Biopharmaceuticals Investor & Analyst Day

Oncology - building on our established strengths

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Merck KGaA
Darmstadt · Germany

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Agenda

Oncology strategy

TH-302

Early-stage portfolio

Our oncology franchise is built on a core set of strategic principles

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Indications		Science-driven approach to deliver personalized therapeutics
Regions		Global oncology franchise with strong presence in emerging markets
Innovation		In-house discovery and development platforms in oncology and immuno-oncology
Technologies		Broad range of discovery technologies, including small molecules, antibodies and antibody-drug conjugates
Combinations		Combination approach leveraging both internal & external partners

Building the Erbitux brand

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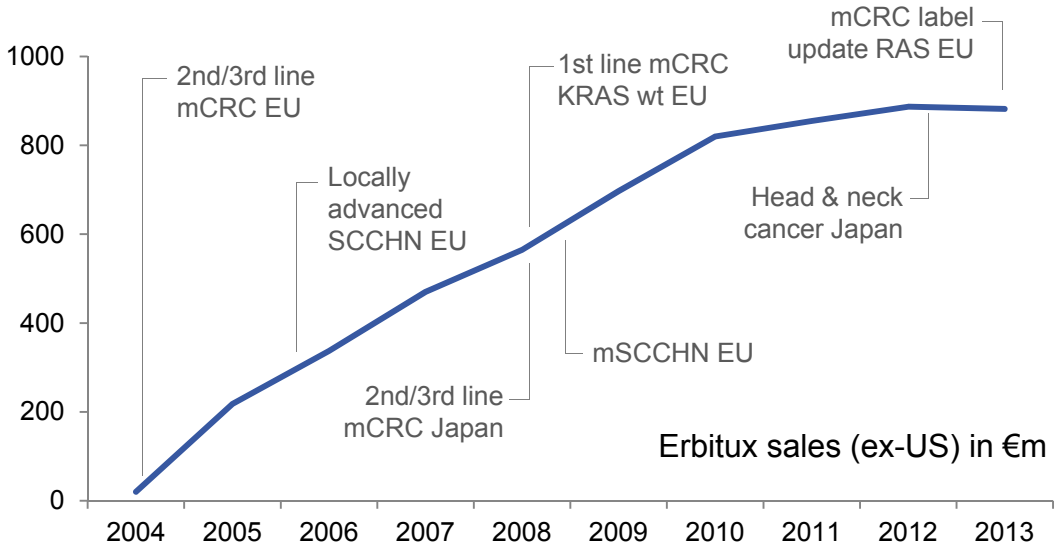
Strong in two solid-tumor indications



Global presence

Marketed by Biopharmaceuticals
Not covered by Biopharmaceuticals

ERBITUX
CETUXIMAB
See the difference

Over 500,000 patients treated with Erbitux since approval in 2004 worldwide

Pipeline progress over the last two years

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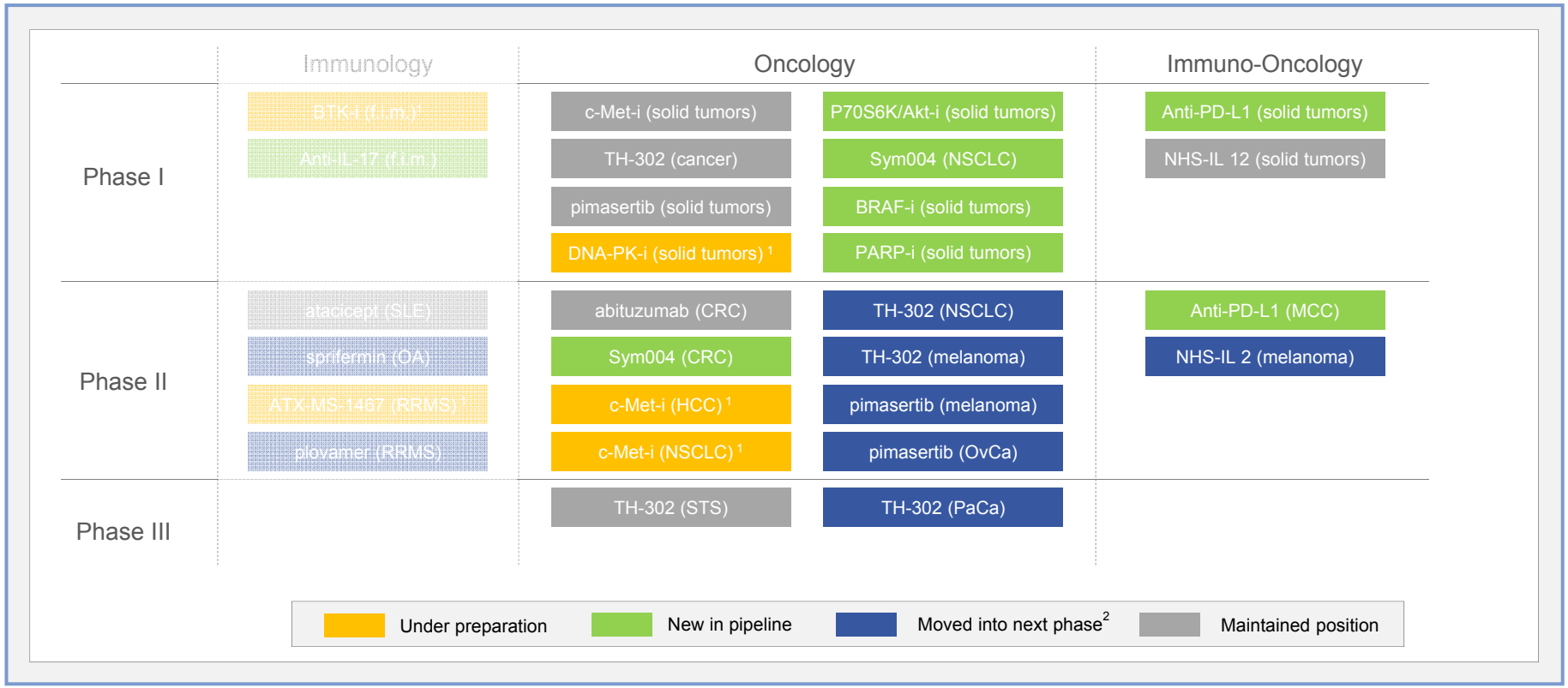

