August 12, 2013

**OUTPERFORM**

Reason for report:

**INITIATION**

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HEALTHCARE EQUITY RESEARCH

# ONCOMED PHARMACEUTICALS, INC.

## A Platform in CSC and a Portfolio of First-in-Class Biologics; Initiate at OP

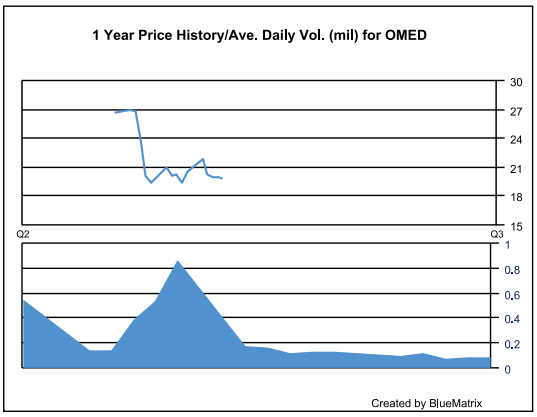
• **Bottom Line:** We are initiating coverage of OMED with an OP rating and a price target of $27. OMED is the longest-standing cancer stem cell (CSC)-focused biotech company. It has a strong technology platform centered on identifying and targeting the critical pathways for cancer stem cells, coupled with monitoring specific surface markers. OMED has developed full pipeline assets internally and possesses a portfolio of five anti-CSC monoclonal antibodies in clinical development. The breadth of the pipeline with a sharp focus on CSC provides multiple shots on goal.

• **All 5 of OMED's clinical candidates are first in class.** Together with 2 additional candidates that are also likely first in class and could enter the clinic in 2014, OMED's portfolio of agents systematically target several of critically important pathways in cancer -- Notch, Wnt, and RSPO-LGR. Although the ultimate success remains to be proven clinically, validations of these targets include mutations identified in genome sequencing. All of OMED's candidates are antibodies or protein-based macromolecules, and its portfolio represents one of the largest clusters of biologics in a small-cap biotech company.

• **OMED has formed partnerships with GSK (MP) and Bayer to co-develop CSC therapeutics targeting the Notch and Wnt signaling pathways, respectively.** The deals provided a cost-effective development path for OMED. In addition, these partnerships provide an independent validation for the platform and targeted CSC therapies.

• **In addition to the 4 partnered programs, OMED has a clinical-stage program as well as two late-preclinical candidates that are wholly owned.** Demcizumab is the most advanced anti-Dll4 antibody targeting the Dll4/Notch signaling pathway. Although cardiovascular (CV) risk was seen as a class toxicity, it may be manageable through truncated dosing. Additionally, the wholly owned bi-specific Dll4/VEGF candidate could potentially provide enhanced activity while potentially mitigating CV toxicity owing to VEGF targeting. Another program targets internally discovered RSPO and could generate high interest as it advances to the clinic.

| **Key Stats:** | **(Symbol:OMED)** |
|---|---|
| **S&P 600 Health Care Index:** | **1,114.02** |
| **Price:** | **$19.84** |
| Price Target: | $27.00 |
| Methodology: | NPV and sum-of-parts |
| 52 Week High: | $31.00 |
| 52 Week Low: | $17.00 |
| Shares Outstanding (mil): | 28.0 |
| Market Capitalization (mil): | $555.5 |
| Book Value/Share: | $(5.49) |
| Cash Per Share: | $4.97 |
| Dividend (ann): | $0.00 |
| Dividend Yield: | 0.0% |




| Dec Yr | 1Q | 2Q | 3Q | 4Q | FY Rev | 1Q | 2Q | 3Q | 4Q | FY EPS | P/E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2012A** | -- | -- | -- | -- | $31.4 | -- | -- | -- | -- | ($21.30) | NM |
| **2013E** | $2.9A | $3.0 | $13.5 | $15.5 | $34.9 | ($0.39)A | ($0.40) | ($0.02) | ($0.04) | ($0.74) | NM |
| **2014E** | -- | -- | -- | -- | $47.0 | -- | -- | -- | -- | ($0.30) | NM |

*Source: Company Information and Leerink Swann LLC Research*
*Revenues in M; EPS are GAAP. OMED went public via an IPO on 7/18/13.*

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*The* Healthcare Investment Bank™

# OncoMed Pharmaceuticals

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# OncoMed Overview

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- Strong technology platform focusing on cancer stem cells with full pipeline assets developed internally.
- Five anti-CSC product candidates in clinical development and have treated an aggregate of over 255 patients. Each program is coupled with prospective testing of predictive biomarker, enhancing probability of success.
- All products are biologics, providing extended market potential beyond patent protection.
- GSK and Bayer partnerships independently validate the platform and provide a cost-effective development path.
- Wholly owned assets provide large economic upside for investors.
- Key financials: 28M dilutive shares, ~$138M cash ($4.97/share)

# Investment Thesis

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- OMED is the longest-standing cancer stem cell (CSC)-focused biotech company. It has a strong technology platform centered on the identifying and targeting of the critical pathways for cancer stem cells, coupled with monitoring specific surface markers. OMED has developed full pipeline assets internally and possesses a portfolio of 5 anti-CSC monoclonal antibodies in clinical development. The breadth of the pipeline with a sharp focus on CSC provides multiple shots on goal.

- All 5 of OMED's clinical candidates are first in class. Together with 2additional candidates that are also likely first in class and could enter the clinic in 2014, OMED's portfolio of agents systematically target several of critically important pathways in cancer -- Notch, Wnt, and RSPO-LGR. Although the ultimate success remains to be proven clinically, validations of these targets include mutations identified in genome sequencing. All of OMED's candidates are antibodies or protein-based macromolecules, and its portfolio represents one of the largest clusters of biologics in a small-cap biotech company.

# Investment Thesis

LEERINK SWANN

- OMED has formed partnerships with GSK and Bayer to co-develop CSC therapeutics targeting the Notch and Wnt signaling pathways, respectively. The deals provided a cost-effective development path for OMED. In addition, these partnerships provide an independent validation for the platform and targeted CSC therapies.
- In addition to the 4 partnered programs, OMED has a clinical-stage program as well as two late-preclinical candidates that are wholly owned. Demcizumab is the most advanced anti-Dll4 antibody targeting the Dll4/Notch signaling pathway. Although cardiovascular risk was seen as a class toxicity, it may be manageable through truncated dosing. Additionally, the wholly owned bi-specific Dll4/VEGF candidate could potentially provide enhanced activity while potentially mitigating CV toxicity owing to its VEGF target. Another program targets internally discovered RSPO and could generate high interest as it advances to clinic.

