Transforming Drug Development at Biopharmaceuticals

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Merck KGaA
Darmstadt · Germany

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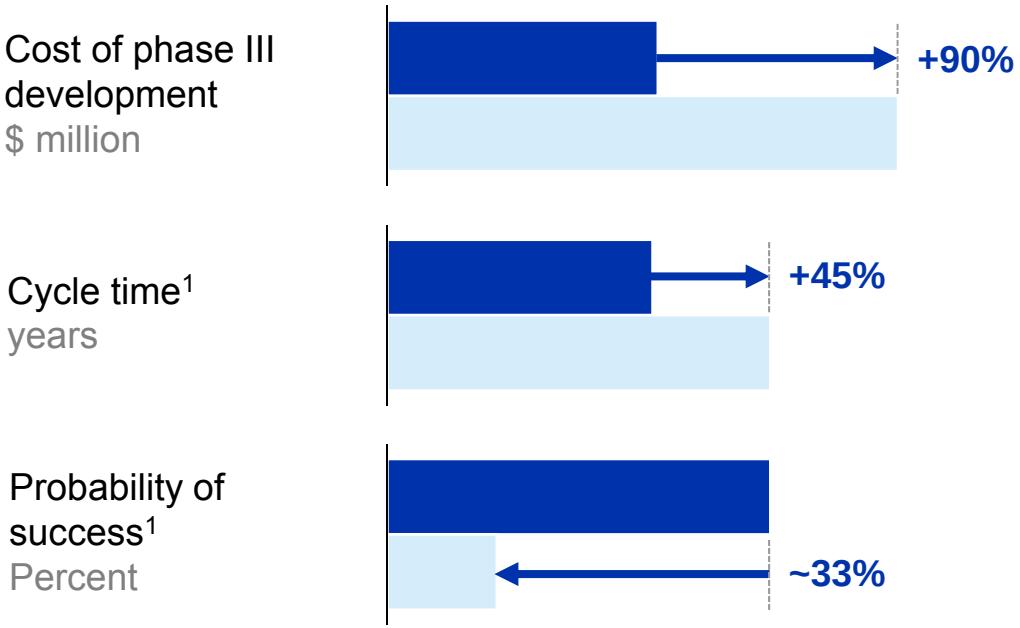
Agenda

1. **Framework to deliver productivity improvements and value**
2. Pipeline
3. Conclusion