[1]under preparation for this phase; [2]since Capital Markets Day in May 2012; f.i.m.: first-in-man trial
As of September 2014

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Agenda

Oncology strategy

TH-302

Early-stage portfolio

The role of hypoxia in cancer

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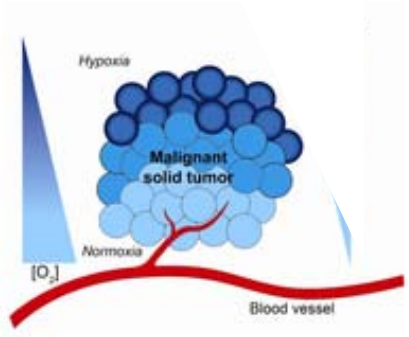
1. Hypoxia is a common feature of many solid tumors
2. Tumor hypoxia can result from rapid cell proliferation and an inadequate disordered vascular network
3. Sustained hypoxia can be associated with an aggressive tumor phenotype
4. Hypoxia is associated with resistance to chemotherapy and radiotherapy



Hypoxia is an attractive target for cancer therapy

Source: Vaupel P, Mayer A. Cancer Metastasis Rev 2007; 26:225-239; Vaupel P, Höckel M, Mayer A. Antioxid Redox Signal. 2007 Aug;9(8):1221-35. Duan JX, et al. J Med Chem. 2008 Apr 24;51(8):2412-20

TH-302: potential broad application in many tumor types

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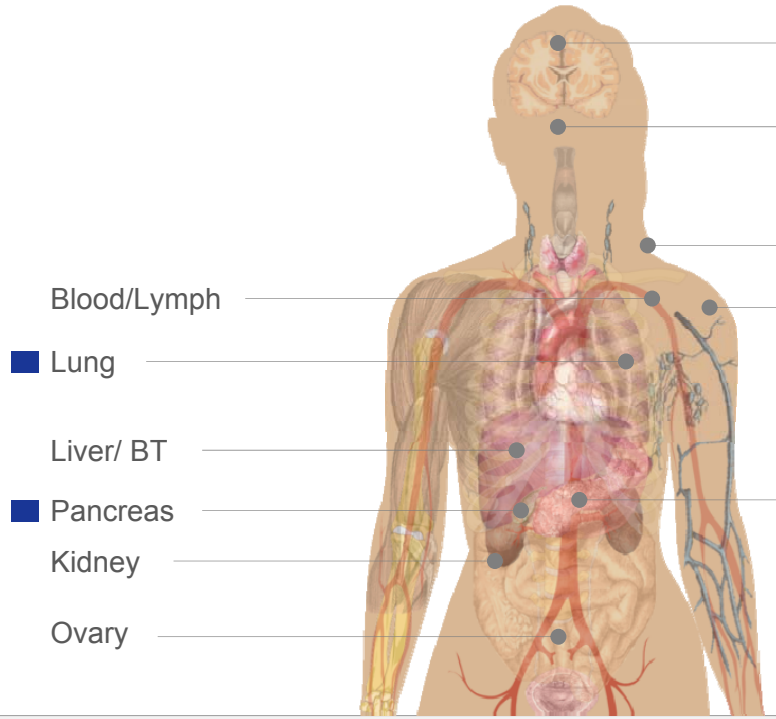

- TH-302 is an investigational hypoxia-activated prodrug designed to be activated under hypoxic (low oxygen) conditions
- TH-302 is essentially inactive under normal oxygen concentrations
- In areas of hypoxia, TH-302 becomes activated and converts to an alkylating cytotoxic agent resulting in DNA cross-linking
- This renders cancer cells unable to replicate their DNA and divide leading to apoptosis
- Potential application in multiple tumor types
- Less likely to produce broad systemic toxicity seen with untargeted comparable chemotherapies

Source: Vaupel P, Höckel M, Mayer A. Antioxid Redox Signal. 2007 Aug;9(8):1221-35. Duan JX, et al. J Med Chem. 2008 Apr 24;51(8):2412-20

Phase IIb resulted in a 2-month increase in PFS for patients with pancreatic cancer treated with TH-302

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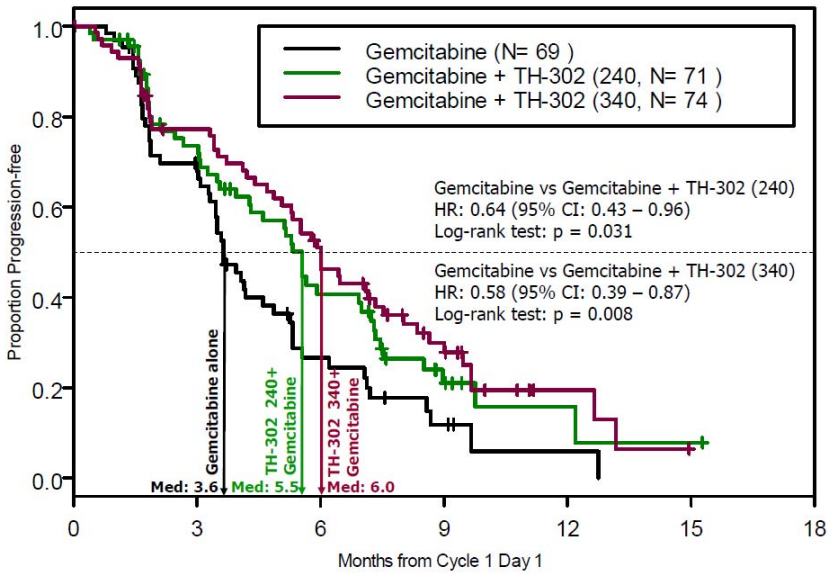
Phase IIb results in pancreatic cancer

