ATACs: a unique new mode of action to fight cancer

H.C. WAINWRIGHT & CO. - 2nd Annual Global Investment Conference - September 2020
Safe Harbor

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Heidelberg Pharma at a Glance

Developing new options to address major challenges in cancer therapy

Our Company

Listed as Heidelberg Pharma AG
Frankfurt Stock Exchange: HPHA
Shares outstanding: 31.03 million
Market cap: ~€130 million
Headquarters: Ladenburg, Germany
~ 78 employees

Our Mission

New option in cancer therapy with a unique mode of action
Overcome resistance mechanisms
Kill dormant tumor cells
Biomarker for patient stratification and expedited development

Our Approach

Inhibition of RNA Polymerase II
Amanitin as toxic payload
Targeted delivery via antibodies (ADC technology)

Antibody Targeted Amanitin Conjugates (ATACs)

Business model: develop proprietary ATAC pipeline, partner ATAC technology platform and generate upside potential from legacy clinical portfolio
ATACs fill the Gap
Missing MoA of Cancer Chemotherapeutics

Amanitin – novel mode of action for cancer therapy

Amanitin specifically binds and inhibits RNA polymerase II – the only currently known inhibitor of RNA polymerase II

Amanitin kills dividing AND quiescent tumor cells by inhibiting mRNA synthesis

→ Potential clinical benefits by
  • Strong efficacy in in vivo and in vitro models
  • Ability to overcome resistance
  • Kill dormant tumor cells causing metastasis & tumor relapse, independent of cell proliferation

Heidelberg Pharma’s technology platform makes highly toxic amanitin accessible for cancer therapy

Adapted from http://chemistry.elmhurst.edu/vchembook/655cancer2.html
Antibody Targeted Amanitin Conjugates (ATACs) Combining the best of two therapeutic modalities

ADCs with Amanitin as toxic payload = ATACs (Antibody Targeted Amanitin Conjugates)

Highly effective payload

Death cap mushroom

From nature to the lab

Chemical synthesis *

Highly specific antibody

• Antibodies for different tumor targets
• Targets determine indications
• Tumor specific delivery
• Internalization of target
• Access to antibodies through licensing or partnering

ATAC technology

Source: pilz-ratgeber.de

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* IP protection includes
Chemical synthesis of toxins, optimal linker attachment sites, portfolio of different linkers, site-specific conjugation technology
Antibody Targeted Amanitin Conjugate Technology – Proven & Established Technology

Antibody specificity + toxin efficacy → improved therapeutic window and fewer side effects

**ATAC:** Antibody-Targeted Amanitin Conjugate

1. ATAC is prepared and released into bloodstream
2. Binding to tumor-associated antigen
3. Internalization
4. Release of Amanitin from the antibody/ATAC
5. Amanitin relocates from the lysosome to the nucleus
6. Amanitin binds to the RNA polymerase II and inhibits mRNA synthesis

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ATACs Overcome Resistance
Early and Explorative Model for Breast Cancer

Complete remission of a breast cancer xenograft model after single-dose application of HER2-ATAC

JIMT-1 Xenograft

Clinical dose of FDA-approved Kadcyla®, a HER2-DM1-ADC, is ineffective

Equivalent dose of HER2-ATAC shows complete remission

→ ATACs are highly potent & superior to existing payloads

→ ATACs can overcome resistance in in vivo models
ATACs Kill Dormant Tumor Cells
Lead candidate HDP-101 ex-vivo model

Anti-BCMA-ATAC (HDP-101) is able to kill non-dividing primary tumor cells

Comparison with MMAF (Auristatin Conjugate as used by GSK) on MM Patient Cells

- Non-dividing (quiescent) cells isolated from multiple myeloma patients bone marrow biopsies
- Dividing tumor cells from lab cell lines

Anti-BCMA-Ab coupled with GSK payload MMAF

HDP-101 (anti-BCMA-Ab coupled with payload Amanitin)

ATACs can kill non-dividing primary tumor cells and may eliminate dormant tumor stem cells
Biomarker approach for multiple tumor entities