We lag industry performance on key metrics

Pre-clinical to launch performance metrics

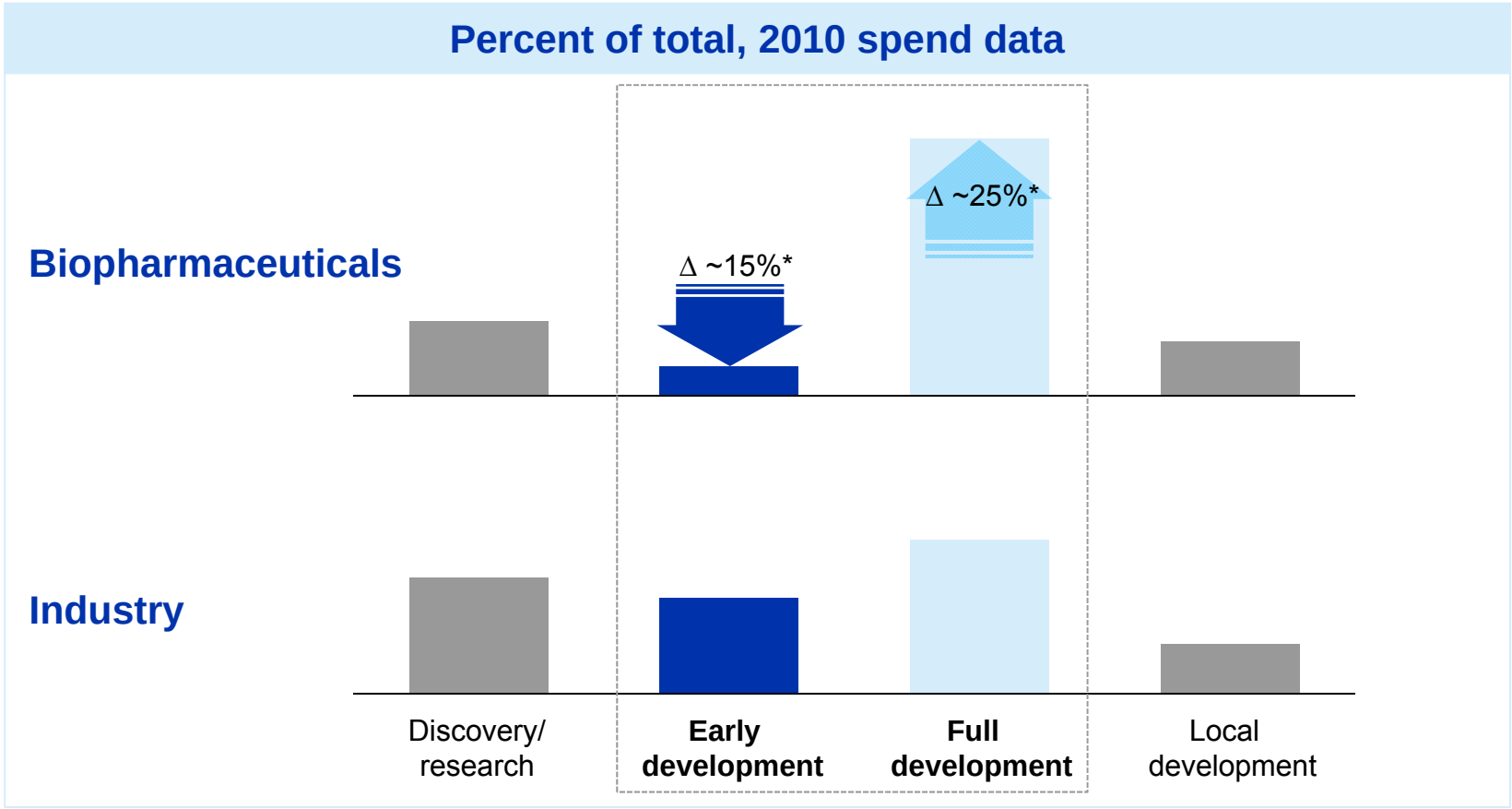


We have had no significant products/ indications reaching the market in the past 5 years

[1] Composite figures from pre-clinical to launch
Source: CMR data

Composite industry benchmark
Biopharmaceuticals

We overinvested in failed late-stage programs while under-investing in mid-stage pipeline



* Absolute difference to industry benchmark

We will focus on cost, competitiveness and culture to deliver value

Reset cost base

- Right size
- Flexibilize[1]
- Globalize
- Renew R&D
- Rebalance

Deliver value

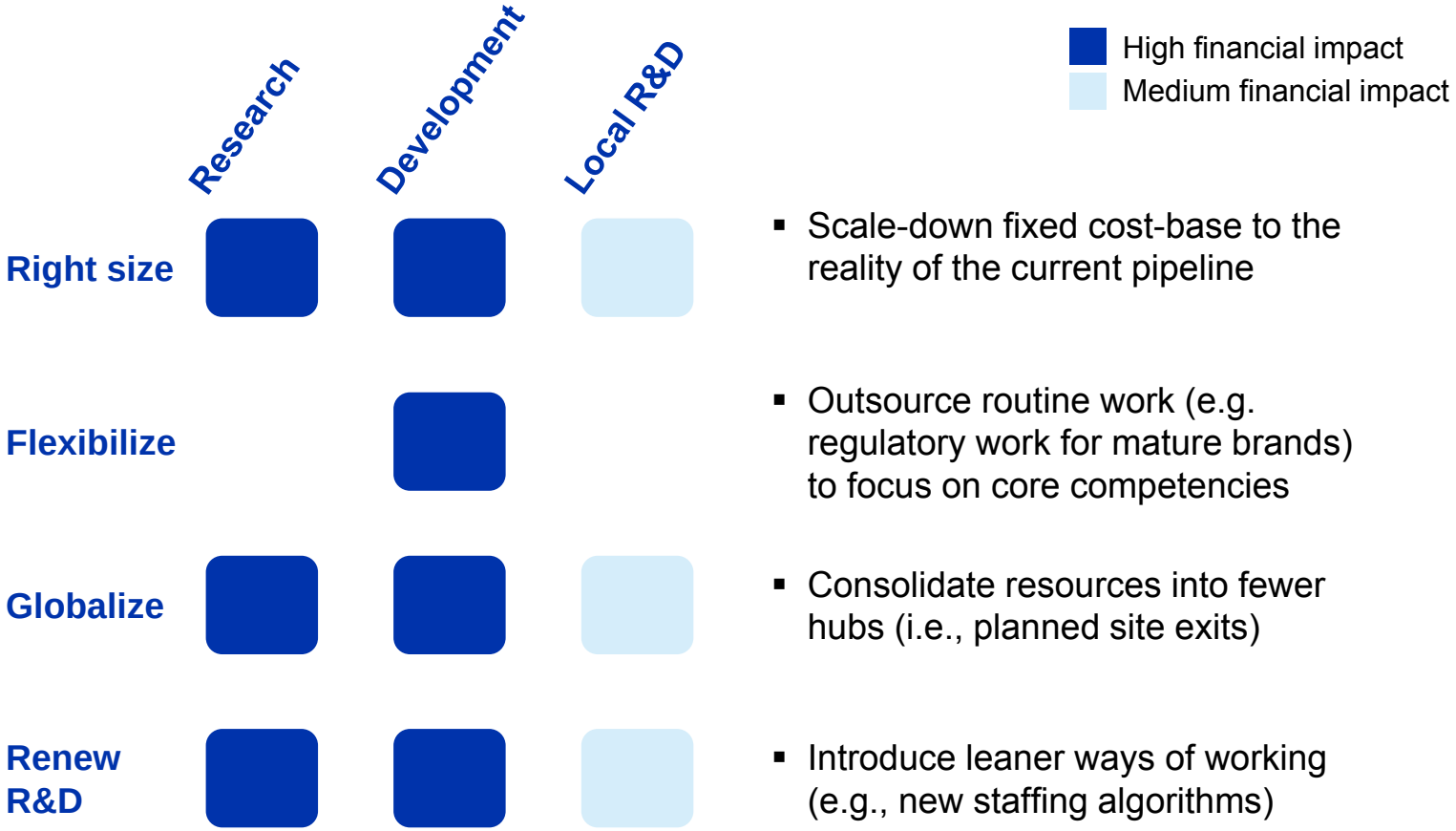
- Innovate
- Improve continuously
- Integrate partnerships
- Embed entrepreneurial biotech mindset

