EQUI-PEERS

Sector: Biotech – epigenetic cancer therapies – HDAC inhibitors

Peers included in the report:

- **4SC AG**
- Onxeo SA
- MEI Pharma Inc.
- Curis Inc.
- Mirati Therapeutics Inc.
- Epizyme Inc.

T .Schießle/D. Großjohann
EQUITS GmbH
16.12.2015

New cancer therapies on the verge of a breakthrough thanks to HDAC inhibitors

HDAC inhibitors (HDACi) are an attractive class of epigenetic compounds that have already shown general clinical efficacy against solid and haematological tumours in mono- and combination therapy and have received initial approval. A forecast by market research institute Visiongain has projected that, for example, in 2018 the market volume of the global **epigenetic market** will be an estimated **$4.3 billion** (2014: $2.5 billion). HDACi can block tumour cell proliferation so as to then induce apoptosis (programmed cell death) and/or promote differentiation. Epigenetic modulators like this communicate their effect in cancer cells by turning on or off dysregulated genes (epigenetic reprogramming). This also explains why epigenetic drugs do not damage healthy body (somatic) cells and therefore have much fewer side effects than conventional cancer drugs. Following the first wave of HDACi approvals from 2006 to 2009 – **vorinostat** (Zolinza®) and **romidepsin** (Istodax®) – HDACi are now on the verge of a breakthrough. In the second wave since 2014, two HDACi drugs – **belinostat** (Beleodaq®) and **panobinostat** (Faridak®) – have already received market approval. Others are positioned extremely promisingly, mainly for combination therapies, including a series of candidates that are currently in clinical trials, such as **resminostat**, **entinostat**, **pracinostat** and **mocetinostat**.

The positioning of Syndax's oral HDAC inhibitor **entinostat** (Phase III in TNBC*) in combination with conventional cancer therapies (e.g. add-on to hormone therapies) also paves the way for other HDACi (breakthrough therapy designation)! Essentially, through targeted epigenetic cell programming, entinostat is designed to make the tumours more vulnerable to the conventional cancer drug (e.g. hormone therapy), allowing breast cancer patients to be treated with this therapy for a longer time before needing chemotherapy, which has more severe side effects. 4SC addresses a similarly large patient group to TNBC* in advanced liver cancer (HCC*). In a Phase I/II clinical development programme that is much broader than those of 4SC's competitors (indications of CTCL*, HCC*, NSCLC*, HL*, CRC*, pancreatic and biliary tract cancer), **resminostat** has been and is being developed by 4SC and its partners in the direction of market approval. Resminostat stands out from the competition thanks to its so far extremely mild side effect profile (safest-in-class), which the compound has already demonstrated in more than 250 patients – at the same time showing promising signs of efficacy in Phase I/IIa trials.

HDAC-Inhibitors – attractive epigenetic class of oncology drugs

Substance	Mode of Action	Indication	Company	Status	Partners
Vorinostat (Zolinza®)	Pan-HDAC-Inhibitor	**CTCL (US, Asia)**	**Merck & Co.**	Marketed in US, Canada, Taiwan, Japan, Australia	-
Romidepsin (Istodax®)	Class-1 Selective-HDAC-Inhibitor	**CTCL (US); rel./ ref. PTCL**	**Celgene**	Marketed in US, Canada, Australia (PTCL)	-
Belinostat (Beleodaq®)	Pan-HDAC-Inhibitor	**rel./ ref. PTCL**	**Onxeo**	Marketed in US	**Spectrum**
Panobinostat (Faridak®)	Pan-HDAC-Inhibitor	**rel./ref. Multiple Myeloma (3rd Line)**	**Novartis**	Marketed in US, EU	-
Resminostat	Class-1,2b-HDAC-Inhibitor	**CTCL (Europe)** **HCC, NSCLC; CRC; HL** Pancreatic/ Biliary-Tract	**4SC**	CTCL* EU: Ph II in preperation CRC* EU: Ph I completed NL*,HCC* EU: Ph IIa completed HCC* Asia: Ph II Data exp. H1/16e NSCLC* Asia: Ph II Data exp. H1/16e Pancreatic-/ Biliary-Tract , Asia: Ph I ongoing	**Yakult Honsha, Menarini AP**
Entinostat	Class-1 Selective-HDAC-Inhibitor	**Breast Cancer, NSCLC**	**Syndax**	TNBC (Breast Cancer): Phase III Phase II in NSCLC	**Kyowa Hakko; Merck & Co.**
Pracinostat	Pan-HDAC-Inhibitor	**MDS; AML**	**MEI Pharma**	AML/MDS: Open Label Phase II ongoing, MDS Phase II completed	-
Mocetinostat	Class-1 Selective-HDAC-Inhibitor	**DLBC; Bladder Cancer**	**Mirati**	DLBCL: Phase II Bladder Cancer: Phase II	**MedImmune**

