



# R&D update call 2022

**More medicines, to more patients, faster**

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Global Head of Research & Development and Chief Medical Officer

**Andrew Paterson**

Chief Marketing Officer

**Klaus Urbahns**

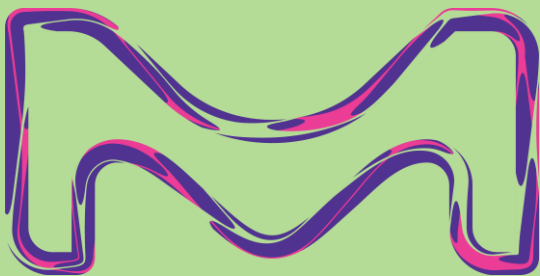
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# Participants in today's call

## R&D and Commercial



**Danny Bar-Zohar**  
Head of Research and  
Development and Chief  
Medical Officer



**Andrew Paterson**  
Chief Marketing  
Officer



**Klaus Urbahns**  
Global Head of Discovery  
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**Victoria Zazulina**  
Global Head of  
Development  
Unit Oncology



**Jan Klatt**  
Global Head of  
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Unit Neurology &  
Immunology



# Today's Call Agenda

- 1 R&D Roadmap**
- 2 Enabling technologies – Antibody Drug Conjugates**
- 3 Oncology - Clinical pipeline**
- 4 Neurology & Immunology – Clinical pipeline**
- 5 Q&A Session**





# R&D roadMap

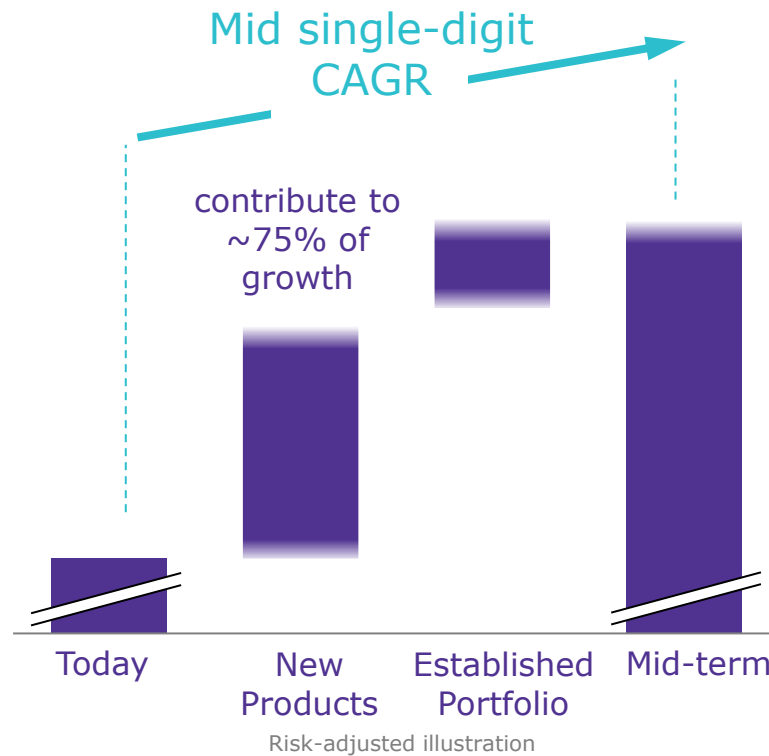
# Healthcare

## Growth driven by innovation, building on a solid established portfolio



Global specialty innovator

Profitable sales growth above global pharmaceutical market<sup>1</sup>



### New products

- Committed to drive **Wave 1** launches Bavencio<sup>®</sup>, Mavenclad<sup>®</sup> and Tepmetko<sup>®</sup>
- Wave 2** expands with evobrutinib (BTKi) with BiC potential in RMS and xevinapant (IAPi) aiming at setting up a new SoC in LA SCCHN

### Sustainable long-term growth

- New pipeline entrants in DNA damage biology, novel ADCs, TLR 7/8 underline an exciting and less risk-correlated approach in oncology and neuroinflammation

<sup>1</sup>Company estimates on pharmaceutical market growth outlook based on industry forecasts and reports from public research institutes (e.g. 3 to 6% in IQVIA Global Use of Medicines Report from January 2022).

Acronyms: TA=Therapeutic Area; FiC=First in Class; RMS=Relapsing multiple sclerosis; IAPi=inhibitor of apoptosis protein; LA SCCHN=locally advanced squamous cell carcinoma of head and neck; TLR=Toll-like receptors; SoC=Standard of Care



# R&D Roadmap

## Performance ambition



## Getting more medicines to more patients, faster

**2x**

Doubling Group's  
historic productivity

**1 in 1.5**

One launch  
every 1.5 years\*

\*rolling average



# R&D Roadmap

## Three strategies to double R&D productivity



**focused  
leadership**

**Building on existing strengths & capabilities**  
in biology, technology and therapeutic areas



**external  
innovation**

Increase contribution from **external innovation**  
**to over 50%** in our core areas of expertise,  
bolstering our capabilities



**agility**

Transforming the R&D to leaner organization  
focused on **flawless execution and resource  
discipline**



R&D budget in line with **industry standard**,  
supported by topline growth



# R&D Roadmap

## Building on R&D focused leadership



### Focus areas of internal innovation

#### Underlying biology



- DDR
- Apoptosis
- Innate immunity
- T-cell modulation

#### Therapeutic areas



- Neuroinflammation
- Multiple Sclerosis
- SCCHN
- Colorectal cancer

#### Technologies



- Track record in NCEs, NBEs
- Antibody drug conjugates
- Protein degradation
- Bi-specifics

> Minimize risks by decorrelation, partnerships and co-development

 Focus of today's call

Acronyms: DDR=DNA damage response; SCCHN=Squamous cell carcinoma of head and neck; NCEs=Novel Chemical Entities; NBEs=Novel Biological Entities



## Further amplifying our external innovation efforts



### Key deals in the last 24 months

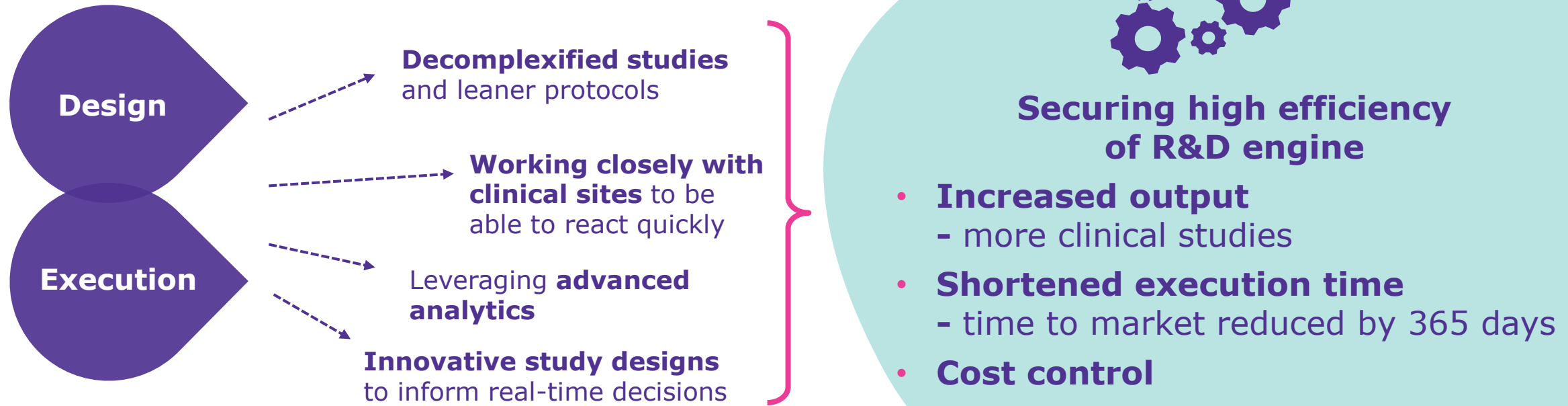
Company	Asset/capacity	Strategic match
Debiopharm	Xevinapant	Expertise in SCCHN, asset post PoC
Nerviano Medical Sciences	NMS-293	Selective PARPi complementing DDR strategy
Chord	Cladribine	Strong understanding of the compound and the area of neuroinflammation
Amphista, Proxygen	Degradation technology	Complementing our expertise in small molecules

➤ Contribution from external innovation to increase to over **50%** of future launches

**Acronyms:** SCCHN=Squamous cell carcinoma of head and neck; PoC=Proof of Concept; PARPi=Poly [ADP-ribose] polymerase inhibitor; DDR=DNA damage response



# Trial design simplicity and agility in execution driving efficiency



**2**

**Enabling  
technologies -  
Antibody Drug  
conjugates**

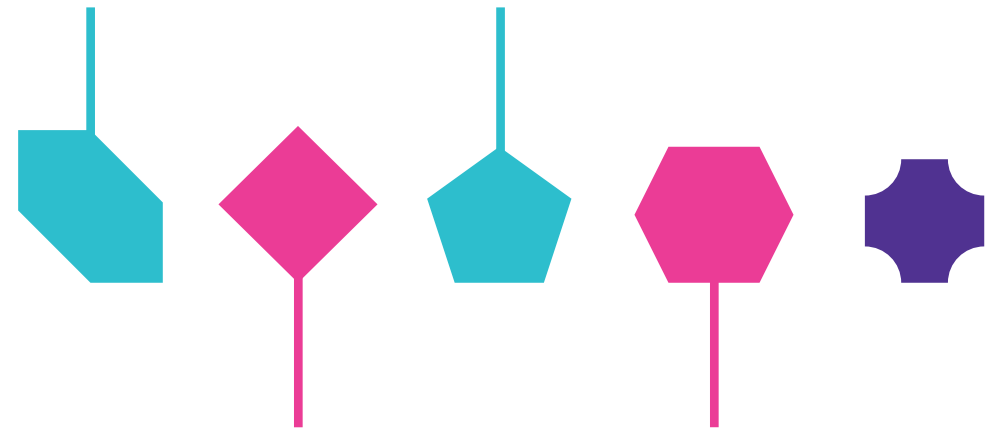
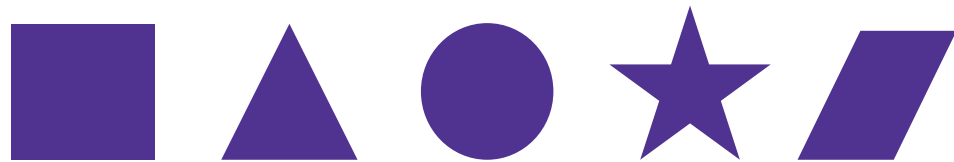
# Enabling Technologies

## Expanding expertise in ADCs and Targeted Protein Degraders

**Established Focused Leadership:**

*Antibodies*

*Protein Kinase Inhibitors*



**Expanding our toolbox:**

*Antibody  
Drug Conjugates*

*Targeted  
Protein Degraders*

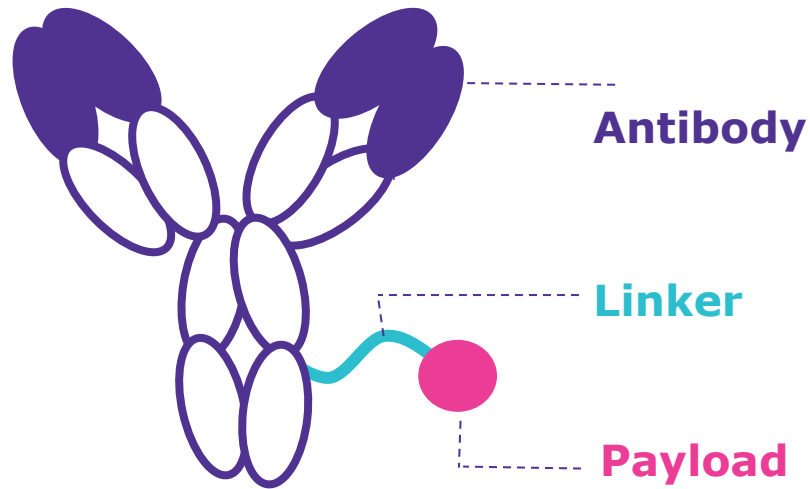
**Aspiring for technology leadership in selected areas.**

**Acronyms:** ADC=Antibody-drug conjugates



# Enabling Technologies: ADCs

## Group's ADC technology addresses the limitations of first-gen ADCs



### First generation ADCs

- Unfavorable target **expression**
- Suboptimal **half-life** and internalization
- **Unstable** linkers, unspecific cleavage
- Undefined **mixtures** from conjugation step
- **Too potent** and **toxic** payloads
- Tumor-**resistant** payloads

Low therapeutic windows

### Group's ADC Platform

- Mono & **bispecific** internalizing binders
- Designed physiochemical properties
- **Tumor-specific** linker cleavage
- **Site-specific** conjugation technologies
- **Next-generation** cytotoxic and immune-mod. payloads
- DNA-alkylators and **TOP1 inh.** fit with DDR ambitions

Improved therapeutic benefits

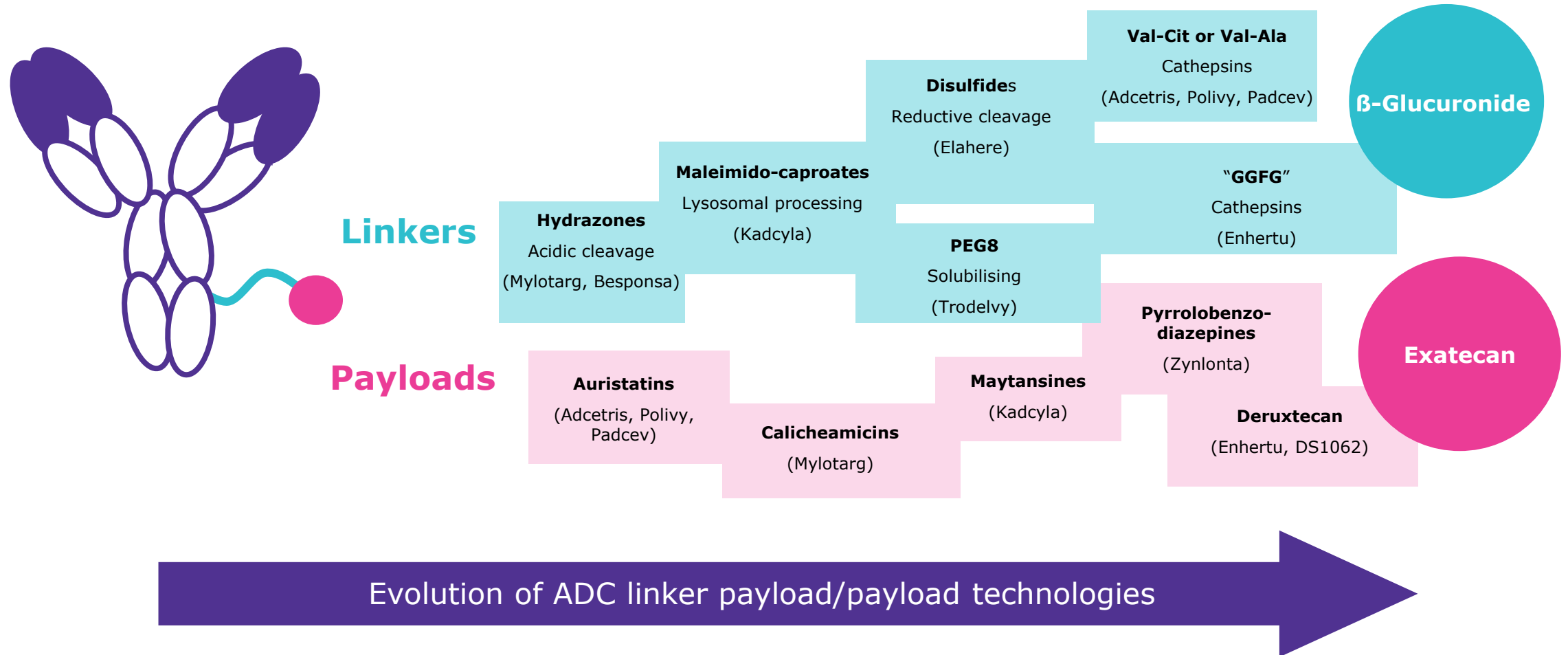
Many opportunities to enhance targeted **delivery of chemotherapy** to tumor cells. Company HC pipeline includes **9 pre-clinical** and **2 clinical assets**.