[1] Reduce fixed cost base to increase agility to scale up or down

Translating science into a differentiated biopharma portfolio through simple, agile and entrepreneurial model

All levers significantly help to reset the cost base

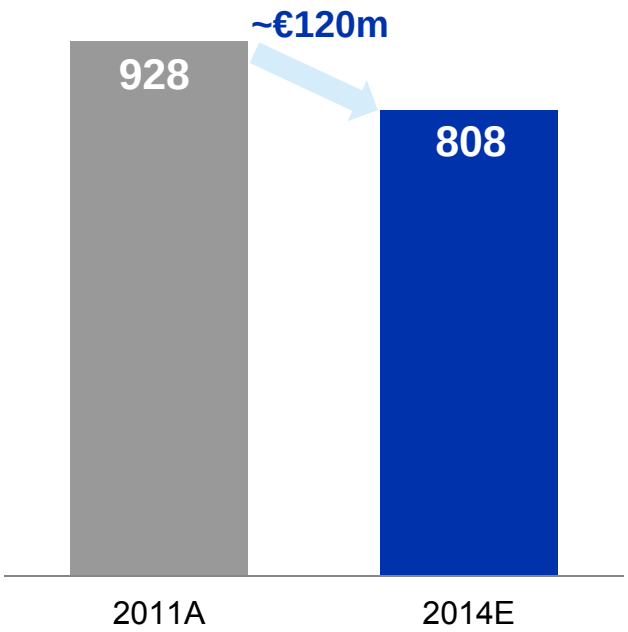
Financial impact



- Scale-down fixed cost-base to the reality of the current pipeline
- Outsource routine work (e.g. regulatory work for mature brands) to focus on core competencies
- Consolidate resources into fewer hubs (i.e., planned site exits)
- Introduce leaner ways of working (e.g., new staffing algorithms)

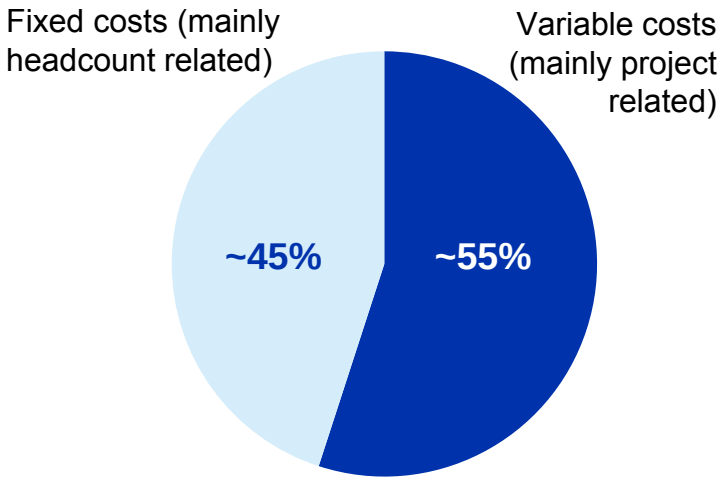
We plan to deliver increased output with substantially fewer R&D personnel

R&D Costs €m[1]



[1] Excludes local R&D, TechOps and other, totaling €297m in 2011, leading to a total annual R&D spend of €1.225m