17p deletion associated with more aggressive tumors

TP53 gene on chromosome 17 is frequently deleted in tumors

Nearby RNA Polymerase II gene POLR2A is frequently co-deleted

Lower levels of RNA Polymerase II in tumor cells with 17p deletion

Higher sensitivity to treatment with ATACs

Incidence is 20-80% dependent on tumor type and stage

→ 17p Deletion / Loss of POLR2A is a potential biomarker to increase therapeutic window and to identify high-risk patients
Tumor cells with less RNA Polymerase II are more sensitive to ATACs

**Normal RNA Pol II levels, Wildtype**

**Reduced RNA Pol II levels, 17pDel**

- **17pDel / Loss of POLR2A**
  - increases the **efficacy** of ATACs
  - is a potential **biomarker** to increase therapeutic window and to identify high-risk patients

**Biomarker offers potential to expedite clinical development by patient stratification**

(e.g. Venetoclax has been approved for CLL patients with 17pDel based on one Ph 2 trial with 107 patients)
**Strategic Cornerstones**

**Build proprietary ATAC pipeline**
- HDP-101 – ATAC targeted against BCMA (multiple myeloma)
- ATACs for additional oncology indications (HDP-102 & HDP-103)
- Antibody discovery for further targets

**ATAC collaborations**
- Licensing collaborations with pharma and biotech
  - Takeda Oncology
  - magenta Therapeutics
  - ETX Therapeutics
- Various research partnerships based on Material Transfer Agreements

**Licensed legacy assets (non-ATACs)**
- Additional upside potential from clinical programs
  - TLX250-CDx – diagnostic imaging agent (REDECTANE®)
  - RHB-107 – uPA/serine protease inhibitor (upamostat / MESUPRON®)

**GMP supply with amanitin**
Multi-Target Research and Option Agreements with Takeda and Magenta

**Research & Option Agreements**

- ATACs using **antibodies** from Takeda/Magenta
- Exclusive target licensing option for **global rights** for development candidates
- Option for several **exclusive targets**
- **Partner is responsible** for preclinical and clinical development as well as commercialization

**Financials**

- **Upfront** technology access fees, R&D support, **option fees** for exercised options
- Regulatory and commercial **milestone payments**:
  - **Takeda**: Up to **USD 113 million** per target; up to three targets
  - **Magenta**: Up to **USD 85 million** per target; two out of four options exercised

**Royalties** on sales

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**Early Validation of ATAC Technology and Cash Through Pharma Collaborations**
## Growing Pipeline of Proprietary and Partnered Programs

<table>
<thead>
<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
<th>Research</th>
<th>Preclinic</th>
<th>Clinic</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary ATAC pipeline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDP-101</td>
<td>BCMA</td>
<td>Multiple myeloma (DLBCL/CLL)</td>
<td></td>
<td></td>
<td></td>
<td>Proprietary</td>
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<tr>
<td>HDP-102</td>
<td>CDXX</td>
<td>NHL</td>
<td></td>
<td></td>
<td></td>
<td>Proprietary</td>
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<tr>
<td>HDP-103</td>
<td>PSMA</td>
<td>Prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td>Proprietary</td>
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<tr>
<td>XX-ATACs</td>
<td>n/a</td>
<td>Solid / Hematological tumors</td>
<td></td>
<td></td>
<td></td>
<td>Proprietary</td>
</tr>
</tbody>
</table>

### ATAC collaborations

| MGTA-ATACs | CD117, CD45 | HSCs, Conditioning programs for blood cancers and genetic diseases | | | | Magenta |
| TAK-ATACs | n/a | Oncology | | | | Takeda/ Millenium |
| ETX-ATAC | Nectin-4 | Solid tumors | | | | JV Emergence |

### Licensed legacy assets (non-ATACs)

| TLX250-CDx | CA-IX | Renal Cancer | | | | Telix |
| TLX250 | CA-IX | Renal Cancer | | | | Telix |
| RHB-107 | Oncology/GI/SARS-CoV-2 | | | | | RedHill |
| LH011 | Breast cancer, Pancreatic cancer | | | | | Link Health |
Multiple Myeloma – Major Unmet Medical Need