*) Explanation on page 7 - December 2015

Attractive future market: combination of HDACi and cancer immunotherapies

Combination tests of HDACi with checkpoint inhibitors (PD1/PDL1*) are being followed with great interest. Combination therapy basically means that two demasking strategies are combined.
Immunotherapies are the bright star in tumour research: they stimulate the human immune system against cancer in a targeted manner. The aim is reduced toxicity and a higher quality of life combined with a longer survival rate. Analysts expect this new class of drugs to generate revenue of between US$30 billion and US$ 40 billion p.a. as of 2025.
The epigenetic-immunotherapeutic combination approach chosen by Merck & Co. and Syndax in March 2015 (Phase Ib/II tests of **entinostat** + **Keytruda®** in NSCLC* and melanoma patients starting in H2 2015) is pointing the way ahead and generates high expectations – also on the stock exchange. 4SC's HDACi **resminostat** could also have this immunomodulatory potential, i.e. to further increase the efficacy of checkpoint inhibitors (PD1/PDL1), immunotherapeutic approaches (e.g. **rituximab**) or immunostimulatory compounds (e.g. TLR ligands), as indicated by initial preclinical data published in March 2015 for the first time. **4SC** is currently testing the immune priming potential of resminostat and 4SC-202 in other preclinical models, for which the Company received funding from the EU's Eurostars programme in September 2015.

4SC AG's business model – with great epigenetics expertise in the fight against cancer

Founded in 1997, 4SC is a biotechcompany focusing on the discovery and development of targeted small molecule drugs used to treat cancer in particular. The development achievement and the commercial potential of the projects are remarkable. Recent years have seen the successful implementation of strategic focusing on 4SC's lead oncology compound resminostat (HDACi), which also showed immunomodulatory properties – useful for immune priming (e.g. on checkpoint inhibitors such as PD1/PDL1*) – in initial clinical tests in 2015. Thus, 4SC operates in what currently are the most exciting areas of pharmaceutical development (epigenetics, cancer immunisation).
Following the most recent capital increase in July 2015: cash reach: 2018e.

Currently, 4SC and its Asian partners clinically develop **Resminostat** for targeted tumour therapies, both in monotherapy and in combination with other cancer drugs, in a broad range of indications.

Partnerships & milestone payments:
Yakult Honsha (Japan): Upfront €6 million + milestone payments up to €127 million + (double-digit) royalties;
Menarini AP (Asia-Pacific excluding Japan): Upfront: n.d. + milestone payments up to €95 million + (double-digit) royalties; further licences (target region: western world) are being pursued.
4SC's development and marketing partner Yakult is currently advancing Phase II development of **resminostat** in blockbuster indications (solid tumours HCC*, NSCLC*). Since June 2015, this has been supplemented by an open Phase I trial with **resminostat** in advanced pancreatic and biliary tract cancer. Thanks to the collaborations with Menarini (Asia) and the Japanese partner Yakult, the entire Asia-Pacific region – which sees 75% of all cases of liver cancer worldwide (peak sales potential of approx. US$800e million p.a.) – is open for **resminostat**.
Important news flow: 2016 Phase II data (in HCC*); followed by potential start of Phase III by Yakult in Asia; start of Phase II in CTCL.