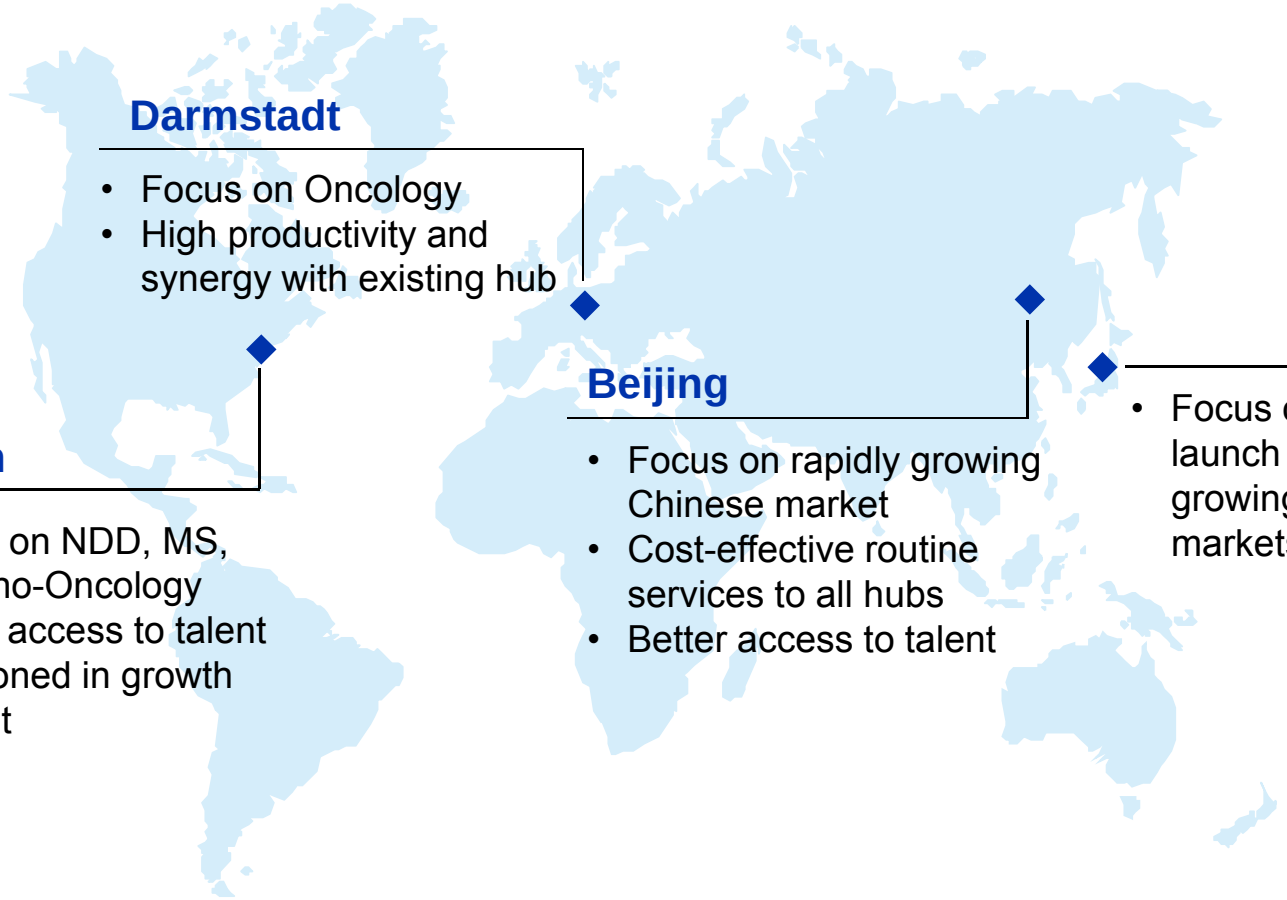
Distribution 2014E[2]



[2] Excluding local R&D, TechOps and other spend

Headcount decrease drives fixed cost base reduction

We plan to evolve our global geographic footprint …



Darmstadt

- Focus on Oncology
- High productivity and synergy with existing hub

Boston

- Focus on NDD, MS, Immuno-Oncology
- Better access to talent
- Positioned in growth market

Beijing

- Focus on rapidly growing Chinese market
- Cost-effective routine services to all hubs
- Better access to talent

Tokyo

- Focus on Japan with launch pad into other growing NE Asian markets

… and plan to globalize the medical & clinical activities conducted locally in countries

Old	New
▪ In-country headcount of over 800 across 60+ countries	▪ First phase of headcount rightsizing and consolidation to 20 major countries and hubs
▪ No consistent single point of accountability for Medical Affairs in all countries ▪ Medical Affairs reporting only to country heads leading to fragmented approach to support brands in countries ▪ All other functions (Pharmaco-vigilance, Regulatory, QA, Clinical Operations) also reporting only into the country organization	▪ Medical director in country reports into Global Medical Affairs and is closely aligned with Commercial Operations ▪ Pharmacovigilance, Regulatory, QA and Clinical Operations part of Development to manage risks better, drive compliance & functional excellence
▪ Unclear career development models	▪ Attractive career path for personnel to help retain and develop talent

New standard model with globalized development functions

We plan to collaborate with partners, while creating an agile and entrepreneurial organization

Innovate	▪ Focus on innovative opportunities with unmet needs ▪ Improve translational medicine capabilities ▪ Continue to build on the ability to successfully drive life cycle management and device opportunities
Improve continuously	▪ Drive operational improvement toward benchmark performance ▪ Strengthen and re-organize quality and compliance functions to address shifting landscape
Integrate partnerships	▪ Access innovative products ▪ Accelerate partnerships to tap into external capabilities
Embed entrepre-neurial mindset	▪ Empower project teams and simplify governance to stimulate innovation ▪ Strengthen R&D leadership team with fresh talent to drive change