Acronyms: ADC=Antibody-drug conjugates; DDR=DNA damage response



# Antibody drug conjugates (ADC's)

## Group HC's ADCs are based on the most advanced linker/payload technologies

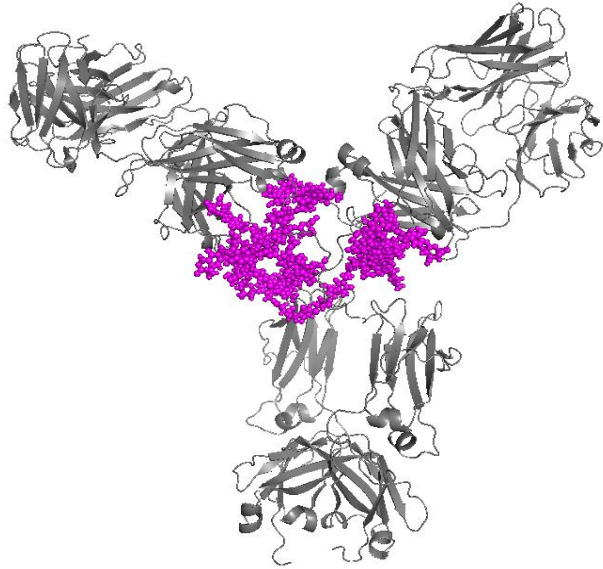


**Acronyms:** ADC=Antibody-drug conjugates; Val-Cit=Valin-citrulline linker; Val-Ala=Valine-alanine linker; PEG8=Polyethylene-glycol octamer; GGFG=Glycine-glycine-phenylalanine-glycine



## Enabling Technologies: ADCs

### Example: Design Features of M9140 (anti CEACAM-5 ADC)



**M9140**

- **Highly specific** CEACAM-5 antibody, with excellent DMPK, long half-life and robust in vitro stability
- High polarity of **glucuronide linker** improves ADC stability and reduces aggregation
- Stable glucuronidase-based linker, **specifically cleaved in tumors**
- Topoisomerase inhibitor-based payload with potential to address **tubulin inhibitor-resistant tumors**
- High bystander activity of **exatecan warhead**
- **Excellent combination opportunities** with our DDR modulator franchise

Group's **predictive modeling** capabilities are enabling the rational design of all components, resulting in ADCs with optimal pharmacokinetics and -dynamics, such as M9140.

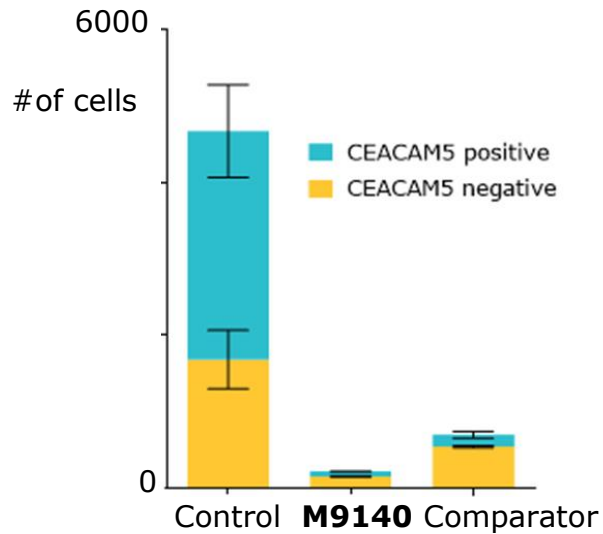
Acronyms: ADC=Antibody-drug conjugates; CEACAM5=Carcinoembryonic antigen-related cell adhesion molecule 5; DDR=DNA damage response; DMPK=Drug metabolism and pharmacokinetics



# Example: Anti CEACAM5 ADC: M9140

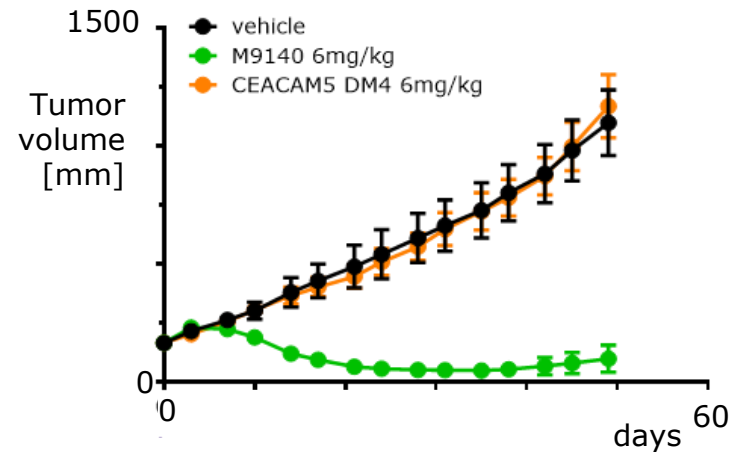
## Group's ADC technologies translate into superior pre-clinical profiles

### In vitro effect on MDA-MB-231 and SK-CO-1 cells



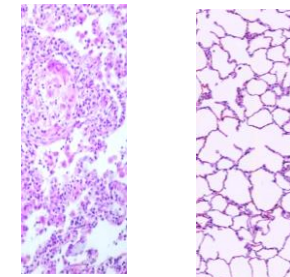
Stronger **bystander effect** than comparator ADCs in vitro.

### In vivo effect in CRC PDX model



Better **in vivo efficacy** in tumor models at 6mg/kg.

### Safety studies in non-human primates



Comparator **M9140**

No pre-clinical evidence of interstitial lung diseases or ocular toxicity (*not shown*) in NHPs at clinically relevant doses

Improved **therapeutic window**

Our superior ADC technologies have the potential to enable a **Best in Class** profile for M9140

**Acronyms:** ADC=Antibody-drug conjugates; CEACAM5=Carcinoembryonic antigen-related cell adhesion molecule 5; NHP=Non-Human Primate; CRC=Colorectal cancer; PDX=Patient derived xenografts; DM4=Maytansine DM4



**3**

**oncology - clinical  
pipeline**

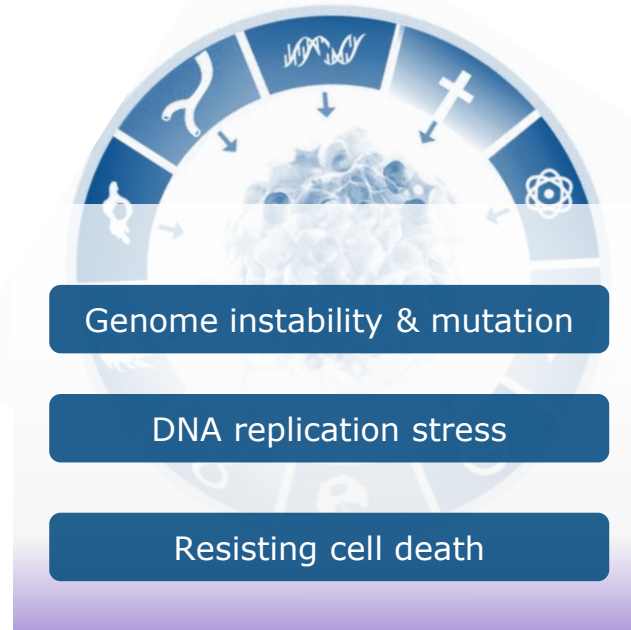
# Oncology

## Building on understanding of cancer biology and unique cancer hallmarks<sup>1</sup>

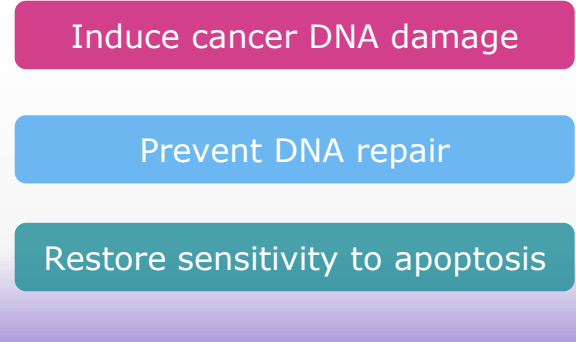
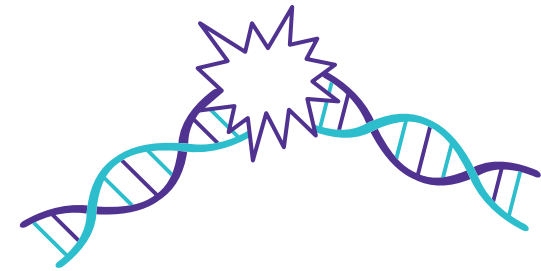
**Cancer is a disease of the genome**, caused by changes to genes which control cell growth and proliferation



**Group's expertise in cancer biology**  
Focus on key hallmarks of cancer<sup>2</sup>



**Killing cancer cells**  
through disruption of DNA

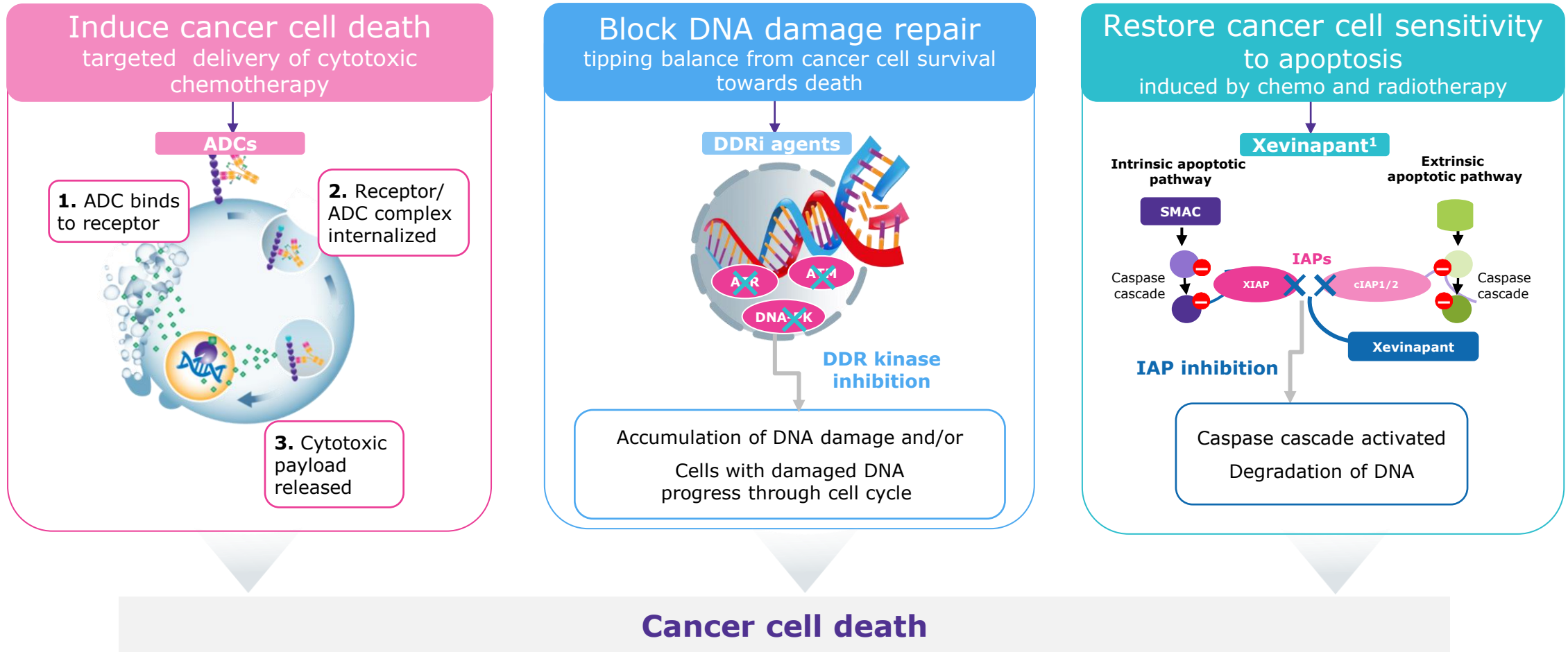


<sup>1</sup>D. Hanahan, Cancer Discov 2022;12:31-46; <sup>2</sup>Negrini et al, Nature 2010