4SC to benefit from lack of approved drugs in the EU for CTCL*. CTCL is the most frequent form of T-cell non-Hodgkin's lymphoma with an extremely high unmet medical need in Europe. Two other HDACi have received market approval in the United States, but not in the EU on account of the single-arm study design chosen at the time! 4SC wants to benefit from this lack of approved drugs and is in the EMA's Scientific Advice process for a trial that could directly lead to market approval if the data is positive. Currently, 4SC is developing **resminostat** for conditional approval (2019e) in the EU using the proceeds from a cash capital increase in July 2015. Positive data from the randomised controlled Phase II trial in CTCL* expected to commence in H1 2016 will ideally be available in H2 2018; start of marketing from H2 2019e. A peak sales potential of the fast-to-market project of €140e million p.a. seems realistic (DCF value: approx. €61e million).

4SC AG – focused oncology pipeline

4SC AG - focused oncology pipeline

New strategy: fast to the market - with HDAC-Inhibitor to „conditional approval" in CTCL* in EU

Corporate
- **Biotech Company** founded: 1997 - HQ Martinsried
- **Compounds** own , licenced in; valid patent protection
- **Focused on oncology & epigenetics** only small molecules
- **Business Model – 2-fold** Prop. Development (Cancer treatment) - Collaborative Business" (services)
- **Senior Management** Enno Spillner (CEO; CFO) Dr. D. Vitt (CDO & CSO) Dr. S. Danhauser (CMO) Dr. E. Enghofer (EVP Oncology& Hematology)
- **Headcount (Q3/15): 60 (31.12.14: 57 FTE`s)** thereof R&D:45 FTE`s

Financials
- **VSC-Shares : Germany, Prime Standard**

Free Float:	38,1%
Santo Holding	48,1%
FCP	7,2%
Wellington Partners	6,8%

- **Financing (no profit till 2017e)** SPO`s + Partnering + Third Party Service Revenues

cash-reach – (11.11.15) „till 2018"

CAPITAL - INCREASE: No.shares (29.07. 2015) 10,2 -> 18,87 Mio. proceeds: € 29 Mio.

Pipeline & Products
- **Pipeline (Phase I/ II)** No of projects: 4 / 5
- **Main Asset: epigenetic cancer drugs**
- **Compounds: 4**
  „**Resminostat**" – HDAC -Inhibitor
  „ **4SC-„202**" – HDAC1,2,3 &LSD1* –Inhibitor, modulating HH* & WNT*
  „**4SC-205**" - Eg5-Inhibitor/Kinasen
  „**Vidofludimus**" – DHODH anti-Inflammation

Newsflow
- **Clinical Newsflow: Resminostat 2016e:**
  -Data „HCC*" 1st Line - Ph II (Yakult)
  -Data „NSCLC*" - Ph II (Yakult)
  -Preclinical (in vivo) data immunomodulation
  -„CTCL" (EU) – Start pivotal Ph II (for conditional Approval) in 2016e
- **Potential deal flow:**
  -„4SC-202" - Partnering / Ph II-Start
  -„Resminostat" - „Western World" Partnering

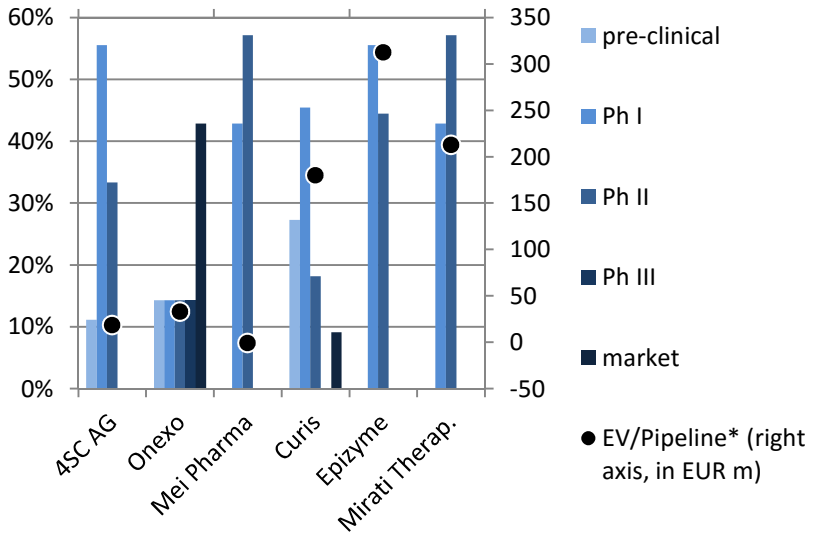
*) Explanation on page 7 - December 2015; EQUITS GmbH

