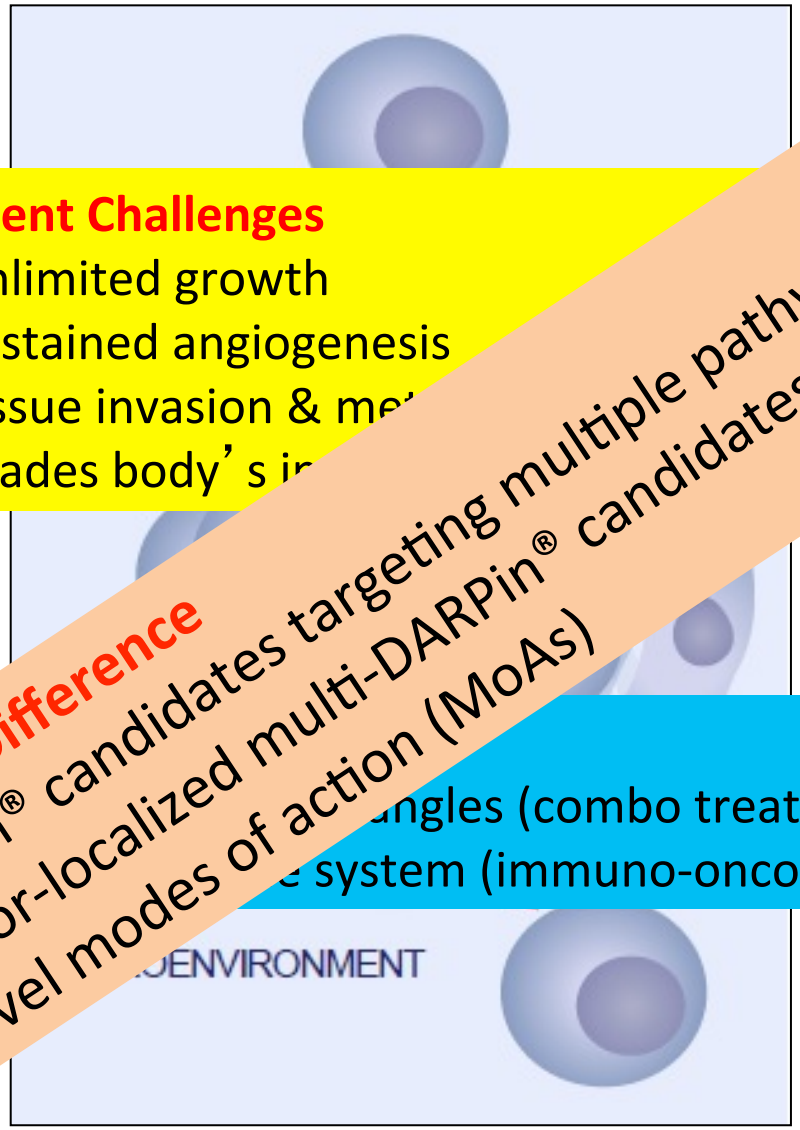


DARPin® Proteins: A Different Class of Therapeutics



Middleton MR, et al. ESMO 2016

The DARPin® Difference in Oncology



Current Challenges

- Unlimited growth
- Sustained angiogenesis
- Tissue invasion & me
- Evades body's i

DARPin® Difference

- DARPin® candidates targeting multiple pathways
- Tumor-localized multi-DARPin® candidates
- Novel modes of action (MoAs)

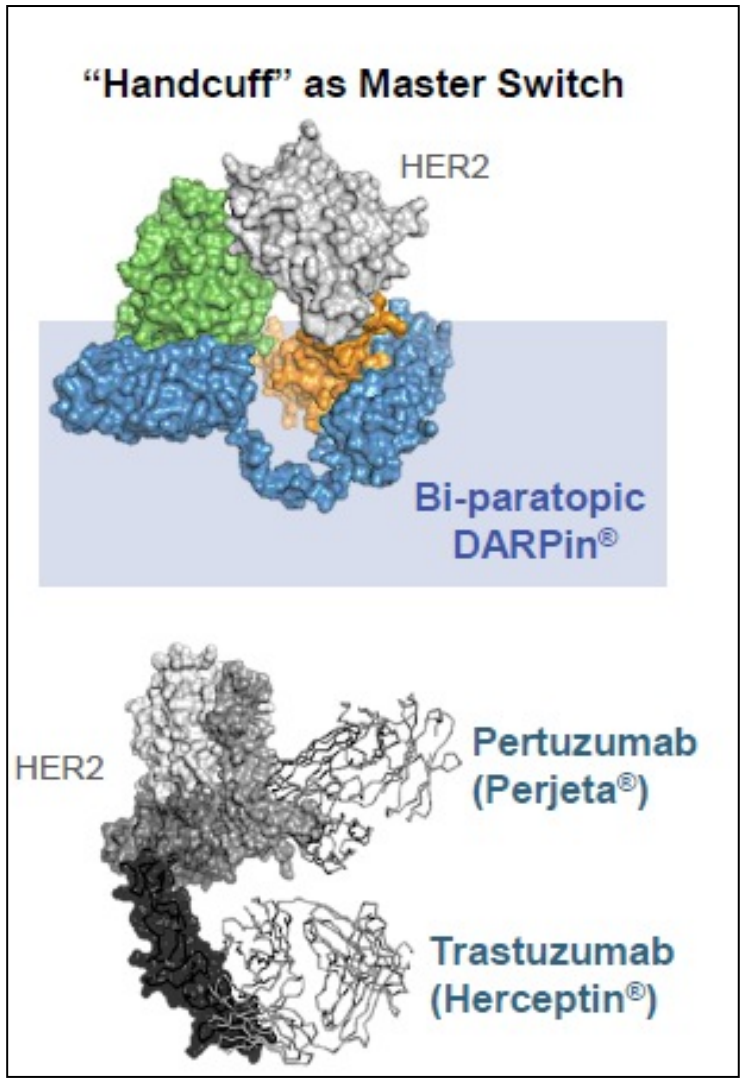
C

angles (combo treatment)

system (immuno-oncology)

ENVIRONMENT

MP0274: Killing HER2+ Cells With New MoA



MP0274

- Multi-DARPin®protein binding two distinct HER2 epitopes
- Indications: patients with HER2-addicted tumors

