MERCK: EVOLVING APPROACHES FOR BIOMARKERS RESEARCH IN DRUG DEVELOPMENT

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Merck is the oldest pharmaceutical and chemical company in the world founded 1668 in Darmstadt, Germany.

Merck KGaA, Darmstadt is a publicly listed company in the DAX at the Frankfurt Stock exchange. The Merck family holds 70% of the shares.

We operate under EMD Serono (or EMD Millipore-Sigma) in North America.

EMD, stands for Emmanuel Merck, Darmstadt, reflecting these roots in Germany.
HEALTHCARE, LIFE SCIENCE & PERFORMANCE MATERIALS

1668 founded
66 countries
50,000 employees
€1.7 bn invested in R&D in 2015
€12.8 bn sales in 2015
Guiding our core research activities is our Translational Innovation Platforms (TIPs). As the cornerstone of our discovery efforts, the TIPs are focused on advancing our science through to first-in-man across our therapeutic areas. An Independent Advisory Board reviews the defined strategies for respective platforms and projects until proof-of-confidence.
Oncology
Targeted Therapies

Our transformative Oncology pipeline of highly selective new molecular entities focuses on targeted therapies in our five Innovation Clusters:

- Oncogenic signaling
- Antibody-drug conjugates
- DNA damage and repair
- Tumor metabolism
- Tumor plasticity

We develop biomarkers and companion diagnostics to guide optimal dosing, for identification of patients who are most likely to benefit from a specific therapy and to increase the benefit/risk ratio in our clinical trials. Translational research is embedded in the whole drug development process to deliver truly differentiated drugs that significantly improve patient’s lives.

We constantly evaluate new therapeutic treatment options by combining our drugs with chemo- / radiotherapy, other targeted therapies or immunotherapies (e.g. checkpoint inhibitors).
### Merck pipeline Oncology

#### Phase I
- tepotinib (c-Met kinase inhibitor)
  - Solid tumors
- M2698 (p70S6K & Akt inhibitor)
  - Solid tumors
- M3814 (DNA-PK inhibitor)
  - Solid tumors
- Beigene-283 (BRAF inhibitor)
  - Solid tumors
- M7583 (BTK inhibitor)
  - Hematological Malignancies

#### Phase II
- tepotinib (c-Met kinase inhibitor)
  - Non-small cell lung cancer
- M2951 (BTK inhibitor)
  - Hematological Malignancies
  - Systemic lupus erythematosus
- sprifermin
  - Osteoarthritis
- atacicept
  - anti-Blys/anti-APRIL fusion protein
  - Systemic lupus erythematosus
- M2951
  - BTK inhibitor
  - Rheumatoid Arthritis

#### Phase III
- avelumab - anti-PD-L1 mAb
  - Non-small cell lung cancer 1L\(^1\)
- avelumab - anti-PD-L1 mAb
  - Non-small cell lung cancer 2L\(^2\)
- avelumab - anti-PD-L1 mAb
  - Gastric cancer 1L\(^3\)
- avelumab - anti-PD-L1 mAb
  - Gastric cancer 3L\(^3\)
- avelumab - anti-PD-L1 mAb
  - Bladder cancer 1L\(^4\)
- avelumab - anti-PD-L1 mAb
  - Ovarian cancer platinum resistant/refractory
- avelumab - anti-PD-L1 mAb
  - Ovarian cancer 1L\(^5\)
- avelumab - anti-PD-L1 mAb
  - Renal cell cancer 1L\(^3\)

#### Registration
- cladirine tablets
  - Lymphocyte targeting agent
- avelumab
  - Anti-PD-L1 mAb
  - Melanoma carcinoid

### Company presentation

**November 7th, 2016**

- First Line treatment
- Second Line treatment
- Third Line treatment
- European Medicines Agency accepted Merck’s Marketing Authorization Application in October 2016

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.
**Selected assets**

**DNA-PK inhibitor**

- M3814 is a selective and potent inhibitor of DNA-PK, a kinase mediating DNA double strand break repair\(^1\)
- Preclinical PoC showing complete responses and/or increased PFS in combination with radiotherapy in several xenograft models (SCCHN, NSCLC, CRC, PaCa) and strong pre-clinical combination data with SoC chemotherapies
- Two Phase Ia trials ongoing: FIM (monotherapy): 5\(^{th}\) dose level completed, MTD not yet reached; RT combination: recruitment ongoing

**Tepotinib**

- Highly selective small molecule c-Met inhibitor
- Active in ligand-dependent and ligand-independent tumor models
- Biomarker-driven approach for patient selection
- Preliminary data show encouraging signs of anti-tumor activity in c-Met positive patients in NSCLC and HCC\(^2,3\)
- Phase II trials in progress in NSCLC and HCC

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Analysis of Phase I data for RT combination expected in H2 2017

