

REDEFINING FRONTLINE IMMUNOTHERAPY

First small-molecule TLR4 agonist rationally designed for effective and safe cancer therapy



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HEPHAISTOS

Raising Series A to advance 3rd generation TLR4 agonist HEPHA440 in first-line cancer therapy



HEPHA440 Solves TLR4 Challenges

- Broad therapeutic window established *in vivo* supports safe systemic clinical administration
- Positioned to optimize frontline immunotherapy



Large Therapeutic Potential

- Deep & durable responses with immune memory effect on many models (TNBC, CRC, sarcoma)
- TME remodeling removes myeloid-cell-related immunosuppression



Robust Clinical Plan

- Clear path for HEPHA440-PD1 combination as front-line treatment for TNBC
- RP2D after 30 months



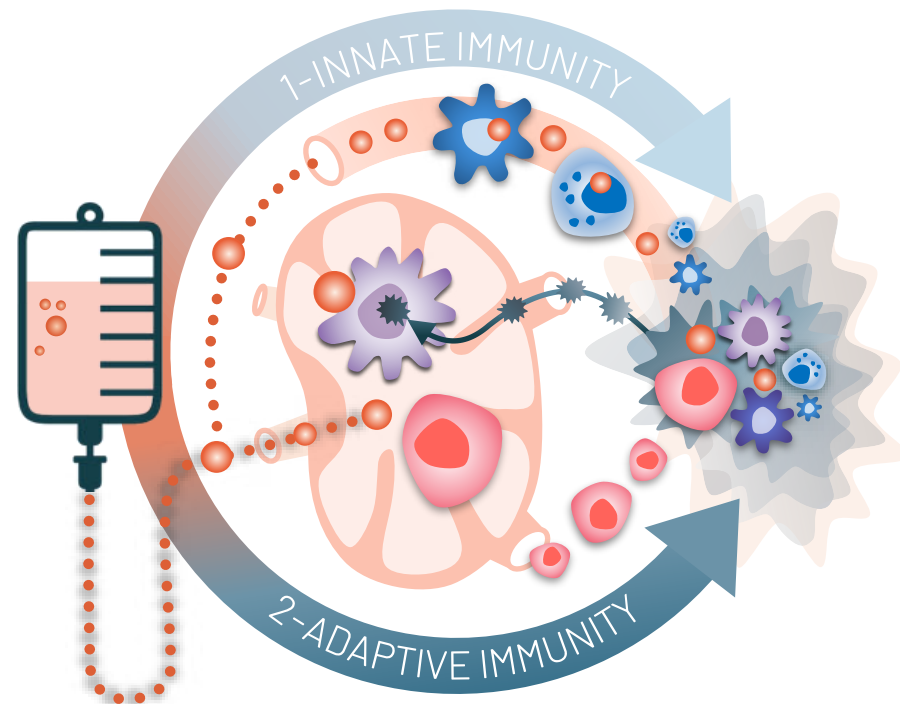
Complete C-Suite

- Leadership, Board, and Scientific Advisors focused on achieving clinical PoC and driving value for patients and shareholders

HEPHA440 activates innate and adaptive immune responses with significant systemic anti-tumor potential

HEPHA440

1. Primary activation of innate immunity
 - M2 to M1 macrophage conversion
 - TME remodeling of 'cold' $\Rightarrow$ 'hot' tumors
 - Inducing tumor antigen presentation by DCs
2. Secondary activation of adaptive immunity
 - Recruitment and priming of CD8⁺ T cells
 - Immune-memory against tumor recurrence
 - Systemic anti-tumor immune effect



● HEPHA440



DC Dendritic cells



T cells



Macrophages
M2 to M1 transition



NK cells



Tumor antigen

HEPHA440 is a differentiated 3rd generation TLR4 agonist with a new chemical structure resolving toxicity by design

CHEMICAL MODIFICATION

HEPHA440

- Rationally designed natural TLR4 agonist
- ~1000x less pyrogenic
- High anti-tumor efficacy
- Anticipated good Therapeutic index



Oligo
saccharide

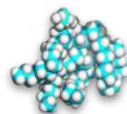
+

Lipid A

"Best in-class" TLR4 agonist

GLA MERCK

- Synthetic MPL[®] analog
- Positive Phase 2 in cancer
- Local administration only
- Narrow Therapeutic Index