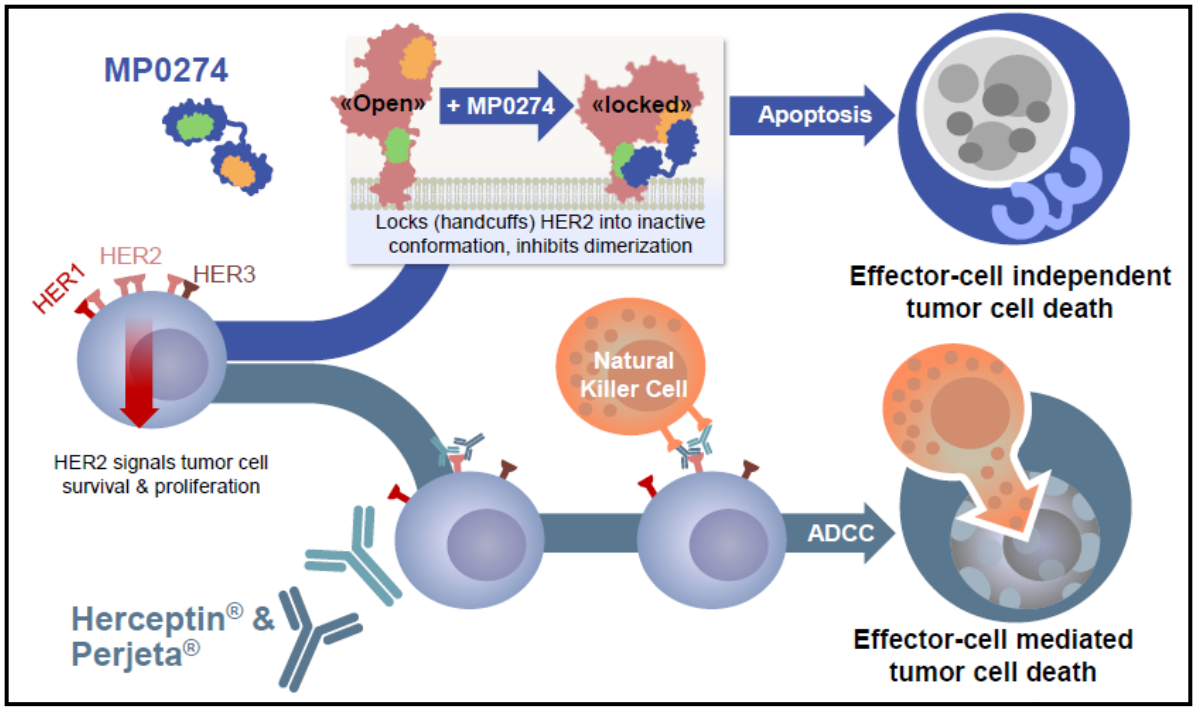
Development/Stage

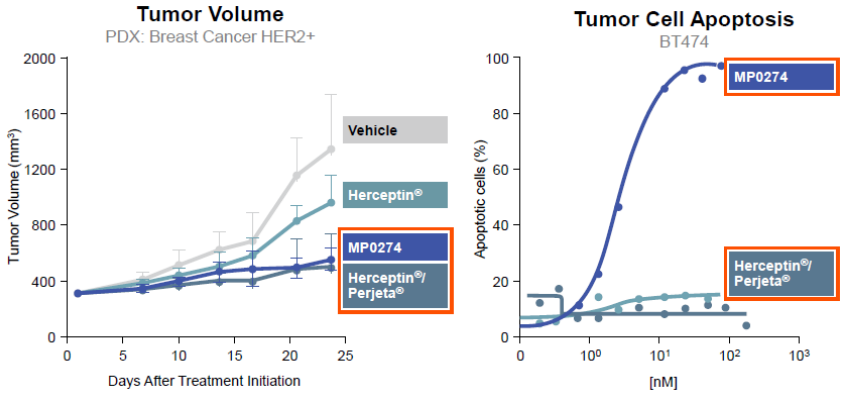
First regulatory submission in Q4/2016

Differentiation & Potential Benefit

- Induces apoptosis (cell death) in HER2+ tumor cells without ADCC
- New MoAmay help patients whodo not adequately respond to current therapies

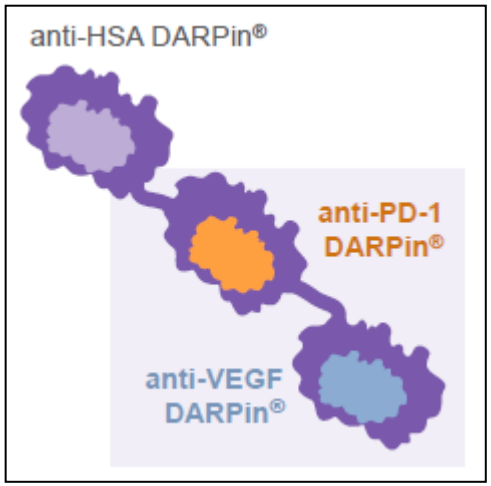
Direct Induction of Tumor Cell Death Is Unique to MP0274





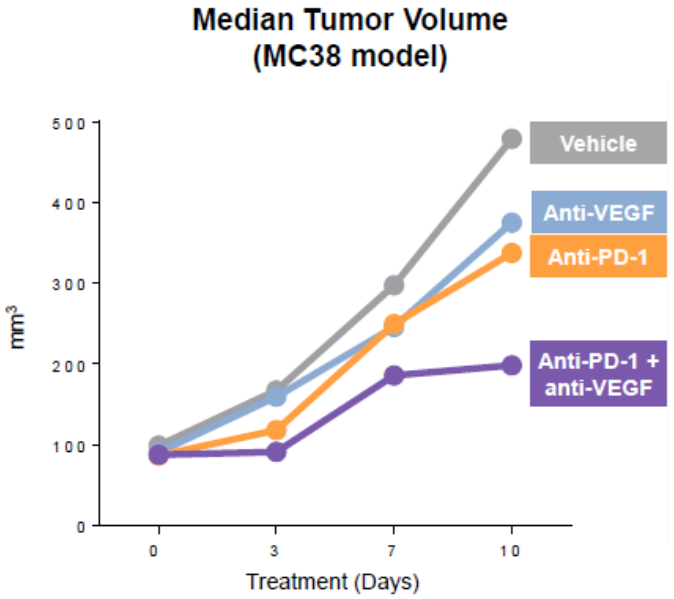
- MP0274 is as efficacious as SOC without the help of the immune system
- New MoAmay help patients who do not adequately respond to current therapies