Quantitative comparison in the epigenetics peer group – pipeline evaluation as a key value driver

(Our evaluation of the research portfolios is based on the maturity and structure of the pipeline;
EV (enterprise value) = market capitalisation + interest-bearing liabilities + non-controlling interests - cash)

Our methodology:

- The pipeline was standardised, taking the number of projects and the structure into account.
- This standardised value is the basis for demonstrating the investors' view of the pipeline.
- **EV/pipeline*** (in millions of EUR) is the indicator we developed for this (where "pipeline*" represents the standardised pipeline).
- The chart shows both the value allocated to the standardised pipeline and the structure of the pipeline (the percentages on the left axis add up to 100 over the portfolios in question).



Currently very broad valuation range: clear division into European and US equities; with/without checkpoints

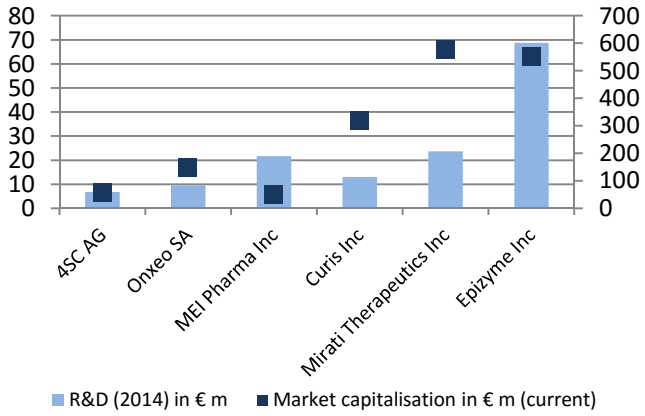
- Valuation premium: In August 2015, MedImmune announced its intention to test its anti-PDL1* immune checkpoint inhibitor durvalumab (MEDI4736) in combination with **Mirati's** mocetinostat in Phase I/II starting in 2016.
- **MEI Pharma** is listed below its cash value of approximately $64 million; EV is currently negative – disappointing Phase II topline data was published in March 2015 – full data was released in December 2015 at the ASH Annual Meeting.
- **Epizyme** made progress with tazemetostat; additional Phase II trials were announced.
- **CURIS** announced the start of the first PDL-1* antagonist (together with Aurigene) for Q4 2015.
- Valuation discount: **4SC** underfinanced up to July 2015, cash capital increase extends cash reach into 2018; **partner Yakult Honsha** starts additional Phase I trials in July 2015; Phase II data (esp. in HCC*) expected in H1 2016.

Research and development expenses in 2014

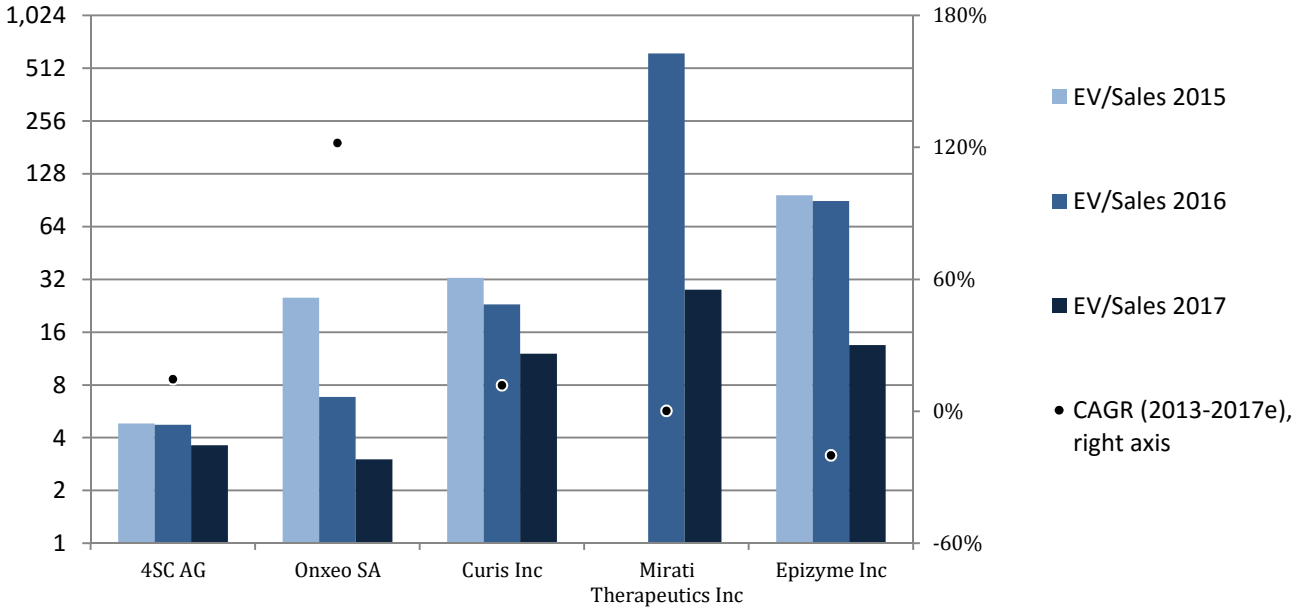
(R&D expenses in millions of EUR; EUR/USD rate=1.10)