# Valuation

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- We value OMED at $27 per share based on an NPV and sum-of-the-parts methodology.
- We assume demcizumab and four partner candidates launch in the front-line settings for pancreatic cancer, NSCLC (non-small cell lung cancer) and ovarian cancer in 2019-20 in the U.S. and in 2020-21 in the EU. Our royalty assumption is 12-15% for two Notch inhibitors and 12-16% for the first Wnt inhibitor and 5-10% for the second Wnt inhibitor.
- Our projection for peak penetration is 12% for NSCLC, 20% for pancreatic cancer, and 18% for ovarian cancer in the U.S. Our projection for probability-weighted (10%) sales for each asset reaches $245M by 2030, two years after patent expiration.
- We include $100M valuation for the platform and other pipeline, and estimated $127M cash at YE:14. We also assign 5X terminal value multiple to account for challenging generic entry for large molecule drugs.
- We use a discount rate of 10%, which we believe is appropriate given probability-weighted sales projection.

# Risks to Valuation

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- Development risk – All of pipeline assets are still in early-stage clinical or preclinical development and they could fail at each development stage. OMED's agents have been all first-in-class. While this improves the upside upon success, the developmental risk may be higher.
- As therapies targeting cancer stem cells by design may only affect a small subpopulation of the tumor cells, observing an anti-tumor signal in early clinical development may be more challenging and demonstration of clinical efficacy may require a randomized study with a longer follow-up.
- Financing risk – OMED has estimated pro forma cash of ~$138M based on a cash balance of $60M as of 3/31/2013 and IPO net proceeds of ~$87M. We believe this could be sufficient to fund operations through the readout of most current ongoing/planned Phase I/II trials.

# OncoMed – Internally Discovered Pipeline

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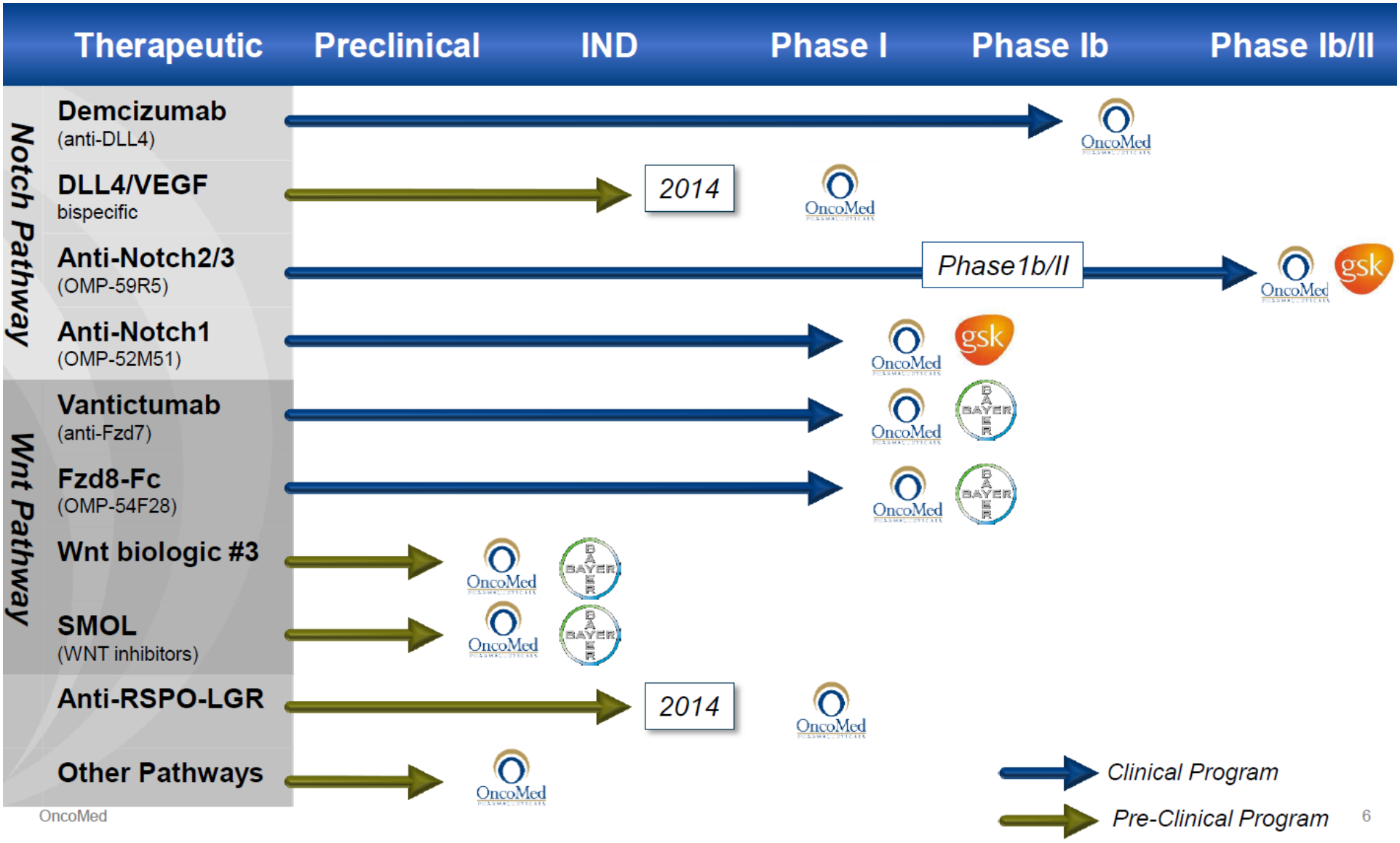
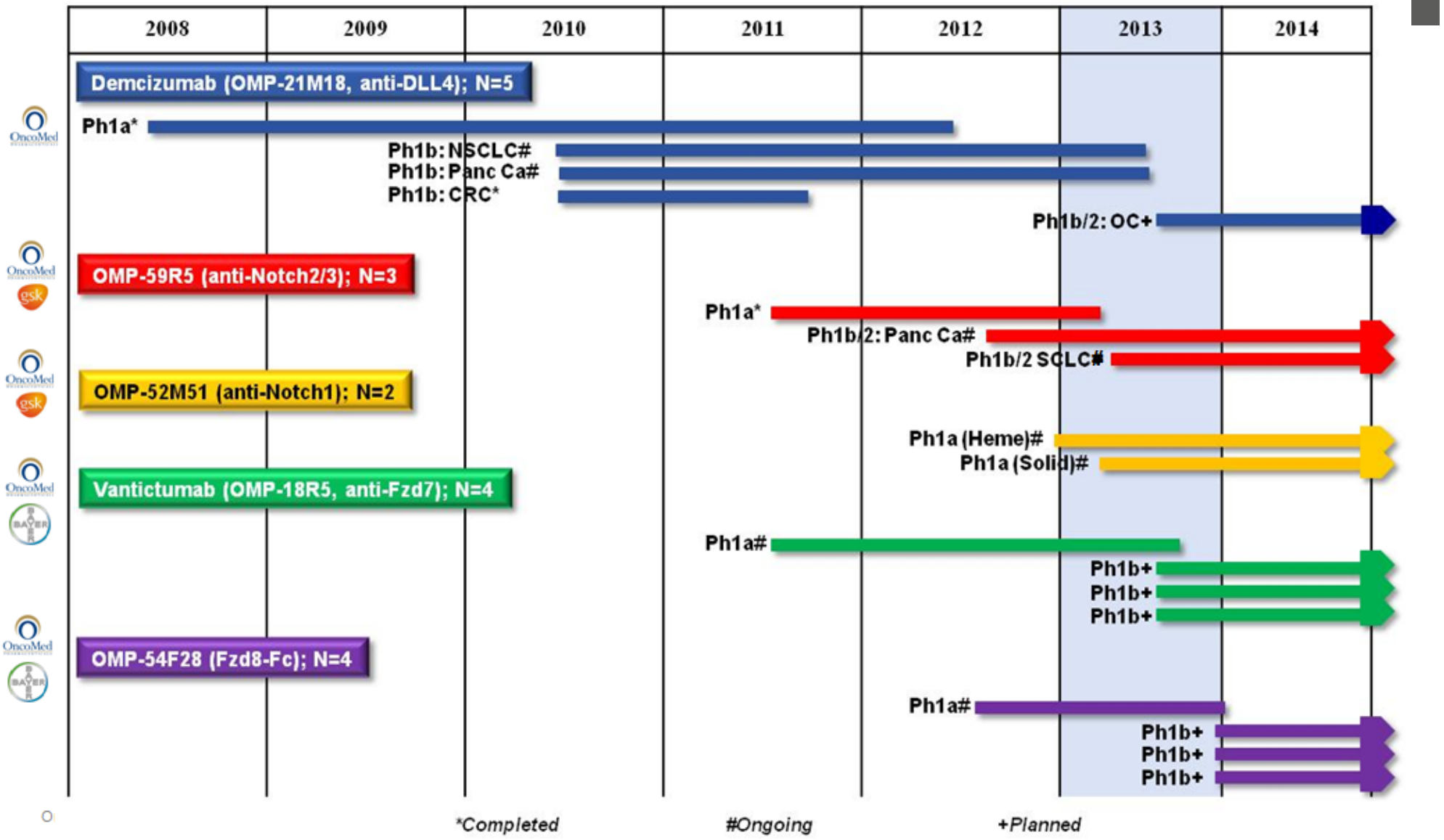