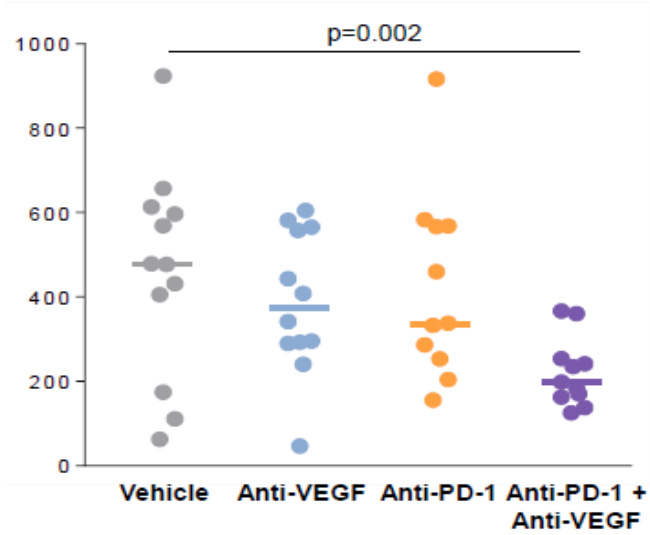
Immuno-Oncology



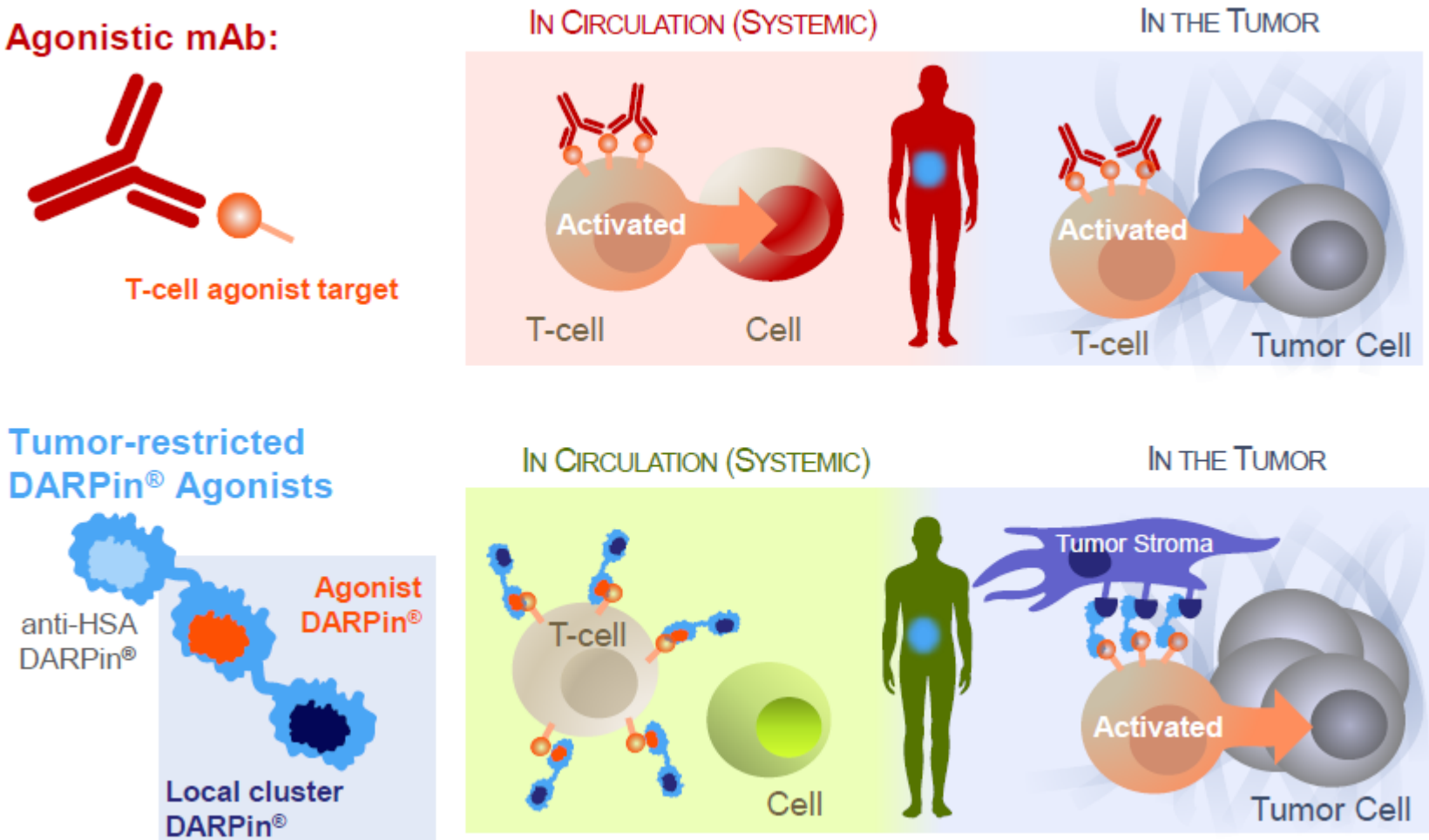
Multi-DARPin® Protein PD-1/VEGF

- Inhibits PD-1 and VEGF
- Rationale: ideal backbone in all indications where PD-1/VEGF will become gold standard
- Normalization of tumor vasculature to enhance immune cell infiltration and PD-1 efficacy
- Opportunity for
  - More patients to respond toanti-PD-1 therapy
  - Use across more indications compared with PD-1 monotherapy

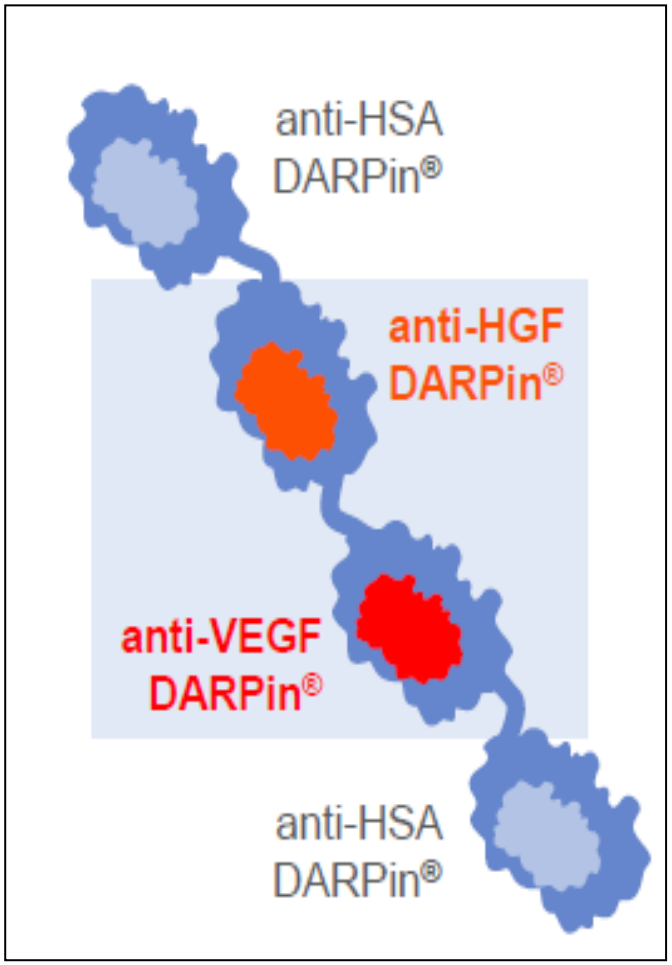




Unleashing Potential of Agonists in I/O



MP0250: An Ideal Combination (anti-VEGF & HGF)



