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:: 2nd World Epigenetics Summit

Munich, 7th-8th of December 2011

Resminostat:

A Novel Oral Histone Deacetylase Inhibitor in
Phase II Clinical Development

Dr. Bernd Hentsch, Chief Development Officer, 4SC AG, Germany

This presentation may contain projections or estimates relating to plans and objectives relating to our future operations, products, or services; future financial results; or assumptions underlying or relating to any such statements; each of which constitutes a forward-looking statement subject to risks and uncertainties, many of which are beyond our control. Actual results could differ materially, depending on a number of factors.

MISSION	<ul style="list-style-type: none"> ▪ 4SC develops targeted small-molecule therapies against inflammation & cancer
BUSINESS FOCUS	<ul style="list-style-type: none"> ▪ Broad & maturing product pipeline – multiple clinical trials in Phase I and II ▪ Integrated drug discovery and development platform ▪ Licensing agreements with biopharmaceutical companies
FINANCE & SHARES	<ul style="list-style-type: none"> ▪ Committed investor base & sufficient cash reserves to reach value inflection points ▪ Listed on Frankfurt Stock Exchange (Prime Standard: VSC)
ATTRACTIVE GOALS AHEAD	<ul style="list-style-type: none"> ▪ Lead inflammation product: <i>Vidofludimus</i> <ul style="list-style-type: none"> • Phase IIb study in IBD in preparation ▪ Lead oncology product: <i>Resminostat</i> <ul style="list-style-type: none"> • Pivotal phase III programme in oncology in preparation

Product	Indication	Mode	Preclinical	Phase I	Phase II	Phase III
AUTOIMMUNE DISEASES						
Vidofludimus (4SC-101)	Rheumatoid Arthritis (RA)	Inhibition of DHODH and IL-17 signaling	COMPONENT			
Vidofludimus (4SC-101)	Inflammatory Bowel Disease (IBD)	Inhibition of DHODH and IL-17 signaling	ENTRANCE			
ONCOLOGY						
Resminostat* (4SC-201)	Hepatocellular Carcinoma (HCC)	Oral Pan Histone-Deacetylase (HDAC)-Inhibitor	SHELTER			
Resminostat (4SC-201)	Hodgkin's Lymphoma (HL)	Oral Pan Histone-Deacetylase (HDAC)-Inhibitor	SAPHIRE			
Resminostat* (4SC-201)	K-ras mut. Colorectal Cancer (CL)	Oral Pan Histone-Deacetylase (HDAC)-Inhibitor	SHORE			
4SC-203	Oncology	Multi kinase inhibition – selective of FLT3 and VEGF-R2				
4SC-205	Solid Tumours and Lymphoma	Oral Eg5 Kinesin inhibitor	AEGIS			
4SC-202	Haematologic and Solid Tumours	Oral selective HDAC inhibitor with strong anti-mitotic effect	TOPAS			
4SC-207	Haematologic and Solid Tumours	Oral resistance breaking cell cycle blocker				

* Cooperation with Yakult Honsha, Japan

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BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS

BIOWORLD® TODAY

FRIDAY APRIL 15, 2011 THE DAILY BIOTECHNOLOGY NEWSPAPER VOLUME 22, No. 73 PAGE 1 OF 7

4SC in \$192M Agreement for Japan Rights to Resminostat

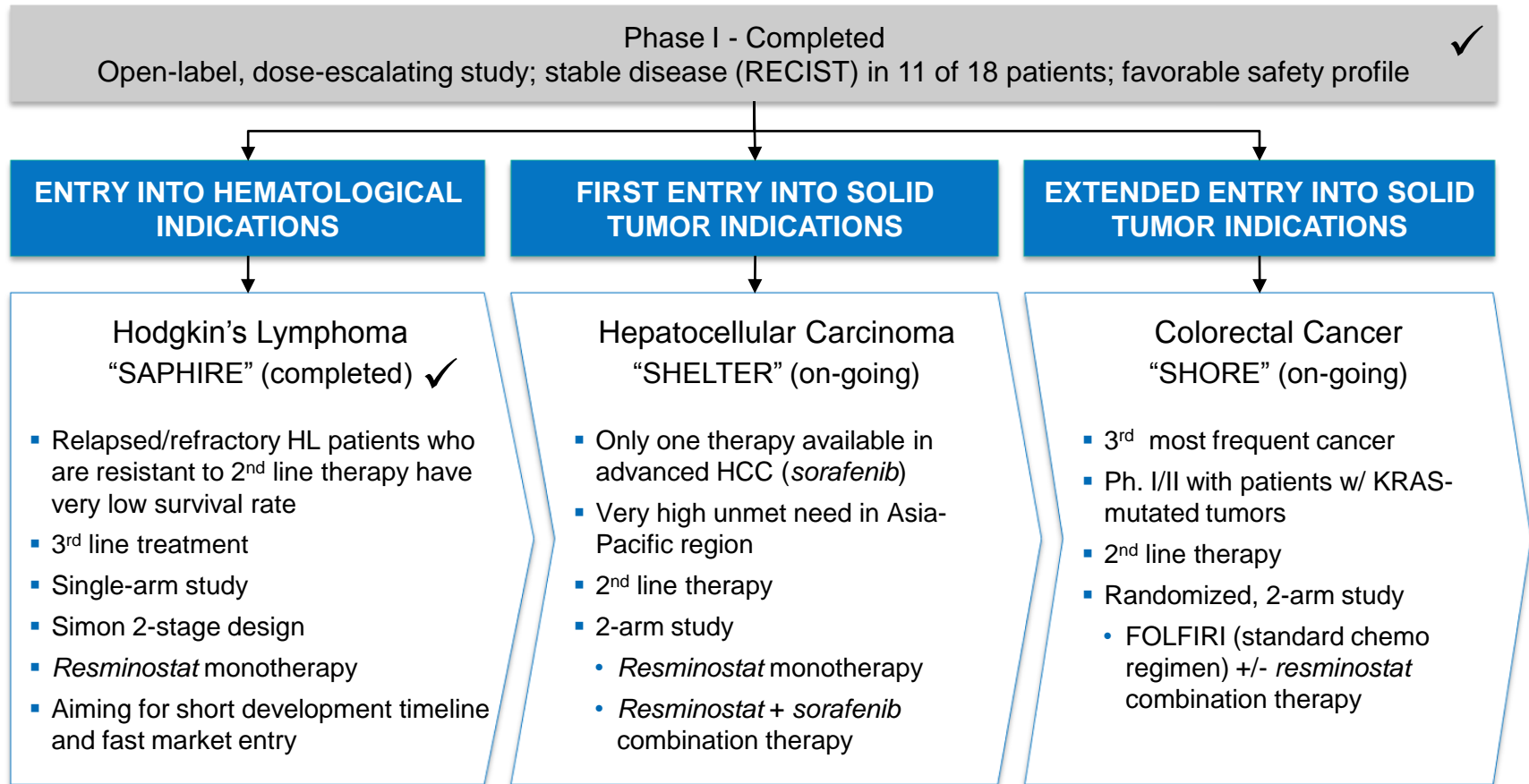
By Cormac Sheridan
BioWorld Today Correspondent