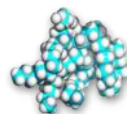


Lipid A

Synthetic TLR4 agonist

MPL[®]

- Detoxified bacterial extract
- Commercialized in 5 vaccines
- Local administration only
- Narrow Therapeutic Index



Lipid A

Modified TLR4 agonist

Therapeutic index	Highly potent	Solubility	Scalability	TRIF-antitumor	MyD88-Pyrogenic
✓	✓	✓	✓	+	-
-	-	✗	✓	-	+
-	-	✗	✗	+	+

Therapeutic Index



1,000

HEPHA440

100

MPL[®]

Commercialized in 5 vaccines

10

GLA

Terminated after Phase 2

1

LPS

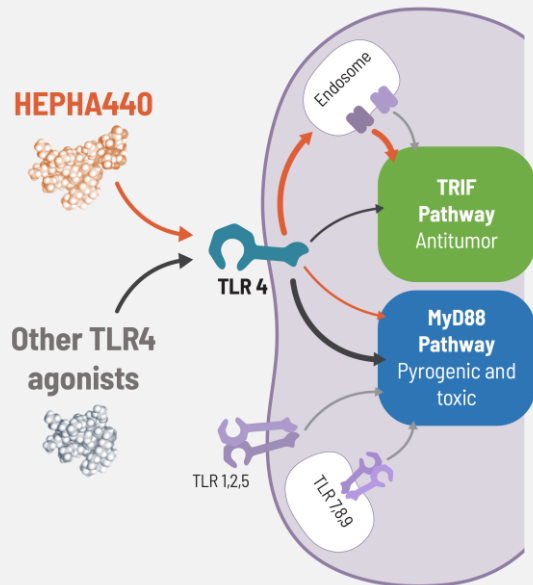
Terminated after Phase 1



Maximum Non-Pyrogenic Dose (ng/kg)

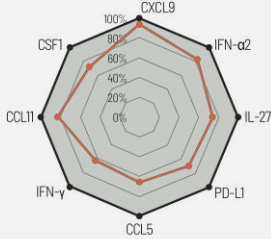
HEPHA440 is designed to have low CRS potential and improved safety profile due to a shift of cytokine balance

Mechanism

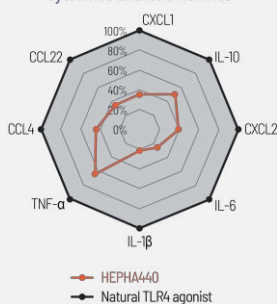


Circulating cytokine production profile in mice

TRIF & Other-related cytokines and chemokines

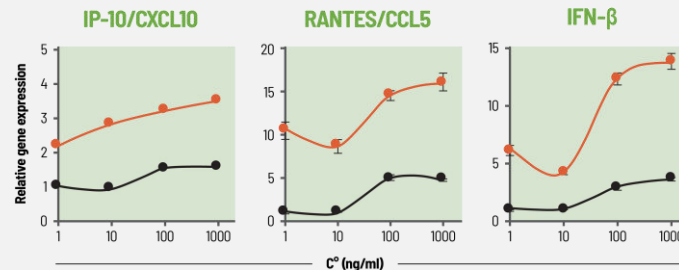


MyD88-related cytokines and chemokines

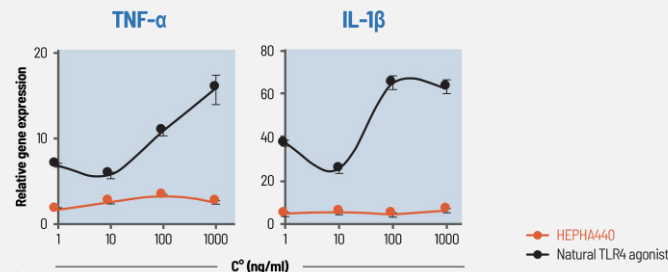


Gene expression profile in human macrophages (THP1 cells)

Type I IFN cytokines (TRIF - related)



Proinflammatory cytokines (MyD88 - related)



(adapted from) Chettab et al., *Frontiers in Immunology*, 2023

Nonclinical toxicology of HEPA440 supports repeated IV dosing at doses up to 1000x higher than known TLR4 agonists