MP0250

First bi-specific biologic targeting VEGF andHGF

Development/Stage

Phase 1: solid tumor study

- Demonstrated good tolerability and exposure, encouraging efficacy

Phase 2: multiple myeloma study

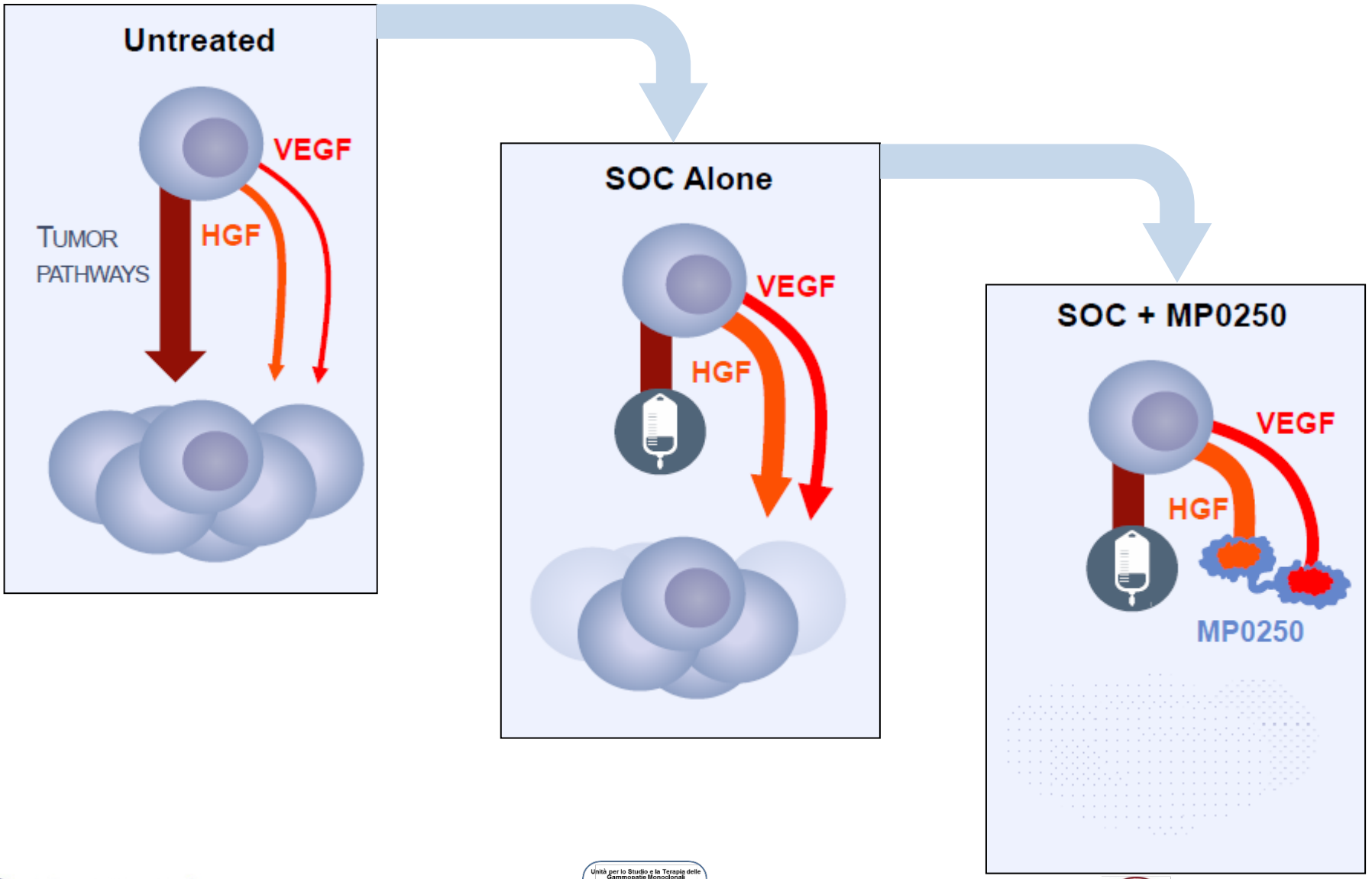
- Regulatory submission Q4/2016
- Initial safety data expected 2017
- Initial efficacy data expected 2018

Additional Phase 2 for solid tumor indication started in 2017

Differentiation & Potential Benefit

- Ideal for patients with likely VEGF-and/or HGF-mediated escape from previous treatment
- Can be combined with standard therapy

MP0250 Blocks Tumor Escape



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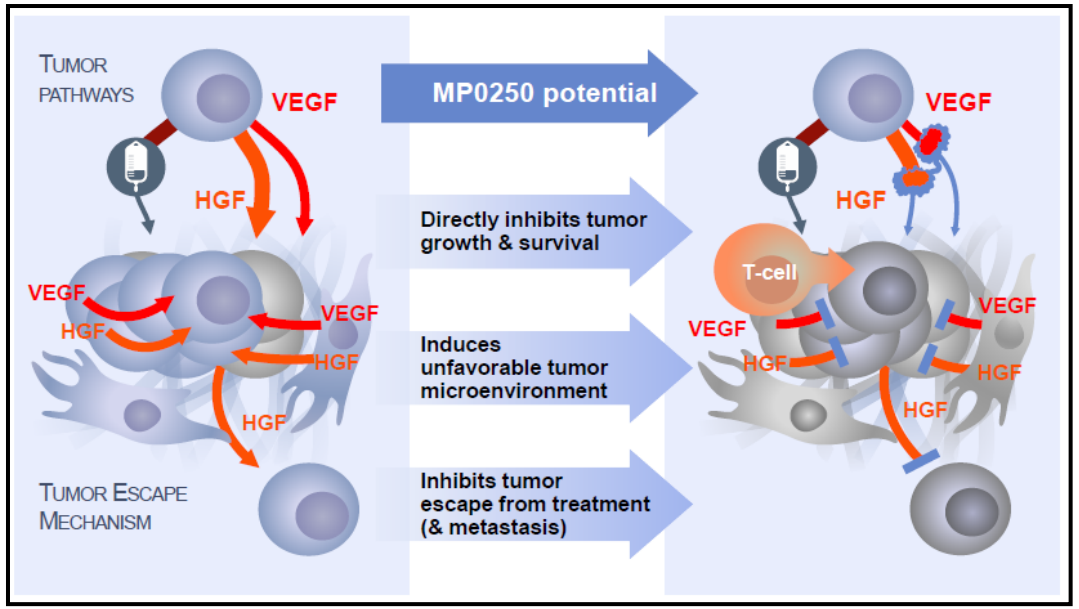
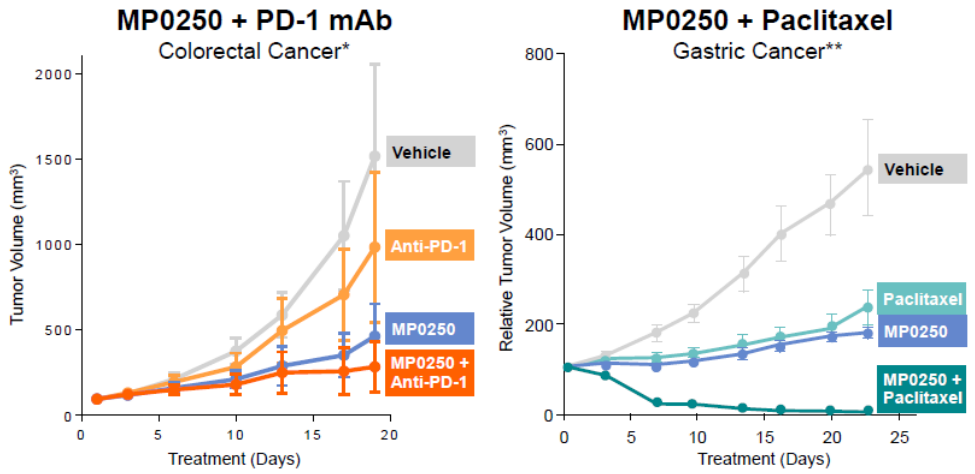
MP0250 Attacks Tumor on Several Levels