Setting down a weighty marker for partnering deals elsewhere, 4SC AG is pocketing €6 million (US\$8.7 million) up front and could earn another €127 million in milestones, for licensing Japanese rights to its oral pan-histone deacetylase (HDAC) inhibitor resminostat (4SC-201).

Tokyo-based Yakult Honsha Co. Ltd. gained exclusive rights to develop and commercialize the compound in all oncology indications in its home country.

It will focus initially on hepatocellular carcinoma (HCC), which has a relatively high prevalence in Asian populations, and on patients with colorectal carcinoma (CRC) who harbor KRAS mutations.

The Martinsried, Germany-based company is pursuing an aggressive development strategy, CEO Ulrich Dauer told *BioWorld Today*.



RESMINOSTAT IS EXPLORED AS SINGLE AGENT ANTI-CANCER DRUG AND AS A (RE-)SENSITIZING AGENT IN COMBINATION WITH ESTABLISHED TUMOR THERAPIES.

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MONOTHERAPY APPROACH:

PHASE II IN HODGKIN'S LYMPHOMA (HL)

- Relapsed and/or refractory HL patients who are resistant to 2nd line treatment have 5-year overall survival rate of only 17%¹
 - High medical need for new 3rd line options with less long-term toxicity²
 - Regulatory agencies open to small pivotal trial(s), allowing for rapid development and near-term launch
- 1st and 2nd line therapies are efficacious, but patients frequently develop secondary malignancies later in life induced by heavy exposure to chemotherapy
 - High medical need for reduction of chemo during earlier lines of treatment
- Orphan drug status granted in USA and EU

RESMINOSTAT IN HL THERAPY:

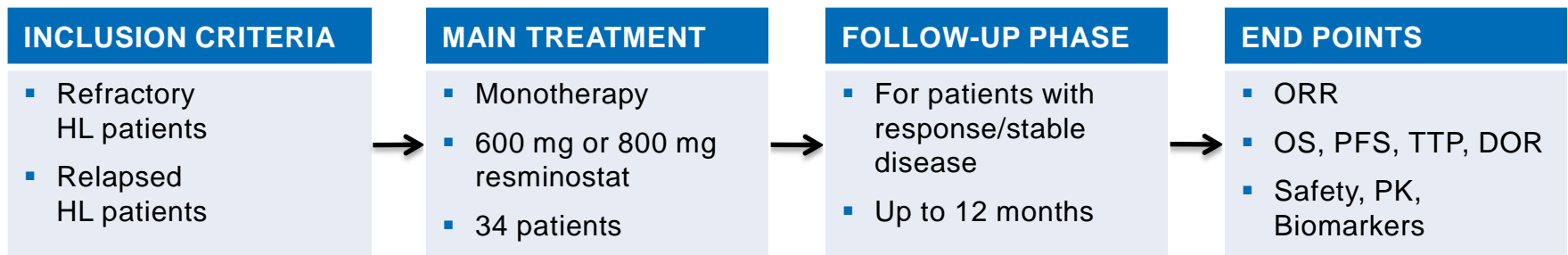
1. ESTABLISHING RESMINOSTAT AS NEW THIRD-LINE OPTION

2. EXTENSION OF RESMINOSTAT TO EARLIER LINES OF TREATMENT, E.G., MAINTENANCE THERAPY APPROACH POST CHEMO / RADIATION / ASCT