New external talent will strengthen the team and help us deliver on our aspirations

> 50% functions across R&D have new leaders

Some key positions have been filled with talent from outside with rich experience

Jacques Mascaro from Elan is new Global Regulatory Head and has prior experience at Johnson&Johnson and Roche

W. Blair Okita from BioPCS Consulting is new Head of Quality and has prior experience at Genzyme and Merck & Co

Kathleen Ford from Millennium is new Global Clinical Operations Head and has prior experience at Alkermes

Dietmar Gross from Bayer Healthcare is new Head of Early Clinical Development and has prior experience at Berlex and Schering

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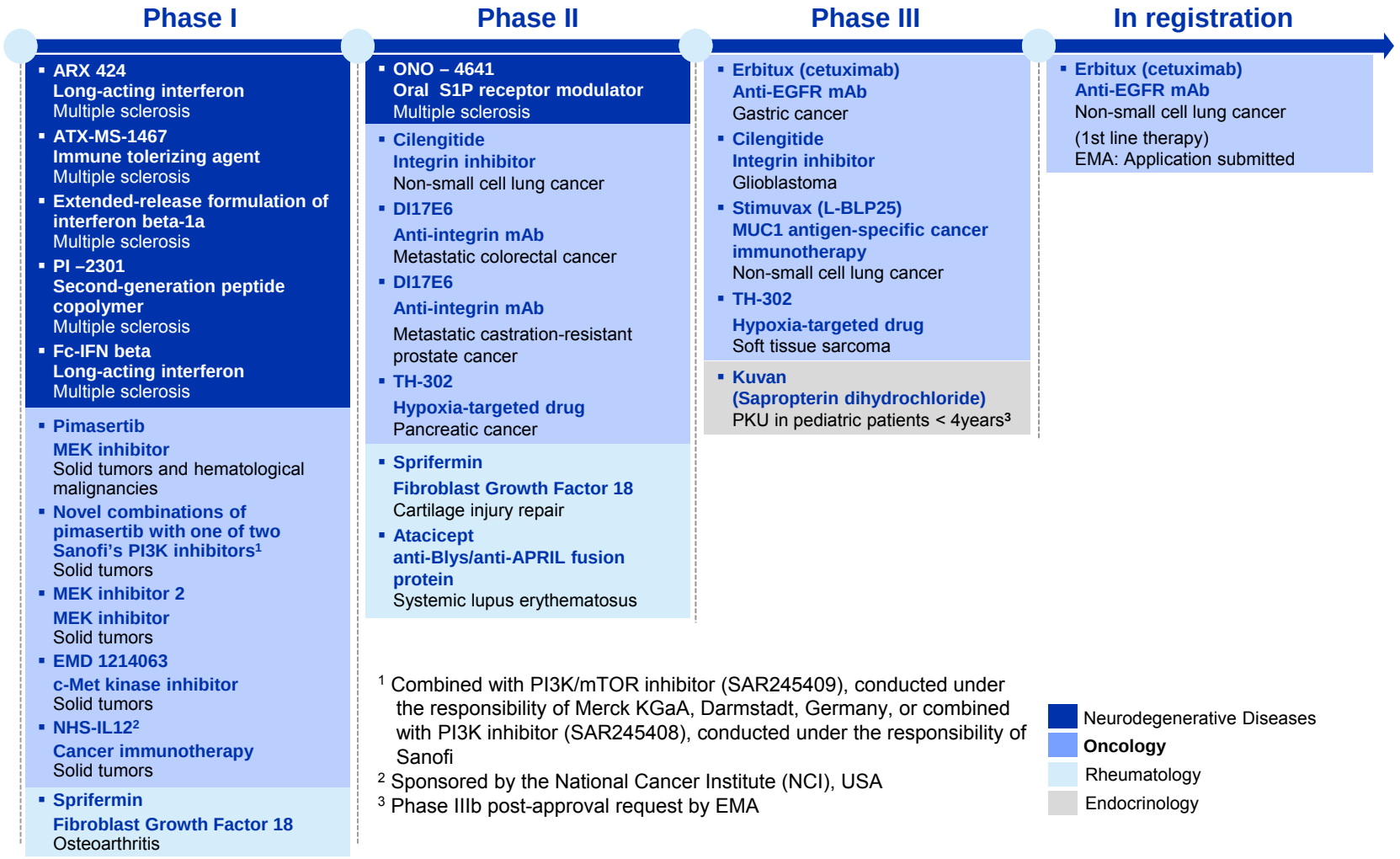
Majority of current projects are in the area of oncology



[1] Combined with PI3K/mTOR inhibitor (SAR245409), conducted under the responsibility of Merck KGaA, Darmstadt, Germany, or combined with PI3K inhibitor (SAR245408), conducted under the responsibility of Sanofi