# Oncology

## Three therapeutic approaches offer combination opportunities to maximize tumor cell killing

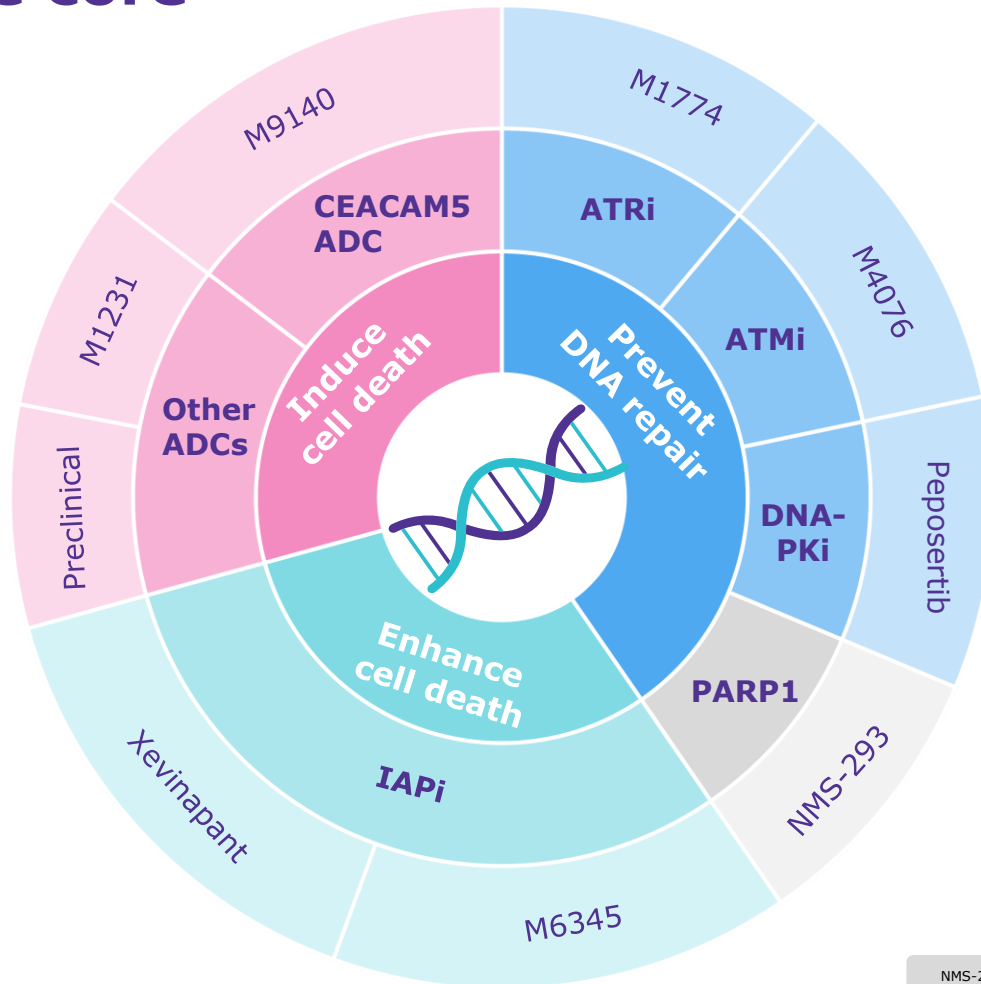


**Acronyms:** ADC=Antibody-drug conjugates, **DDRi** **DDR** **DNA**=damage response inhibitors, **DDR** **DNA**=damage response, **SMAC** =second mitochondria-derived activator of caspases; **XIAP**&**cIAP1/2**=Inhibitor of apoptosis IAPs  
<sup>1</sup>Xevinapant is not approved for any use anywhere in the world



# Oncology - Cancer DNA

## Exploiting major vulnerability of tumor cells and striking them right at the core



### Validated therapeutic approaches, with strong innovation potential:

ADC

DDRi

Chemo/radio sensitizers

### Ability to drive new standard of care:

- In all-comer indications  
e.g. Xevinapant
- In biomarker-defined populations  
e.g. CEACAM-expressors, BRCA1 mut, ATMloss

### Combination potential:

- With current standard of care  
e.g. IAPi+chemo, ATRi+IO
- Utilize synergy within Group's pipeline  
e.g. ATRi+ATMi, ATRi+ADC

### Guiding inorganic opportunities

NMS-293

Collaboration agreement with licensing option with Nerviano Medical Sciences S.r.l.

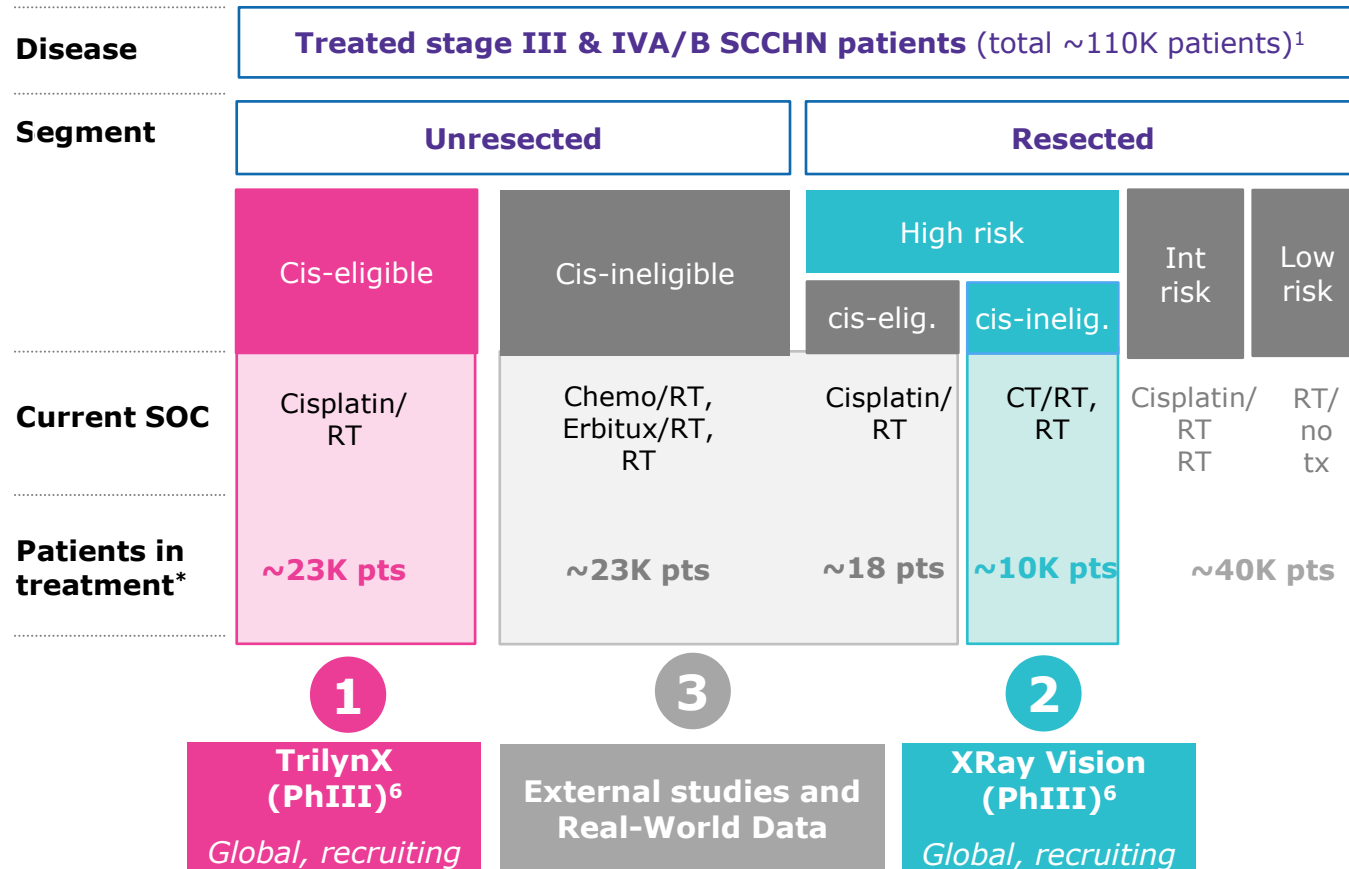
**Acronyms:** ATRi=ataxia telangiectasia and Rad3-related protein, inhibitor; ATMi=ataxia-telangiectasia-mutated protein, inhibitor; DNA-PKi=DNA-dependent protein kinase inhibitor; PARP1=Poly [ADP-ribose] polymerase 1; IAPi=Inhibitor of apoptosis inhibitor; CEACAM5=Carcinoembryonic antigen-related cell adhesion molecule 5; IO=Immunooncology; BRCA1=Breast cancer type 1 sus



# Oncology - Xevinapant

## Leveraging our long-lasting expertise in SCCHN

Treatment paradigm of LA SCCHN



**>50%**  
with recurrence and/or distant metastasis within 2 years of RT-based curative treatment for LA SCCHN <sup>2,3</sup>

**>20yrs**  
of limited progress in SOC, including failed trials of immunotherapy <sup>4,5</sup>

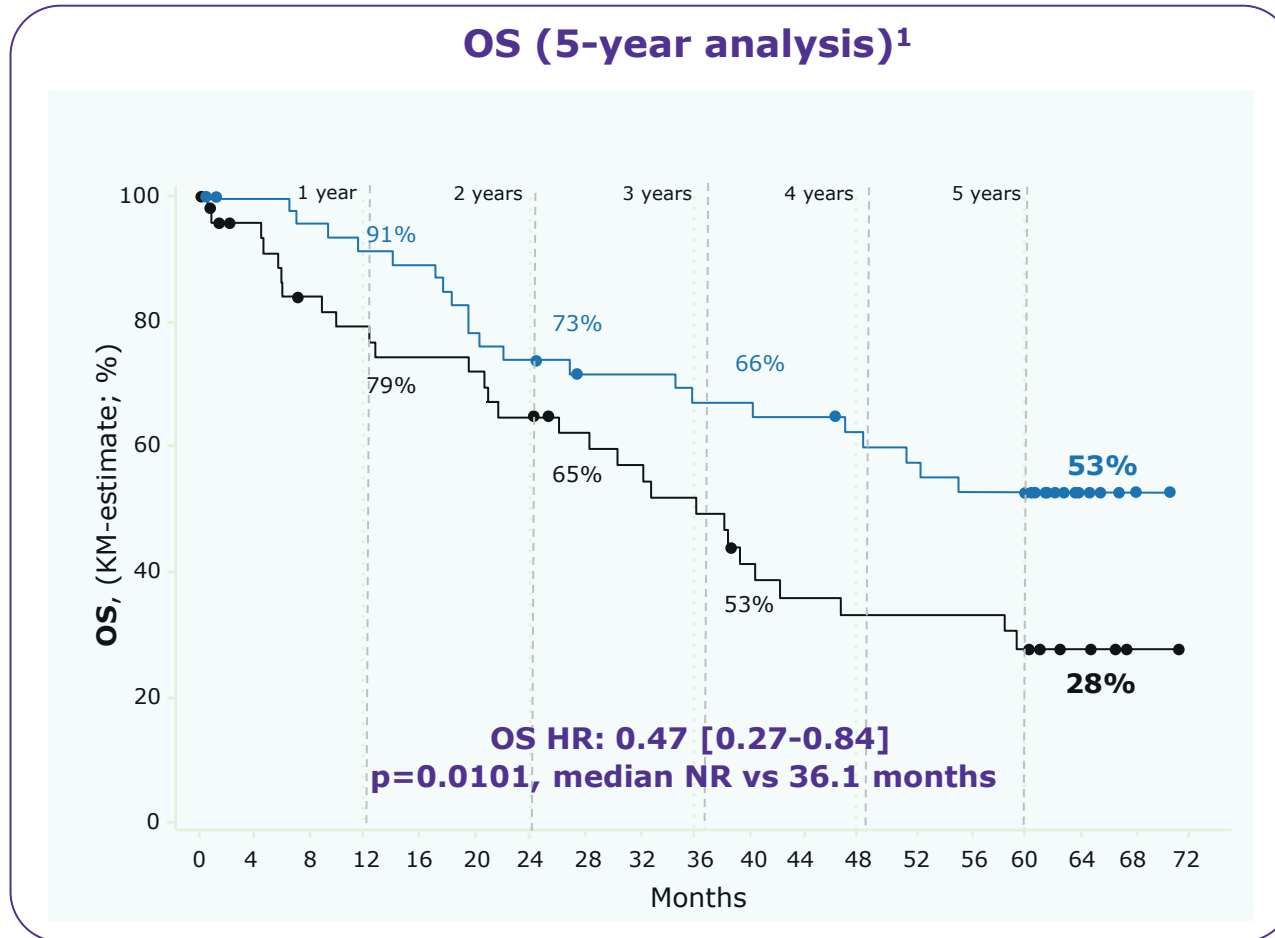
<sup>1</sup>Treated patient numbers are for US and EU combined (Kantar/Cerner Enviza 2021); <sup>2</sup>Denaro N, et al. Clin Exp Otorhinolaryngol. 2016;9(4):287-297.; <sup>3</sup>Ahn J-S, et al. Cancer Res Treat. 2007;39(3):93-98.; <sup>4</sup>NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers. v1.2021.; <sup>5</sup>Machiels JP, et al. Ann Oncol. 2020;31(11):1462-1475. <sup>6</sup>Global trials, including strong presence in China and Japan; \*Global trials, including strong presence in China and Japan

**Acronyms:** SCCHN=squamous cell carcinoma of head and neck; LA SCCHN=locally advanced squamous cell carcinoma of head and neck; RT=Radiotherapy; SOC=Standard of care



# Oncology - Xevinapant

## Phase II: Addition of xevinapant to chemoradiotherapy nearly doubled cure rate in patients with LA SCCHN



The risk of death was more than halved and median OS was prolonged with xevinapant vs placebo.

<sup>1</sup>Bourhis J. et al. Ann Oncol 2022;33:S1400. Oral presentation at ESMO 2022 (LBA33).