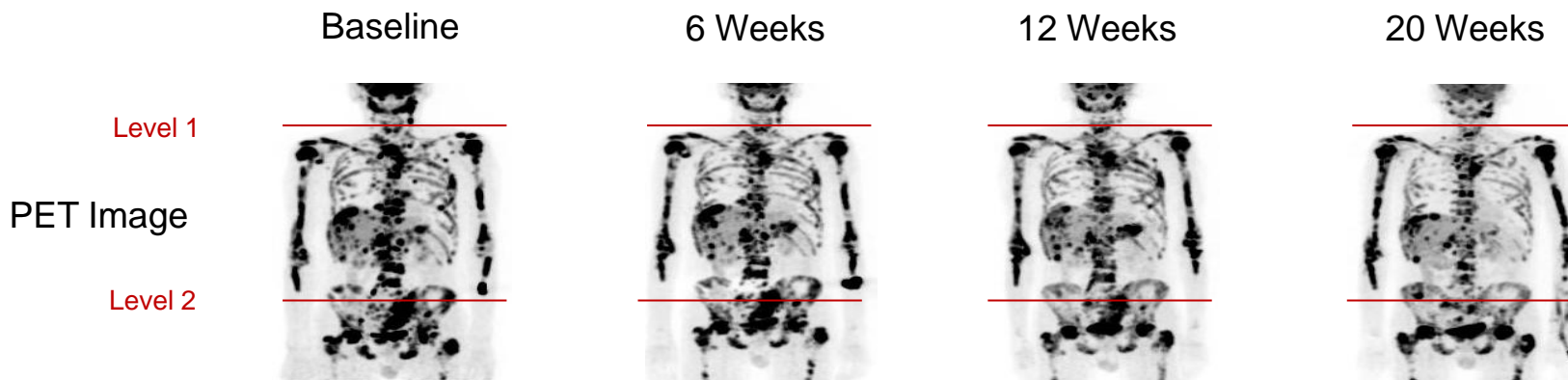
¹ Sirohi *et al.*, *Ann. Oncol.* 2008; 19(7):1312-9

² Datamonitor, Pipeline Insight: *Lymphomas, Multiple Myelomas and Myelodysplastic Syndromes* (2010)

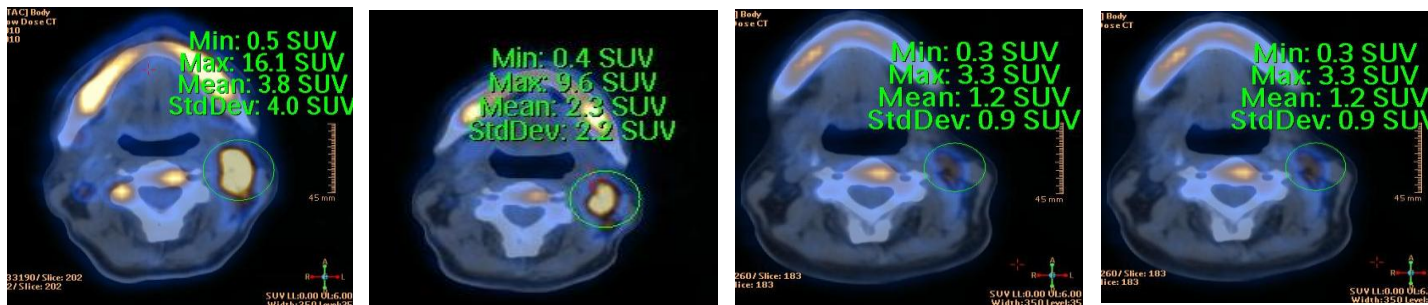
- Phase II open-label, single-arm, multi-center, multinational trial¹
- Once-daily oral dosing of *resminostat* (600 mg and 800 mg); Simon two-stage design; 14-day treatment cycles (“5+9”, *i.e.* 5 days on, 9 days off)
- 12 weeks of therapy during main treatment phase; optional treatment extension thereafter upon demonstration of clinical benefit