R&D:

- **4SC** has intensive and efficient R&D
- With the exception of **MEI Pharma** (which has had a low valuation since March 2015 owing to disappointing Pracinostat data in MDS), the ranking of the R&D expenses follows the ranking of the market capitalisation
- Reported R&D expenses at **Mirati** "squeezed" because of cost absorption by MedImmune
- The inherent connection is the respective pipeline; more advanced projects require a higher R&D budget (and are a key value driver)



Conventional valuation methods are only partially applicable – growth v. EV/sales without a clear statement (except MEI Pharma – see below)

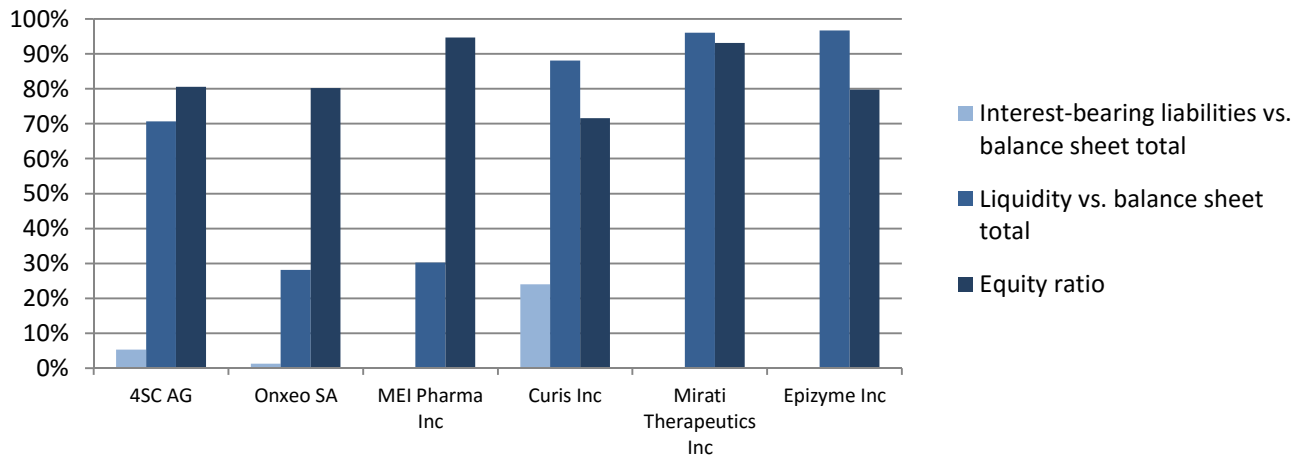


Valuation and growth:

- Limited significance of shown sales (the focus is more on the pipeline/future) and growth rates (since sales can vary considerably from one year to the next).
- When EV/sales (logarithmic left scale) is taken as the starting point, **4SC** currently is the epigenetics company with the most favourable valuation in the peer group, alongside **Onxeo.**
- **MEI Pharma** traded below cash value; EV is currently negative (disappointing Ph-II-topline-data).