MP0250: Combination with chemotherapy and biologics across diverse cancers: renal, liver and lung cancer

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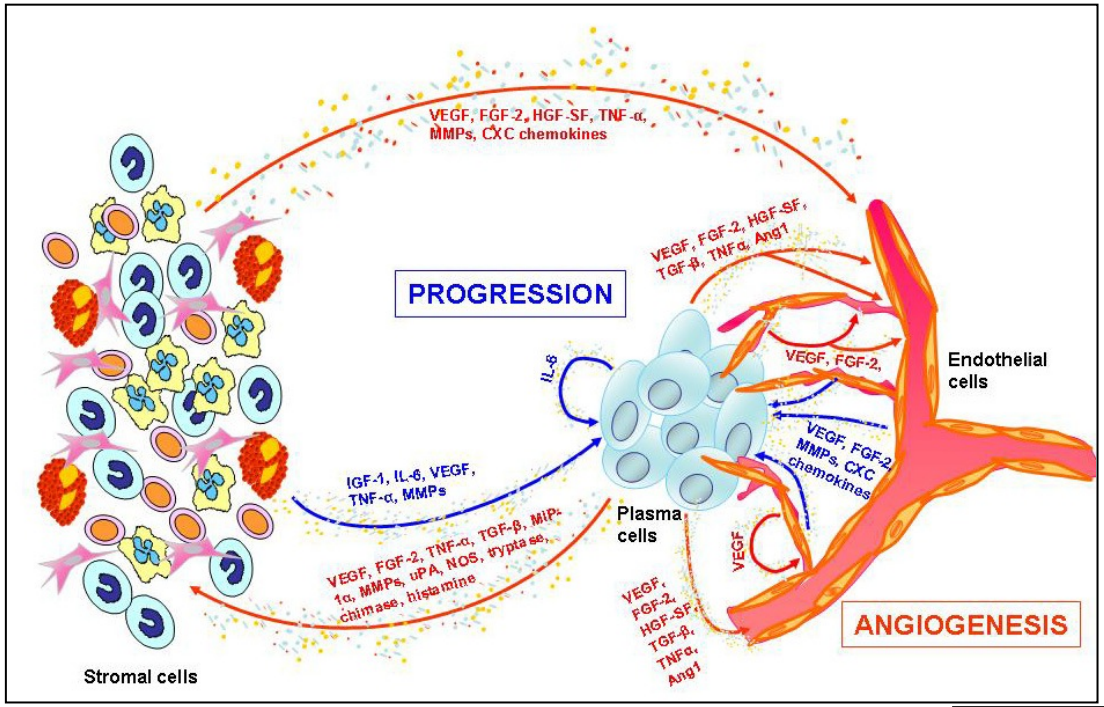
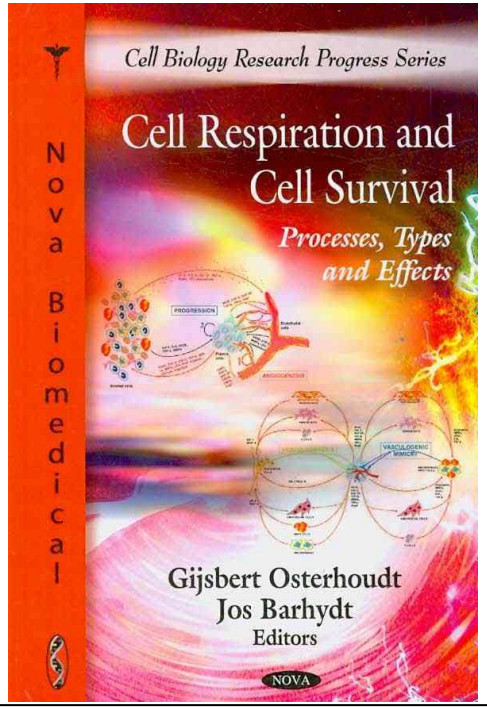
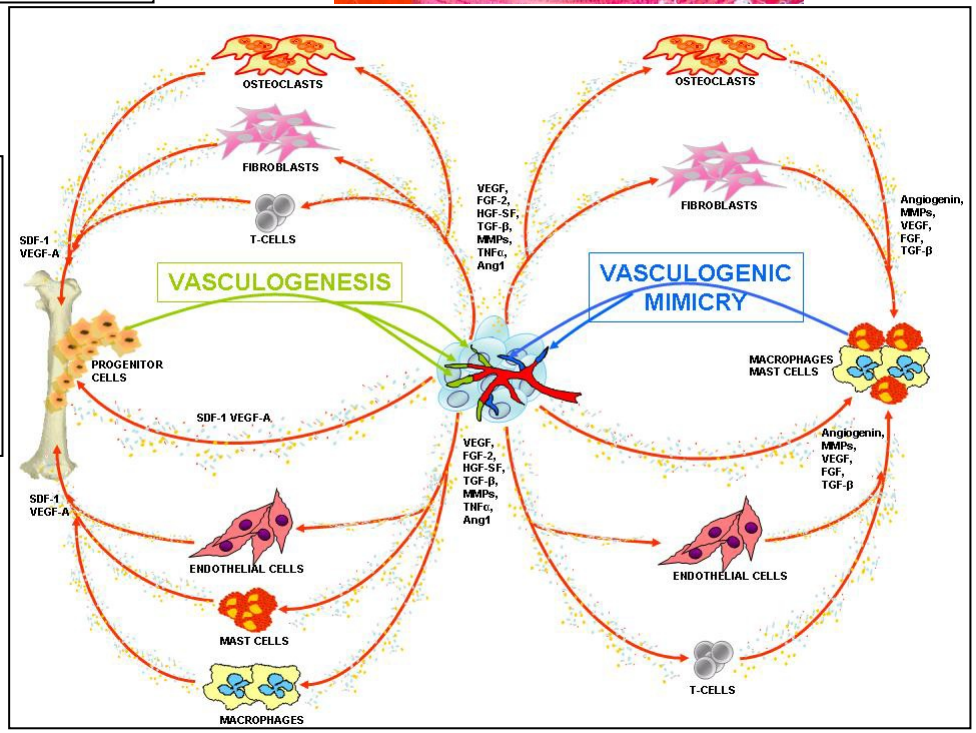




The Bone Marrow Microenvironment in Multiple Myeloma: Cellular and Molecular Basis of Disease Progression