Progression-free survival (primary endpoint)



- Randomized controlled trial that enrolled 214 previously untreated patients with locally advanced unresectable or metastatic pancreatic cancer
- Patients receiving gemcitabine alone whose disease progressed were permitted to be randomized to treatment with gemcitabine plus either the low or high dose of TH-302
- Trial was 80% powered to detect a 50% improvement in PFS with a p-value of 0.20

	Gemcitabine (N=69)	Gemcitabine + TH-302 (240, N=71)	Gemcitabine + TH-302 (340, N=74)
6-month survival (p-value, vs. gem)	57 %	69 % 0.123	73 % 0.037
12-month survival (p-value, vs. gem)	26 %	37 % 0.178	38 % 0.130

Source: Borad et al., AACR Annual Meeting, April 2012; PFS = progression-free surival
Note: no formal statistical power analysis for overall survival since confounded by crossover contribution

Dose-limiting hematological toxicities observed, skin and mucosal toxicities not dose limiting

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Phase II PaCa results (hematological adverse events)

	Gemcitabine (n = 69)	Gemcitabine + TH-302 (240mg) (n = 71)	Gemcitabine + TH-302 (340mg) (n = 74)
Platelets Grade 3/4	5/2 (11%)	11/16 (39%)	23/23 (63%)
ANC Grade 3/4	19/2 (31%)	31/8 (56%)	26/18 (60%)
Hemoglobin Grade 3/4	6/0 (9%)	15/2 (24%)	20/0 (27%)
Creatinine (N) Grade 3/4 (increase)	0/0 (0%)	0/0 (0%)	1/0 (1%)
Bilirubin (N) Grade 3/4 (increase)	3/1 (6%)	9/1 (13%)	5/1 (8%)
Mean cum. gemcitabine dose intensity end cycle 6	88%	81%	72%

- 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
- No increase in study discontinuations for adverse events

Source: Borad et al., AACR Annual Meeting, April 2012

TH-302: Phase III in pancreatic cancer recruiting well

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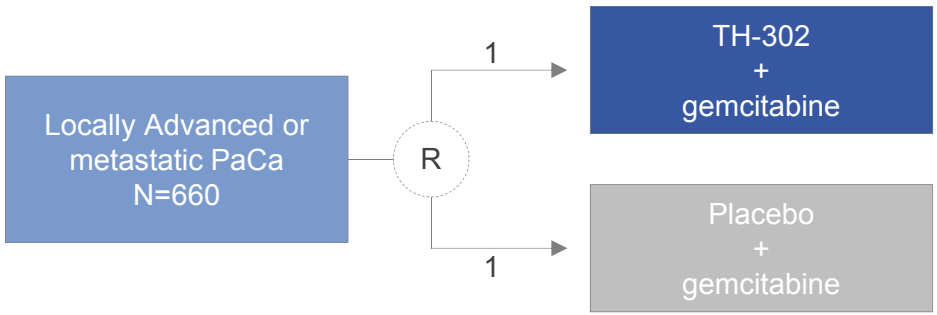
Phase III (MAESTRO) – Study design

TH-302 – Pancreatic Cancer

Double-blind, placebo-controlled, randomized, multicenter



- Primary endpoint: overall survival
- Secondary endpoints include: Progression-free survival, overall response rate, duration of response
- Predictive biomarkers: CAIX, ENO-2+
- Under FDA Special Protocol Assessment (SPA)agreement
- Locations: >120 sites including US, Europe, Latin America, Asia, Australia
- Initiated: Jan 2013
- Aim to complete enrolment early 2015
- Orphan drug designation in US and EU

Final analysis planned for 2016

Phase II results suggest an improvement in efficacy over standard of care in patients with STS

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Phase II results in soft tissue sarcoma (STS)

Endpoint		Value (N=89)
Progression-Free Survival (PFS)	mPFS	6.7 months
	3-month PF rate	83%
	6-month PF rate	63%
Overall Survival (OS)	mOS	21.5 months
	12-month survival rate	73%
	24-month survival rate	44%
RECIST Best Response	Overall response rate	36%
	Complete response	2%
	Partial response	34%
	Stable disease	48%
	Stable disease or better	84%
	Progressive disease	16%

- Phase 1/2, multicenter, single-arm dose escalation trial to determine the safety, efficacy and pharmacokinetics of TH-302 in combination with doxorubicin in patients with advanced STS
- Initiated in September 2008
- Enrolled 101 patients
- 91patients were included in the analyses
  - including 89 patients with at least one evaluable post-treatment tumor assessment
- Nausea and fatigue were the most commonly reported adverse events

Source: Chawla SP, et al., CTOS Annual Meeting, October 2011; PFS = progression-free surival; OS = overall survival

TH-302: Phase III in STS fully enrolled

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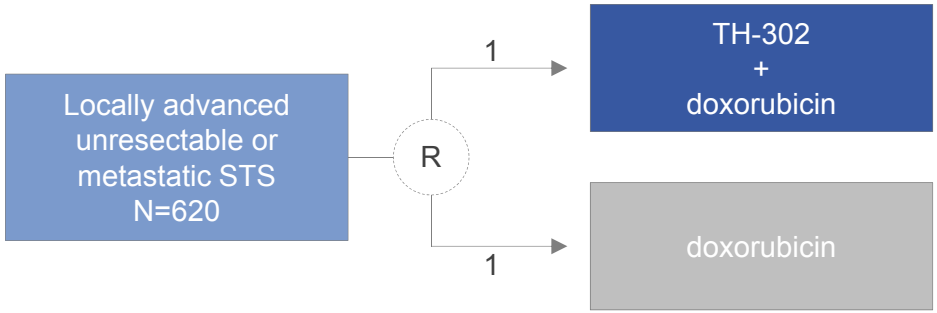
Phase III (TH-CR-406) – Study design

TH-302 – Soft Tissue Sarcoma

Open-label, randomized, multicenter



Patients on the treatment arm who are responding or who have stable disease and have acceptable toxicity may elect to continue on **maintenance therapy** with single-agent TH-302 until PD