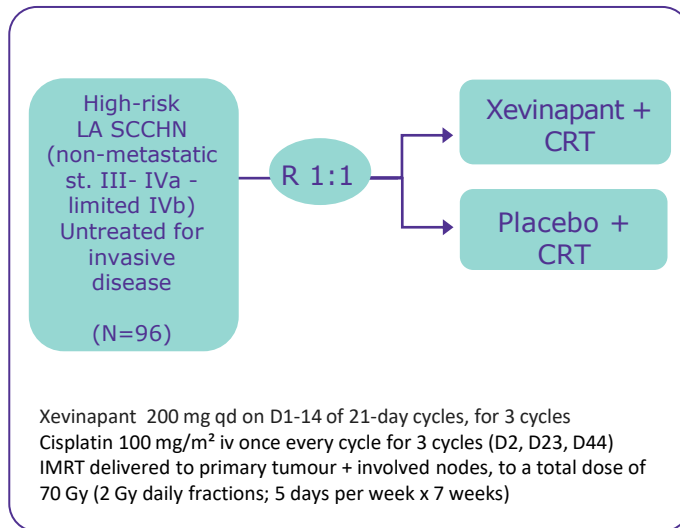
**Acronyms:** NR=Not Reported; LA SCCHN=locally advanced squamous cell carcinoma of head and neck; RT= Radiotherapy; SOC= Standard of care; OS= Overall survival; HR=homologous recombination



# Oncology - Xevinapant

## Phase II: Consistent improvement across all efficacy endpoints with no compromise in delivery of backbone chemoradiotherapy (CRT)

### PhII: Double-blind, multi-centre, randomized trial<sup>1</sup>



### Selected efficacy endpoints

Efficacy Endpoint	Xevi + CRT	Pbo+ CRT	
<b>LCR at 18mo</b> (primary endpoint)	54%	33%	<b>OR 2.69</b> [1.13-6.42], p=0.026
<b>PFS</b> (3-year analysis)	NR	16.9 mo	<b>HR 0.34</b> [0.17-0.68], p=0.0023
<b>DoR<sup>2</sup></b> (3-year analysis)	NR	17.3 mo	<b>HR, 0.21</b> [0.08-0.54], p=0.0011
<b>OS<sup>3</sup></b> (3-year analysis)	NR	36.1 mo	<b>HR, 0.49</b> [0.26-0.92]; P=.0261

### Combination tolerability profile

Category of AEs	Xevi + CRT	Pbo+ CRT
Any TEAE	100%	100%
Gr ≥ 3	85%	87%
Serious AEs	63%	60%
Fatal AEs	0	4%
Late toxicity (mostly gr.1-2)	73%	66%

### Delivery of CRT

Treatment	Xevi + CRT	Pbo+ CRT
Median dose of Cis (mg/m <sup>2</sup> )	288	288
Pts with ≥ 2cycles of Cis (%)	88	83
Pts with all 3 cycles of Cis (%)	58	53
Median cumulative dose of RT (tumor/lymph nodes), Gy	70/ 51.8	70/ 51.8

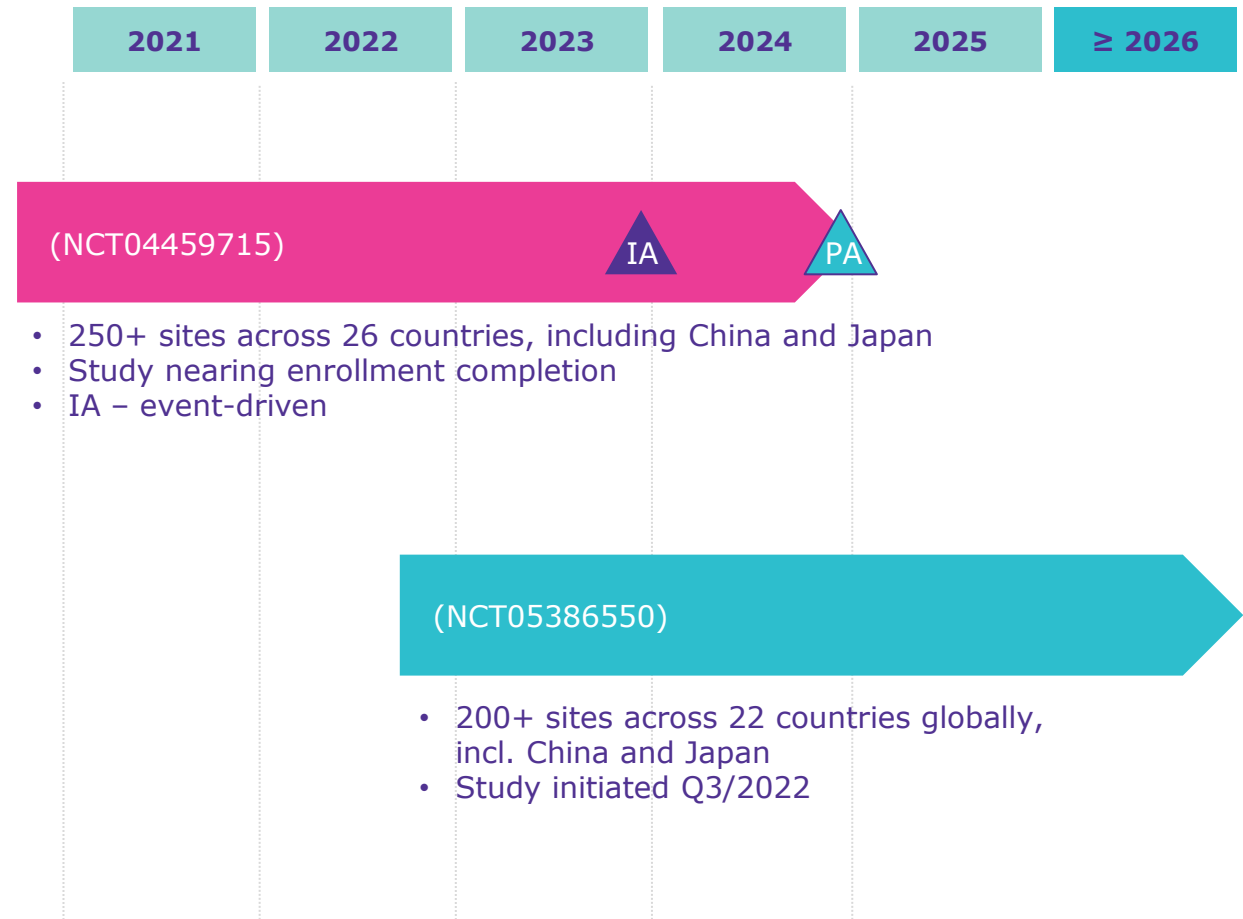
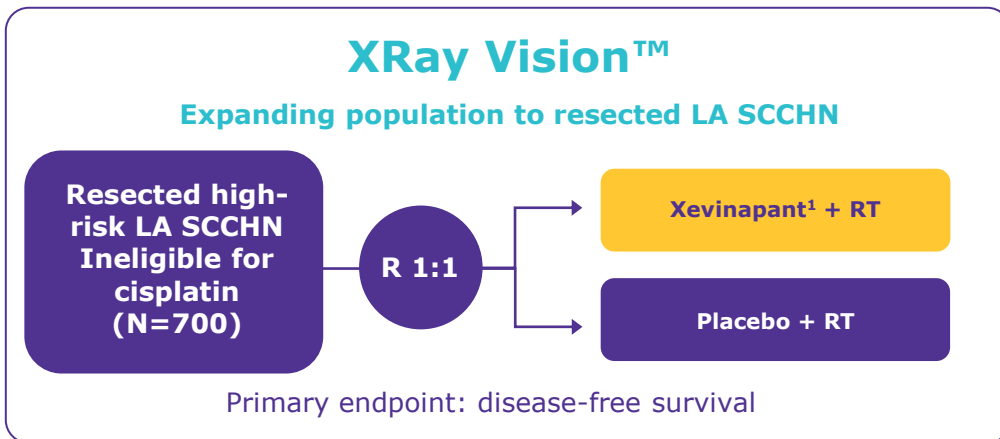
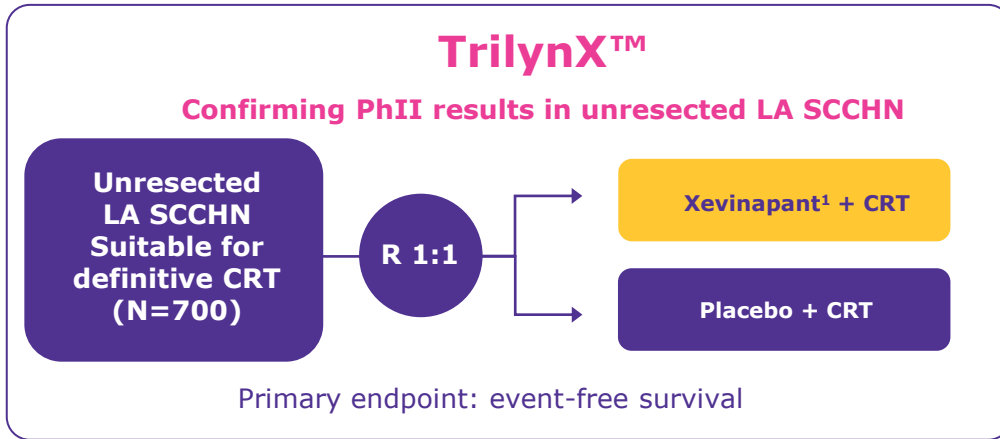
<sup>1</sup>Sun XS, et al. Lancet Oncol. 2020;21(9):1173-1187; <sup>2</sup>Bourhis J. et al. Ann Oncol 2022;33:S1400. Oral presentation at ESMO 2022 (LBA33); <sup>3</sup>Bourhis J. et al. Ann Oncol (2020) 31 (suppl\_4): S1142-S1215.

**Acronyms:** AE=adverse event; NR=Not reported; CRT=Chemoradiotherapy; LCR=Locoregional control; PFS=Progression-free survival; DoR=Duration of Response; OS=Overall survival; OR=Overall response



# Oncology - Xevinapant

## Phase III program on track to deliver on a blockbuster potential



- 250+ sites across 26 countries, including China and Japan
- Study nearing enrollment completion
- IA – event-driven

(NCT05386550)

- 200+ sites across 22 countries globally, incl. China and Japan
- Study initiated Q3/2022

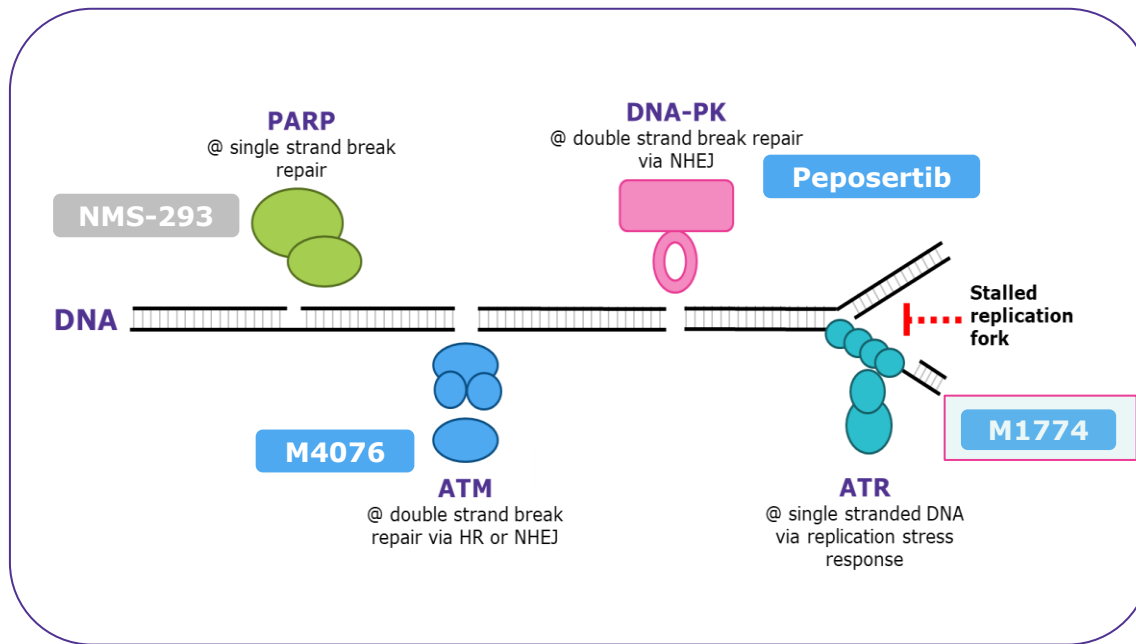
<sup>1</sup>Xevinapant administration: 3 cycles of oral solution at a dose of 200 mg/day once daily from Day 1 to 14, per 3-week cycle in combination with CRT/RT followed by 3 cycles of Xevinapant monotherapy

**Acronyms:** AE=adverse event; NR=Not reported; CRT=Chemoradiotherapy; LCR=Locoregional control; PFS=Progression-free survival; DoR=Duration of Response; OS=Overall survival; OR=Overall response; IA=Interim Analysis



# Oncology - DNA Damage Response (DDR)

## Unique portfolio of DDR inhibitors testing three distinct hypotheses to enhance tumor cell killing



Selectively kill tumors with DDR mutations  
**(Synthetic Lethality)**

Amplify **DNA damage-inducing** chemotherapy and radiotherapy

Activating **immune response**  
(through activation of cGAS–STING innate immune pathway and type I IFN signaling)

- Different types of DNA damage are repaired by different mechanisms
- Key proteins involved are **PARP, ATR, ATM, and DNA-PK**
- **DDR inhibitors accumulate DNA damage, leading to cancer cell death**