Larger Therapeutic Index



Non-GLP			- Repeated dose + Biodistribution studies - Good tolerance in IV (MTD > 100µg)
			- Repeated Dose escalation - Good tolerance in IV (MTD > 1600 µg/kg). Low grade adverse effects (Leukopenia, Fever & Liver tox). Reversible within 12-24h
GLP		2026	- CRO selected for regulatory tox studies - DRF study + GLP tox studies

Rabbits accepted as relevant species by French regulatory agency

HEPHA440 recruits CD8 T Cells and converts macrophages removing myeloid cell-based immunosuppression



C3H/HeN WT (n=6)
C3H/HeJ - TLR4 KO
(n=6)

LM8 - metastatic osteosarcoma mouse model

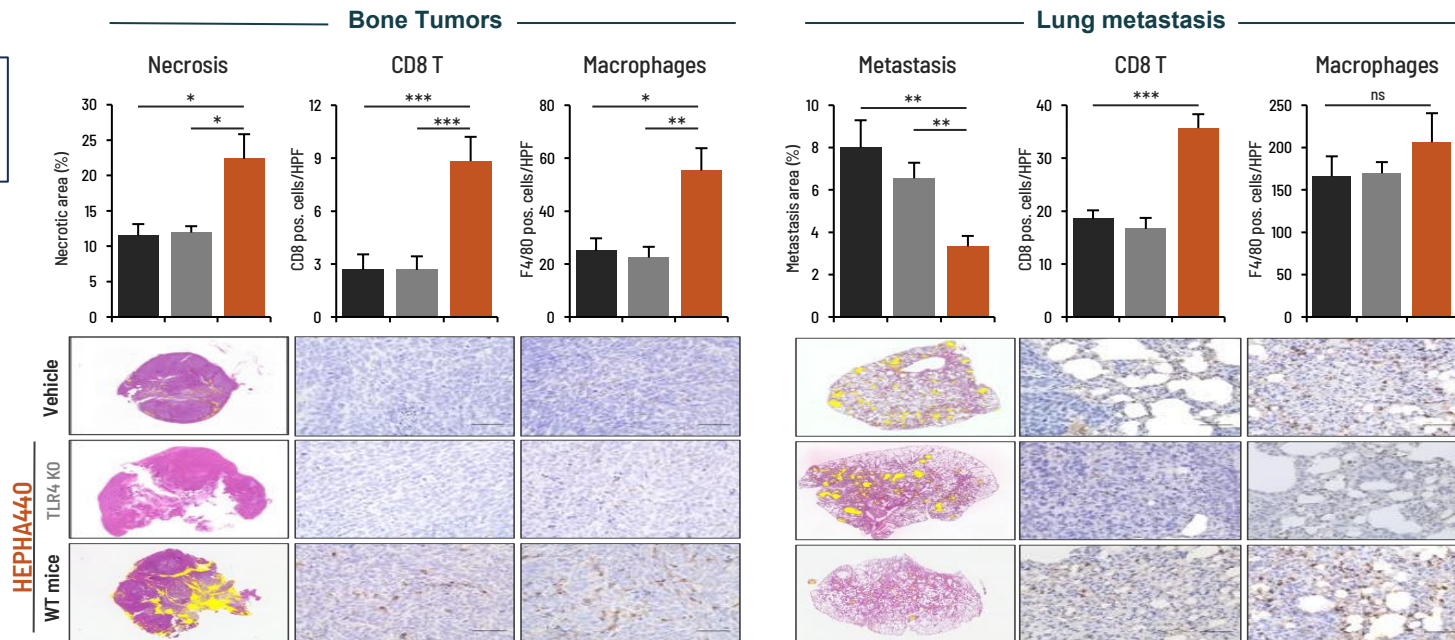
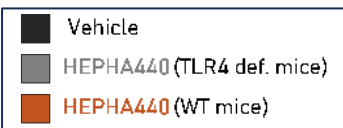
Tumor implantation D0

HEPHA440 (100µg in i.p.; Batch (B5P10); F7 Formulation)

H&E staining - Quantification of necrotic areas (tumor) and lung metastasis

IHC analysis - CD8 and F4/80 (macrophages) positive cells in tumors and Lung metastasis at D25

Intraperitoneal injection



* P<0.05, ** P<0.01, *** P<0.005, ns: Not significant

HEPHA440 increases checkpoint expression in TME explaining the combination potential with immune checkpoint inhibitors



C3H/HeN WT (n=6)