- Second most prevalent hematopoietic malignancy*
- 70,000 deaths due to MM annually; median age at diagnosis is 65-70 years
- Malignancy characterized by the proliferation of single clone of plasma cells derived from B-cells which produce abnormal antibody proteins
- MM is initially confined to bone marrow, natural progression of disease can result in end organ damage
- Current treatment options: Chemotherapy, immunomodulatory drugs, proteasome inhibitors and autologous stem cell transplantation (ASCT)
- MM is still considered incurable, median survival ~30-60 months

# Multiple Myeloma: Big Market with Big Need for New Treatment Options

## Standard of Care

### Approved therapies

**Approved agents, e.g.:**

- **Immunomodulators**: Revlimid (revenue 2018: $9.17 billion), Pomalyst/Imnovid (Celgene)
- **Proteasome inhibitors**: Velcade, Ninlaro (Takeda), Kyprolis (Amgen);
- **DNA Alkylators**: Treanda, Bendeka (Teva), Ygalo (Oncopeptides);
- **HDAC inhibitor**: Farydak (Novartis);
- **BCL-2 inhib.**: Venclexta (AbbVie);
- **CD38 mAbs**: Darzalex (J&J), Sarclisa (Sanofi);
- **SLAMF7 mAb**: Empliciti (BMS)

→ All patients eventually relapse

### New BCMA therapeutic agents in development

#### BCMA Bispecifics

- Need for continuous infusion
- Cytokine Release Syndrome (CRS)
- No clinical data for half-life extended yet

e.g.: Amgen, Regeneron/Sanofi, Pfizer, J&J, TeneBio, Celgene

#### BCMA CAR-Ts

- Safety concerns
- Limited eligibility, applicability and accessibility
- Complex manufacturing, not off-the-shelf
- Only 1 year PFS

e.g.: Celgene/Bluebird, Celgene/Juno, Autolus, Legend, Poseida

#### BCMA ADCs

- Targeted delivery of potent toxin
- Available off-the-shelf;
- Only a few players in the field:
  - GSK (GSK2857916): BCMA-MMAF; FDA approval August 5, 2020
  - Prevalent ocular toxicity
  - Medimmune (MEDI-2228): Phase I
  - BMS (Celgene) / Sutro (CC-99712): Phase I, undisclosed payload

#### BCMA ATAC

- Potential improvement ocular tox
- Active on dormant cells
- Active in 17p-del high-risk patients

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*Global MM market growing (2026): $31 billion*

**BCMA-ATAC (HDP-101) offers potential advantages over other approaches**

*Fortune Business Insights (29 April 2020)*

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17p Deletion – Use of Biomarker Could Provide Opportunity for Accelerated Clinical Development

**Case study: HDP-101 for multiple myeloma**

- MM patients with 17p deleted tumors have a very high medical need for new treatment options
- HDP-101 has preferential activity on 17p deleted tumor cells derived from MM patients
- Potential options to speed-up market approval for such a selected patient population if preclinical data translate into clinical benefits
- Potentially broader therapeutic window resulting in lower development risk and new treatment option for patient segment with bad prognosis

**Overall survival of MM patients with and without 17p deletion**

*Blood 2009, Jul 16;114 (3): 522-525*

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**Plan to apply for FDA Fast Track designation for HDP-101**
# HDP-101 – Next Development Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete GLP toxicity study</td>
<td>July 2020</td>
</tr>
<tr>
<td>Long-term stability studies of HDP-101</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Complete GMP production of HDP-101 to supply the planned clinical trial</td>
<td>July 2020</td>
</tr>
<tr>
<td>Outline of the study design for the clinical trial</td>
<td>Completed</td>
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<tr>
<td>Contracts with the study centers in the US and GER</td>
<td>In negotiation</td>
</tr>
<tr>
<td>FDA pre-IND Meeting</td>
<td>Q3 2020</td>
</tr>
<tr>
<td>Submission of the Investigational New Drug Application (US)</td>
<td>Q4 2020</td>
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<tr>
<td>Submission of the Clinical Trial Application (Germany)</td>
<td>Q1 2021</td>
</tr>
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</table>