Highly liquid peers – capital increase at 4SC in July 2015 will safeguard financing until 2018

(The basis of the calculations is the last published financial report)

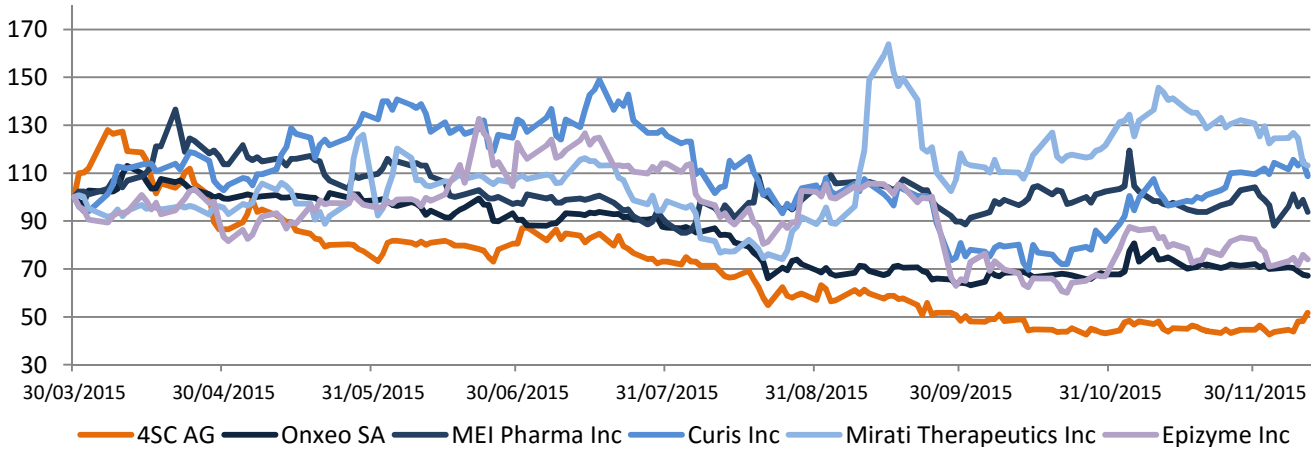


Finance:

- In the last reports, the peers disclosed equity ratios of over 70%, as did 4SC after completing its capital increase.
- With effect from 20 July 2015, **4SC** increased its share capital by €8.75 million (to €18.99 million), generating gross proceeds of approximately €29 million. In addition, interest-bearing liabilities of €6 million were converted into equity. In the course of the capital increase, 4SC generated net cash of around €27.5 million.
- **Mirati** is financed through a development alliance with MedImmune; the cash capital increase in September 2015 generated US$95 million (net).

Standardised share price charts – Outperformance of US peers

(Daily closing prices at the respective main exchange were indexed (30.03.2015=100) to make the figures comparable)



Market price commentary:

- In August 2015, MedImmune announced its intention to test its anti-PDL1 immune checkpoint inhibitor durvalumab (MEDI4736) in combination with **Mirati's** HDACi mocetinostat in Phase I/II starting in 2016.
- A massive valuation premium was set up; a cash capital increase swiftly followed (US$95 million). **4SC**, like **Onxeo**, is an underperformer as a **European equity**; the inadequate financing up to July 2015 is no longer a fundamental justification.

CONCLUSION:

- Second wave of HDACi oncology compounds is in late clinical trials – US stock market valuation indicates the direction!
- The expected news flow at **4SC** (Phase II data in HCC* from Yakult from 2016e, start of Ph II in CTCL/EU) is in contrast to a fundamental undervaluation. In our opinion, the potential of immunomodulatory compounds is completely ignored (from 2016e: decision regarding combination tests with Resminostat + PD-1/PD-L1).

Analyst coverage and recommendations

Data source: Thomson Reuters (11 December 2015)

	Analyst recommendation			Price target (local currency)			Stock price	Highest price target	Lowest price target
	Buy	Hold	Sell	increased	unchanged	decreased	(11.12.15)		
4SC AG	2	0	0	0	1	1	€ 2.90	€ 18.00	€ 5.50
Onxeo SA	2	0	0	0	0	2	€ 3.65	€ 9.60	€ 6.44
MEI Pharma Inc	2	3	0	0	1	1	$ 1.64	$ 7.00	$ 3.00
Curis Inc	5	0	0	1	3	1	$ 2.72	$ 7.00	$ 5.00
Mirati Th. Inc	4	2	0	3	2	1	$ 32.95	$ 50.00	$ 43.00
Epizyme Inc	6	1	0	0	1	5	$ 14.49	$ 42.00	$ 22.00

Analysts:

- The fair values determined are often very disparate (especially in the case of **MEI Pharma**, **Epizyme** and **4SC**).
- Buy recommendations feature prominently, though in the majority of cases upside targets are currently being reduced due to increased volatility on the capital markets as a whole (debate about whether to raise US interest rates).