- Primary endpoint: overall survival
- Secondary endpoints include: Progression-free survival, overall response rate, duration of response, quality of life
- Crossover from control arm is not permitted
- Under FDA Special Protocol Assessment (SPA) agreement
- Locations: >80 sites in 14 countries including US & Europe
- Orphan drug designation in US and EU

Interim analysis in Q3 2014, final analysis planned for 2015

PD = progressive disease

TH-302: Phase II in 2nd line NSCLC now underway

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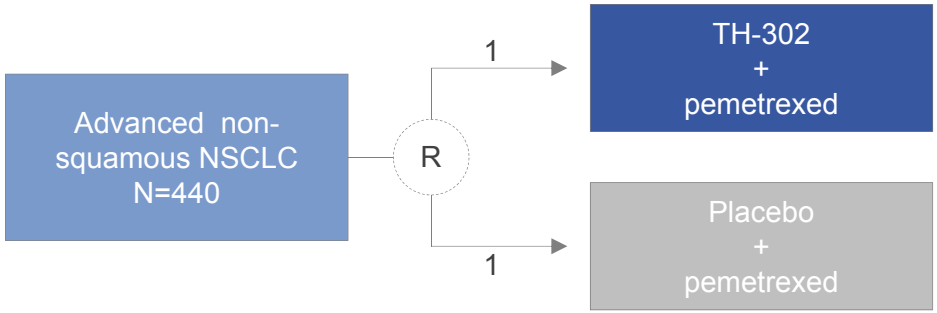
Phase II (TH-CR-415) – Study design

TH-302 – Non-small Cell Lung Cancer

Double-blind, placebo-controlled, randomized, multicenter



- Primary endpoint: overall survival
- Secondary endpoints include: Progression-free survival, overall response rate, disease control
- Locations: >75 sites including US, Europe

Data available in 2016

TH-302: potential broad therapeutic application

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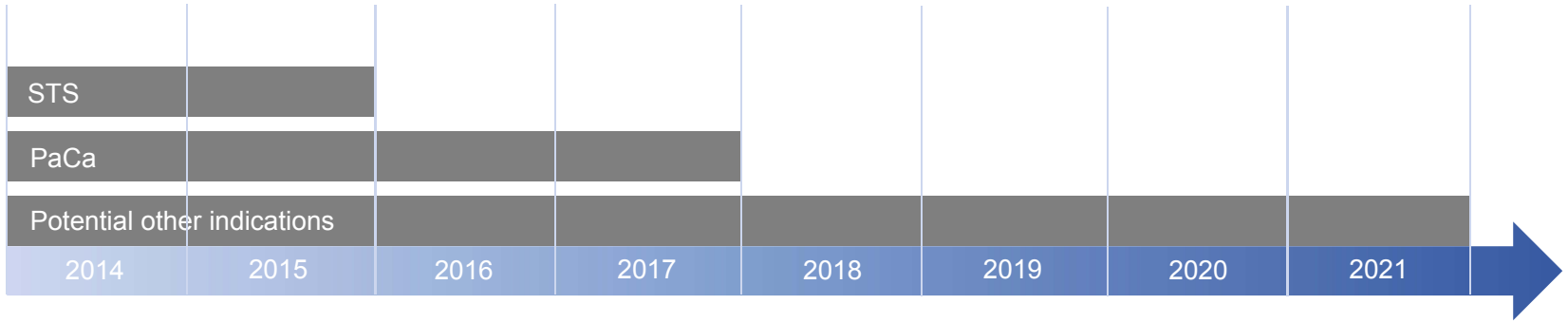
Development strategy

1. Combination with chemotherapy and/or targeted therapies (doublets/triplets)
2. Combination with anti-angiogenic agents
3. Combination with radiotherapy
4. Selected monotherapy indications based on the MoA of TH-302

Filing timelines



Summary

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Strategy

- Biopharmaceuticals Oncology starts in a position of strength with well-respected market leading team ex-US
- Two key products in full development (TH-302 and anti PD-L1) provide basis for growth in US and globally
- Early candidates in both Oncology and Immuno-Oncology TIPs provide basis for additional growth & partnerships

TH-302

- Activated in the hypoxic areas of tumors that are resistant to or not significantly impacted by other therapies
- Efficacy signals from early phase trials across multiple tumor types with no unexpected adverse events
- Pivotal trial readouts in 2015 & 2016

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Agenda

Oncology strategy

TH-302

Early-stage portfolio

In the Translational Innovation Platform Oncology we pursue a risk-balanced R&D approach

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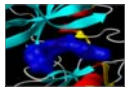
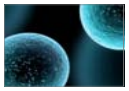
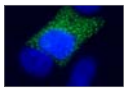
Innovation Cluster