Analysis of Phase II data for HCC and NSCLC expected in H1 2018

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Note: timelines are event-driven and may change

\(^1\)Graphics only illustrative; Acronyms: SCCHN = Squamous Cell Carcinoma of the Head and Neck, NSCLC = Non-small Cell Lung Cancer, CRC = Colorectal Cancer, PaCa = Pancreatic Cancer, HCC = Hepatocellular Cancer, PFS = Progression-free Survival, SoC = Standard of Care, FIM = First-in-Man, RT = radiotherapy, CT = chemotherapy, MTD = maximum tolerated dose; \(^2\)Qin, ECC 2015; \(^3\)Kim et al, IASLC-WCLC 2015

Source: MERCK – Q3 2016 ROADSHOW
Personalized Medicine towards Precision Medicine

Patient stratification based on simple drug → target interaction and single biomarker, e.g. targeted therapies in oncology

Linear R&D approach

- Biomarker proposal based on modulation of target by drug candidate
- Translation of biomarker into assay for early clinical trials
- Validation of biomarker hypothesis in early clinical trials and stratification of patients in pivotal trials
- Transfer, validation, and regulatory approval of companion diagnostics by (internal/external) partner
- Securing access to drug and cDX in all markets

Source: Merck internal analysis
Biomarkers are biological characteristics used in the diagnosis, prognosis and treatment of cancer in order to optimally tailor treatment to the patient. Biomarkers from the RAS gene family can be used to determine whether a patient is likely to benefit from treatment with Erbitux®.
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Source: Merck internal analysis
Example: Merck Partnership on cDx

Collaboration with Sysmex Inostics (HQ Kobe, Japan) on a Blood-Based RAS Biomarker Test

- Development and commercialization agreement on blood-based RAS biomarker mutation status test for metastatic colorectal cancer (mCRC)
- This collaboration reflects Merck’s commitment to leveraging the company’s expertise in precision medicine and predictive biomarkers
Example: Merck Partnership on cDx

Strategic Collaboration with Biocartis to collaborate on new liquid biopsy technology for RAS biomarker testing

- First pharma company to collaborate with multiple diagnostic providers to support RAS biomarker testing
- Collaboration will allow Merck to provide complementary molecular testing solutions to various laboratory segments
- New diagnostic test will be fast, minimally invasive, easy-to-perform and support timely decision making
Liquid biopsy RAS biomarker test based upon AmoyDx’s real-time PCR technology, Adx-SuperARMS®, will be made available in China in 2017.

- **Merck is the first pharmaceutical company** to collaborate with multiple diagnostic providers to support liquid biopsy RAS biomarker testing worldwide.
## Merck pipeline Immuno-Oncology

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  - Fibroblast growth factor 18
  - Osteoarthritis
- atacicept
  - anti-Blys/anti-APRIL fusion protein
  - Systemic lupus erythematosus
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  - Rheumatoid Arthritis

### Phase III

- avelumab
  - anti-PD-L1 mAb
  - Solid tumors
- avelumab
  - anti-PD-L1 mAb
  - Hematological Malignancies
  - M9241
- MSB 11022
  - proposed biosimilar of adalimumab
  - Chronic Plaque Psoriasis

### Registration

- cladribine tablets
  - lymphocyte targeting agent
  - Relapsing-remitting multiple sclerosis
- avelumab
  - anti-PD-L1 mAb
  - Merkel cell carcinoma

### Neurodegenerative Diseases
- Oncology
- Immunology
- Immuno-Oncology
- Biosimilars

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**Company presentation**

1 First Line treatment
2 Second Line treatment
3 Third Line treatment
4 European Medicines Agency accepted Merck’s Marketing Authorization Application in October 2016

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.
Immuno-oncology is a top priority for Merck and Pfizer. The global strategic alliance between Merck and Pfizer enables the companies to benefit from each other’s strengths and capabilities and further explore the therapeutic potential of avelumab*, an investigational anti-PD-L1 antibody initially discovered and developed by Merck. The immuno-oncology alliance will jointly develop and commercialize avelumab and advance Pfizer’s PD-1 antibody.

The alliance is focused on developing high-priority international clinical programs to investigate avelumab, as a monotherapy, as well as in combination regimens, and is striving to find new ways to treat cancer.