Glossary

CTCL = Cutaneous T-cell lymphoma (CTCL) is a type of cancer with a very high unmet medical need. In Europe, there are currently only a few treatment options available for advanced stages of the disease, none of which offers chances of recovery. Two HDAC inhibitors have already been approved for treating CTCL in the US, but none in Europe.

Checkpoint inhibitors = The immune system features a series of mechanisms to prevent excessive defence reactions by T-lymphocytes. Tumours misuse these checkpoints to override the immune defence set up against them. This is where checkpoint inhibitors intervene. They inhibit signalling pathways, thereby releasing the T-cells' brakes, and hence restore the immune system's potential to attack the tumour.

Hh pathway = Hedgehog (Hh) signalling pathway - A signal transduction pathway enabling cells to react to external signals. The signalling pathway is named after its ligand *hedgehog* (Hh), a signalling protein. Inhibition of the hedgehog signalling pathway is a novel therapeutic principle in the treatment of certain kinds of cancers, such as basal-cell carcinoma.

HCC = Abbreviation for hepatocellular carcinoma. Malignant tumour starting from the hepatocytes in the liver, often called "liver cancer".

HDAC = Abbreviation for histone deacetylases. These are enzymes that play an important role in gene regulation by modifying histones (proteins that package the DNA in the cell nucleus). As a result, they directly regulate the transcription (i.e. the reading of genetic information) and therefore also epigenetic modifications, i.e. whether certain genetic information can be used for the organism or not. Therefore, the development of HDAC inhibitors is regarded as a meaningful strategy in the fight against cancer.

HL = Hodgkin's lymphoma (HL) is a malignant tumour of the lymphatic system, also classifiable as refractory (stubborn, unresponsive to treatment) or relapsed (recurring).

NSCLC = Non-small-cell lung cancer – In German-speaking regions, this form of lung cancer is the third-most common malignant tumour in women and the second-most common malignant tumour in men. There are different therapeutic recommendations for patients with non-small-cell and with small-cell lung cancer. NSCLC is the most common form of the disease, accounting for around 85% of lung cancer cases.

PD1 = Abbreviation for the programmed cell death 1 protein. Anti-PD-1 antibodies block the interaction between the programmed cell death and its ligand PDL1. Programmed cell death (PD-1) is an important receptor protein that is expressed by activated T-cells.

TNBC = A type of breast cancer. The classification as TNBC (triple negative breast cancer) is based on the immunohistological analysis of an invasive mammary carcinoma by the pathologist, who examines the expression of the estrogen receptor (ER), the progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2). A carcinoma is termed triple negative when it does not demonstrate a clinically relevant expression pattern for the three above-mentioned markers.

Disclaimer

A. Disclosures in accordance with § 34 b WpHG (German Securities Trading Act), Finanzanalyseverordnung (FinAnV) (Ordinance on the Analysis of Financial Instruments):

I. Disclosures on authorship, responsible company, regulatory authority:

Company responsible for the publication: EQUI.TS GmbH

Authors of this financial analysis: Daniel Großjohann, Analyst, and Thomas Schießle, Analyst.

EQUI.TS GmbH is subject to regulation through the Federal Financial Supervisory Authority (BaFin).

Reference pursuant to section 4 subsection 4 point 4 FinAnV:

Company	Analyst	Rating	Price Target

II. Additional information:

1. Information sources:

Material sources of information for preparing this document are publications in domestic and foreign media such as information services (including but not limited to Reuters, VWD, Bloomberg, DPA –AFX), business press (including but not limited to Börsenzeitung, Handelsblatt, Frankfurter AllgemeineZeitung, Financial Times), professional publications, published statistics, rating agencies as well as publications of the analysed issuers.