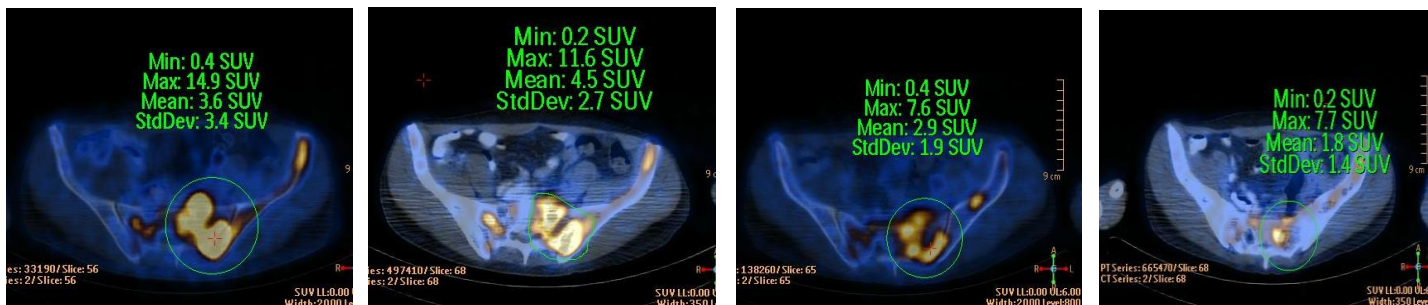
¹ www.clinicaltrials.gov: NCT01037478

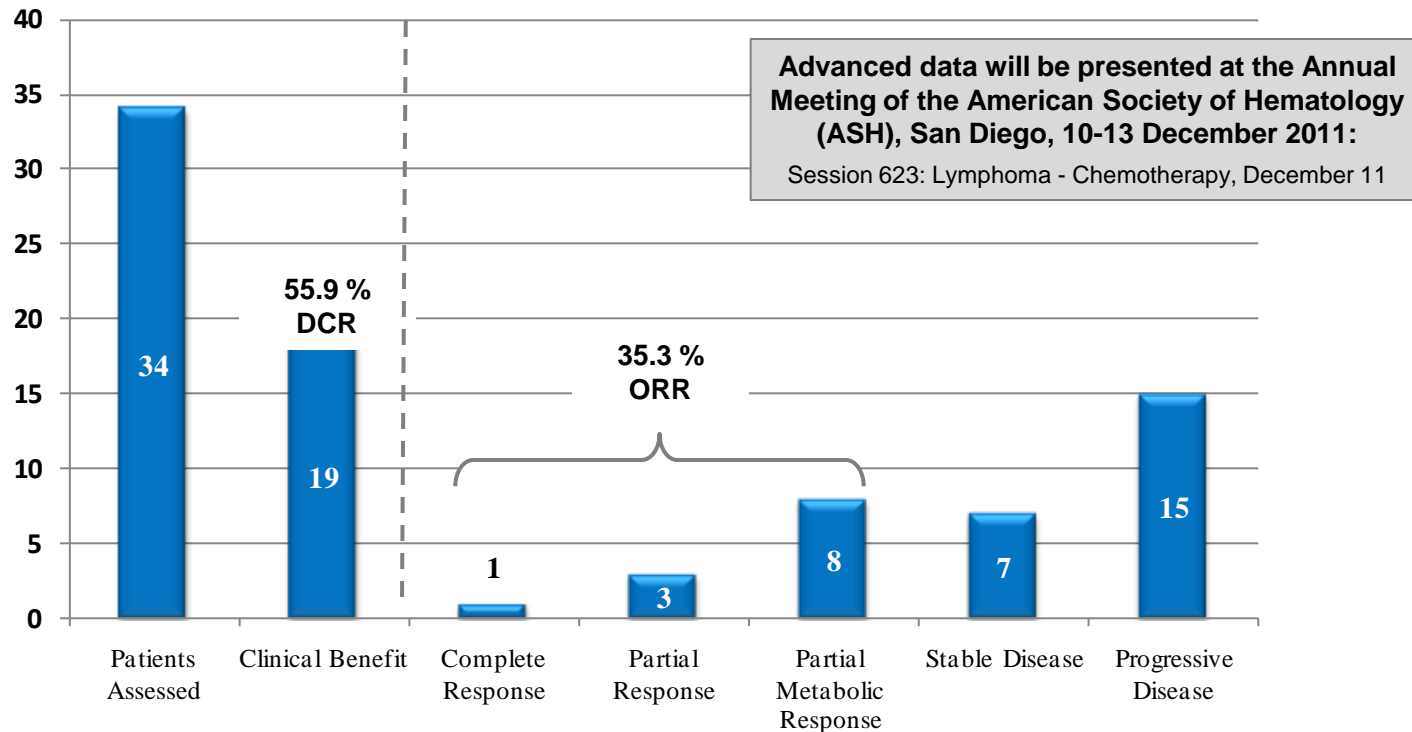


PET/CT Image at Level 1



PET/CT Image at Level 2





* Clinical activity was measured through PET/CT, *i.e.*, combination of positron-emission tomography (PET) and computer tomography (CT). Complete and partial responses were measured according to Cheson criteria,¹ and metabolic responses according to EORTC criteria.²

DCR = Disease Control Rate | ORR = Overall Response Rate

**19 PATIENTS (55.9%) WITH CLINICAL BENEFIT;
12 PATIENTS (35.3%) QUALIFIED AS RESPONDERS.**

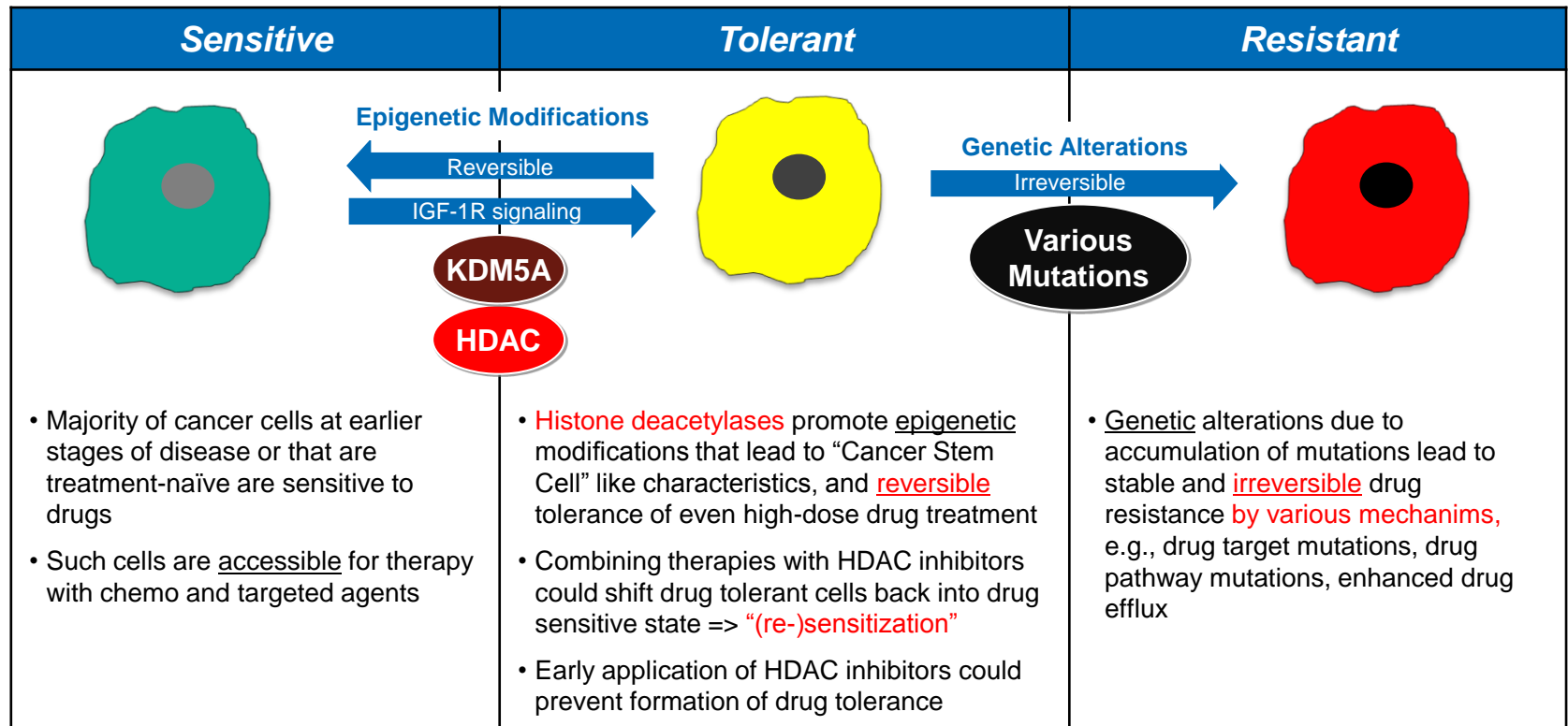
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THE PRINCIPLE OF (RE-)SENSITIZATION OF DRUG TOLERANT CANCER CELLS