*Source: Company Reports and Leerink Swann*

# OncoMed – Ongoing and Planned Trials




*Source: Company Reports*

# Key Expected Events – Data News Flow

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| Drug | Time | Event |
|---|---|---|
| **Notch Pathway** | | |
| Demcizumab ('21M18, anti-DLL4) | 2H:13 | Initiation of Phase Ib/2 (Taxol+DEM) at MDACC in recurrent ovarian cancer |
| OMP-59R5 (anti-Notch2/3) | 2H:13/2014 | Advancing ALPINE in front line pancreatic cancer and PINNACLE in front line small cell lung cancer |
| OMP-52M51 (anti-Notch 1) | 2H:13/2014 | Advancing Phase Ia trials in hematologic and solid tumors |
| DLL4/VEGF | 2014 | IND filing |
| **Wnt Pathway** | | |
| Vantictumab ('18R5, anti-Fzd7) | 2H:13 | Initiation of 3 Phase Ib combination therapy in solid tumors |
| OMP-54F28 (anti-Fzd8-Fc) | 2H:13/2014 | Initiation of 3 Phase Ib studies in solid tumors |

*Source: Company reports and Leerink Swann*

# Expected Data Readouts Through 2016 – from Potentially 11 Randomized Phase II

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| Program | Objective |
|---|---|
| Demcizumab | Phase Ib NSCLC: results |
| | Phase Ib Pancreatic Cancer: results |
| | Phase Ib/II Ovarian Cancer: Phase Ib* initiation and results |
| | Phase Ib/II Ovarian Cancer: Phase II* initiation and results |
| Anti-Notch2/3 | Phase Ib/II ALPINE: Phase Ib* results |
| | Phase Ib/II ALPINE: Phase II* initiation and results |
| | Phase Ib/II PINNACLE: Phase Ib* results |
| | Phase Ib/II PINNACLE: Phase II* initiation and results |
| Anti-Notch1 | Phase Ia Hematologic: results |
| | Phase Ia Solid Tumor: results |
| | Phase Ib Hematologic: initiation and results |
| | Phase Ib Solid Tumor: initiation and results |
| | Phase II Hematologic: initiation and results |
| | Phase II Solid Tumor: initiation and results |
| Vantictumab | Phase Ia: results |
| | Phase Ib: indication #1 initiation and results |
| | Phase Ib: indication #2 initiation and results |
| | Phase Ib: indication #3 initiation and results |
| Fzd8-Fc | Phase Ia: results |
| | Phase Ib: indication #1 initiation and results |
| | Phase Ib: indication #2 initiation and results |
| | Phase Ib: indication #3 initiation and results |

- Additional data expected from OMED's preclinical programs

*Source: Company reports*

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# KEY INVESTMENT CONSIDERATIONS

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# TARGETING CANCER STEM CELLS – RATIONALE AND CONTROVERSIES

# Hypothesis of Cancer Stem Cells for Why Most Current Cancer Therapies Are Ineffective

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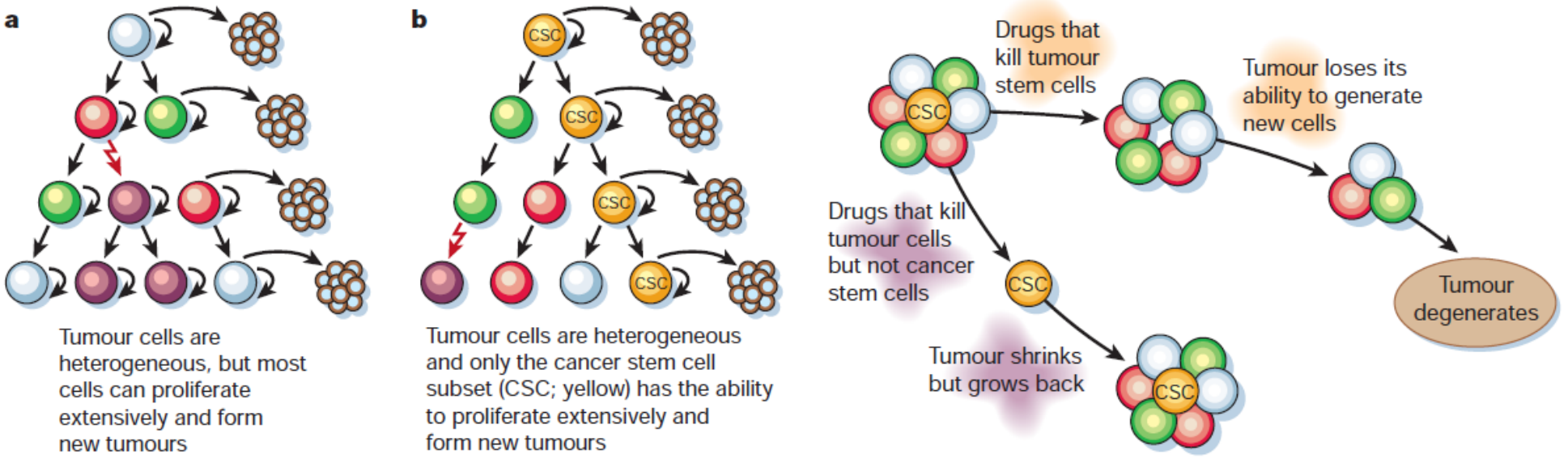
- Two general models of heterogeneity in solid tumor cells.
  a) Tumor cells are heterogeneous and most cells can proliferate to form new tumors.
  b) Tumor cells are heterogeneous and only cancer stem cell (CSC) has the ability to proliferate to form new tumors
- The existing therapeutic approach has been based largely on the model “a”; however, the failure of these therapies to cure most solid tumors suggests that model “b” might be more accurate.