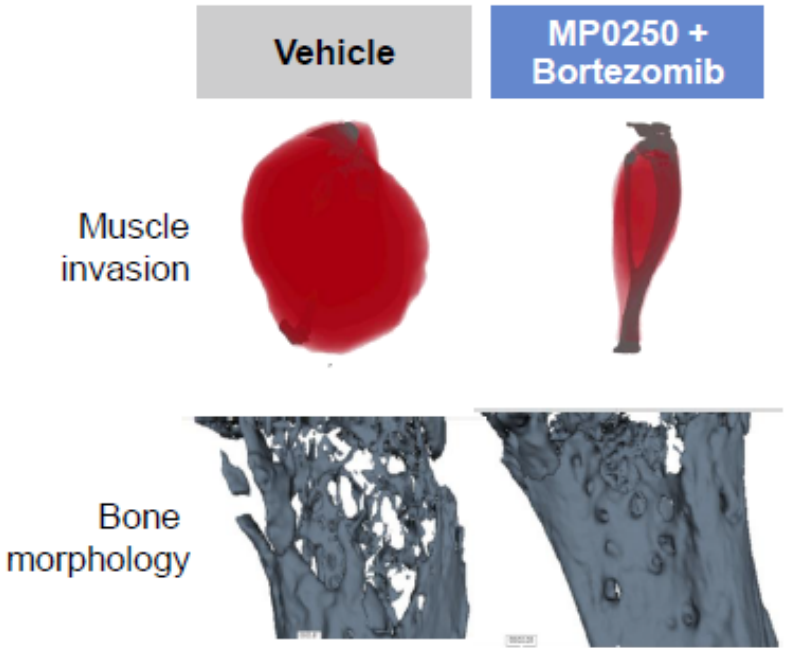
R. Ria[1], A. Reale[1], G. Mangialardi[1], D. Dammacco[1], F. Ribatti D.[2] and A. Vacca[1]*



Preclinical and Clinical Data Support MP0250 + SOC for Multiple Myeloma

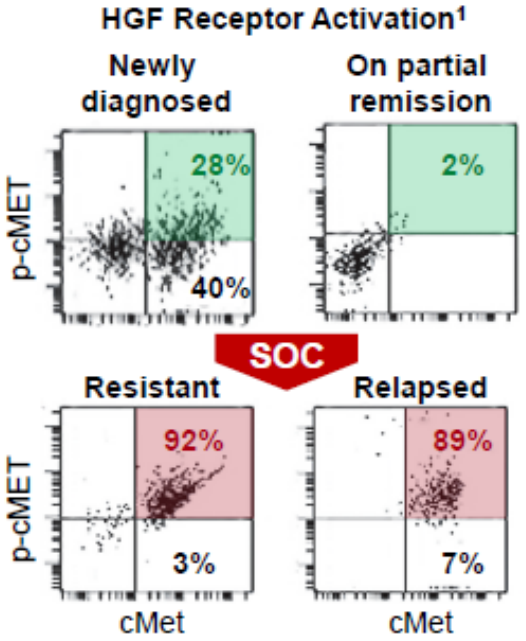
Preclinical Rationale

Tumor Growth
H929 Xenograft



Clinical Rationale

HGF Rationale



VEGF Rationale

A small MM study of bevacizumab (Avastin®) + bortezomib (Velcade®) demonstrated benefit over bortezomib alone[2]

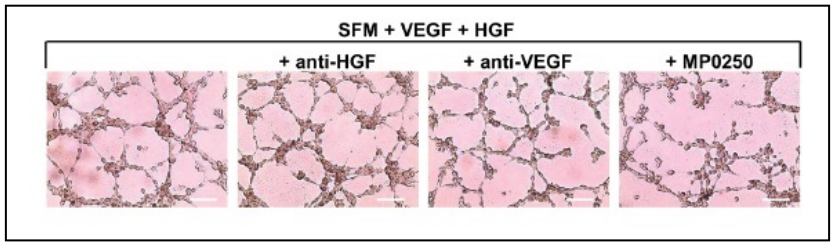
1. Moschetta M, et al. Clin Cancer Res 2013;19:4371-82; 2. White D, et al. Cancer 2013;119:339-47.

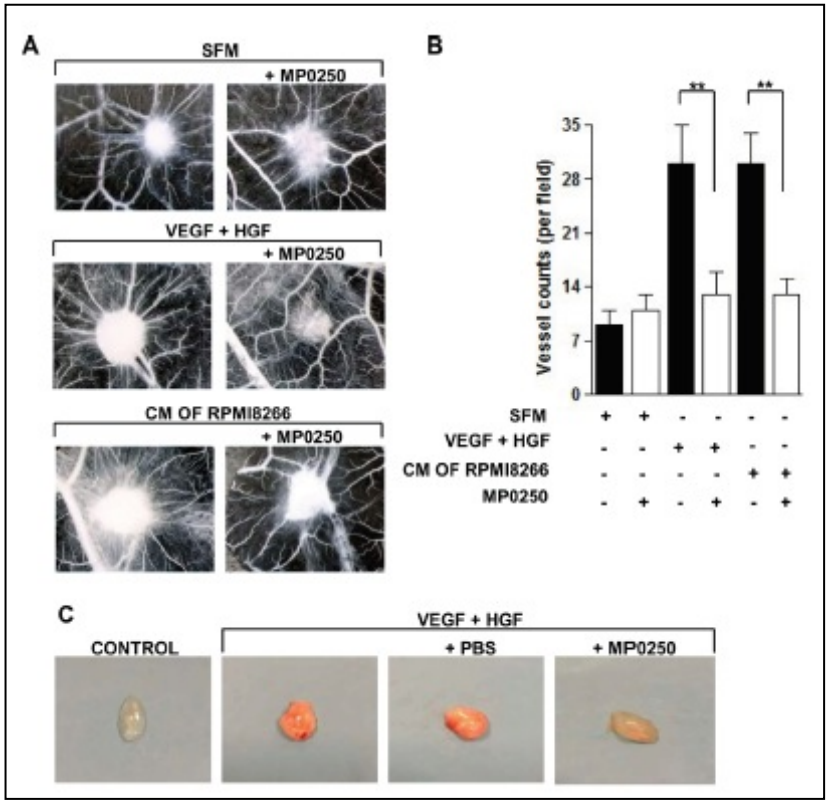
www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 17), pp: 13366-13381