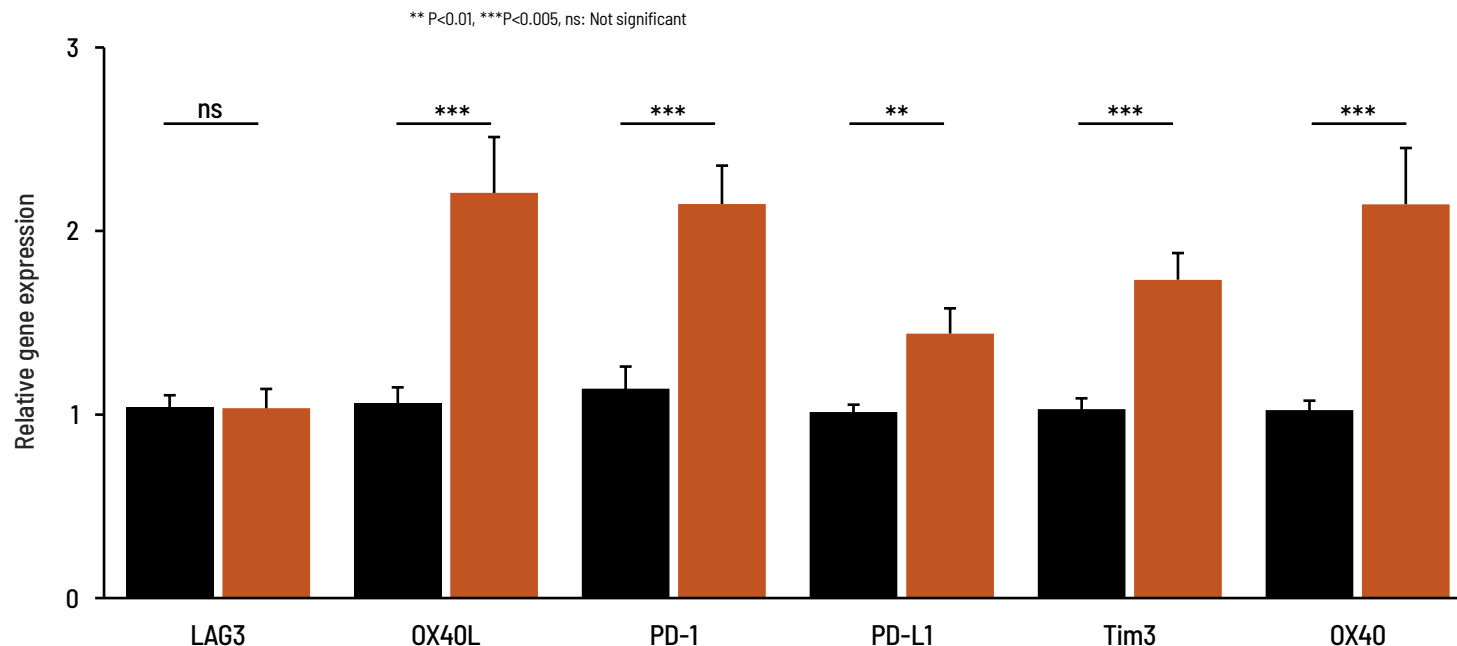
LM8—Metastatic mouse osteosarcoma model

Tumor implantation D0
Treatment : HEPHA440 (60µg in i.v.) 2x/week for 3 weeks
D25: Analysis ICP expression in TME (RT-qPCR)

■ Control (PBS)

■ HEPHA440

Oyama et al., BJC, 2025



HEPHA440 has been shown to potentiate ICI anti-tumor activity by TME remodeling

HEPHA440 in combination with PD1 inhibition induces deep and durable response with memory effect against colorectal cancer



C57BL/6 mice (N=8)