**Approval of IND and CTA in the US and GER**
Initiate study centers and enroll patients
Financials and Shares

<table>
<thead>
<tr>
<th>in € m</th>
<th>FYR 2019</th>
<th>HY 2020</th>
<th>Guidance 2020</th>
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<tbody>
<tr>
<td>Sales revenue and other income</td>
<td>8.0</td>
<td>3.8</td>
<td>8.0 to 10.0</td>
</tr>
<tr>
<td>Operating expenses</td>
<td>18.1</td>
<td>13.2</td>
<td>20.0 to 24.0</td>
</tr>
<tr>
<td>Operating result (EBIT)</td>
<td>(10.1)</td>
<td>(9.4)</td>
<td>(11.0) to (15.0)</td>
</tr>
<tr>
<td>Funds required</td>
<td>9.6</td>
<td>9.1</td>
<td>11.0 to 15.0</td>
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<tr>
<td>Funds required per month</td>
<td>0.8</td>
<td>1.5</td>
<td>0.9 to 1.3</td>
</tr>
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</table>

**Financing**
- €14.4 m gross proceeds from private placement with dievini and selected institutional investors in April 2020
- Cash as of 31 May 2020: €15.1 m, Cash reach is secured until mid-2021 based on current budget planning
- **New financing commitment of €15 million, planning update after nomination of development candidates**

**Shares**
- Shares outstanding: 31,030,572 (as of 30 June 2020)
- Average daily trading volume: ~50,000 shares (all stock exchanges, ytd)
- Majority shareholder: Dietmar Hopp and affiliated companies*

**Analysts**
- MainFirst (Stifel) 06/20: target €6.30
- Pareto 07/20: target €4.40
- EQUI.TS 04/20: target €6.15

*dievini Hopp BioTech holding GmbH & Co. KG + DH Holding Verwaltungs GmbH
Operational Outlook

ATAC technology

- **HDP-101 – next steps planned**
  - Submission of IND (US) and CTA (Germany)
  - Site activation & First Patient In
  - Continue biomarker development

- **Proprietary pipeline**
  - HDP-102 & HDP-103 to advance as next proprietary development candidates
  - Expansion of development capacities

- **ATAC technology und partnerships**
  - Advance ongoing research projects on an MTA basis und Amanitin GMP supply
  - Sign additional license and collaboration agreements
Investment Summary

Developing new options to address major challenges in cancer therapy

- **Unique anti-tumor strategy** through targeted inhibition of RNA polymerase II in cancer cells by ATACs

- **Disruptive first-in-humans** mode of action provides **high efficacy** and potential for **unique clinical advantages**, including treatment of dormant tumor cells

- **Increased efficacy against 17p deleted and aggressive** tumor cells based on biomarker

- Platform validated by **high quality collaborations** (early validation and cash)

- **High value potential** with growing proprietary portfolio, expansion of application areas in partner projects and progress of the licensed legacy portfolio
## Upcoming conferences & events

<table>
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<tr>
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<th>Venue</th>
<th>Date</th>
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<tbody>
<tr>
<td>PEGS: The Essential Protein Engineering &amp; Cell Therapy Summit</td>
<td>Delivered digitally</td>
<td>31 Aug – 04 Sept 2020</td>
</tr>
<tr>
<td>International HealthTech Innovation Days</td>
<td>Paris</td>
<td>05 – 06 October 2020</td>
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<tr>
<td>BioCapital Europe</td>
<td>Amsterdam</td>
<td>07 October 2020</td>
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<tr>
<td>BIO-Europe</td>
<td>Delivered digitally</td>
<td>26 – 29 October 2020</td>
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<tr>
<td>German Equity Forum</td>
<td>Delivered digitally</td>
<td>16 – 18 November 2020</td>
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<tr>
<td>World ADC Asia</td>
<td>Tokyo</td>
<td>07 – 09 December 2020</td>
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## Financial Calendar

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Q3 – Interim Results</td>
<td>08 October 2020</td>
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## Ticker data

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