  Focus of today's call

**NMS-293** Collaboration agreement with licensing option with Nerviano Medical Sciences S.r.l.

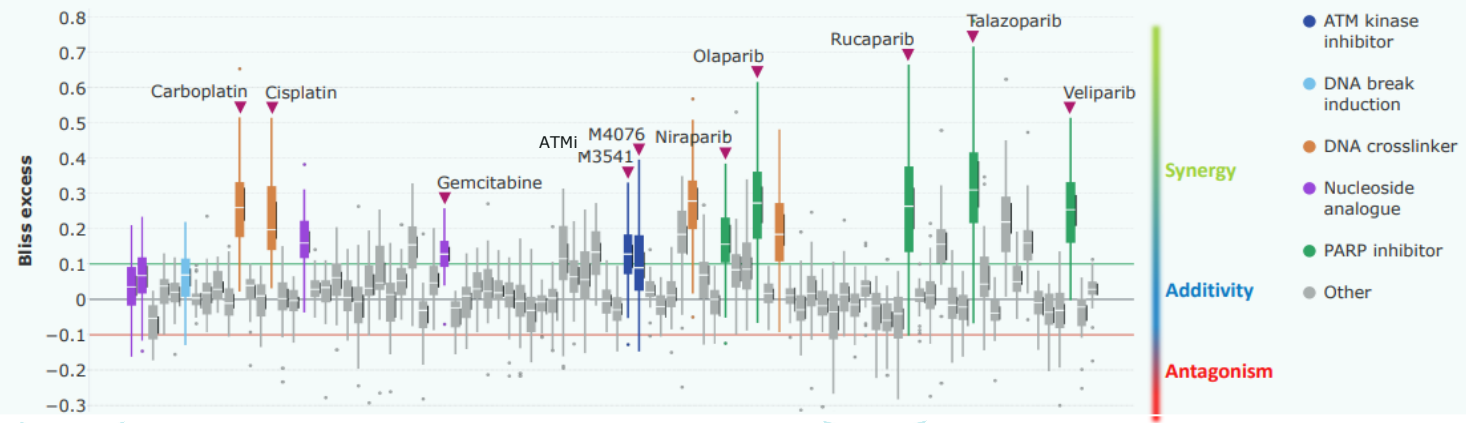
**Acronyms:** HR=homologous recombination; NHEJ=non-homologous end joining; PARP= Poly [ADP-ribose] polymerase; DNA-PK= DNA-dependent protein kinase; ATM= ataxia-telangiectasia-mutated protein; ATR= ataxia telangiectasia and Rad3-related protein



# Oncology - DNA Damage Response (DDR)

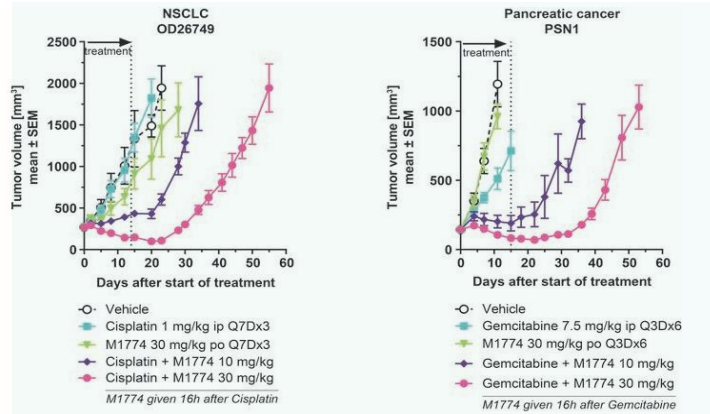
## M1774 strongly synergizes with multiple drug classes<sup>1</sup>

**COMBINATION screen *in vitro*:**  
(platinum, Topo-I inhibitors, PARPi, and other DDRi)



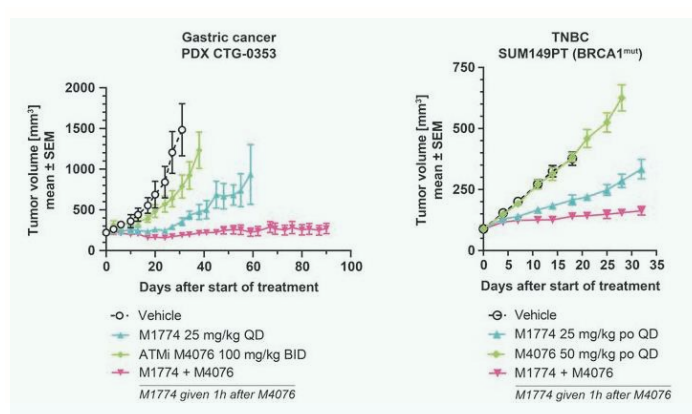
*In vivo* efficacy studies confirm the combination potential suggested from *in vitro* studies

### Chemotherapy combination



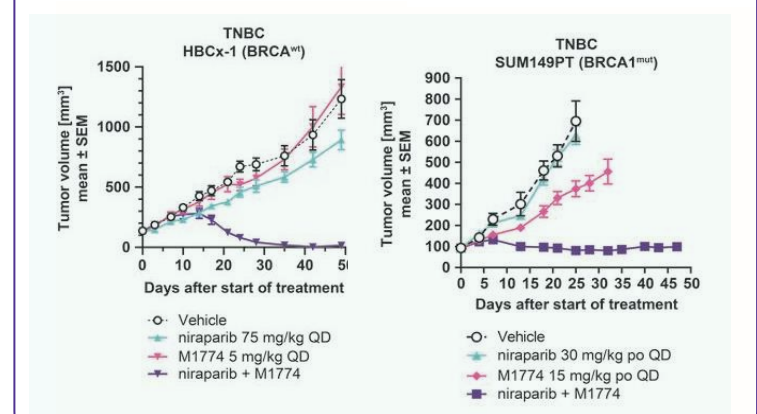
**M1774 enhances the effect of DNA-damaging chemotherapy**

### ATMi combination (M4076)



**M1774 synergizes *in vivo* with other DDR inhibitors, together creating or exploiting pre-existing defects in DNA repair pathways**

### PARPi combination



<sup>1</sup>Zimmermann et al. AACR 2022 abstract 2588



# Oncology - DNA Damage Response (DDR)

## M1774 Phase I study: integration of potency, exposure and safety supports strong combination potential

### DDriver Solid Tumors 301 (PhI) NCT04170153

- Continuous and intermittent doses between 5 mg - 270 mg QD explored
- **Favorable PK profile:**
  - steady state concentration significantly above target for *in vivo* potency
- **Robust target engagement** in PBMC assay at doses  $\geq$  130mg
- **Well tolerated** up to 180 mg QD (MTD)
  - Anemia – the only hematological toxicity
- Recommended dose for expansion (RDE) **180 qd 2w on/1w off** achieves right balance mitigating anemia vs. providing adequate pharmacological coverage to test PoC

### Pharmacologically robust ATRi that achieves strong target coverage

M1774 Dosing regimen	C <sub>av</sub> fold for pCHK1 IC <sub>90</sub>	% of time typical patient above pCHK1 IC <sub>90</sub>
130 mg QD	19 x IC <sub>90</sub>	100 %
180 mg QD	36 x IC <sub>90</sub>	100 %
<b>180 mg 2w on/1w off</b>	24 x IC <sub>90</sub>	71 %

### Compares favorably on early safety data

	<b>M1774</b> 180 mg QD 2w on/1w off (N=28)*	<b>Elimusertib<sup>1</sup></b> 40 mg BID 3d on/4d off (N=143)	<b>Camonsertib<sup>2</sup></b> 160 mg QD, 3d on/4d off (N=34)
Gr. $\geq$ 3 Anaemia (%)	10.7	65.7	26.5
Gr. $\geq$ 3 Neutropenia (%)	0	47.6	14.7
Gr. $\geq$ 3 Thrombocytopenia (%)	0	10.5	5.9
Any AEs leading to dose reduction (%)	10.7	37.1	17.6
AE leading to treatment discontinuation (%)	3.6**	5.6	NR
Transfusion (%)	28.6	88.1	32.4

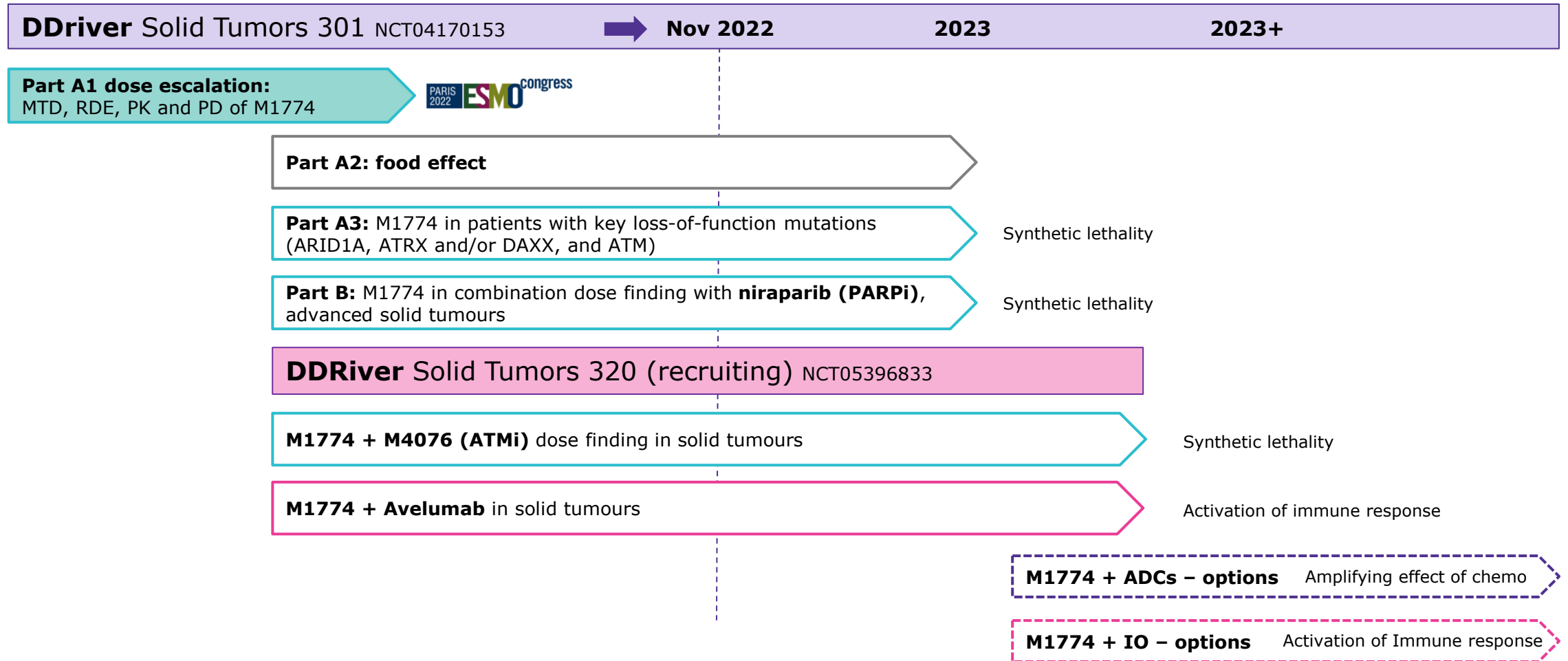
\*Data from dose escalation (n=7) and preliminary in-house data from dose expansion (n=21) \*\* AE unrelated to M1774

**Acronyms:** PBMC=Peripheral Blood Mononuclear Cells; MTD=Maximal Tolerated Dose; AE=adverse event; RDE=Recommended Dose for Expansion; NR=Not Reported; Pchk1=Phosphorylated Checkpoint Kinase 1; ATRi=ataxia telangiectasia and Rad3-related protein, inhibitor; IC=inhibitory concentration; QD=once-a-day; BID=twice-a-day



# Oncology - DNA Damage Response (DDR)

## Exploring combination potential of M1774 in a broad DDRiver development program



**Acronyms:** PK=Pharmacokinetics; RDE=Recommended Dose for Expansion; NR=Not Reported; MTD=Maximal Tolerated Dose; PD= Pharmacodynamics; ARID1A= AT-Rich Interaction Domain 1A; ATRX= AT-Rich Interaction Domain 1A; DAXX= Death- associated protein 6; ATMi= ataxia-telangiectasia-mutated protein, inhibitor; PARPi= Poly [ADP-ribose] polymerase inhibitor; ADC=Antibody-drug conjugates; IO= Immunooncology; ATM=ataxia-telangiectasia-mutated protein



# Oncology - Antibody-Drug Conjugates

## M9140: specifically designed to fight CRC and other GI cancers, with optionality in additional tumors

### Scientific Rationale

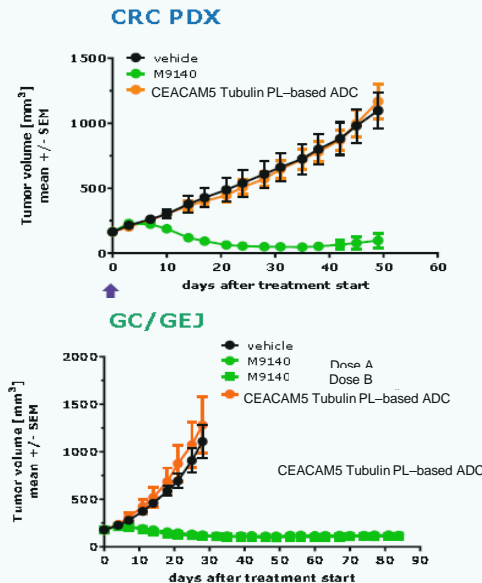
#### CEACAM5 expression

CEACAM5 antigen expression by tumor type	
CRC (AD)	98%
Gastric Cancer	60%
Pancreatic Cancer	54%
nsq NSCLC	47%
Cervical	31%
ESCC	23%
sq NSCLC	17%
SCCHN	12%
UC	9%
TNBC	1%

- **CEACAM5** is expressed in CRC, GC/GEJ, lung & other cancers with low expression in normal tissues, making it an ideal target
- **TOP1 inhibitor (exatecan)** payload optimized for tumors with target expression & sensitivity to TOP1i

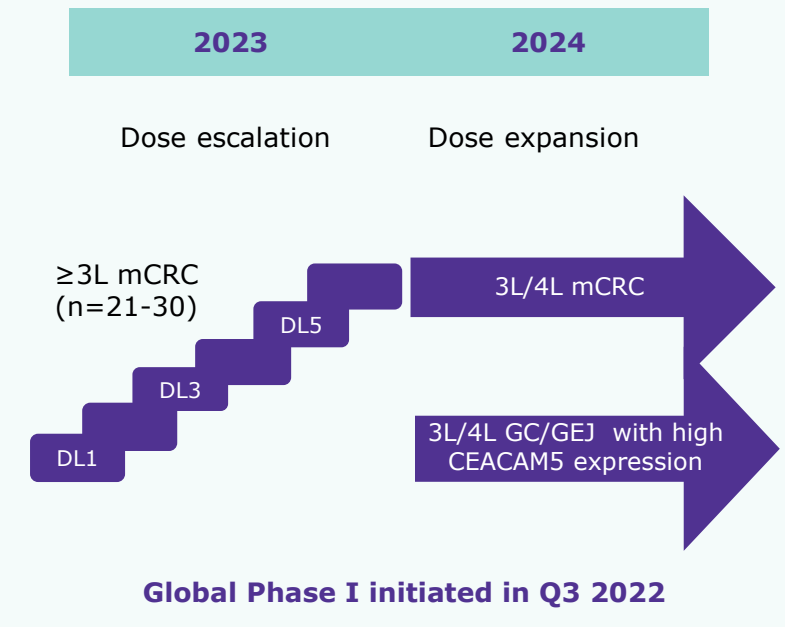
### Differentiation

#### M9140 vs DM4 ADC



- **Superior pre-clinical efficacy** vs antimicrotubule payload (ravtansine) ADCs
- **Synergistic potential** and durable efficacy with DDRi