*Source: *Reya et al, Nature (2001) 414:105-111*

# What Are Cancer Stem Cells?

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- Cancer stem cells (CSC) are cells within a tumor that has the capability of self-renewal as well as generating the heterogeneous lineages of cancer cells that comprise the tumor*.
- CSC has three distinctive functional characteristics**:
  - Self-renewal – transplantability and capability to form tumors when injected into nude mice
  - Lineage capacity – ability to recreate the full phenotypic heterogeneity of the parent tumor
  - Distinctive surface markers
- The standard assay to identify CSC is serial transplantation in animal models, where human cancer cells are transplanted ("xenografted") into an orthotopic site (corresponding site of the human tumor) of immuno-compromised mice and are analyzed at various time points for tumor formation*.

*Source: *Clarke et al., Cancer Res (2006) 66:9339-9344; **Tomao et al., J Exp Clin Cancer Res (2012) 32:48*

# The Original Experiment that Establishes CSC in Acute Myeloid Leukemia (AML)

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- Most human AML cells have limited proliferative capacity, suggesting that the leukemic clone may be maintained by a rare population of stem cells.
- Using transplantation experiment with severe combined immune-deficient (SCID) mice, Lapidot et al. in 1994 identified AML-initiating cells that are able to home to the bone marrow and proliferated extensively in response to in vivo cytokine treatment, resulting in a pattern of dissemination and leukemic cell morphology similar to that seen in the original patients.
- Limiting dilution analysis showed that the AML-initiating cells are very rare. The frequency is on average 1 per $10^6$ cells, although it can vary by more than 1000-fold between donors.
- By fractionating AML cells on the basis of cell-surface-marker expression, it was found that AML-initiating cells that could produce large numbers of colony-forming progenitors were CD34+CD38-.
- This in vivo model was found to replicate many aspects of human AML and defines a new leukemia-initiating cell, which is less mature than colony-forming cells.

*Source: Lapidot et al, Nature (1994) 367, 645-648; Dick, Blood (2008), 112, 4793 -4806,*

# Original AML Study Leads to a Hierarchical Model of CSC and Similar Findings in Other Tumors

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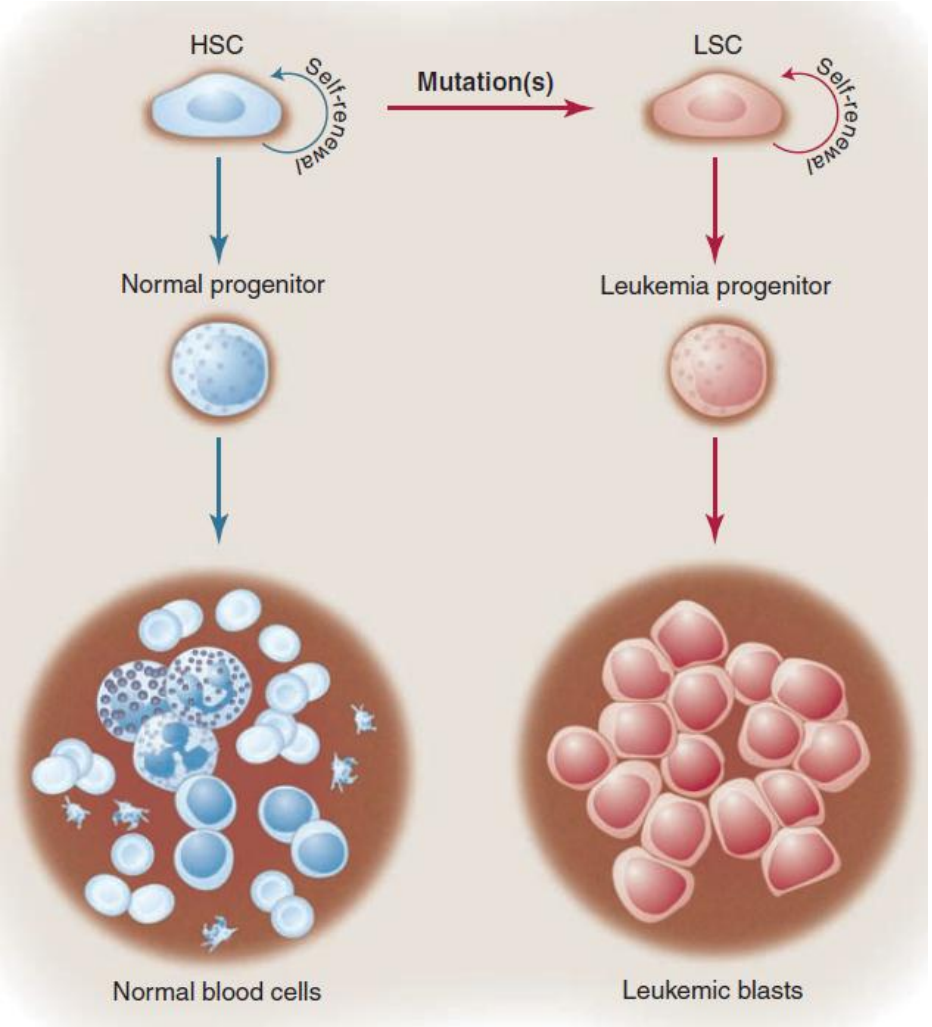
- The AML study establishes a cancer development paradigm in which CSC is at the top of the hierarchical pyramid.
- CSC paradigm refers to the ability of a subpopulation of cancer cells to initiate tumorigenesis by undergoing self-renewal and -differentiation, like normal stem cells, whereas the remaining majority of the cells lack these properties.
- In addition to leukemias (also including acute lymphoblastic leukemia and chronic myeloma leukemia), similar findings have been reported for melanoma, brain, breast, pancreatic and colorectal cancers.




HSC: hematopoietic stem cell; LSC: leukemia stem cell

*Source: Rosen and Jordan, Science 2009; Frank et al., Journal of Clinical Investigation, 2010*

# Controversies Surrounding CSC

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- Some of the controversy seems rather academic and centers on the definition of CSC – whether they are truly bona fide stem cells and can give rise to multiple differentiated cell types.
- A more salient objection involves a different view of cancer cell development and evolution. Instead of the hierarchical, intrinsic view of CSC, an alternative is the “clonal evolution” theory in which cancer cells experience a more stochastic process with tumor cells acquiring various phenotypical changes during tumorigenesis by responding to the microenvironment (extrinsic model – see next page).
- One objection to the intrinsic model proposed based on the original AML study by Lapidot et al. is that the xenograft mouse model used to test tumor-initiating capacity lacks an appropriate microenvironment because of the differences between mouse and human and the lack of an intact immune system.