[2] Sponsored by the National Cancer Institute (NCI), USA

[3] Phase IIIb post-approval request by EMA

Neurodegenerative Diseases
Oncology
Rheumatology
Endocrinology

As of May 15, 2012

Oncology immunotherapy: a four pronged strategy

Immuno Oncology Strategy

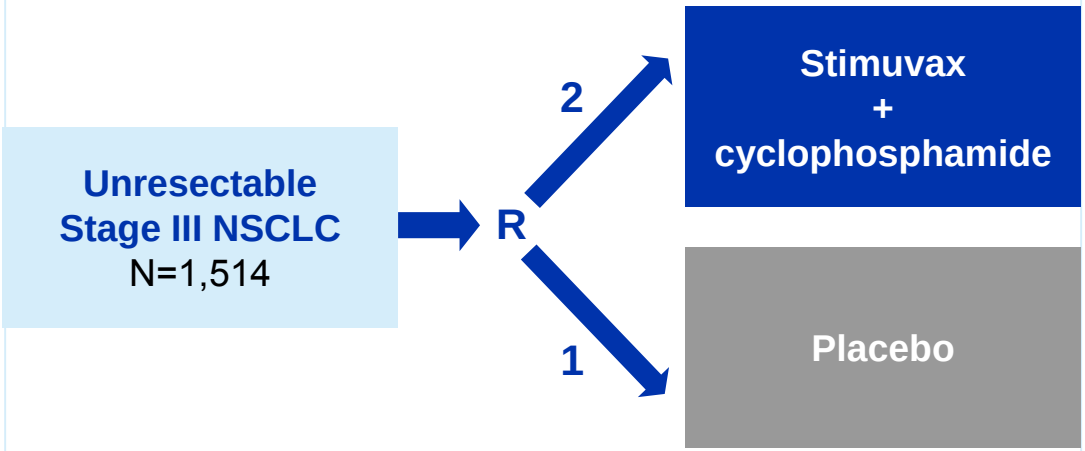
Therapeutic Cancer vaccines	Immuno-modulation	Immune environment	Cancer stem cells
Tumor Vaccines ▪ Stimuvax ▪ Nanovacc	**Blockade of Inhibitory Signals** ▪ Anti-PD-L1 **Activation of APCs and Expansion of T cells** ▪ NHS-IL12 ▪ Selectikine	**Inhibition of Cancer Inflammation** ▪ FERi **T regs and Metabolic Effects** ▪ TGFβRi ▪ GCN2 ▪ Combo with CTX	▪ Anti-CD47 ▪ Anti-Muc1

Treatment of Chronic Disease → **Curative Aim**

Phase III

Stimuvax in stage III NSCLC

Trial design



Facts

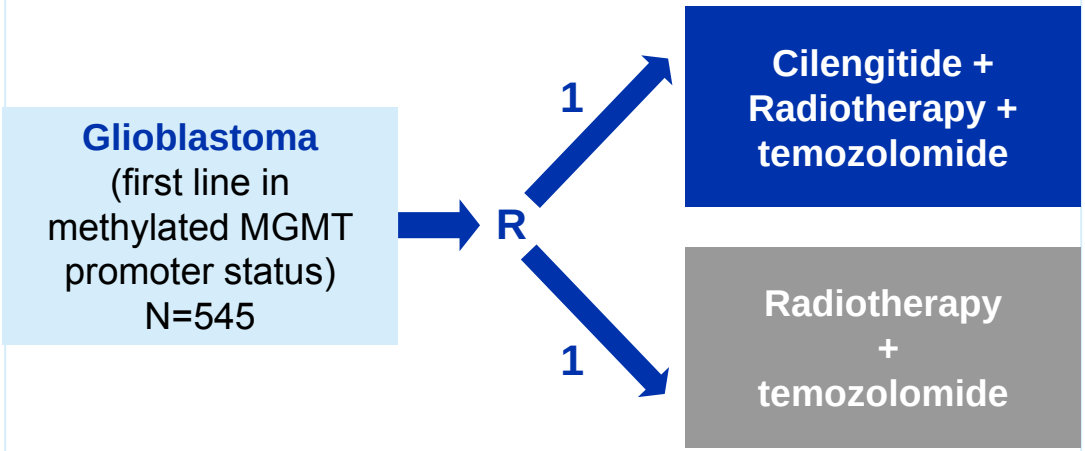
- **Name:** START
- **Design:** Randomized, double-blind, placebo controlled
- **Locations:** Europe, North America, Latin America, Asia, Australia
- **Primary analysis:** Overall Survival
- **Initiated:** Feb 2007
- **Enrollment:** Completed
- **Status:** Study continuing as planned following second interim analysis