Established

1.  Oncogenes
2.  Receptor Tyrosine Kinases & Antibody-Drug Conjugates

Exploratory

1.  Wnt & Developmental Pathways
2.  DNA Damage & Repair
3.  Metabolism & Autophagy

Pipeline progress over the last two years

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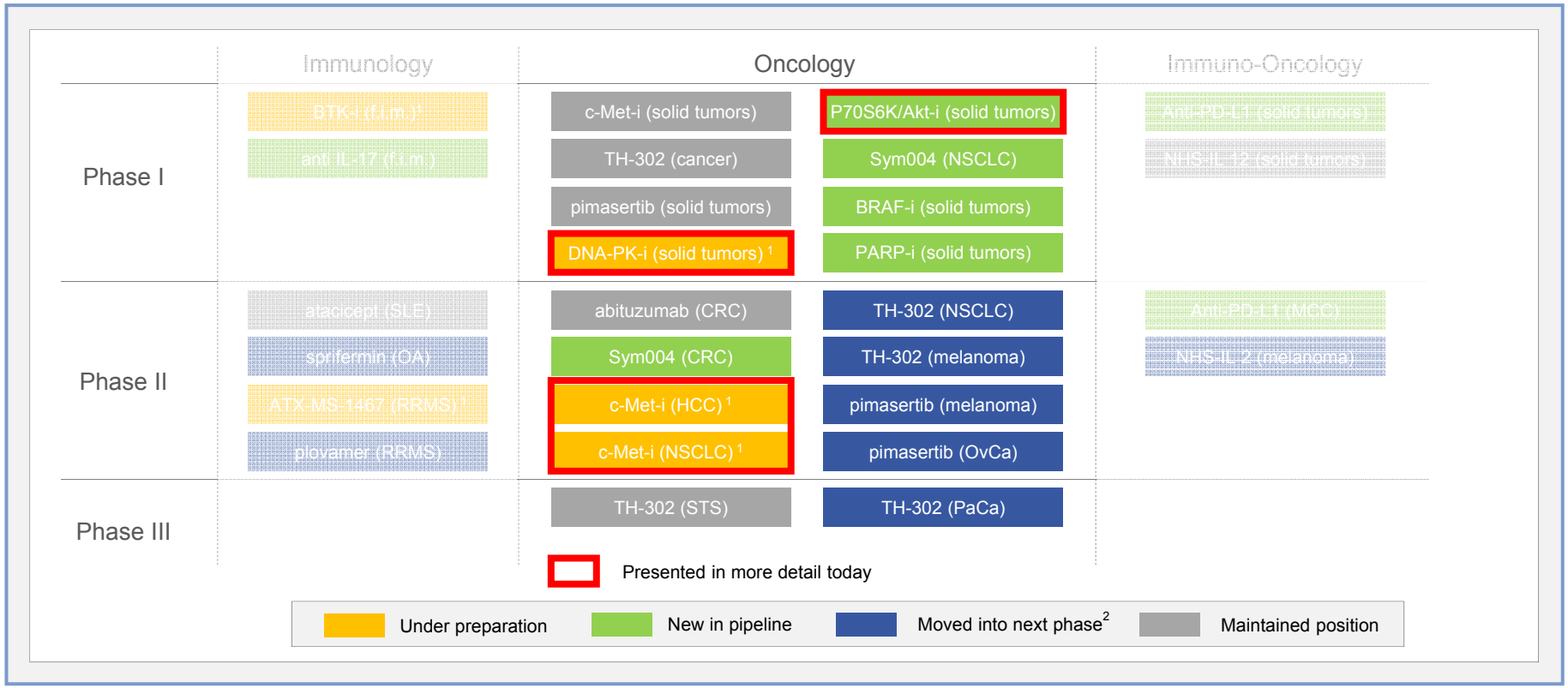

[1]under preparation for this phase; [2]since Capital Markets Day in May 2012; f.i.m.: first-in-man trial
As of September 2014

c-Met inhibitor: A highly potent and selective compound in biomarker-driven clinical development

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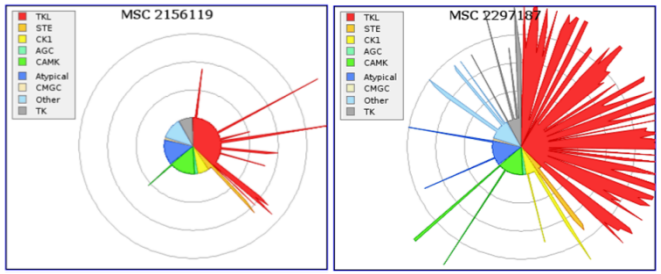
Mode of action

- MSC2156119J: highly potent and selective small molecule c-Met inhibitor with strong activity in preclinical models
- c-Met amplification as well as c-Met and HGF (hepatocyte growth factor) over-expression preclinically validated as predictive biomarkers

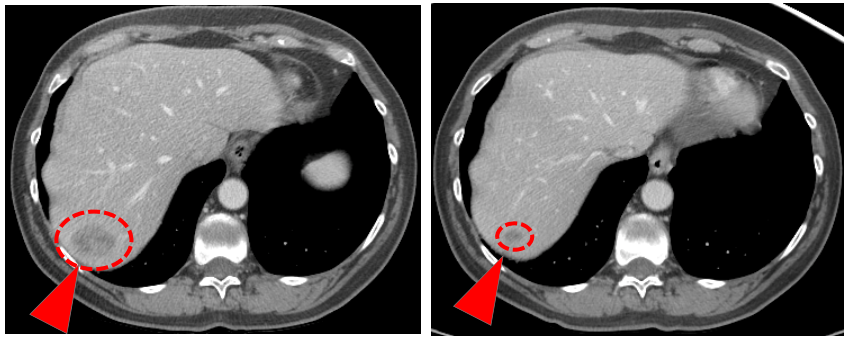
MSC2156119J | A competitor



Kinase inhibitor selectivity: >240 kinases tested at 10 µM, each bar represent a kinase and the length of the bar the degree of inhibition

Highlights

- 76% of patients had no drug-related AEs > G1
- Optimal biological dose (OBD) of 500 mg qd used in Phase II, based on quantitative assessment of target inhibition in on-treatment tumor biopsies, PK and PK/Pd modelling
- 2 confirmed PRs, 2 unconfirmed PRs, and 18 patients with SD ≥ 4 months in all-comers during dose-escalation