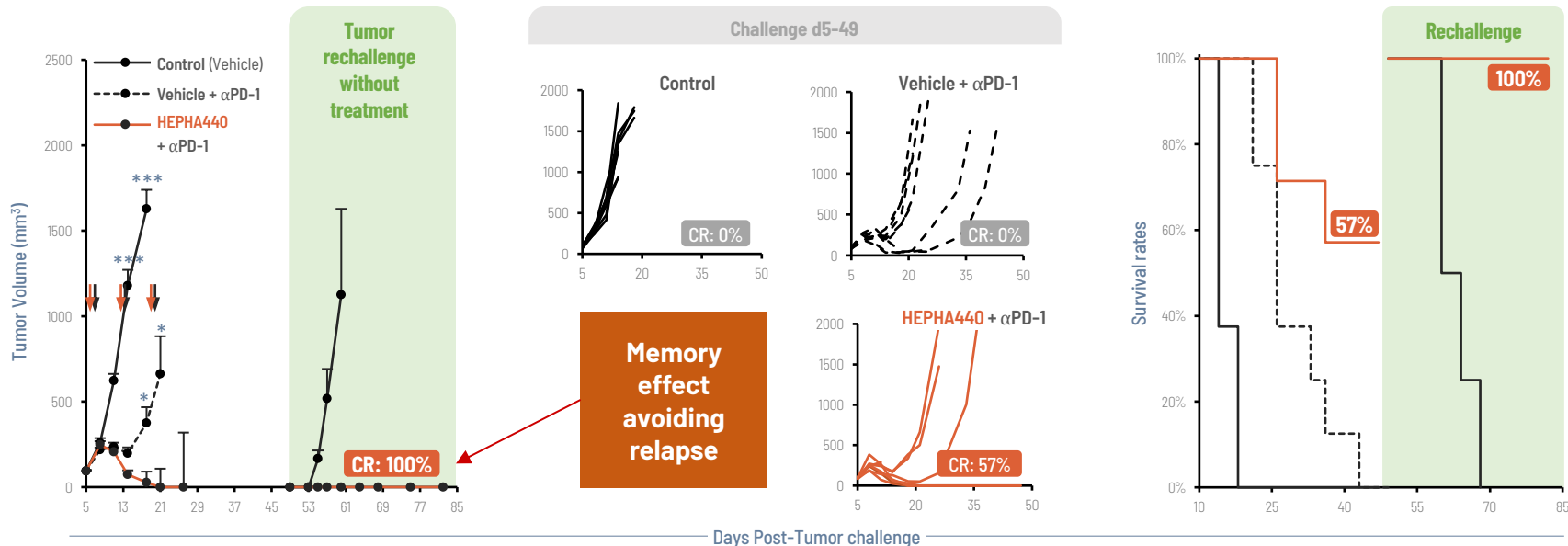
MC38—Mouse CRC model

Tumor implantation D0 (5x10⁶ cells)

Doses - Anti-Mouse PD-1 RMP1-14 (12.5mg/kg in i.p.), HEPHA440 (25µg in i.v.)

CR - Complete Remission

Benchmark - Human anti-PD1 mAb (Pembrolizumab)



Chettab et al., Frontiers in Immuno., 2023

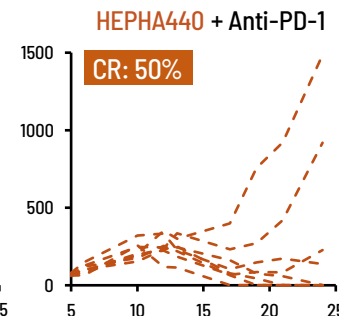
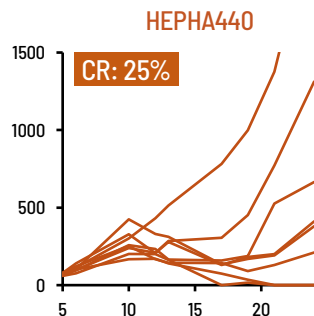
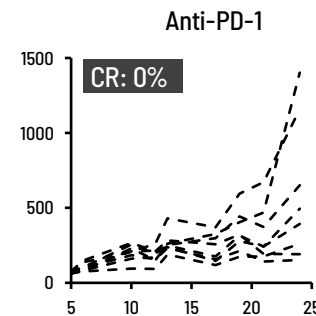
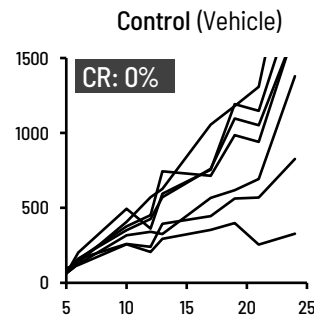
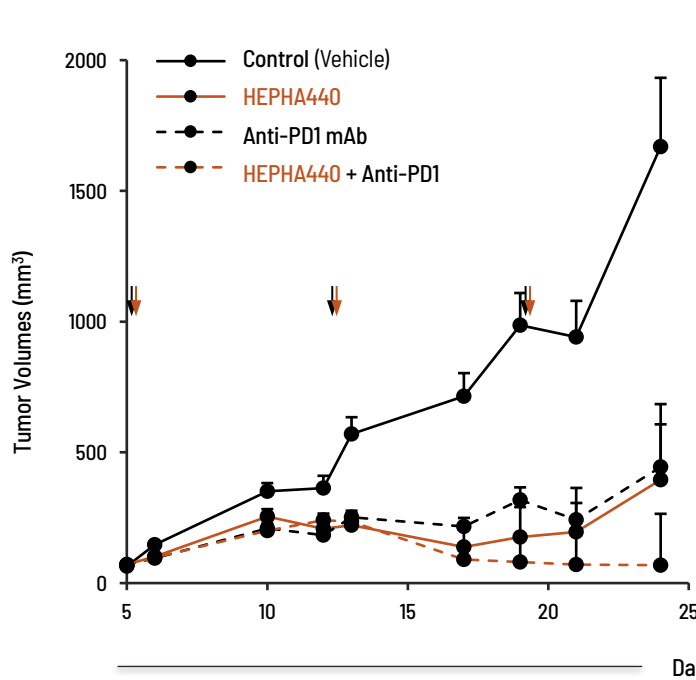
HEPHA440 demonstrates anti-tumor activity in aggressive triple-negative breast cancer model