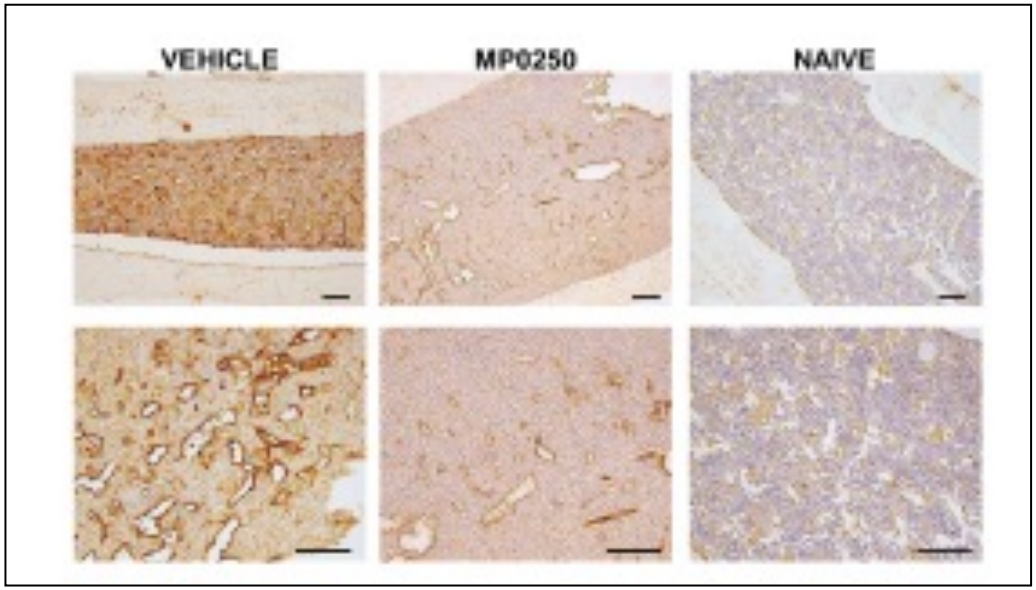
Research Paper

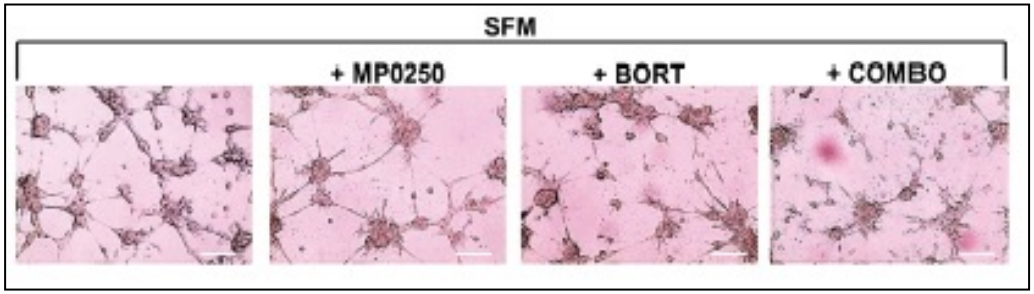
Targeting angiogenesis in multiple myeloma by the VEGF and HGF blocking DARPin® protein MP0250: a preclinical study

Luigia Rao[1,*], Kim De Veirman[2,*], Donato Giannico[1], Ilaria Saltarella[1], Vanessa Desantis[1], Maria Antonia Frassanito[1], Antonio Giovanni Solimando[1], Domenico Ribatti[3], Marcella Prete[1], Andreas Harstrick[4], Ulrike Fiedler[4], Hendrik De Raeve[5], Vito Racanelli[1], Karin Vanderkerken[2,*] and Angelo Vacca[1,*]









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Abstract B25

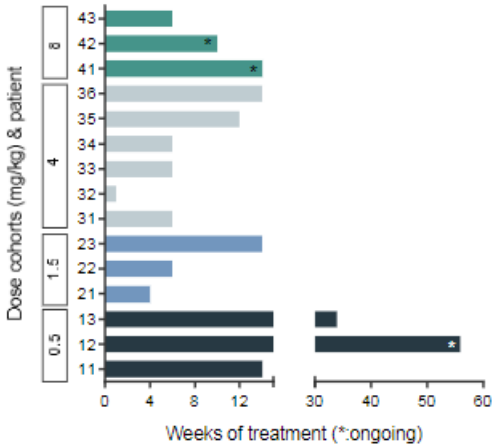
First-in-human Phase I study to evaluate MP0250, a DARPin® blocking HGF and VEGF, in patients with advanced solid tumors

Jordi Rodon[1], Aurelius Omlin[2], Karin H. Harbschieb[2], Javier Garcia-Corbacho[1], Jan Steiner[3], Ignacio Dolado[3], Christof Zitt[3], Daniel Feurstein[3], Dascha Turner[3], Keith M. Dawson[3], Michael T. Stumpp[3], Patrick Gilboy[4], Andreas Haratrick[5], Analia Azaro[1], Christoph J. Ackermann[3], Mark R. Middleton[3], Richard D. Baird[4]

[1]Vall d'Hebron, Institute of Oncology, Barcelona, Spain; [2]Kantonsspital St Gallen, St Gallen, Switzerland; [3]Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, UK; [4]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK; [5]Oxford Therapeutics Consulting Ltd, Cowthorne, UK; [6]Molecular Partners, Zurich, Switzerland

Characteristics of patients enrolled (total and per dose cohort)

Cohort	Dose mg/kg	# Patients	Age (Med., Range)	Male / Female	Tumor types	# Infusions (Med., Range)	# prior Tx (Med., Range)
All	0.5-8	15	63 (20-78)	5/10		5 (1-29)	3 (1-7)
1	0.5	3	70	female	Endometrial sarcoma	8	2
			20	female	Nasopharyngeal carcinoma	29	2
			57	female	Cervical adenocarcinoma	18	3
2	1.5	3	67	male	Colorectal carcinoma	3	7
			60	male	NSCLC	4	4
			62	male	Carcinoma of the tongue	8	1
3	4	6	41	female	Adenocarcinoma of unknown primary	4	1
			67	male	Colorectal carcinoma	1	4
			70	female	Renal cell carcinoma	4	3
			78	female	Breast cancer	4	7
			61	female	Breast cancer	7	1
			63	female	Salivary gland carcinoma	8	0
4	8	3	69	female	NSCLC	8	4
			70	male	Colorectal carcinoma	6	4
			63	female	Ovarian carcinoma	4	2

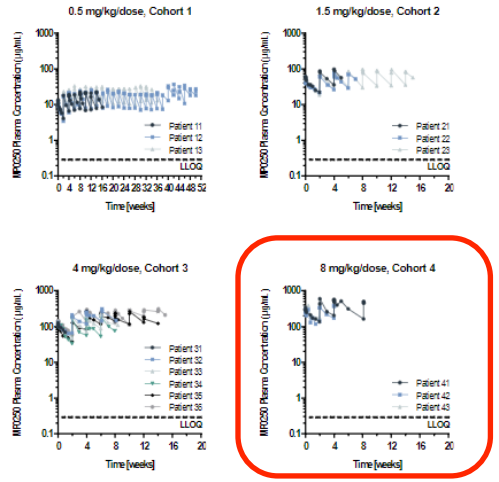


Treatment duration was ≥3 months in about 50% of patients with 2 patients exceeding 8 months.

List of all adverse events in more than two patients.

Dose cohort (mg/kg)	0.5		1.5		4		8		Total
N	3		3		6		3		15
Severity (NCI-CTC v4.03)	1-2	3	1-2	3	1-2	3*	1-2	3	
Hypertension				1	1	3		2	7
Diarrhea	1		2		2		1		6
Fatigue	1		2		1		2		6
Nausea			1		3		2		6
Cough	2		1		1		1		5
Anorexia	1				2				3
Back pain	1				2				3
Blood bilirubin increased					2		1		3
Vomiting					2		1		3

* Two patients died due to progressive disease; of whom one presented in addition grade 4 hyperglycemia and thrombocytopenia.