HDACs PROMOTE REVERSIBLE DRUG TOLERANCE THROUGH EPIGENETIC MODIFICATION

- Growing evidence indicates that resistance to cancer drugs involves a reversible “drug-tolerant” state, and that HDACs play crucial role in drug tolerance development¹



THE POTENTIAL ABILITY TO PREVENT AND REVERSE DRUG TOLERANCE EXPLAINS THE SUITABILITY OF HDAC INHIBITORS AS PROMISING COMBINATION AGENTS.

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MONOTHERAPY & (RE-)SENSITIZATION: PHASE II IN HEPATOCELLULAR CARCINOMA

HEPATOCELLULAR CARCINOMA (HCC) IS LACKING EFFECTIVE TREATMENT OPTIONS



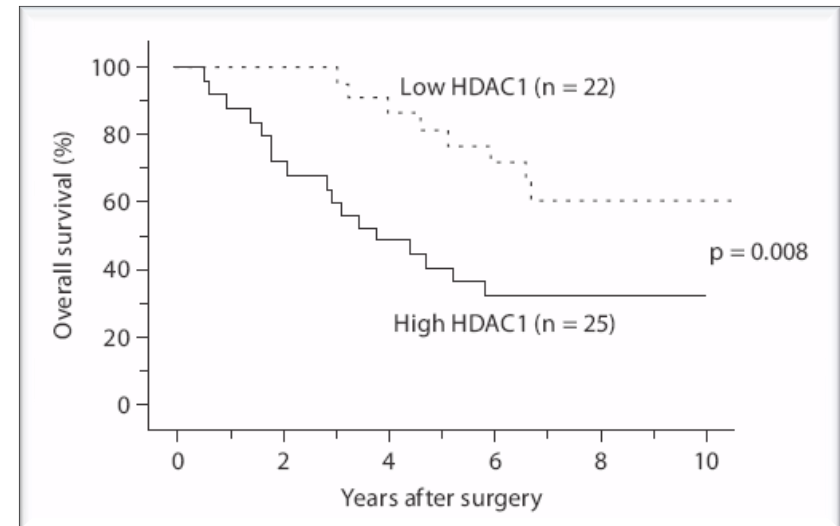
- High unmet medical need due to limited treatment options
 - Prognosis of patients with unresectable HCC is poor, with median survival of less than 1 year¹ and ca. 700,000 deaths/year worldwide²
 - Sorafenib is the only approved 1st line therapy for advanced-stage HCC; no 2nd line therapy available after progression on sorafenib
 - High medical need to improve 1st line options, and urgent need for 2nd line options with focus on re-sensitization of sorafenib-refractory tumors

Liver Stage	Treatment intervention	1 st line systemic regimens used	2 nd line regimens used
Resectable <i>BCLC 0,A: 30%-40%</i>	<ul style="list-style-type: none"> • Surgery • Liver transplantation • Local ablation 	<ul style="list-style-type: none"> • NA 	<ul style="list-style-type: none"> • NA
Unresectable/metastatic <i>BCLC B: 20%</i> <i>BCLC C: 40%</i> <i>BCLC D: 10%</i>	<ul style="list-style-type: none"> • Chemoembolization (B) • Sorafenib (C) • Best supportive care (D) • Exploratory drugs 	<ul style="list-style-type: none"> • Sorafenib OS: 10.7 months TTP: 5.5 months Placebo TTP: 2.8 months 	<ul style="list-style-type: none"> • Exploratory drugs • Best supportive care OS: 3 to 6 months TTP: ~ 1.5 months

¹Llovet et al. J. Natl. Cancer Inst. 2008;100:698-711

²GLOBOCAN 2008, available from <http://globocan.iarc.fr>

- In HCC patients, high HDAC-1 expression correlates with:¹
 - Higher incidence of cancer cell invasion into the portal vein
 - Poorer histological differentiation
 - More advanced TNM stage
 - Lower survival rates after surgical resection