### Phase I study ongoing NCT05464030



**Acronyms:** ADC=Antibody-drug conjugates; RDE=Recommended Dose for Expansion; NR=Not Reported; CRC=Colorectal cancer; GC=Gastric cancer; GEJ= Gastric and gastroesophageal junction; TOP1i=Topoisomerase inhibitor type 1 inhibitor; DDRi=DDR DNA damage response inhibitors; GI=Gastrointestinal; CRC=Colorectal cancer; CEACAM5=Carcinoembryonic antigen-related cell adhesion molecule 5



# Oncology

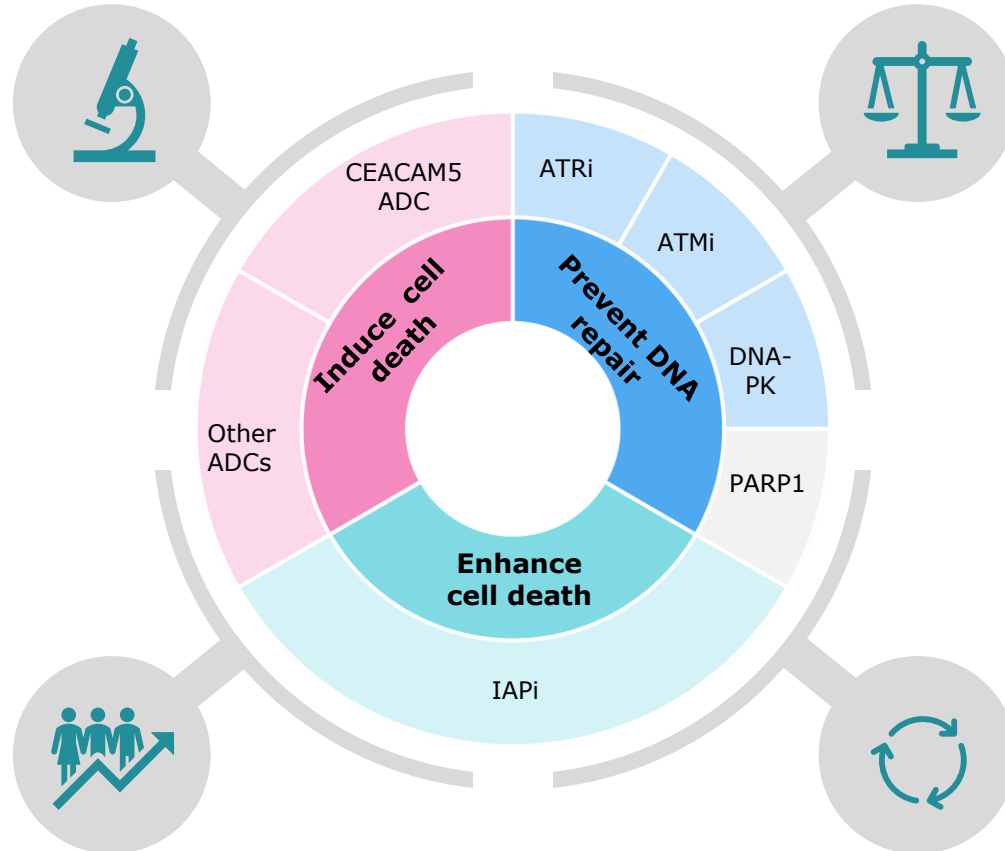
## Company Oncology – building focused leadership in core areas while balancing risks

### Right Science

- Exploits major vulnerability of cancers
- Multiple pipeline and SOC synergies

### Right Ambition

- A chance to lead in next-generation DDR and ADC therapies
- Double down on indications of interest
- Solid commercial potential



### Right Balance

- Clinically validated approaches (ADC, PARPi), but still with lots of innovation potential (FiC/BiC)
- Diversity of MoA across 3 pillars
- No risk concentration in a single area

### Sustainable Play

- Multiple unique opportunities within today's portfolio
- Substantial scope for expansions through organic and inorganic targets

**Acronyms:** ADC=Antibody-drug conjugates; SOC=Standard of care; PARPi=Poly [ADP-ribose] polymerase inhibitor; FiC=First in Class; BiC=Best in Class; MoA=Mode of Action; DDR=DNA damage response



A large, stylized number '4' in a vibrant pink color, positioned on a dark purple rounded rectangular background. The background is set against a larger pink area on the left side of the slide.

# Neurology & Immunology – clinical pipeline

# N&I - Strategy

## Gradual expansion on a solid foundation



### MAXIMIZE MS PORTFOLIO

#### Area of focused leadership

World-class launch of a potential for Best-in-Class BTKi

Evobrutinib

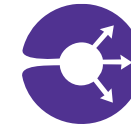


### EXPAND IN NEUROLOGY

Focus on rare neurological diseases where **inflammation is the primary biology**

Expand into neurological areas that support **focused leadership**

Oral Cladribine



### DIVERSIFY WITH IMMUNOLOGY

**Accelerate discovery & development** on targets with proven biology via novel modalities

Maximize potential for TLR7/8 inhibition

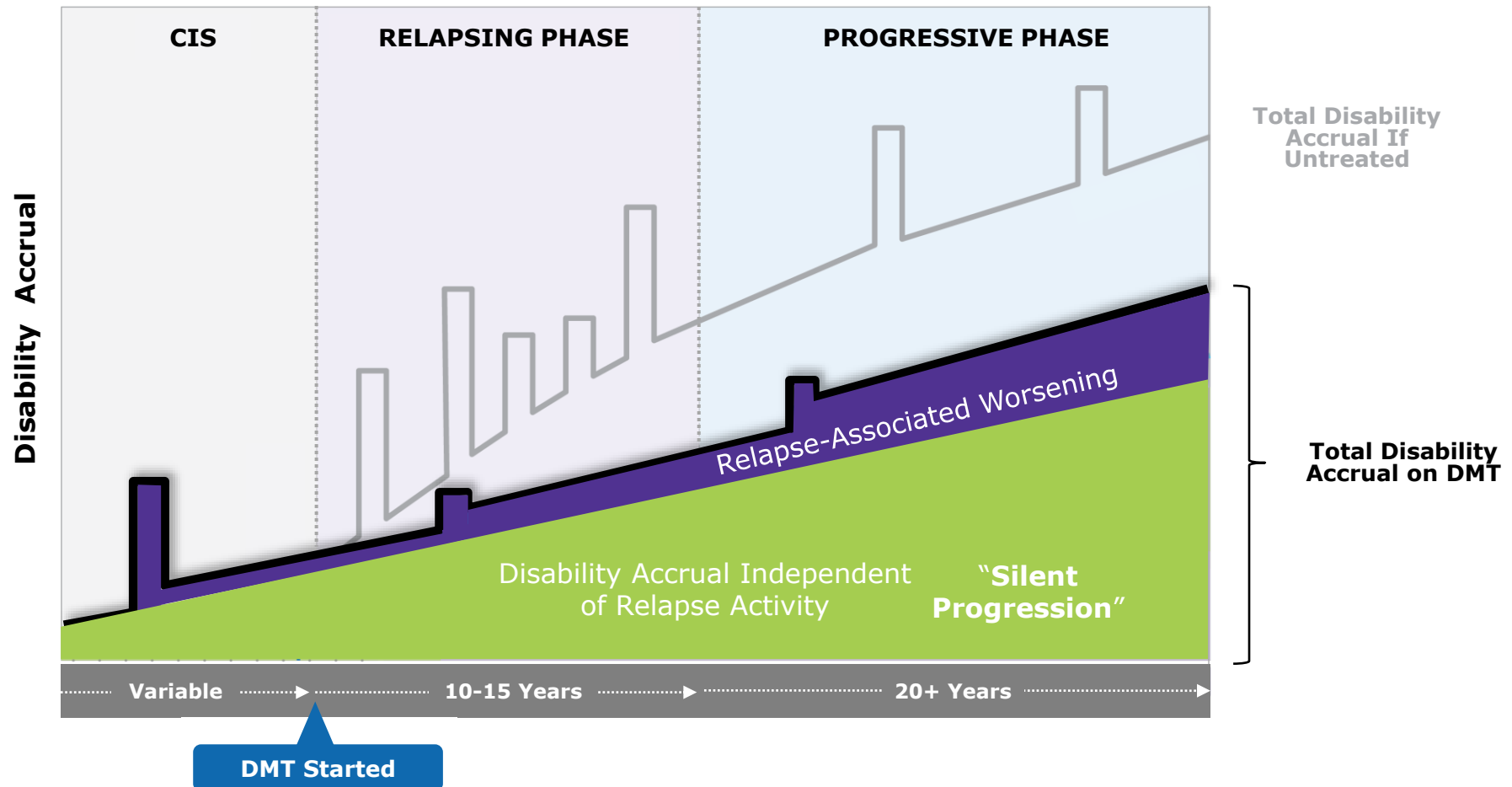
Enpatoran

Acronyms: **BTKi**=Bruton's tyrosine kinase inhibitor; **MS**=Multiple Sclerosis



## N&I - Evobrutinib

# Silent progression - disability accumulation despite DMT in the absence of focal MRI lesions and relapses is a persistent critical unmet need in MS



Acronyms: CIS=clinically isolated syndrome; DMT=disease-modifying therapy; MRI=Magnetic resonance imaging; MS=Multiple Sclerosis  
Adapted from Hauser SL, Cree BAC. *Am J Med.* 2020;133(12):1380-1390.



# N&I - Evobrutinib

## Dual Mode of Action for dual efficacy potential

### Dual MOA



BTK inhibition modulates<sup>1-5</sup> B cells and microglia in the CNS **AND** B cells & monocytes in the periphery\*

### Dual efficacy



Reduction in progression associated with relapses **AND** independent of relapses (i.e. silent progression)

## Clinical Excellence



- ✓ **Optimal BTK occupancy<sup>6</sup>** with BID dosing for sustained BTK inhibition and maximal efficacy
- ✓ **Most comprehensive Phase II study** including novel endpoints
- ✓ **Thorough safety profile characterization and management** through appropriate monitoring

**Acronyms:** BTKi=Bruton's tyrosine kinase; CNS=central nervous system; BID=twice-a-day

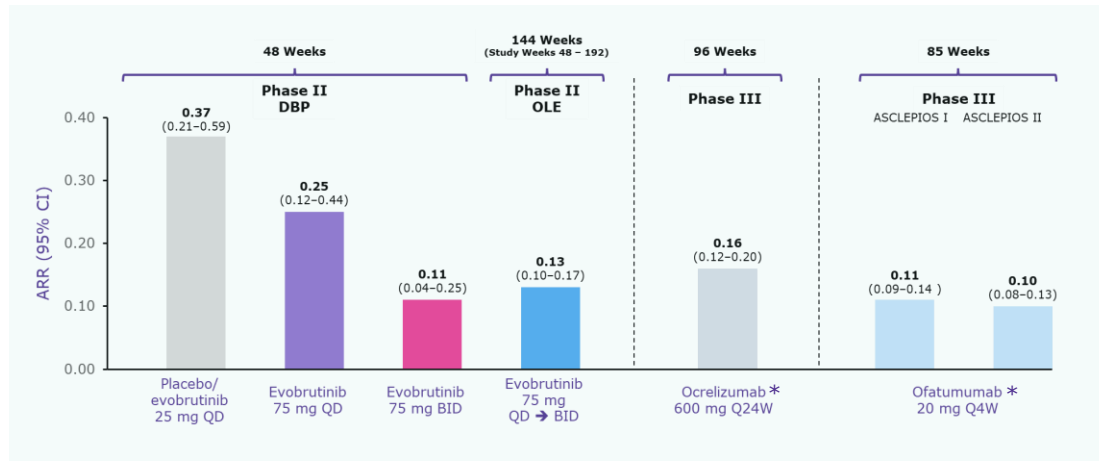
<sup>1</sup>Haselmayer P. et al. J Immunol. 2019 May 15;202(10):2888-2906; <sup>2</sup>Bhargava P. et al. Brain. 2021 Jun 22;144(5):1396-1408; <sup>3</sup>Martin E. et al. Brain Plast. 2020; 5(2): 123-133; <sup>4</sup>Alankus Y-B. et al. 2019 Annual Meeting of the Consortium of Multiple Sclerosis Centers; <sup>5</sup>Geladaris A. et al. 2021;ECTRIMS 2021(LB-ECTRIMS-2021-01631); <sup>6</sup>Papasouliotis O. et al. Clin Transl Sci. 2022 Sep 20.; \*in pre-clinical studies



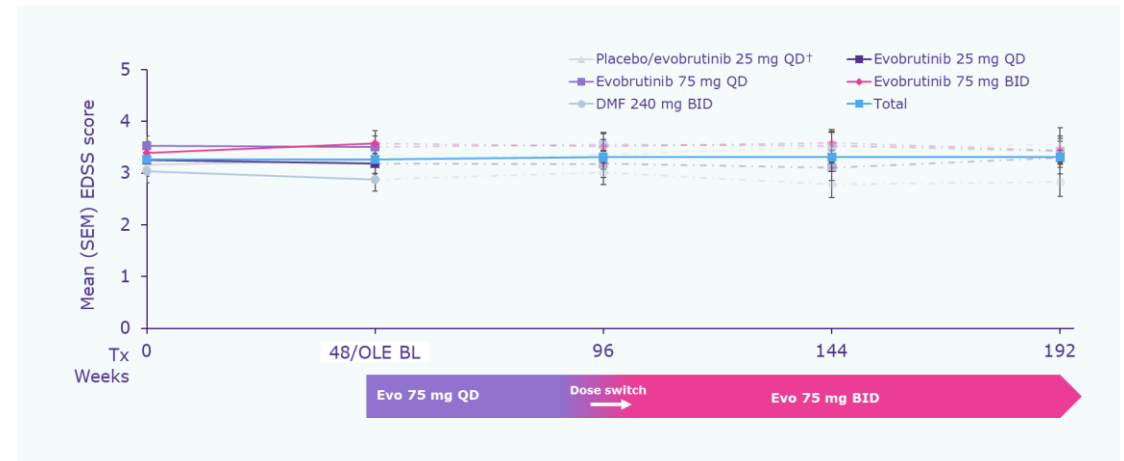
# N&I - Evobrutinib

## Compelling clinical data in Phase II and the ongoing extension

### Very low and sustained ARR



### Long-term Clinical Stability (EDSS)



**Acronyms:** ARR=annualized relapse rate; BID=twice daily; BTKi=Bruton's tyrosine kinase inhibitor; CI=confidence interval; CNS=central nervous system; DBP=double-blind period; OLE=open-label extension; Q24W=every 24 weeks; QD=once-a-day.