Final analysis planned in H1 2013

Phase III

Cilengitide in glioblastoma

Trial design



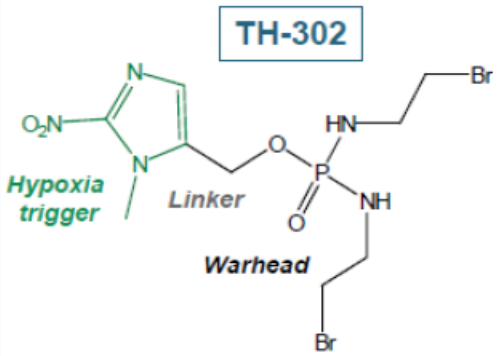
Facts

- **Name:** CENTRIC
- **Design:** Randomized
- **Locations:** US, Canada, Europe, Asia, Australia, Latin America
- **Primary analysis:** Overall Survival
- **Initiated:** Sept 2008
- **Enrollment:** Completed

Final analysis planned in H1 2013

TH-302 is a hypoxia activated prodrug

Molecule



THRESHOLD PHARMACEUTICALS

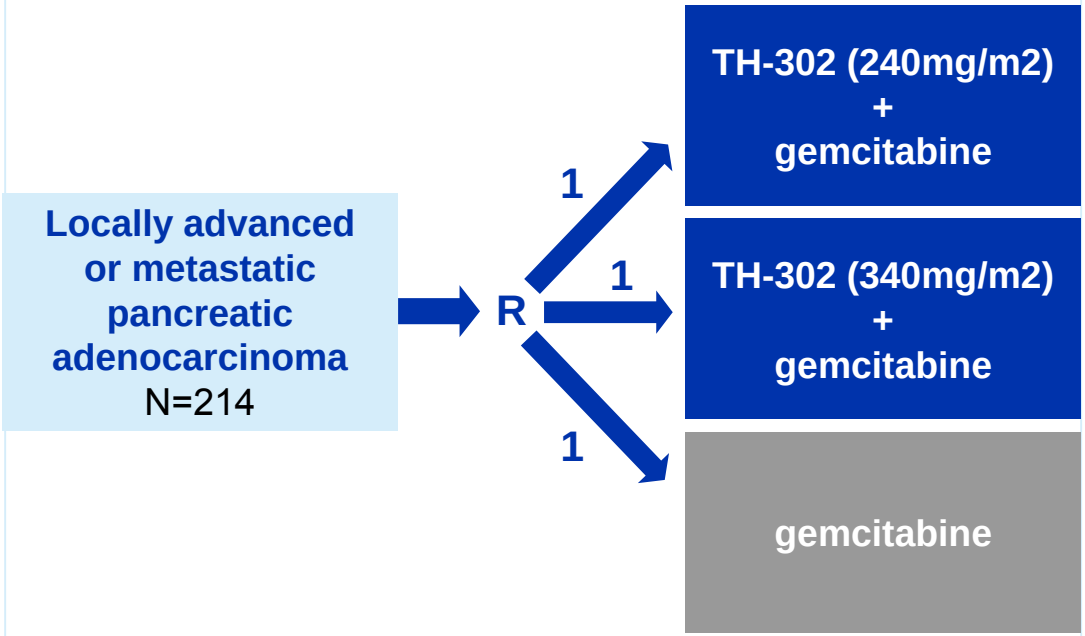
Facts

- Small molecule hypoxia activated prodrug (HAP)
- Covalently coupled Hypoxia-Trigger renders Warhead inactive under normal oxygen concentrations
- Under hypoxic conditions the Trigger is released and the drug becomes activated resulting in DNA crosslinking
- Phase I monotherapy studies in advanced hematologic malignancies; combination trials in various solid tumours (e.g., NSCLC, renal cell carcinoma, prostate cancer)
- Phase II combination trial on-going in pancreatic cancer (Study 404)
- Phase III combination trial on-going in soft tissue sarcoma (Study 406)
- Administration: 1 hour i.v. infusion
- Collaboration with Threshold Pharmaceuticals