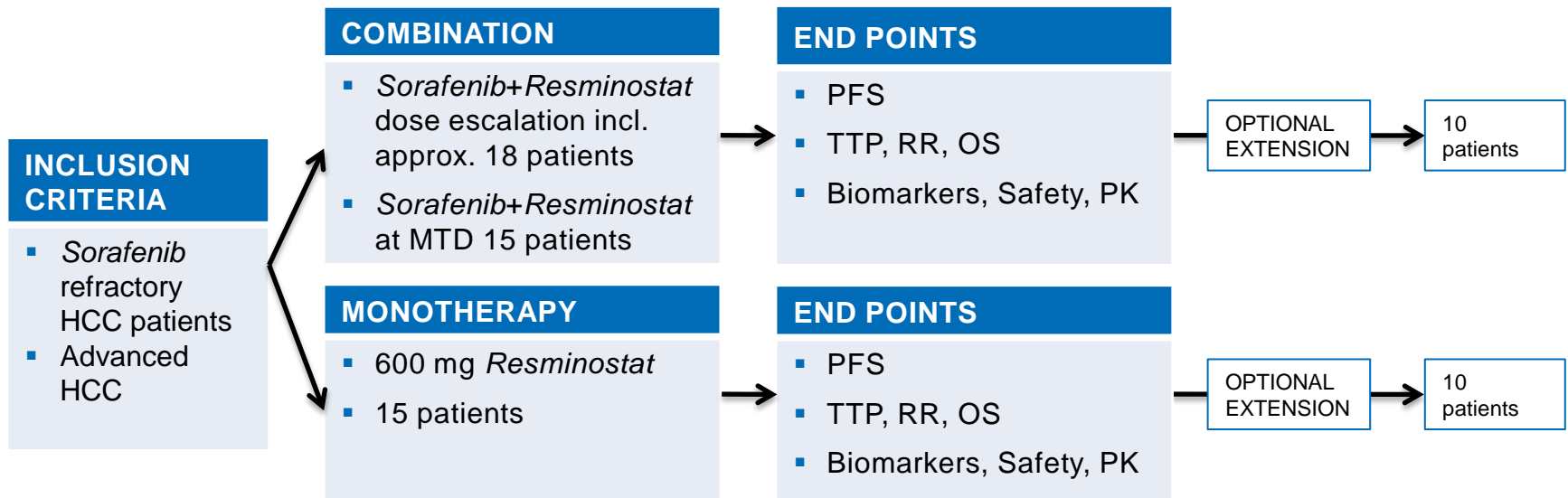
- Furthermore, expression levels of HDAC-1, -2 and -3 correlate with HCC recurrence rate following liver transplantation²
- Resminostat acts synergistically in combination with sorafenib
- Orphan drug status for resminostat in HCC granted in USA and EU

HIGH LEVELS OF HDAC EXPRESSION ARE LINKED TO POOR PROGNOSIS IN HCC.

¹ Rikimaru *et al.*, *Oncology* 2007; 72:69-74

² Wu *et al.*, *PLoS One* 2010; 5:e14460

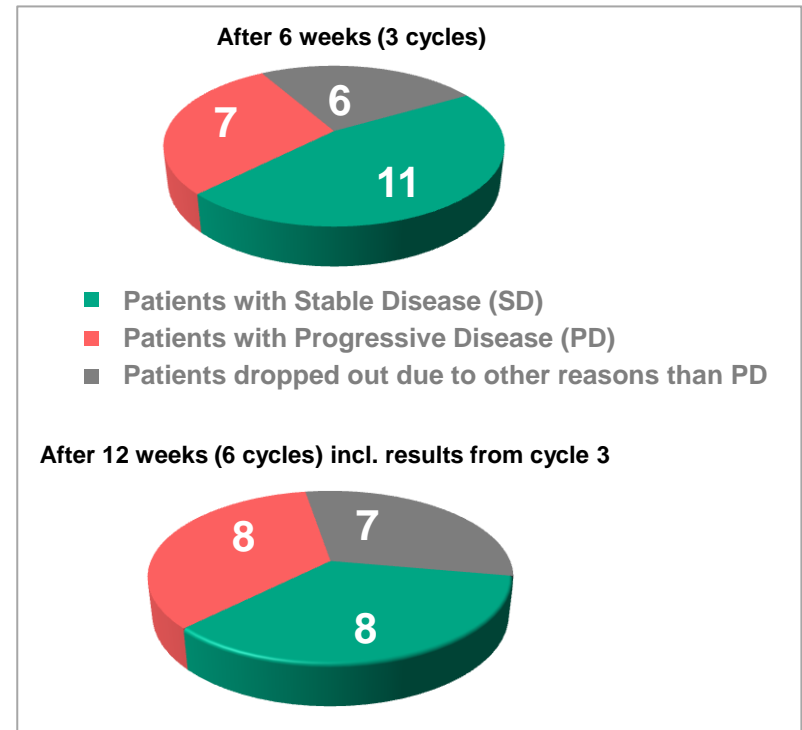
- Ph. II open-label, two-arm, multi-center trial in Germany and Italy¹
- Once-daily oral dosing of *resminostat*; 14-day treatment cycles (“5+9”, *i.e.*, 5 days on, 9 days off; continuous administration of *sorafenib*)
- 12 weeks of therapy during main treatment phase; optional treatment extension thereafter upon demonstration of clinical benefit



¹ www.clinicaltrials.gov: NCT00943449

- Interim Progression Free Survival Rate (PFSR, n=18):¹
 - After 6 weeks (Cycle 3): 61% (11/18)
 - After 12 weeks (Cycle 6): 50% (8/16)
- Resminostat and sorafenib can be combined in advanced HCC patients
- New therapy opportunity for **1st and 2nd line** development

Advanced data to be presented at the
 2012 ASCO Gastrointestinal Cancers Symposium,
 San Francisco, 19-21 January 2012:
 Abstract ID #262; General Poster Session B



**INTERIM PFSR* (PROGRESSION FREE SURVIVAL RATE):
 AT 6 WEEKS (CYCLE 3) = 61% (11/18) / AT WEEK 12 (CYCLE 6) = 50% (8/16)**

¹ Data represent the total patient population from both study arms, i.e. monotherapy and combination (dose escalation and maintenance).
 See www.4sc.de/product-pipeline/publications-posters