*Source: Gupta et al., Nature Medicine, 2009; Rosen and Jordan, Science 2009*

# Controversies Surrounding CSC, Continued

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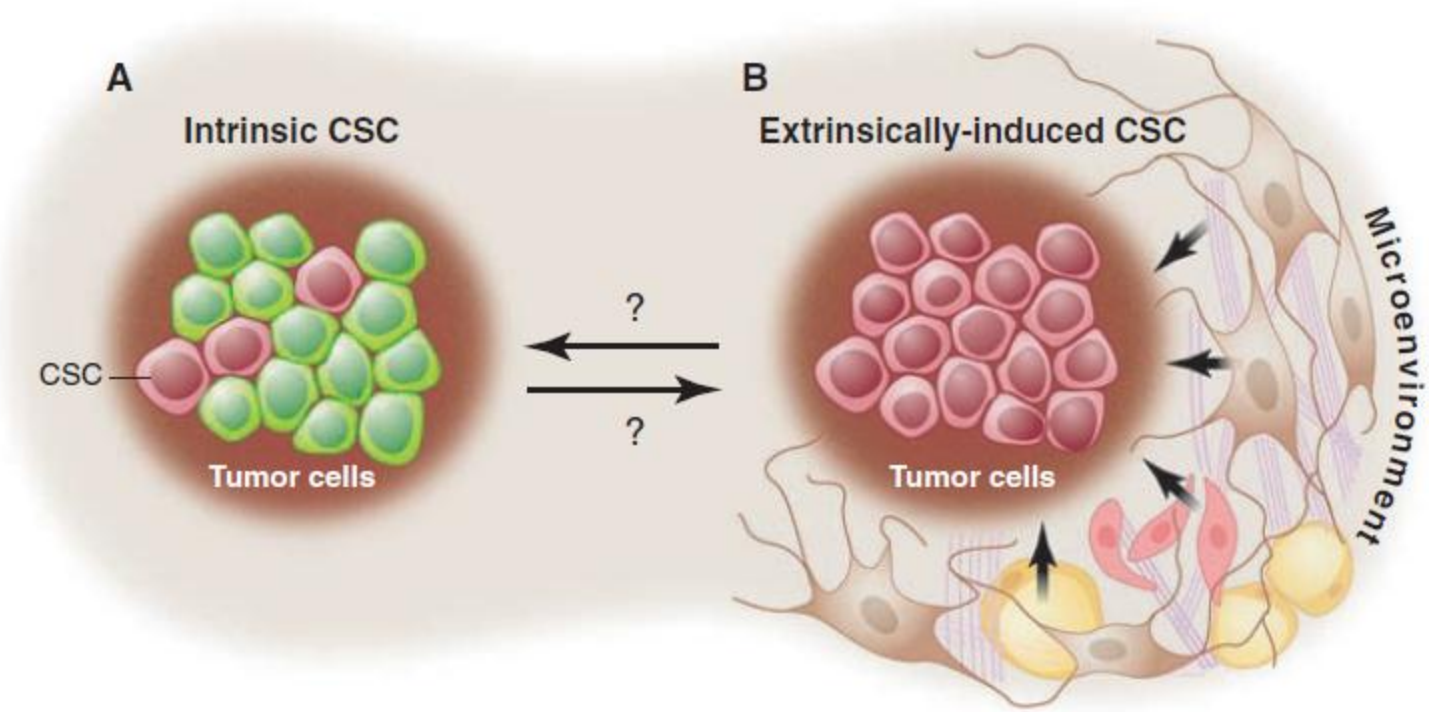
- Experiments have found that the relative frequency of cells with tumor-initiating capability can depend highly on the experimental system and the tumor type. Modified xenotransplantation conditions, including the use of more highly immuno-compromised mice, increased the detection of tumorigenic melanoma cells by several orders of magnitude. One in four unselected melanoma cells formed tumors in these studies, arguing that CSCs are not always rare.
- Despite these controversies, it appears that there are a subpopulation of cancer cells, regardless of whether they are bona fide stem cells or their frequency, that have the capacity of self-renewal. There exists a therapeutic need to successfully target these cells.

*Source: Gupta et al., Nature Medicine, 2009; Rosen and Jordan, Science 2009*

# Two Views of Cancer Cell Evolution and Development




CSC: cancer stem cell

- The intrinsic model (left) suggests that a specific subpopulation within a tumor (pink cells) possesses the functional properties of CSCs.
- The extrinsic model (right) proposes that all tumor cells are functionally equivalent and display heterogeneous behaviors as a function of extrinsic (microenvironmental) cues.

*Source: Rosen and Jordan, Science 2009*

# Cancer Stem Cells Do Not Always Originate from Stem Cells

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- Some cancer stem cells may arise from normal stem cells through mutations of genes that cause stem cells to become carcinogenic. Examples include acute myelogenous leukemia (AML) where cancer stem cells display a CD34+CD38- cell surface phenotype, similar to the normal primitive hematopoietic progenitors.

- Cancer stem cells can also arise from more differentiated cells that had multiple mutagenic events and then acquired the self-renewal capacity and immortality. For example, in chronic myelogenous leukemia (CML), the more differentiated granulocyte-macrophage progenitor acquires self-renewal capacity and "reacquires" stem-like properties due to the later mutations.

- Epithelial-to-mesenchymal transition (EMT) may account in part for the diversity of abundance of CSCs. Recent studies have suggested that induction of EMT in immortalized human mammary epithelia cells results in cells with stem-like properties, and cells at the leading invasive edge of solid tumors, such as colon, breast, pancreatic cancers, exhibit more mesenchymal features and are characterized by the expression of CSC markers.

*Source: Clarke et al, Cancer Res (2006) 66:9339-9344; Rosen and Jordan, Science (2009), 1670-1673*

# Cell Surface Markers by Themselves Are Not Sufficient to Define CSC

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- It is not sufficient to define a CSC solely on surface markers in the absence of linking marker expression to a self-renewal assay.
- None of the markers used to isolate stem cells in various normal and cancerous tissues is expressed exclusively by stem cells. For example, CD133 was a marker for brain tumor stem cells, but also expressed on normal brain stem cells in various tumors and tissues. The same is true for CD44, Sca1 and Thy1. In fact, the vast majority of the cells expressing these markers are not CSC.
- CSC markers differ from one tissue to another tissue.
- Genetic and epigenetic signatures
  - Bmi-1, Tie-2, Shh, Notch, and Wnt/beta-catenin signaling pathways have been shown to have important regulatory functions for some stem cells.