\*Comparison not based on head-to-head study. 1. Montalban X et al. N Engl J Med, 2019;380:2406-178. 2. Vermersch P, et al. ECTRIMS 2022 [P731]; 3. Hauser SL, et al. N Engl J Med 2017; 376:221-234; 4. Hauser SL, et al. 2020; 383:546-557

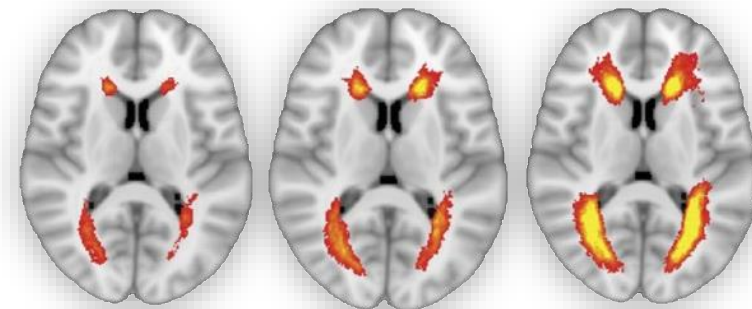
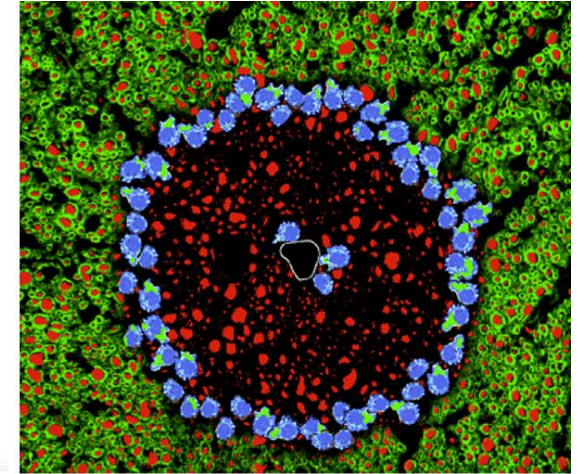
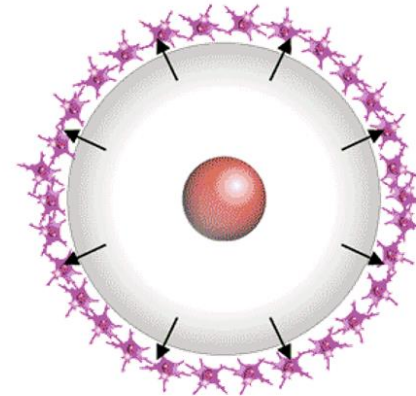


## N&I - Evobrutinib

# Slowly Expanding Lesions (SELs) are associated with long-term disability progression in patients with RMS

### Slowly Expanding Lesions are:

- Chronically active, demyelinated MS lesions
- **Driven by sustained microglial activity** resulting in progressive accumulation of irreversible neural tissue damage and axonal loss<sup>1</sup>
- Visible on conventional MRI/T2 images MRI showing gradual, radial expansion over time
- **Predictive of long-term disability<sup>2</sup>**
- **Not highly impacted by approved MS therapies**

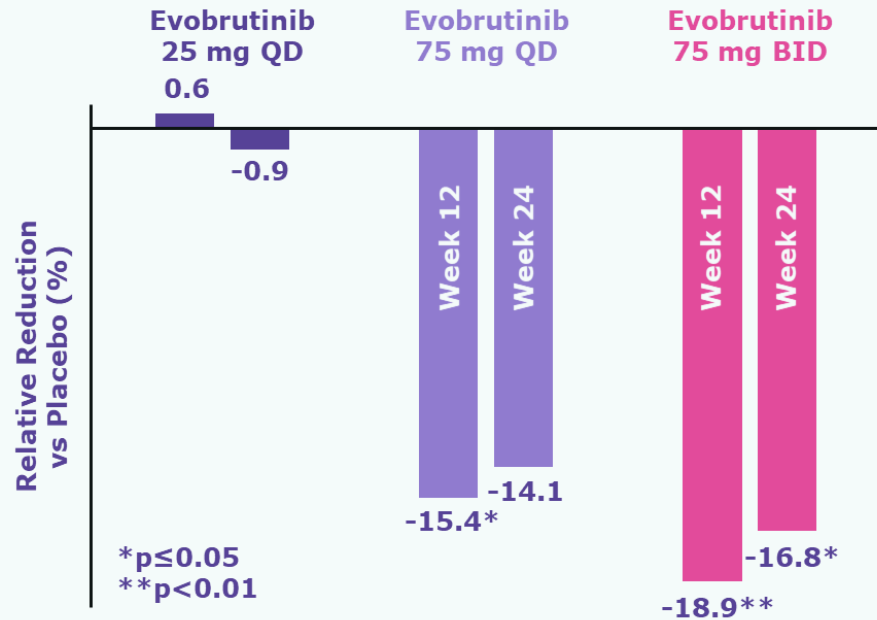


<sup>1</sup>Arnold DL, et al. CMSC 2022 [DMT17]; <sup>2</sup>Elliott C, et al. *Brain*. 2019,142:2787:2799  
Acronyms: RMS= Relapsing multiple sclerosis, MRI=Magnetic resonance imaging; MS=Multiple Sclerosis

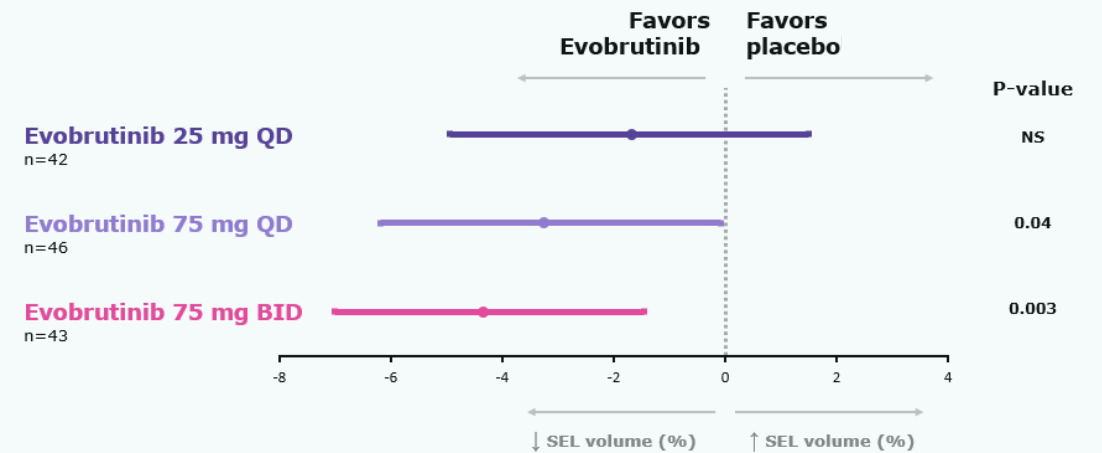
# N&I - Evobrutinib

## Biomarker data further supports impact on silent progression in Phase II

### Reduction in established biomarkers of neuronal damage (NfL)



### Reduction in SEL volume



Acronyms: BTKi=Bruton's tyrosine kinase inhibitor; CNS=Central Nervous System; SEL=Slowly Expanding Lesions; NfL=Neurofilament light polypeptide  
1. Kuhle J et al. AAN 2021. [Emerging Science 005]. 2. Arnold DL et al ECTRIMS 2021 [115]. 3. Arnold DL et al. AAN 2022 [S.14.009]



## N&I - Evobrutinib

# Broad and comprehensive assessment of disability in the Phase III program



- Composite measures: CDP, NEP, NEPAD, RAW, PIRA, PIRMA
- Disability improvement: CDI
- Manual dexterity: 9 Hole Peg Test
- Walking ability: T25FW
- Biomarkers: NfL
- Cognition: SDMT
- Fatigue: PROMIS Fatigue
- Quality of life: PROMIS Physical function
- Imaging: Conventional MRI measures, SEL

(Secondary endpoints)

### Additional studies to start:

- PET (Imaging) study
- 5-year umbrella extension

**Acronyms:** CDI=confirmed disability; CDP=confirmed disability progression; NEP=no evidence of progression; NEPAD=no evidence of progression with active disease; 9HPT=9-hole peg test; SDMT=symbol digital modality test; RAW=relapse-associated worsening ; PIRA=progression independent of relapse and MRI activity; SEL=Slowly Expanding Lesions; NfL=Neurofilament light polypeptide; MRI=Magnetic resonance imaging; PET=Positron emission tomography



## N&I - Evobrutinib

# Evobrutinib – potential for Best-in-Class and on track for Q4 2023 readout



### Rapid Response to Emerging Operational Challenges

- Protocol switched to an event-driven design
- Extension of study period to 3 years
- Re-opened sites outside of UKR/RUS crisis region



### Study Analysis Approach

- Analysis strategy is to utilize data from UKR/RUS with confirmed high data quality
- Confirmed by external advisors and agreed upon by FDA



### Next Steps

- Recruitment closed in Q4 2022
- Program on track for readout in Q4 2023

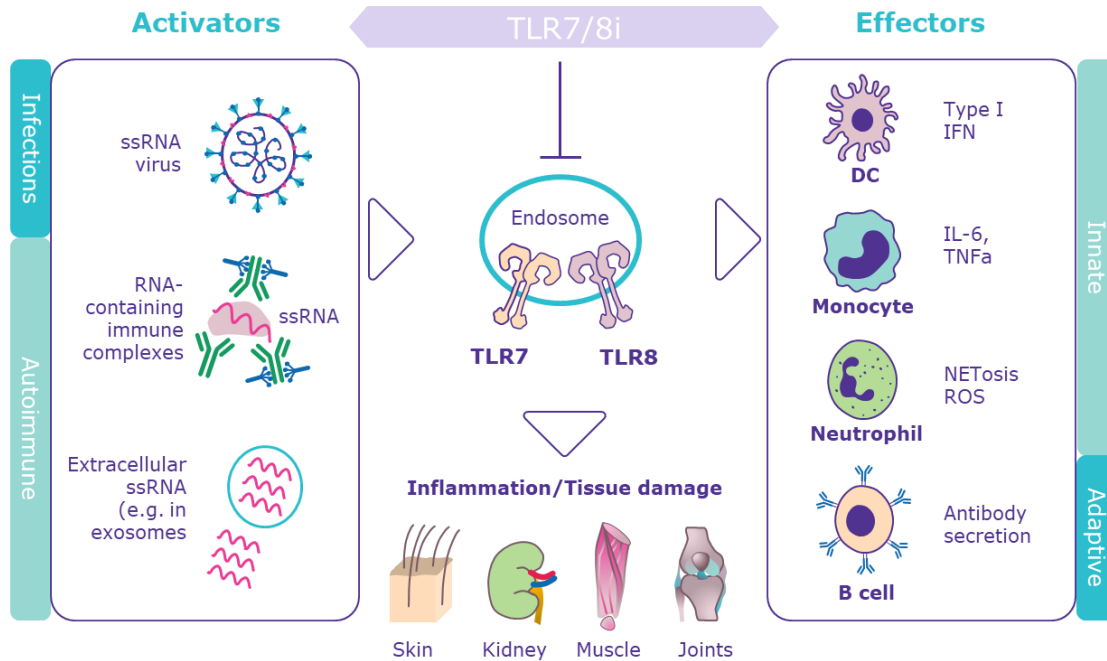


**Readout  
in Q4 2023**



# N&I - Enpatoran

## TLR7/8 inhibition: Potential to transform treatment of autoimmune diseases



## Rationale

- TLR7 and TLR8 detect ssRNA, triggering activation of both innate and adaptive immune cells<sup>1,2</sup>
- Aberrant TLR7/8 activation is linked to multiple autoimmune and inflammatory diseases<sup>3</sup>
- Monogenic gain-of-function TLR7 mutation leads to childhood-onset lupus<sup>4</sup>

**Acronyms:** ssRNA=Single-stranded RNA.

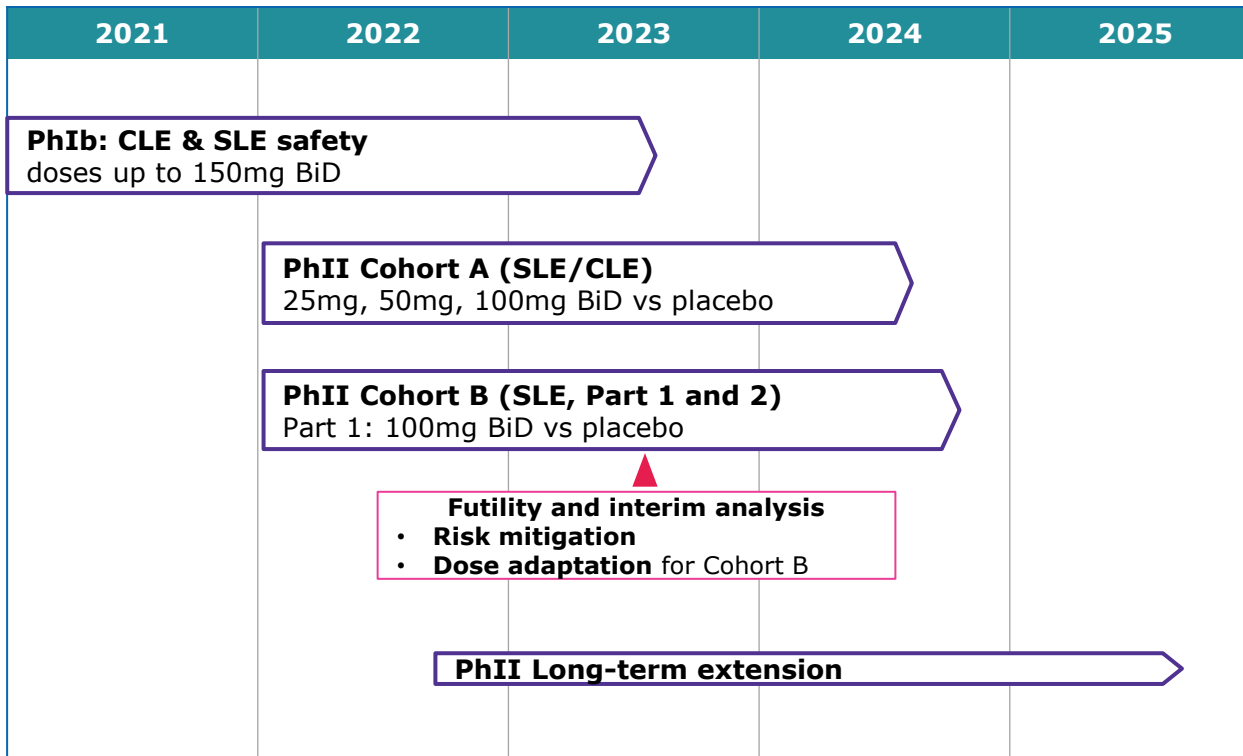
Figure created with BioRender.com. <sup>1</sup>Chow KT et al Annual Review of Immunology 2018. <sup>2</sup>Lind NA et al. Nat. Rev. Immunol. 2022. <sup>3</sup>Joosten LAB et al. Nat. Rev. Rheumatol. 2016.