*Avelumab is the proposed nonproprietary name for the anti-PD-L1 monoclonal antibody (MSB0010718C). Avelumab is under clinical investigation and has not been proven to be safe and effective. There is no guarantee any product will be approved in the sought-after indication by any health authority worldwide.

www.powerofcombination.com

The clinical development program for avelumab now includes more than 2,200 patients across more than 15 tumor types, including breast cancer, gastric/GEJ cancers, head and neck cancer, Merkel cell carcinoma, melanoma, mesothelioma, non-small cell lung cancer, ovarian cancer, renal cell carcinoma and urothelial (e.g. bladder) cancer.
MCC 2L: Clinical results support avelumab as potential therapeutic option – planned to apply for marketing authorization in H2 2016*

Encouraging response rates

- ORR: 31.8%
  - 9.1% complete response
  - 22.7% partial response
  - Rapid (78.6% responding within 7 weeks of treatment)
  - Durable (82.1% still responding at time of analysis)
- 6-mo OS: 69% (median OS: 11.3 months)
- 6-mo PFS rate: 40%
- Manageable safety profile; no unexpected safety signals

Potential for differentiation

- Largest international multicenter, open-label study of anti-PD-L1/PD-1 reported in this patient population (88 patients) – Responses observed in large number of patients
- Improved response rates observed when used earlier, i.e. fewer lines of prior chemotherapy appeared to be associated with better response to avelumab in MCC 2L and beyond
  - ORR of 40.4% for patients with one prior systematic treatment
  - ORR of 19.4% for patients with two and more prior treatments

Note: timelines are event-driven and may change

Note: avelumab is the proposed nonproprietary name for the anti-PD-L1 monoclonal antibody (MSB0010718C)


Source: MERCK – Q3 2016 ROADSHOW, *: EMA filling announce on Oct 31st
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Linear R&D approach

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Personalized Medicine towards Precision Medicine

Partnership with Dako on PD-L1 ICH

September 24, 2015

Merck and Pfizer Collaborate with Dako, an Agilent Technologies Company, on Development of Companion Diagnostic for Investigational anti-PD-L1 Antibody, Avelumab

- Merck and Pfizer collaborate with Dako in developing an immunohistochemistry (IHC)-based companion diagnostic (CDx) in immuno-oncology

Darmstadt, Germany, and New York, U.S., September 24, 2015 – As part of the global strategic alliance between Merck and Pfizer to jointly develop and commercialize

The three-party agreement, signed recently, enables Dako, Merck and Pfizer to work to develop the CDx to assess programmed death-ligand 1 (PD-L1) protein expression levels in tumor tissue, and its microenvironment, including tumor-associated immune cells. The investigational CDx is part of the protocols in ongoing clinical trials of avelumab, some of which will be reported at upcoming scientific congresses.
Personalized Medicine towards Precision Medicine

Drugs addressing multifactorial disease pathways (e.g. iONC) need to incorporate multiple data sources to develop biomarker signatures

Integration of omics data to anticipate multifactorial biomarker signatures
Integration of clinical data from academia, PPPs, and competitors to refine biomarker hypothesis
Collaboration to align biomarker signatures across industry

Integrative, still linear R&D approach

Biomarker proposals based on multifactorial disease pathways and modulation of target
Translation of biomarkers into multiple exploratory assays for early clinical trials
Exploration of multiple biomarker hypotheses in early clinical trials. Stratification in pivotal trials based on signatures.
Transfer, validation, and regulatory approval of companion diagnostics signatures by (multiple) partners
Securing access to drug and cDX in all markets

Source: Merck internal analysis
Going forward, avelumab combinations will drive differentiation strategy

- Phase II 2L MCC (BTD, ODD and FTD)
- Phase III 1L and 2L Plat res/ref ovarian
- Phase III 1L MN and 3L gastric
- Phase III 1L and 2L NSCLC
- Phase III 1L MN bladder
- Phase I Hodgkins Lymphoma
- Multiple other tumor types

Combinations
- Phase III, RCC 1L (avelumab + Inlyta)
- Phase Ib/II, NSCLC 1L ALK+ (avelumab + Xalkori/Lorlatinib)
- Phase I/II (avelumab + 4-1BB)
- Phase Ib/II, ovarian (avelumab + Entinostat; Syndax collaboration)
- Phase I/Ib, ovarian (avelumab + VS-6063; Verastem collaboration)
- Phase I/II, HPV+ H&N (avelumab + TG4001; Transgene collaboration)
- Phase Ib/II, NSCLC (avelumab + VX15/2503; Vaccinex collab.)
- Phase I/Ib, NSCLC (avelumab + Debio1143; Debiopharm collab.)

- Further combination trials under consideration

Note: avelumab is the proposed nonproprietary name for the anti-PD-L1 monoclonal antibody (MSB0010718C)

PD-L1–TGF-beta indicates potential to move beyond checkpoint inhibitors

Four focus areas for exploration

- Replace current IO SOC (leveraging Dual MOA)
- Identify opportunities where current IO SOC is not established yet
- Explore non-immunogenic tumor types (alter micro-environment)
- Explore opportunity in PD-x Failures

Status and next steps

- Novel, first-in-class bifunctional immunotherapy
- Bifunctional mode should result in broader application vs. respective mono-functional agents
- Great potential when combined with Standard of Care, immunotherapy and internal pipeline drug candidates
- Dose level finding of Phase I completed
- Expansion into Ib cohorts expected for Q3 2016

Note: timelines are event-driven and may change

Source: MERCK – Q3 2016 ROADSHOW
Combinations of drugs for multifactorial disease pathways need to be explored in iterative development processes to develop precision medicine treatment algorithms.