Furthermore, discussions were held with the Management for the purpose of preparing the company study. The analysis was provided to the issuer prior to publication; no substantial changes were made afterwards.

2. Summary of the valuation principles and methods used in preparation of the analysis: EQUI.TS GmbH uses a 3-level absolute share rating system. The ratings pertain to a time horizon of up to 12 months.

BUY: the expected price trend of the share amounts to at least +15%. NEUTRAL: The expected price trend lies between -15% and +15%.

SELL: The expected price trend amounts to more than -15%.

The following valuation methods are used when valuing companies: Multiplier models (price/earnings, price/cash flow, price/book value, EV/revenues, EV/EBIT, EV/EBITA, EV/EBITDA), peer group comparisons, historical valuation approaches, discounting models (DCF, DDM), break-up value approaches or asset valuation approaches. The valuation models are dependent upon macroeconomic measures such as interest, currencies, raw materials and assumptions concerning the economy. In addition, market moods influence the valuation of companies. Furthermore, the approaches are based on expectations that can change quickly and without warning, according to industry-specific developments. As a result, the results of the valuation and target prices derived from the models can change correspondingly. The results of the valuation are based on a period of 12 months. They are, however, subject to market conditions and

represent a snapshot. They can be reached more quickly or more slowly or be revised upwards or downwards.

3. Date of initial/original publication of the financial analysis: (12/16/2015)

4. Date and time of the prices of financial instruments disclosed therein:

(Closing price on 12/11/2015)

5. Updates:

We have currently not yet set a fixed date to provide a precise update of this analysis. EQUI.TS GmbH reserves the right to update the analysis unannounced.

III. Disclosure on possible conflicts-of-interest by the use of the following numeration as reference:

1. the author has a shareholding in an amount of more than 5% of the share capital,

2. the author has participated in the management of a consortium which has publicly issued financial instruments of the issuer within the last twelve months,

3. the author has carried out sales/purchase transactions on the analysed contents,

4. there exists personnel ties between the author and the issuer,

5. the author belongs to a controlling body of the issuer or by any other means exercises a corresponding control function,

6. the author has an agreement with the issuer on the preparation of analysis (assignment),

7. the author receives payments from the issuer,

8. the author concluded an agreement on services in connection with investment banking transactions in the last 12 months, and he has received consideration or promise of consideration from such agreement

In the present financial analysis the conflict-of-interest mentioned under 6. applies.

B. General disclosures/liability arrangement:

This document was prepared by EQUI.TS GmbH exclusively for information purposes.

This publication, if sold in the UK. may only be made available to those persons who, in the meaning of the Financial Services Act 1986 are authorised and exempt, or persons as defined in section 9 (3) of the Financial Services Act 1986 (Investment Advertisement) (Exemptions) Decree 1988 (amended version) and must not be transmitted directly or indirectly to other persons or groups of persons.

Neither this document nor any copy of it may be taken into, transferred to or distributed within the United States of America or its territories and possessions. The distribution of this document in Canada, Japan or other jurisdictions may be restricted by law. and persons who come into possession of this publication should find out about any such restrictions and respect them. Any

failure to respect these restrictions may represent a breach of the US, Canadian or Japanese securities laws or laws governing another jurisdiction.

By accepting this document you accept all disclaimers of liability and the restrictions cited above.

This document is neither a recommendation nor an offer nor application of an offer for the purchase, sale or subscription of any security or investment. It is by no means meant to provide investment advice.

This document, prepared by EQUI.TS GmbH, is based on information from sources (publicly available information and tax rates at the time of publication, which can, however, change), which, according to EQUI.TS GmbH, are dependable, yet not actually available for independent verification. Despite diligent verification, EQUI.TS GmbH cannot provide a guarantee, assurance or warranty for completeness and correctness; responsibility and liability is therefore excluded insofar as there is no intent or gross negligence on the part of EQUI.TS GmbH. All statements and opinions are exclusively those of EQUI.TS GmbH and can be changed without prior notice. Any error-caused misstatements of the document can be corrected by EQUI.TS GmbH, without EQUI.TS GmbH being held responsible for damages as a result of these misstatements.

This document is a translation of the legally binding German original version of **December 16, 2015**.