*Source: *Clarke et al, Cancer Res (2006) 66:9339-9344; **Tomao et al, J Exp Clin Cancer Res (2012) 32:48*

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# ONCOMED IS SYSTEMATICALLY DEVELOPING ANTIBODY-BASED AGENTS AGAINST TARGETS IN KEY PATHWAYS FOR CANCER STEM CELLS

# Cancer Stem Cells – Validated Pathways

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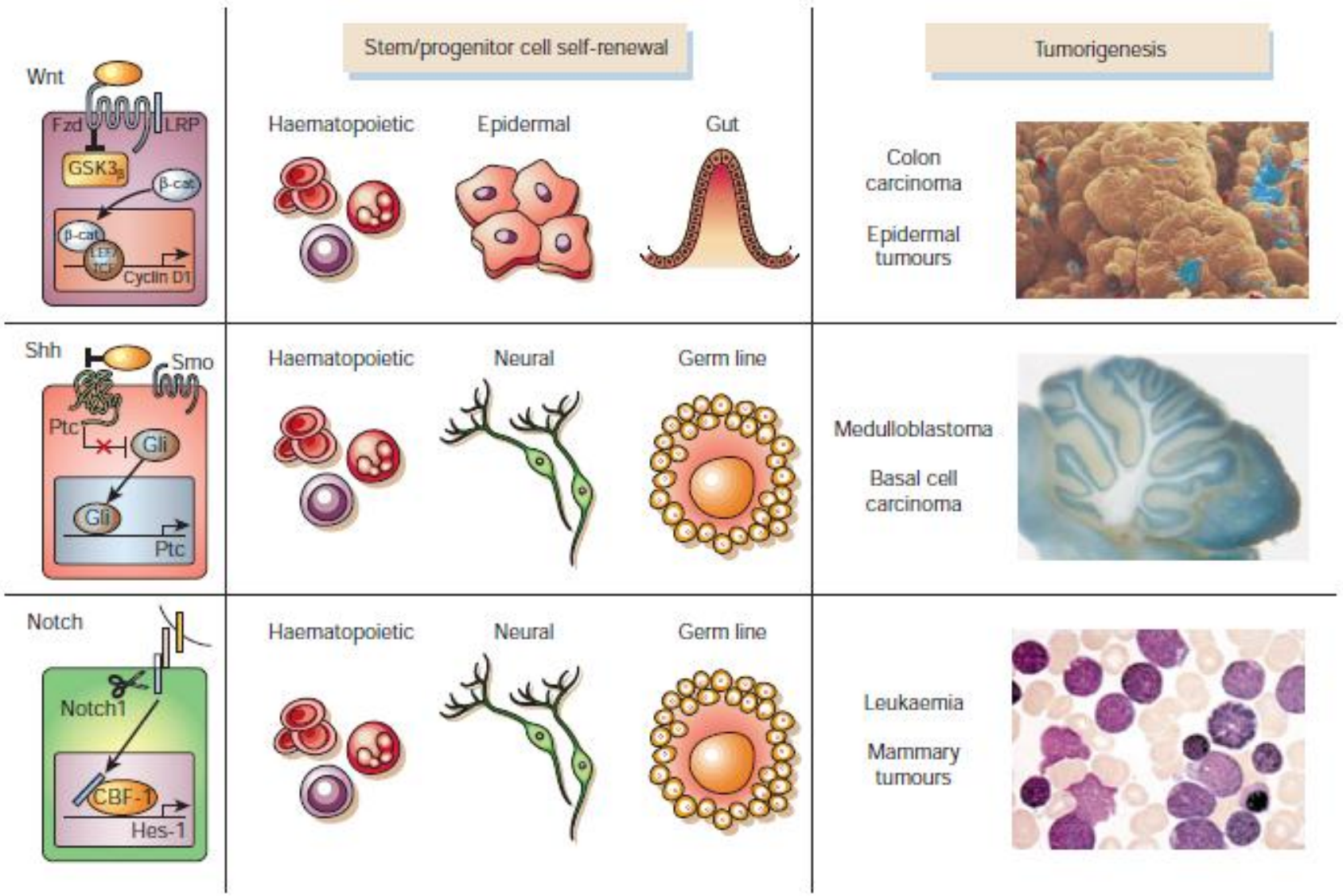


*Source: *Reya et al., Nature (2001) 414:105-111*

# Wnt Pathway Is Involved in Many Major Cancers and CSCs

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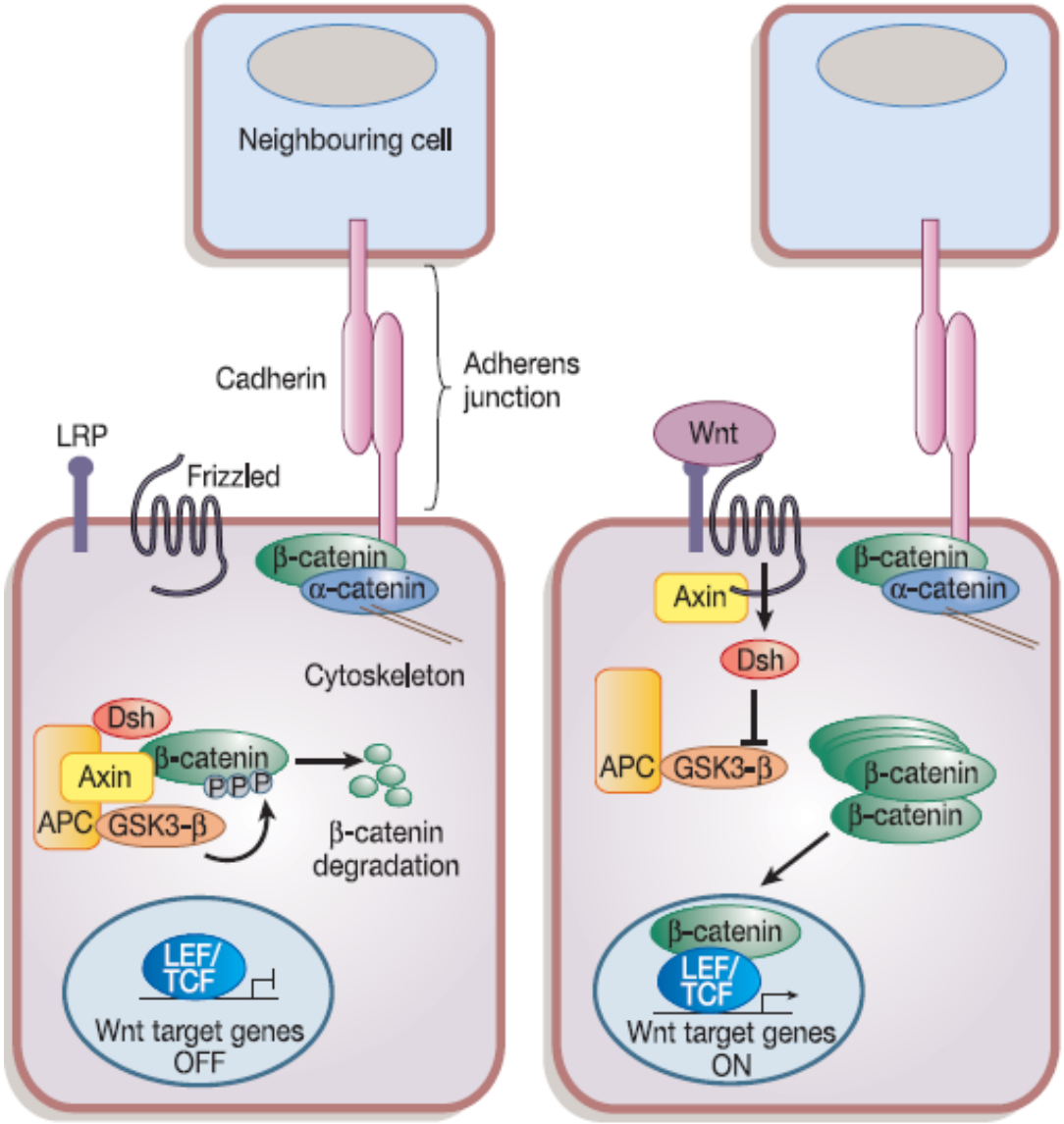
- The Wnt signaling pathway is an evolutionarily conserved pathway that regulates crucial aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development.
- Members of Wnt family through the Frizzled (Fz) receptor have been shown to induce several signaling events including a Wnt/β-catenin dependent (canonical) pathway and a Wnt/β-catenin independent (non-canonical) pathway.
- The canonical Wnt pathway has emerged as a critical regulator of stem cells. Activation of Wnt signaling has also been associated with cancer. It is hypothesized that tightly regulated self-renewal in stem and progenitor cells mediated by Wnt signaling is subverted in a cancer cell, which leads to malignant proliferation.
- The Wnt pathway is strongly implicated in many major cancers. It is also required for tumor growth in CSCs from patient-derived tumors.