Phase II

TH-302 in first-line pancreatic adenocarcinoma

Trial design



Facts

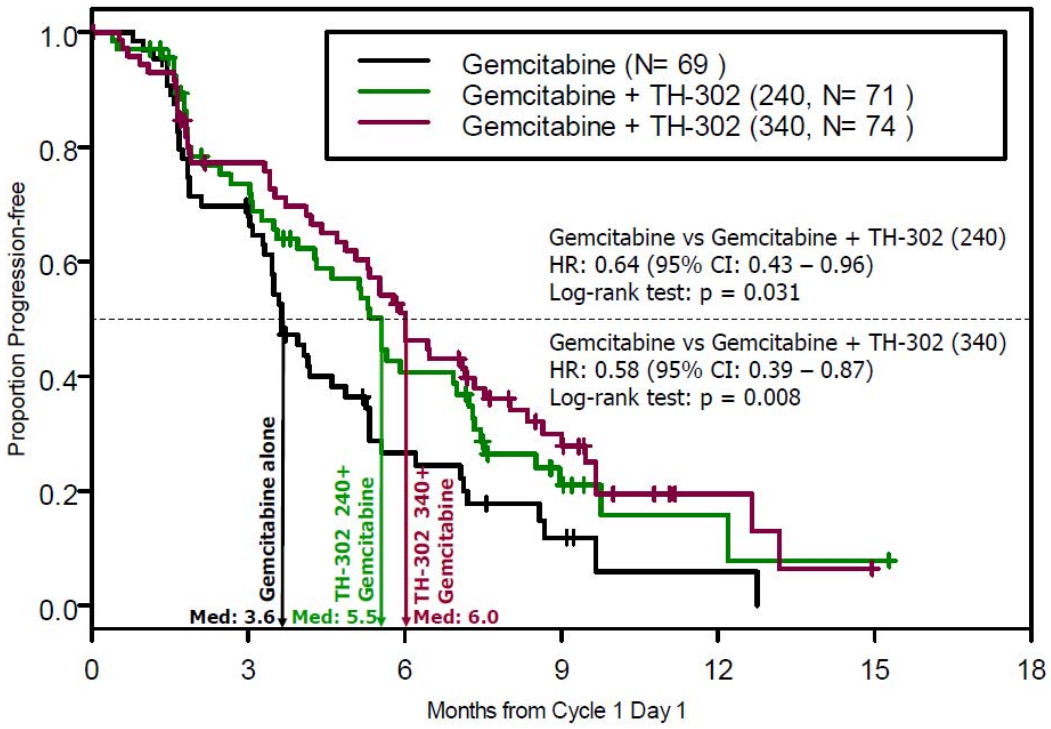
- **Name:** Study 404
- **Design:** Open label, randomized, crossover
- **Locations:** US
- **Primary analysis:** Progression Free Survival
- **Secondary endpoints:** RECIST Response, Overall Survival, CA 19-9 biomarker
- **Initiated:** June 2010
- **Enrollment:** Completed
- **Status:** Primary endpoint met

Final analysis planned for H2 2012

Phase II

Primary endpoint met: significant prolongation in progression free survival

Phase II data presented at AACR



Facts

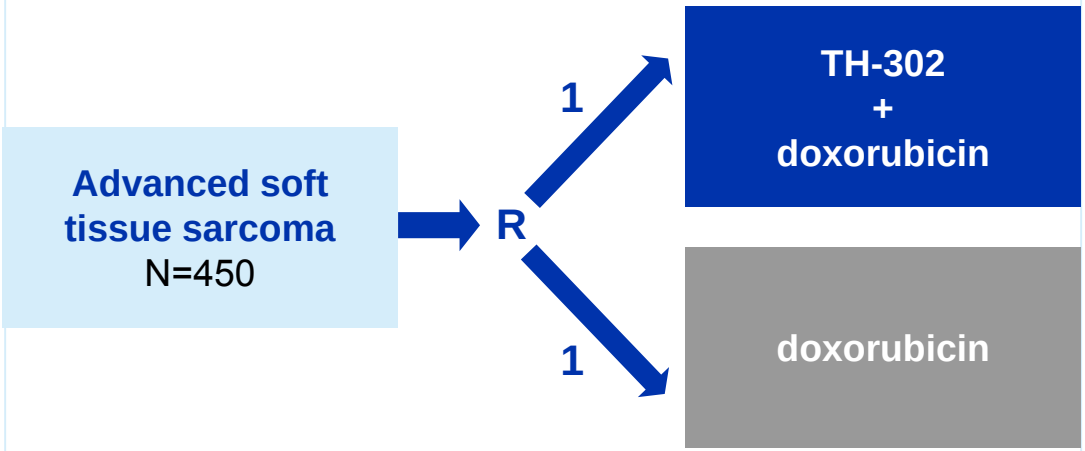
- Safety: Combination was well tolerated
- Skin and mucosal toxicities were TH-302 dose-dependent but not dose-limiting
  - Myelosuppression was TH-302 dose-dependent and dose-limiting but reduction in gemcitabine dose intensity was not associated with loss of efficacy
- Phase III study design under discussion

Borad et al., AACR Annual Meeting, April 2012

Phase III

TH-302 in first-line soft tissue sarcoma

Trial design



Facts

- **Name:** Study 406
- **Design:** Open label, randomized (FDA Special Protocol Assessment agreement)
- **Locations:** US, Europe
- **Primary analysis:** Overall Survival
- **Initiated:** Sept 2011
- **Enrollment:** Ongoing
- **Note:** Orphan drug designation in US and EU March 2012

Final analysis planned for 2015

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Conclusion

1 We will deliver net annual savings in R&D of €120m driven by a footprint change and substantial headcount reduction

2 We will transform into an agile and entrepreneurial organization that delivers differentiated products in areas of unmet need

3 We will implement a project-team centric approach and better leverage internal and external capabilities

4 We are well-positioned to benefit from our presence in oncology through our portfolio of 7 clinical stage molecules

Our aspirations to fuel future growth

Biopharmaceuticals R&D

- Become competitive and unlock value through continuous improvement
- Harness a biotech mindset
- Focus on disease areas where we bring unique advantages

> Our R&D aspiration over the longer-term is to deliver one new medicine or a significant LCM opportunity every year across core therapeutic areas