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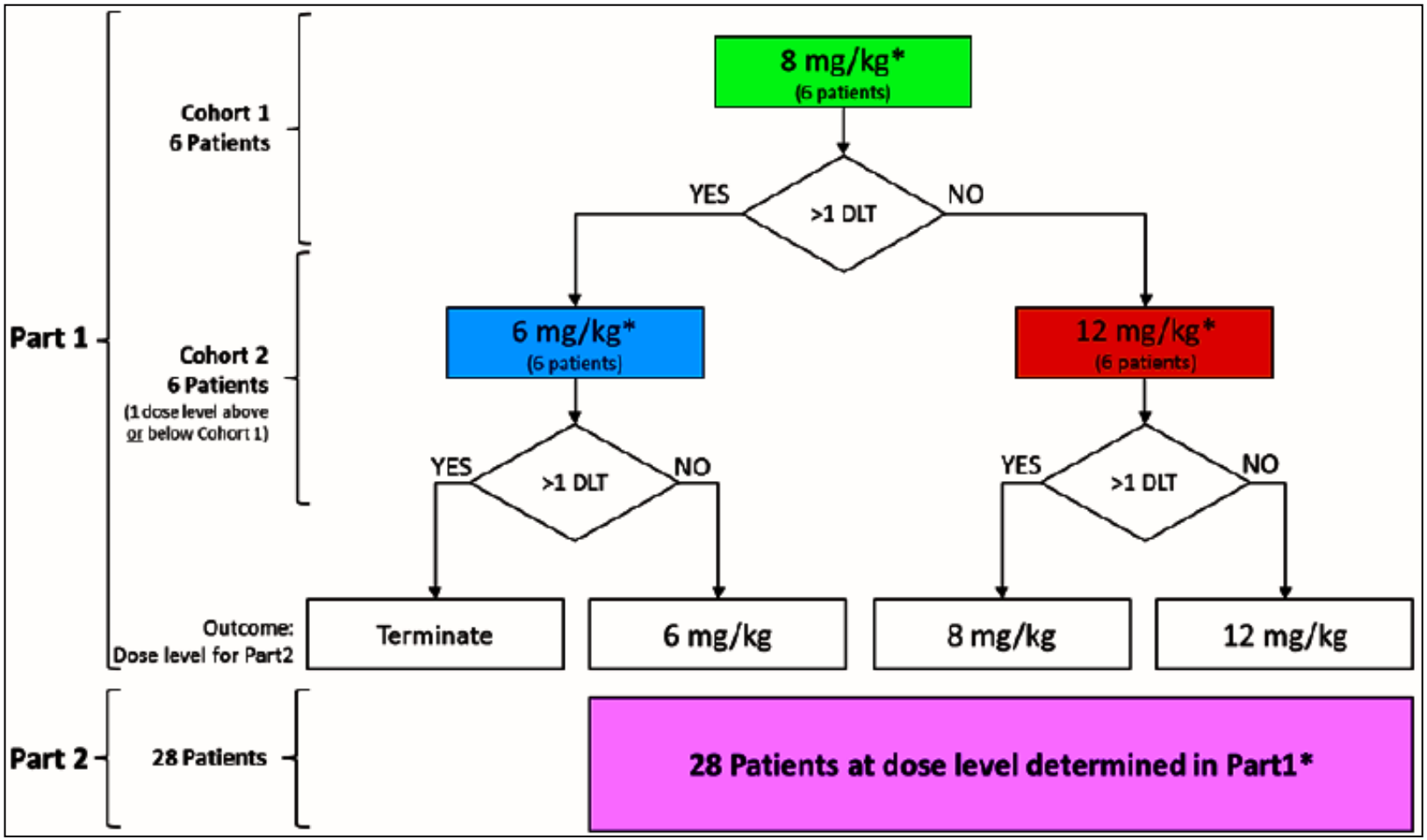
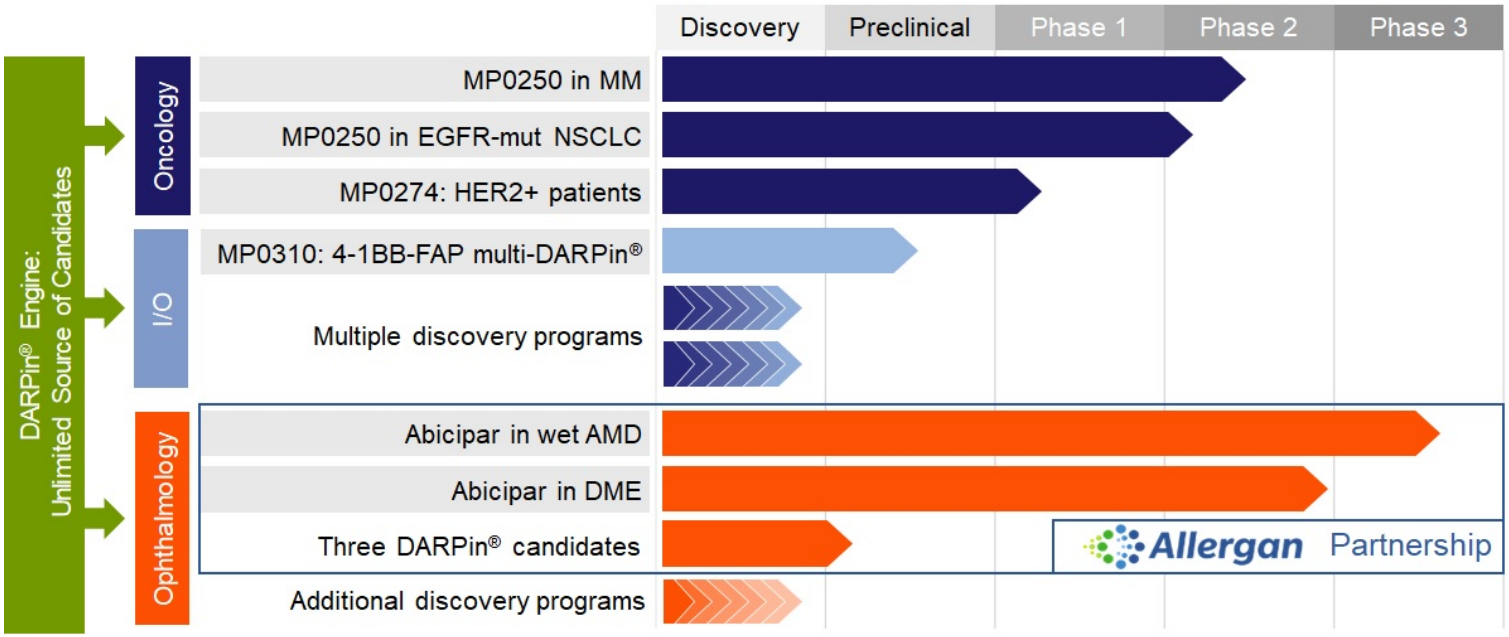
MP0250 Plus Bortezomib + Dexamethasone: Phase II MiRROrStudy



Conclusions

- **Natural principle:** repeat proteins were evolved as binders in multifunctional contexts.
- **Ideal properties:** mono-& multi-DARPin®are soluble, stable with a high-yield production.
- **Preclinical and clinical efficacy and safety**.
- **Broad range of application:** Oncology, Immuno-Oncology, Immunology, Ophthalmology.



AMD, age-related macular degeneration; DME, diabetic macular edema; MM, multiple myeloma; NSCLC, non-small cell lung cancer.


Thanks for your attention