Confirmed partial response in a NSCLC patient with c-Met overexpression

AE = adverse event; PK = pharmacokinetics; Pd = pharmacodynamics; qd = once daily; PR = partial response; SD = stable disease; NSCLC = non-small cell lung cancer
Source: Falchook et al, ASCO 2014, J Clin Oncol 32:5s, 2014 (suppl; abstr 2521), Bladt et al., Clin. Cancer Res. 19(11), 2013

c-Met inhibitor: Asia-focused proof-of-concept studies in HCC and NSCLC

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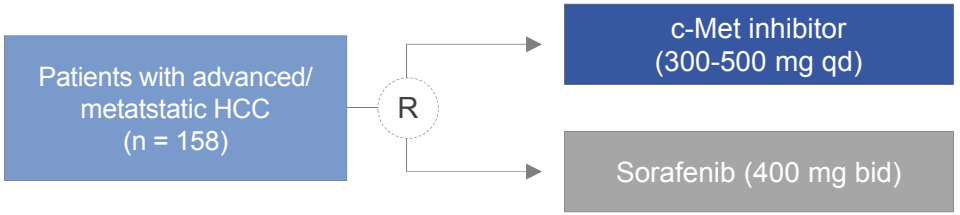
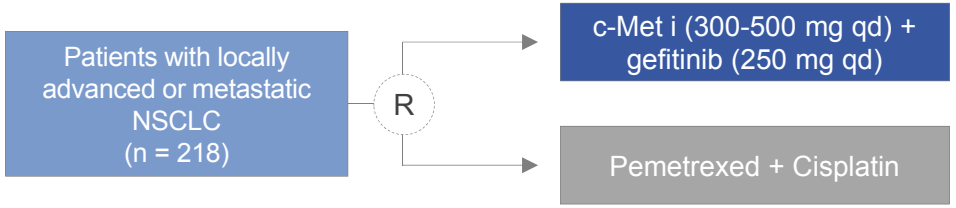
HCC - Phase I/II

- Open-label, randomized trial vs. sorafenib to determine the RP2D and evaluate efficacy (TTP)
- Enrolling biomarker-positive Asian subjects with advanced 1st line hepatocellular carcinoma
- Supportive single-arm trial in biomarker-positive 2nd line HCC in EU



NSCLC - Phase I/II

- Open-label, randomized trial vs. chemotherapy to determine the RP2D and evaluate efficacy (PFS)
- 2nd line treatment in biomarker-positive subjects with NSCLC with acquired resistance to 1st line gefitinib => test hypothesis of reversing EGFR inhibitor resistance



Currently recruiting, data available in 2016/2017

HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer; RP2D = Recommended phase II dose; TTP = time to progression; PFS = progression free survival; EGFR = epidermal growth factor receptor; qd = once daily; bid = twice daily

MSC2363318A, a dual p70S6K/AKT inhibitor for a key oncogenic pathway

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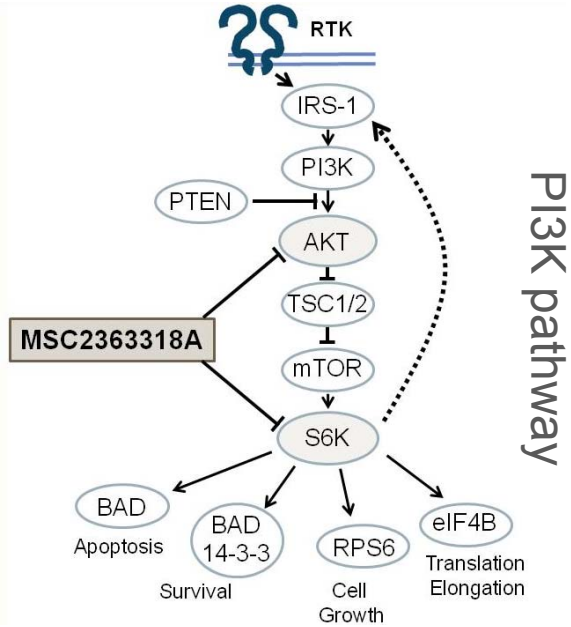

Mode of action

- Aberrant activation of the PI3K pathway in >30% of all tumors, e.g. by PTEN loss of function or PIK3CA mutations
- Single-node pathway inhibitors with limited activity, potentially due to induction of a compensatory feedback loop
- MSC2363318A: orally available, brain penetrant, small molecule inhibitor of p70S6K and AKT providing sustained pathway inhibition including neutralization of the feedback loop

Highlights

- Biomarker-driven Phase I: only including patients with diagnosed pathway mutations and tumor types with known high prevalence of them
- First patient treated in Dec. 2013, 5 of first 6 patients with SD
- Options for Phase II single-agent development in selected tumors (e.g. brain cancers and metastasis, based on good brain penetration) and for combinations under evaluation

Phase I currently recruiting, data available in 2016

RTK = receptor tyrosine kinase; SD = stable disease
Source: Liu et al., Nat. Rev. Drug Discov. 8(8), 2009; Rodon et al., Nat. Rev. Clin. Onc. 10(3), 2013; Huck et al., Mol Cancer Ther 12(11 Suppl):A162, 2013

Potential as monotherapy and in combination with SoC or novel agents, based on translational research

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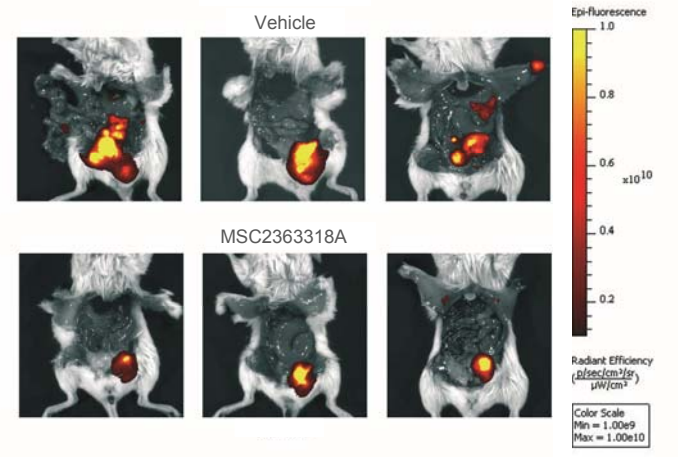
p70S6K/AKT inhibitor: monotherapy

- Anti-tumor activity shown in models with PI3K pathway genomic alterations from multiple indications including Her2+ and triple negative breast cancer, glioblastoma, ovarian cancer, endometrial cancer, and pancreatic cancer