EMT6—Mouse TNBC model

BALB/c mice (N=8)

Tumor implantation D0
Doses - HEPHA440 (25µg i.v.), Anti-mouse PD-1 mAb (RPM1-14; 12.5mg/kg i.p.)
CR - Complete Regression



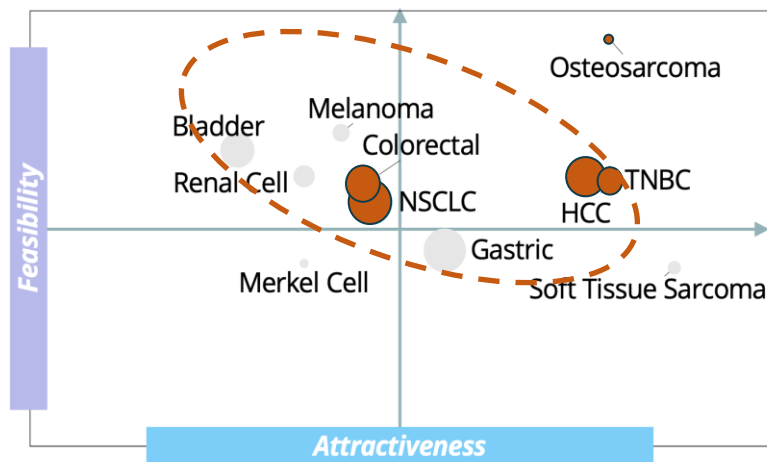
Benchmark :
0% Complete Regression

25% CR as single agent

50% CR in combination w/ ICI

We are prioritizing high unmet medical need and fast value creation

Indication Priorization Matrix



We will prioritize indications with myeloid infiltration and high unmet medical need (TNBC, CRC, NSCLC).

HEPHA440 can be used in frontline TNBC in combination with PD1 inhibitor

We will enroll patients with any PD1 expression/immunoscore

Feasibility : Myeloid infiltration + clinical evidence + patient recruitment

Attractiveness : Unmet medical need + broad life-cycle management opportunities

Bubble size : relevant size of advanced-stage 2L or 3L treatment segment

Blockbuster potential in frontline immunotherapy for triple-negative breast cancer (TNBC)