System biology approaches, but most likely power of prediction of biomarker signatures limited.

Establishment of unbiased x-omics approaches to deal with complexity of potential biomarker signatures.

Big data creation and identification of signatures in early clinical trials. Stratification in pivotal trials based on signatures.

Validation and regulatory approval of companion diagnostics signatures ideally on one omics platform.

Exploratory trials (basket, bucket, adaptive) with x-omics analysis with evolution of criteria to match drugs to suitable patient with increasing precision.

Securing access to drug and cDX or omics platform in all geographies.

Integration of omics data to support identification multifactorial biomarker signatures.

Iterative R&D approach necessary.

Personalized Medicine towards Precision Medicine

Research

Non-clinical

ClinDev

BD/cDx

Commercial

Source: Merck internal analysis

Personalized Medicine towards Precision Medicine
Example: Merck Partnership on cDx

Strategic Collaboration with Illumina on development of companion diagnostics

- Development and commercialization agreement on a universal next-generation sequencing-based oncology diagnostic
- Joint development of assays that aim to detect and simultaneously measure multiple genetic variants in a single tumor sample
- Complementing Merck’s existing partnerships in the area of diagnostics, allowing Merck to choose from a wide variety of technologies in implementing a precision medicine strategy
Discrepancy between data per patient and # of patients

**Standard trials are designed to provide power for 1 endpoint**

Balance between # of patients and amount of data
(few patients with little data ≠ big data)

1 primary
~5 secondary endpoints

100 to 2000 patients
~20 pre-specified subgroups

Source: Merck internal analysis
Discrepancy between data per patient and # of patients

*omics data induces imbalance in standard clinical trials*

Omics data

1 primary
~5 secondary
Endpoints

Imbalance between # of patients and amount of data
(big data per patient, but lack of significant # of patients)

100 to 2000 patients
~20 pre-specified subgroups based on baseline characteristics
Infinite # of subgroups possible based on omics data

Source: Merck internal analysis
Discrepancy between data per patient and # of patients

**Complementation of clinical trials data by large cohorts**

1 primary
~5 secondary
Endpoints

100 to 2000 patients
~20 pre-specified subgroups based on baseline characteristics

omics data

omics data from large cohorts (10,000 to 1mio patients/volunteers)

Source: Merck internal analysis
Big data from outside clinical trials applied to clinical data

**Big data help to identify meaningful patterns**

- 100 to 2000 patients
- ~20 pre-specified subgroups based on baseline characteristics
- # of subgroups restricted to meaningful omics patterns

Source: Merck internal analysis
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Research  Non-clinical  ClinDev  BD/cDx  Commercial

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**Integration of omics data to anticipate multifactorial biomarker signatures**

**Integration of clinical data from academia, PPPs, and competitors to refine biomarker hypothesis**

**Collaboration to align biomarker signatures across industry**

### Integrative, still linear R&D approach

- **Research**: Biomarker proposals based on multifactorial disease pathways and modulation of target
- **Non-clinical**: Translation of biomarkers into multiple exploratory assays for early clinical trials
- **ClinDev**: Exploration of multiple biomarker hypotheses in early clinical trials. Stratification in pivotal trials based on signatures.
- **BD/cDx**: Transfer, validation, and regulatory approval of companion diagnostics signatures by (multiple) partners
- **Commercial**: Securing access to drug and cDX in all markets

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Iterative R&D approach necessary.

Source: Merck internal analysis

Personalized Medicine towards Precision Medicine

Research Non-clinical ClinDev BD/cDx Commercial
Merck Partnership
Preferred Partner

• In a world of constant change, we benefit from the long-term view of Merck with its 350-year tradition in pharmaceuticals and chemicals, while maintaining the agility to adapt to market requirements

• As a midsize company, we offer our partners the flexibility, agility and lean structures of a biotech company, while providing global reach and large-scale capabilities

• Strategy focused on precision medicine and biomarkers approach. Strong experience in commercialization of therapeutic antibodies, delivering personalized treatments for patients
MINILABS – FIGHTING COUNTERFEIT MEDICINES

Millions of people depend on crucial medications, but unknown to them – end up taking a pill made of nothing more than flour, sugar or sawdust. This happens because up to 30% of medicines sold worldwide are counterfeit. However, counterfeits can be quickly and easily detected using the GPHF-Minilab, a compact analysis kit in a briefcase.

Thanks to Merck, more than 700 Minilabs are being used in over 80 countries to detect counterfeit antibiotics, antimalarials, and analgesics. We also provide training on how to properly use the kits.