*Source: Polakis et al., Cold Spring Harb Perspect Biol (2012) 4:a008052; Reya and Clevers, Nature (2005) 434:843-850.*

# The Canonic Wnt Pathway




- In the absence of Wnt signaling (left panel), β-catenin is in a complex with axin, APC and GSK3-β. This destruction complex then phosphorylates β-catenin, leading to its degradation. β-catenin also binds Cadherin & regulates cell-cell adhesion.
- In the presence of Wnt signaling (right panel), β-catenin is uncoupled from degradation complex and translocates to the nucleus, where it binds Lef/Tcf transcription factors and actives targeted genes.

*Source: Reya and Clevers, Nature (2005) 434:843-850.*

# Wnt Pathway in Colon Cancer

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- Initial evidence of Wnt pathway in cancer was derived from the discovery of the APC mutation in familial adenomatous polyposis (FAP) patients, where dysfunction of one APC allele leads to development of large numbers of colon polyps early in life.
- Mutational inactivation of APC leads to the inappropriate stabilization of β-catenin, suggesting disruption of APC function transforms epithelial cell through activation of Wnt signaling. This hypothesis was supported by in vitro studies in APC mutant cancer cell lines where Tcf was inappropriately transcribed in the absence of Wnt signaling.
- In some tumor cases where APC is not mutated, rare mutations in both the scaffolding protein axin2 and β-catenin have been found including point mutations in β-catenin, which removes its N-terminal Ser/Thr destruction motif. In all cases, these mutations lead to inappropriate accumulation of β-catenin-Tcf4 complexes in the transformation of epithelial cells.
- Various studies suggest that colorectal cancer almost unanimously starts with an activating mutation in the Wnt signaling pathway. This is largely due to the unique physiological dependence of the intestinal progenitor/stem cell on the Wnt cascade.

*Source: Reya and Clevers, Nature (2005) 434:843-850.*

# Wnt Pathway in Epidermal Development and Cancer

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- In vitro studies showed that mutations in Lef1 gene display a reduction of hair follicles while its over-expression leads to invaginations in epidermis. Similarly, when over-expressed a constitutively stable form of β-catenin, pronounced hair follicle morphogenesis was observed in interfollicular epidermis.
- β-catenin and Lef1 mRNA accumulate in embryonic skin placodes (structural precurors to hair follicles) while conditional deletion of β-catenin leads to loss of these placodes. These findings suggest that Wnt signaling contributes to the placode induction and ultimately the formation of hair follicles during embryonic development.
- Although evidences suggest some aspects of hair follicle biology are controlled by the Wnt signaling pathway, it remains unclear whether the Wnt pathway is also required in the interfollicular epidermis and mutated in tumors derived thereof.

*Source: Polakis et al., Cold Spring Harb Perspect Biol (2012) 4:a008052; Reya and Clevers, Nature (2005) 434:843-850.*

# Aberrant Wnt Pathway in Leukemia

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- The substantial influence of Wnt pathway on hematopoietic stem and progenitor cells suggests that dysfunction of the pathway may lead to leukemia.
- Activated Wnt signaling was identified in granulocyte-macrophage progenitors (GMPs) from chronic myelogenous leukemia and blast crisis cells from patients resistant to therapy. Additionally, inhibition of β-catenin decreases the replating capacity of leukemic cells. These evidences suggest that leukemia precursors are dependent on Wnt signaling for growth and renewal.
- Additional supporting evidences have been found in acute myelogenous leukemia (AML). In hematopoietic stem cells transfused with mutations found in AML, re-plating efficiency of HSCs was decreased upon inhibition of γ-catenin. Conversely, over-expression of γ-catenin in mice showed AML-like symptoms.
- Stabilized form of β-catenin has been found in a number of primary myelomas and cell lines. Although no mutations have been identified, high expression of Wnt proteins such as Wnt5A and Wnt10B were detected. These data suggest that, different from colon cancer or epidermal tumors where mutations may lead to tumor formation, autocrine/paracrine use of Wnt signaling may be crucial in leukemia for sustaining cancerous self-renewal.

*Source: Polakis et al, Cold Spring Harb Perspect Biol (2012) 4:a008052; Reya and Clevers, Nature (2005) 434:843-850.*

# Uncontrolled Wnt Signaling Leads to Cancerous Tissues; Inhibition of Wnt Signaling May Prove to Be an Effective Approach for Cancer Therapy