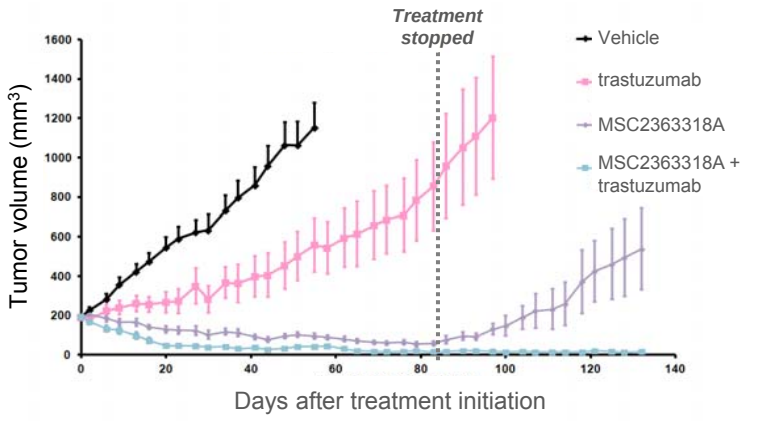
Ovarian cancer model



p70S6K/AKT inhibitor: combination

- Complete response in combination with trastuzumab in a patient-derived, lapatinib-resistent breast cancer model

Patient-derived Her2+ breast cancer model



SoC = standard of care

DNA-PK inhibitor: potentially enhancing the activity of DNA-damaging anti-cancer therapeutics

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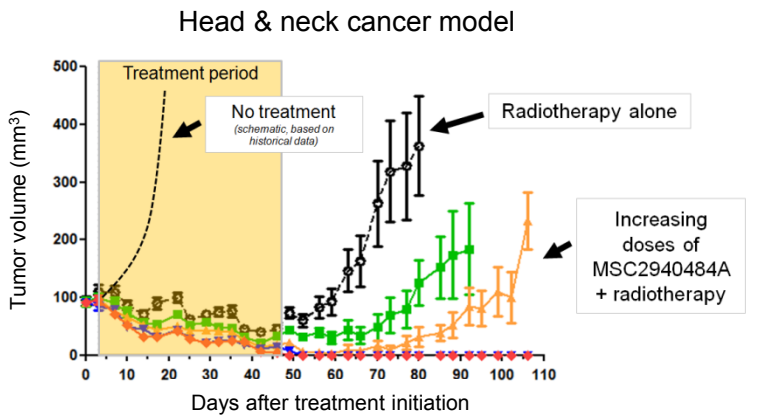
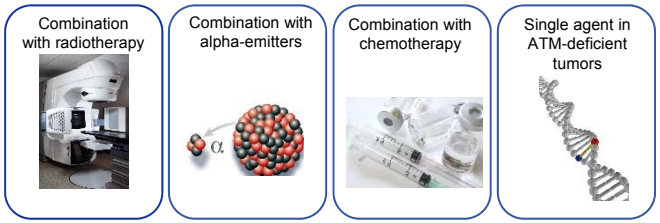
Mode of action

- Many anti-cancer therapeutics cause DNA double strand breaks (DSB), leading to cancer cell death if left unrepaired
- DNA-PK is a key enzyme in the most important DSB repair pathway
- MSC2940484A: orally available, selective and potent DNA-PK inhibitor potentially enhancing the efficacy of DNA damaging agents, such as radiotherapy and many chemotherapies

Highlights

- 100% cure rate in a head & neck cancer model in combination with radiotherapy in a clinically relevant setting (5x2 Gy/week for 6 weeks)
- Multi-track development strategy with single-agent potential in a biomarker-defined patient population
- >50% of cancer patients receive radiotherapy, providing development opportunities in multiple indications





Phase I to start in Q4/2014

DSB = double strand breaks; Gy = Gray; ATM = ataxia telangiectasia mutated

Sym004: building on our deep knowledge in the EGFR area

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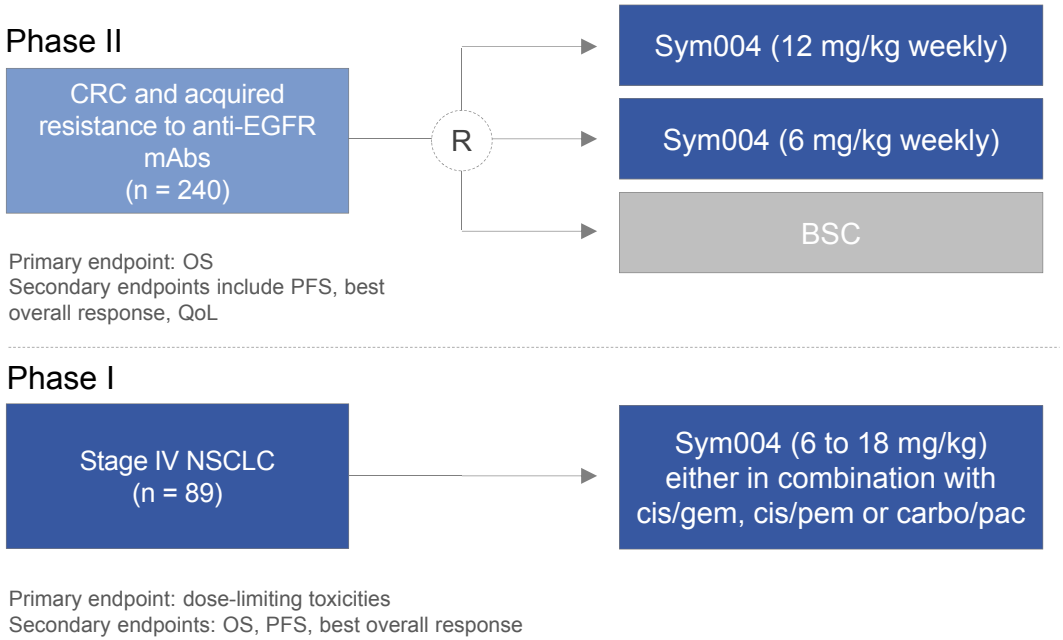
Mode of action