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CLINICAL SAFETY SUMMARY

■ Profile of Adverse Events¹

- GI disturbances (nausea, vomiting) and fatigue (esp. in long-term treatment)
- Hematological effects (thrombocytopenia, anemia) → predominant in SAPHIRE
- Mild to moderate in most cases; manageable, generally not treatment-limiting
- Cardiovascular effects typical of other HDAC inhibitors were not prominent (analysed via central ECG assessments)

■ Profile of Serious Adverse Events¹

- Heterogeneous; mostly related to the underlying advanced disease stages
- In the majority, hematological events (thrombocytopenia, anemia) in SAPHIRE; causal relationship to the heavily pretreated HL population; manageable and only in rare cases treatment-limiting

RESMINOSTAT'S FAVORABLE SAFETY PROFILE RENDERS IT A COMBINATION PARTNER FOR VARIOUS CANCER THERAPIES, INCL. CYTOTOXICS AND NOVEL TARGETED THERAPIES IN SOLID AND HEMATOLOGICAL TUMORS.

¹ Phase I, SHELTER, SAPHIRE, and SHORE trials

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PHASE I/II IN COLORECTAL CANCER (CRC)

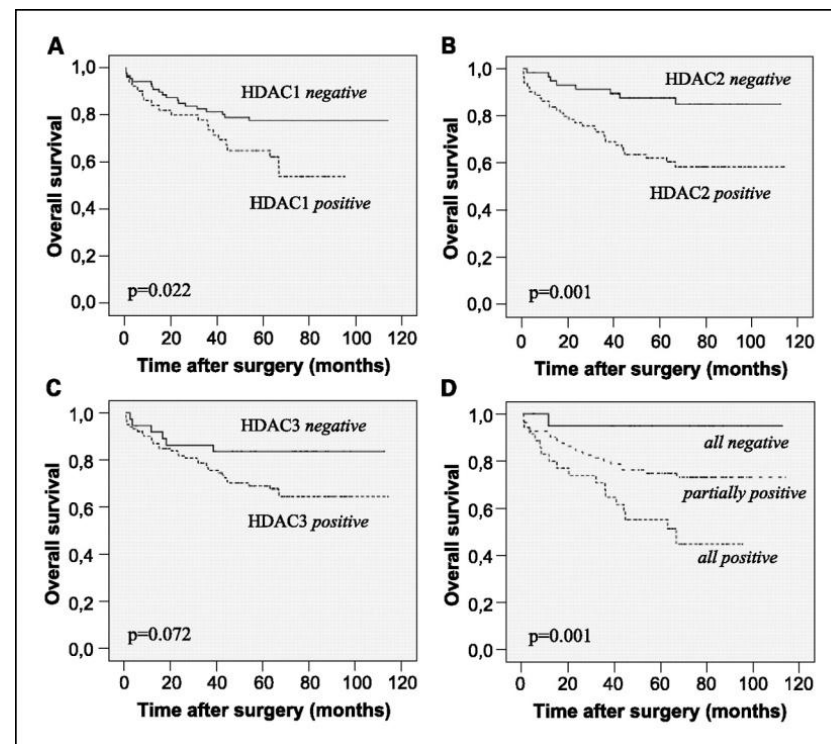
- Colorectal carcinoma (CRC) is third most common cancer (~1.2M cases worldwide in 2008) and fourth leading cause of cancer-related mortality (~600,000 deaths in 2008)¹
- Epidermal growth factor receptor (EGFR) inhibitors have expanded CRC treatment options, *e.g. cetuximab* and *panitumumab*
- Substantial evidence now exists that KRAS mutations, which are present in approx. 35%-45% of CRC patients, are associated with insufficient response to EGFR targeting therapies²
- Patients with CRC harboring KRAS mutations with high medical need for additional therapy options

RESMINOSTAT OFFERS NEW SECOND-LINE TREATMENT OPTION
FOR KRAS-MUTANT CRC PATIENTS.

¹ GLOBOCAN 2008, available from: <http://globocan.iarc.fr>;

² Van Cutsem *et al.*, *N. Engl. J. Med.* 2009; 360(14):1408-17.

- Class I HDACs found to be highly expressed in colorectal adenocarcinomas¹
- HDAC-3 is overexpressed in ~50% of all colon adenocarcinomas²
- HDAC-2 is upregulated in APC-mutant cells and in most colon cancers, and confers survival advantage to colon tumor cells³
- Patients showing overexpression of class I HDAC isoforms had dramatically reduced survival times¹