2.3 million

breast cancer cases globally/year¹



20%

of all breast cancers is TNBC



NO

sustainable disease control with current treatments²



<50%

advanced/metastatic TNBC patients reach 2L treatment³

\$5 billion

Current global revenue for TNBC⁴

\$7,3 billion

Global revenue⁵ for TNBC by 2035

4.8%

CAGR for TNBC⁵

¹<https://www.who.int/news-room/fact-sheets/detail/breast-cancer>

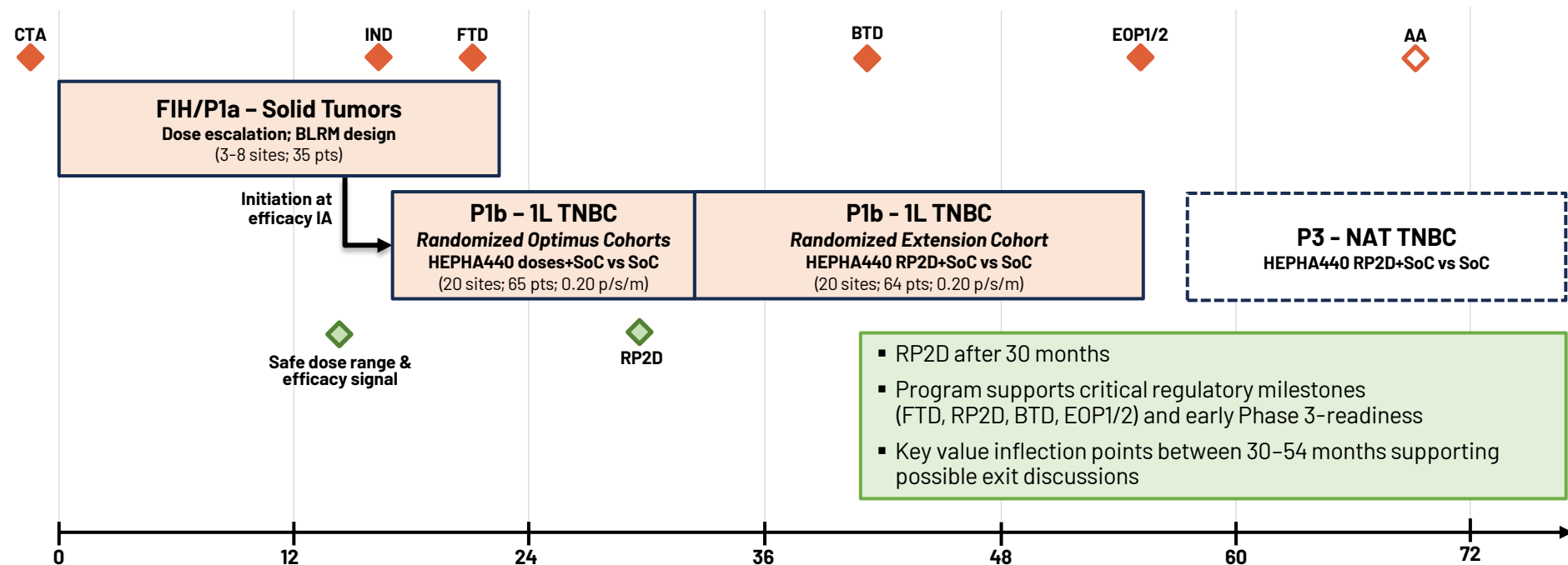
²<https://www.nature.com/articles/s41523-022-00468-0>

³<https://www.nejm.org/doi/full/10.1056/NEJMoa2508959>

⁴<https://www.delveinsight.com/report-store/triple-negative-breast-cancer-tnbc-market>

⁵<https://www.insightanalytics.com/report/global-triple-negative-breast-cancer-treatment-market/1038>

Phase 1 trial designed to rapidly achieve value inflection points and Phase 3-readiness for TNBC patients



Abbreviations: 1L, first-line treatment; AA, Accelerated Approval; BTD, Breakthrough Therapy Designation (FDA); EOP1/2, End-of-Phase 1/2 (Type C) meeting; FIH, first-in humans; FTD, Fast Track Designation (FDA); IA, interim analysis; NAT, neoadjuvant treatment; P1/3, Phase 1/3 study; RP2D, recommended Phase 2 dose; SoC, standard of care.

OUTCOMES:

- **FIH/Phase 1a** – Confirmation that HEPHA440 is safe and tolerated in humans and efficacy signals with biopsies, DNAc, PK, disease control rate
- **Phase 1b Optimus** – RP2D and optimal benefit-risk profile for 2 doses, with acceleration and expansion option for Phase 3-readiness of NAT

FUNDING

4.5M€ in equity raised
Seed round in early 2024

**13.6M€ in non-dilutive
funding secured**



2024

2025

TEAM



Chairman
David SOURDIVE
PhD



CEO
Frédéric CAROFF
MSc, MBA



CSO
Jérôme KERZERHO
PhD



CMO
Stephan BRAUN
MD PhD



CDO
Frederique BRUNE
PharmD



CFO
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