- Monoclonal antibody mixture targeting two different, non-overlapping EGFR epitopes
- Both antibodies bind EGFR with high affinity but have only limited preclinical activity individually
- Synergistic activity has been demonstrated by the Sym004 mixture both in vitro and in vivo
- Proposed cross-linking of EGFR that leads to internalization and degradation
- Formulated as one drug product



Currently recruiting, data available in 2016

EGFR = epidermal growth factor receptor; CRC = colorectal cancer; BSC = best supportive care; OS = overall survival; PFS = progression-free survival; QoL = quality of life; NSCLC = non-small cell lung cancer; cis/gem = cisplatin/gemcitabine; cis/pem = cisplatin/pemetrexed; carbo/pac = carboplatin/paclitaxel

Pimasertib (MEK inhibitor): employing a scientifcally-rationalized development

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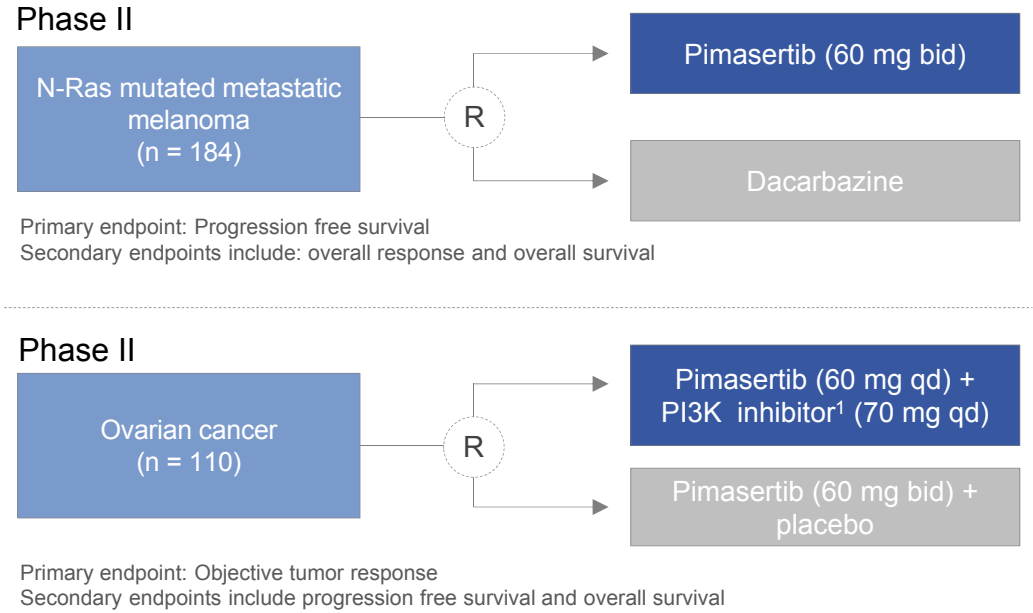
Clinical program

- Phase II: Open-label trial vs. standard of care in patients with previously untreated cutaneous melanoma harboring N-Ras mutations
- Phase II: Double-blind trial investigating a novel-novel combination of MEK and PI3K[1] in patients with previously treated unresectable low-grade serous ovarian cancer
- Phase I: Open-label trial investigating a novel-novel combination of MEK and hDM2[2] in patients with solid tumors to determine the recommended Phase II dose and assess the anti-tumor activities



bid = twice daily; qd = once daily
[1]SAR245409/Sanofi; [2]SAR405838/Sanofi

Strategic alliances for the development of next-generation antibody-drug conjugates (ADC)

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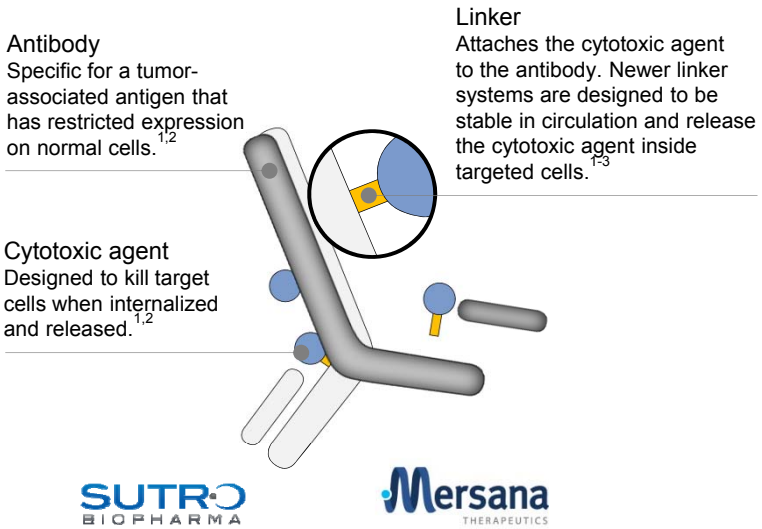
Mode of action

- Antibody chemically linked to a cytotoxic drug, whereby the antibody specifically targets tumor antigens for selective delivery of the cytotoxic drug and subsequent cancer cell elimination
- Critical success factors:
  - Antibody against a tumor-specific and internalizing antigen
  - Stable linker to prevent systemic release of the cytotoxic agent
  - Highly active cytotoxic agent
  - Drug-antibody ratio (DAR) that has to be optimized case by case

Highlights

- Partnerships with Mersana Therapeutics and Sutro Biopharma to access improved next-generation technologies
- Collaborations with academic partners for antibodies against tumor-specific targets to complement the internal portfolio

Elements of an Antibody-Drug Conjugate (ADC)



References: [1]Cater PJ et al. Cancer J. 2008;14(3):154-169. [2]Senter PD. Curr Opin Chem Biol. 2009;13(3):235-244. [3]Polson AG et al. Cancer Res. 2009;69(6):2358-2364.

Summary

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- Risk-balanced pipeline with R&D projects in established and exploratory Innovation Clusters
- Highly selective molecules for a biomarker-driven, personalized medicine approach
- Promising early-stage assets
- Intensified partnering efforts to complement the pipeline and to access innovative technologies

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