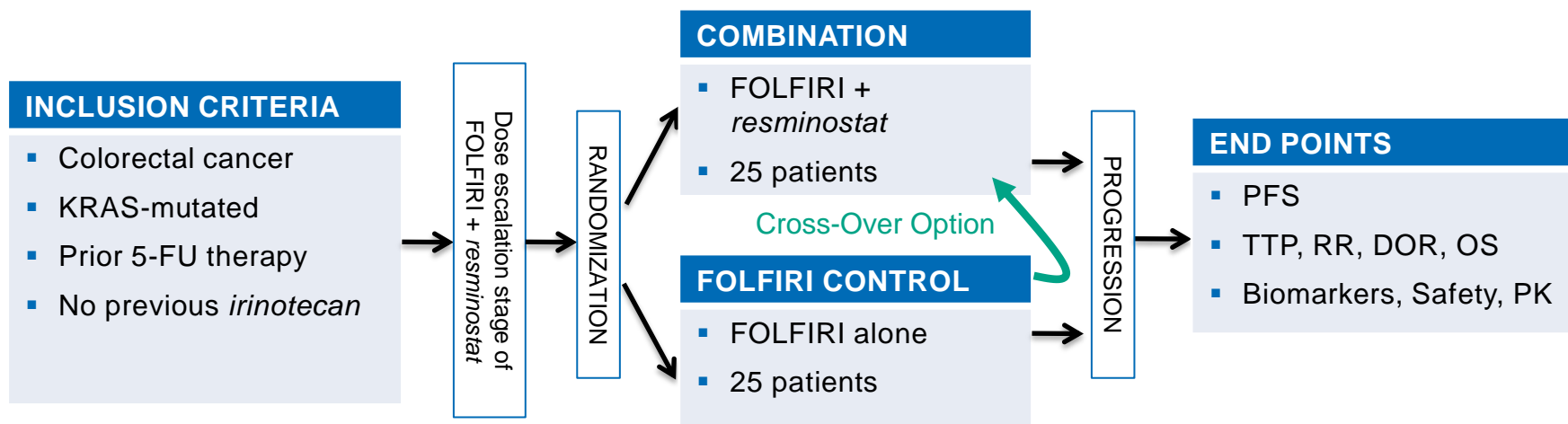
Kaplan-Meier survival curves dependent on HDAC isoform expression patterns. Overall survival dependent on HDAC-1 (A), HDAC-2 (B), HDAC-3 (C), and combined HDAC (D) expression. P values were calculated with log-rank test.¹

HDAC EXPRESSION CORRELATES WITH POOR PROGNOSIS IN CRC PATIENTS.

¹ Weichert *et al.*, *Clin. Cancer Res.* 2008; 14(6):1669-77;

² Ashktorab *et al.*, *Dig. Dis. Sci.* 2009; 54(10):2109-17; ³ Zhu *et al.*, *Cancer Cell* 2004; 5(5):455-63.

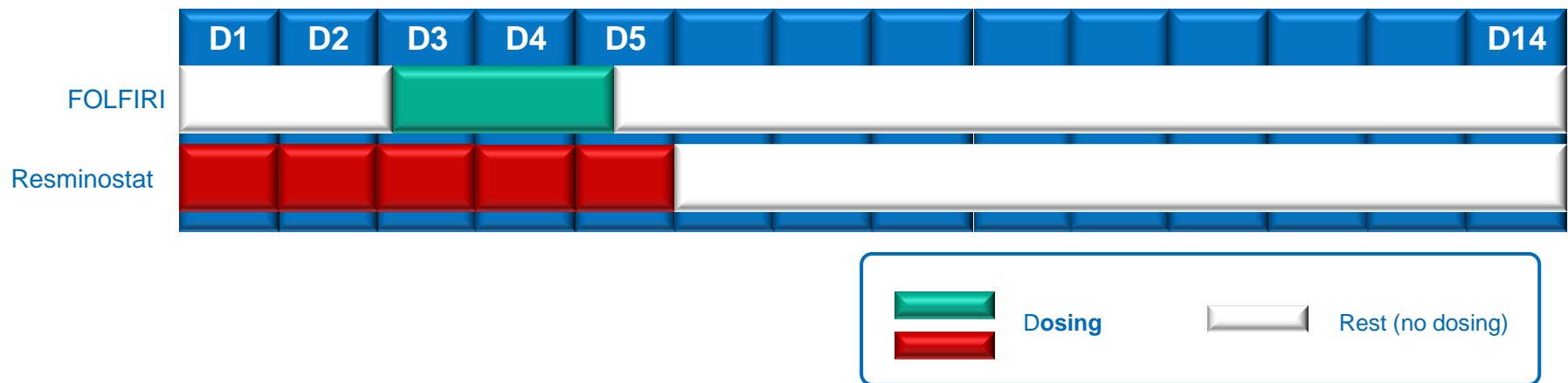
- Ph. I/II trial recruiting up to 70 patients¹
- Randomized, open-label, multi-center, 2-arm study in combination with FOLFIRI vs. FOLFIRI alone in 2nd line therapy
- Once-daily oral dosing of *resminostat* at MTD (determined through dose escalation arm in 20 patients) with FOLFIRI; “5+9” treatment cycles until progression



¹ www.clinicaltrials.gov: NCT001277406

www.4sc.de/product-pipeline/publications-posters: 22nd EORTC-NCI-AACR Symposium, Berlin, 2010

- SHORE Study Status
 - First dose levels completed
 - Dose escalation ongoing
- Resminostat is administered prior to, during and after FOLFIRI dosage
- Treatment duration (number of cycles) is not limited
 - Treatment up to progression, toxicity or withdrawal of consent



- Clinical development program in 3 indications ongoing:

HL

- Low survival rate among relapsed/refractory HL patients resistant to 2nd line therapy
- Clear, objective responses to *resminostat* **monotherapy** in heavily pretreated patients
- Target lesion size reductions of >50%; frequent decreases in metabolic tumor activity
- Excellent safety profile in heavily pretreated patient population

HCC

- Only single therapy line available, i.e. sorafenib
- Interim data show frequently 3 months PFS reached
- Very good safety profile in severely debilitated patients
- Large commercial potential in Asia-Pacific, incl. China
- Novel mode of action of “**(Re-)Sensitization**” in this solid tumor; preclinical synergism with *sorafenib*

CRC

- CRC patients with KRAS-mutant tumors have limited treatment options
- Extension to KRAS-wild type patients possible
- Combination may be expandable to 1st line
- Combination with cytotoxics suitable for other cancers
- “**(Re-)Sensitization**” approach, strong preclinical activity with *irinotecan*

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ACKNOWLEDGEMENT

THANKS TO THE PATIENTS AND THEIR FAMILIES

THANKS TO THE CLINICAL INVESTIGATORS AND STUDY GROUPS

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THANK YOU VERY MUCH !

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