<sup>4</sup>Brown, G.J. et al. Nature. 2022



# N&I - Enpatoran

## Unique adaptive design of WILLOW study in SLE & CLE



### WILLOW Design Features

- Cohort B part 2 – **dose adaptation**, informed by Phase Ib and Phase II Cohort A at the interim analysis
- Investigation of predictive biomarkers to support PhIII design

### Study Status:

- Global active enrollment of patients in up to 174 sites in 22 countries

➤ **Faster development via streamlined clinical study design**

Acronyms: TLR=Toll-Like Receptor; SLE=Systemic lupus erythematosus; CLE=Cutaneous lupus erythematosus; PoC=Proof of Concept; PoS=Probability of Success; BiD=twice-a-day



# N&I - Enpatoran

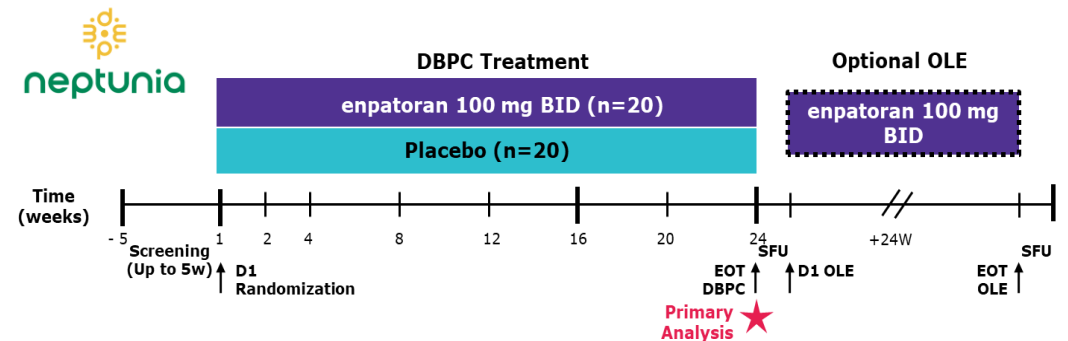
## Expansion into myositis, First-in-Class Potential

### Development Rationale

- **G7 prevalence of 100 – 120K**
- Debilitating autoimmune disease, characterized by muscle weakness, fatigue and disability
- **Patients show lupus-like patterns** of immune activation and TLR7/8 expression
- **High unmet need for effective treatment options:** Large proportion of patients refractory to SoC high dose CS/immunosuppressants



### Neptunia Study



- PoC study in dermatomyositis and polymyositis
- Start in early 2023

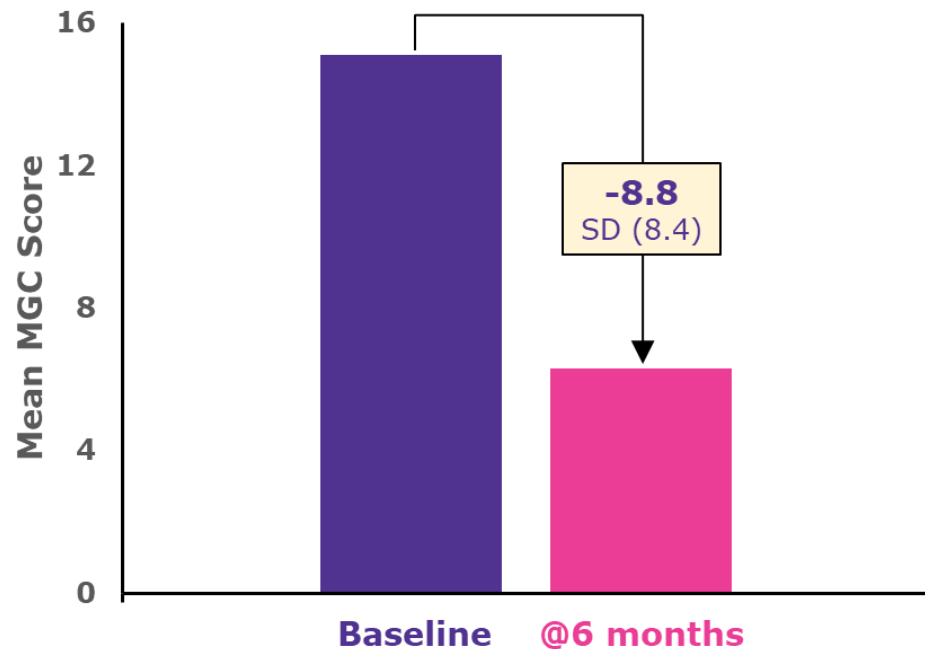
> **An oral therapy with novel MoA and potential for a steroid-sparing effect could be transformative for myositis patients**

Acronyms: **PoC**=Proof of Concept; **MoA**=Mode of Action; **SoC**=Standard of care



## Cladribine – going beyond multiple sclerosis

### s.c. Cladribine Open Label Study in MG



### Development Rationale

- **Myasthenia gravis** is a neuromuscular disease with high unmet need
- There is **potential for a highly differentiated therapy** that can deliver high efficacy and convenience with an oral short-course treatment cycle
- Initial **supportive clinical data available**



**Clinical study planned for early 2024**





5

## KEY TAKEAWAYS & Q&A SESSION

# R&D Update call 2022

## Upcoming milestones

### Significant readouts

#### 2023

- Evobrutinib PhIII program
- Enpatoran PhII CLE/SLE - futility analysis
- Xevinapant (cis-eligible) PhIII - IA
- Tepotinib NSCLC EGFRm/METamp PhII
- M9140 PhIa RDE
- M1069 PhIa RDE

#### 2024

- Xevinapant (cis-eligible) PhIII - full analysis
- Avelumab UC Medley PhII (IA read-out)

### Study initiations

#### 2023

- Enpatoran PhII DM/PM
- Evobrutinib PET Study PhIIIb
- M1774 + ICI PhII
- M9140 PhIb expansions

#### 2024

- Cladribine new formulation in gMG
- M1774 + ADC PhII
- M6345\* PhI study
- GD-2 ADC\* PhI study

**Acronyms:** SLE=Systemic lupus erythematosus; CLE=Cutaneous lupus erythematosus; ADC=Antibody-drug conjugates; NSCLC=Non-small cell lung cancer; IA= Interim analysis; cisPt=cisplatin; FIS=First in Human; RDE=Recommended Dose for Expansion; gMG=Myasthenia Gravis; NSCLC=Non-Small Cell Lung Cancer; UC=urothelial carcinoma; ICI=Immune Checkpoint Inhibitor; PM=Polymyositis; DM=Dermatomyositis  
\*asset in preclinical profiling phase



# R&D Update call 2022

## Key take-away points

### 1 More medicines to more patients, faster



### 2 Expanding focused leadership

- Building on strong internal expertise and capabilities to advance biology understanding, technology development, and therapeutic focus
- Determined to establish technology leadership in ADCs and protein degradation

### 3 Strong progress in clinical development

- Building on leadership in H&N: **xevinapant**
  - ✓ 5ys OS data indicating nearly doubling of cure rates
  - ✓ TrilynX Interim Analysis (IA) in 2023
- Maximizing presence in MS: **evobrutinib**
  - ✓ dual MoA for dual efficacy
  - ✓ Potential for BiC, FiC
  - ✓ on track for Q423 readout
- Driving innovation in focus area of DDRi with **M1774** and combinations.
- Driving focus areas of ADC tech and CRC with **M9140**
- **Enpatoran**:
  - ✓ Interim readout in 2023
  - ✓ Broaden development beyond lupus
- Expand in neuroinflammation with oral **cladribine** in gMG

**Acronyms:** **FiC**=First in Class; **BiC**=Best in Class; **MoA**=Mode of Action; **DDRi** **DDR** **DNA**=damage response inhibitors; **ADC**=Antibody-drug conjugates; **MS**=multiple sclerosis; **CRC**=Colorectal cancer



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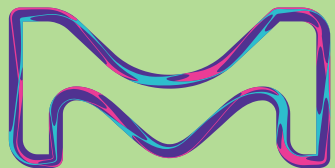


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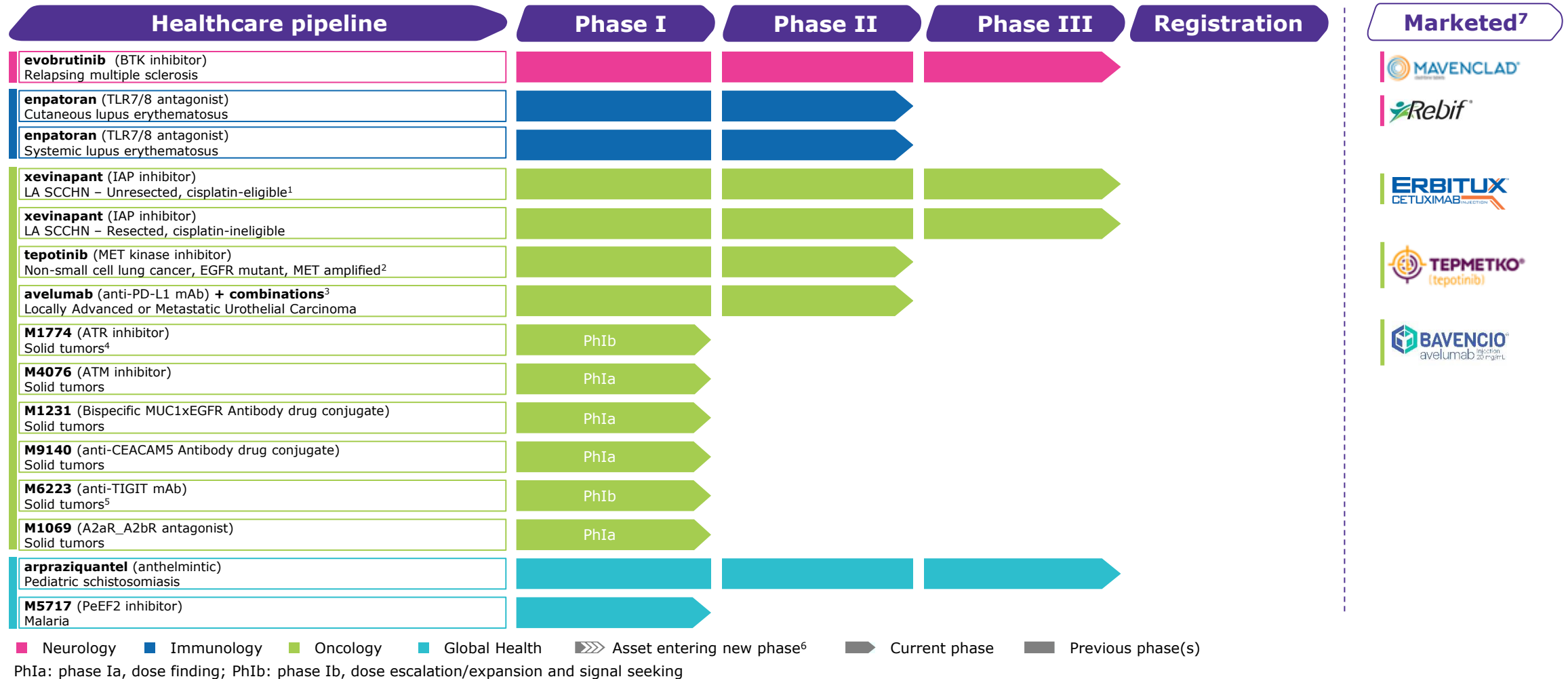


# Appendix

healthcare pipeline

# Merck KGaA, Darmstadt, Germany pipeline

November 21, 2022



<sup>1</sup> In combination with cisplatin and radiotherapy in unresected LA SCCHN patients eligible for cisplatin. <sup>2</sup> In combination with osimertinib. <sup>3</sup> Combinations include Sacituzumab Govitecan, NKTR-255 and M6223. <sup>4</sup> Study as monotherapy and in combination with niraparib and M4076 ATMi. <sup>5</sup> Includes combinations other than avelumab. <sup>6</sup> Registered study with open enrollment; subjects may not yet be enrolled. <sup>7</sup> Marketed products for information only. Unless noted otherwise, clinical programs conducted in collaboration with external partners are not shown unless Merck KGaA, Darmstadt, Germany has co-ownership of data. In such cases the indication is shown in italics.

Pipeline products are under clinical investigation and have not been proven to be safe and effective. There is no guarantee any product will be approved in the sought-after indication.