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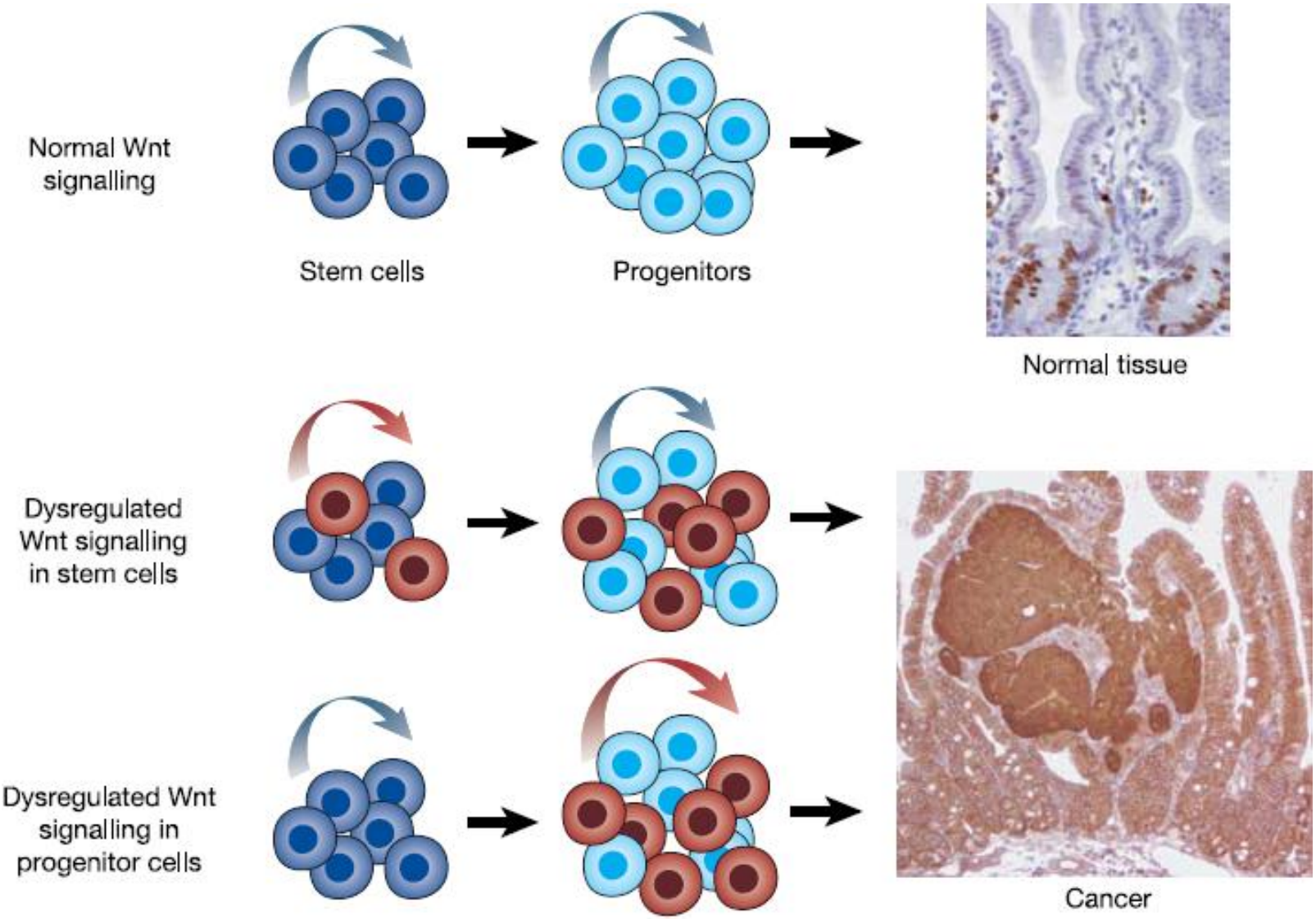
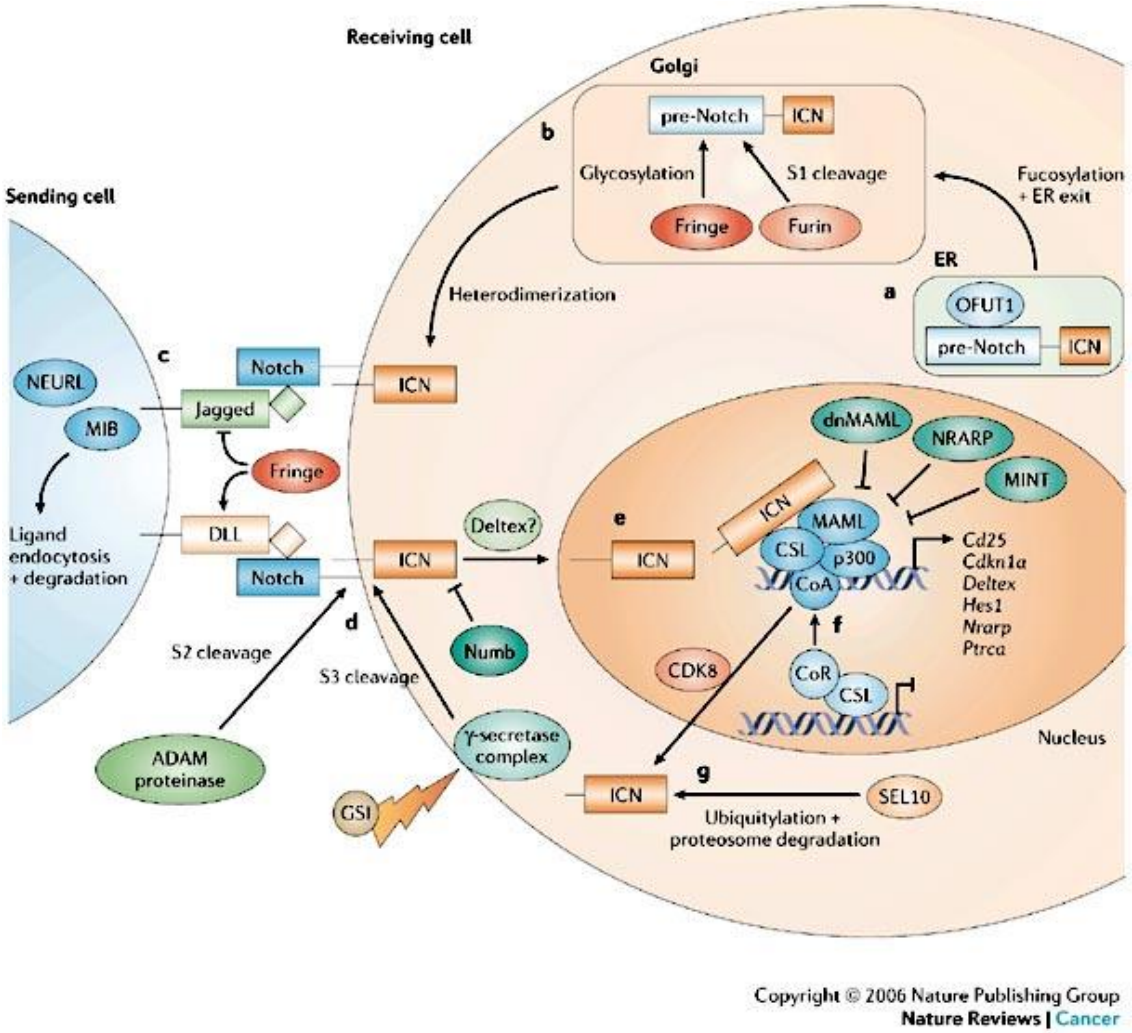



*Source: Reya and Clevers, Nature (2005) 434:843-850.*

# Notch Pathway Is Involved in Many Major Cancers and CSCs






- The Notch signaling pathway is a highly conserved pathway involved in embryogenesis and development of central nervous, cardiovascular and endocrine systems.
- Notch signaling is dysregulated in many cancers, and Notch mutations have been found in CLL, T-ALL and many other tumor types.
- While the oncogenic functions of Notch pathway have been well documented, the role in cancer stem cells is just emerging.

*Source: Grabher et al., Nature Rev Cancer (2006) 6:347-359; CLL – chronic lymphocytic leukemia; T-ALL – T-cell acute lymphoblastic leukemia*

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# GENOME SEQUENCING IDENTIFIED MUTATIONS IN NOTCH THAT ARE ASSOCIATED WITH CANCER

# Notch1 Mutations Have Been Identified in CLL Patients

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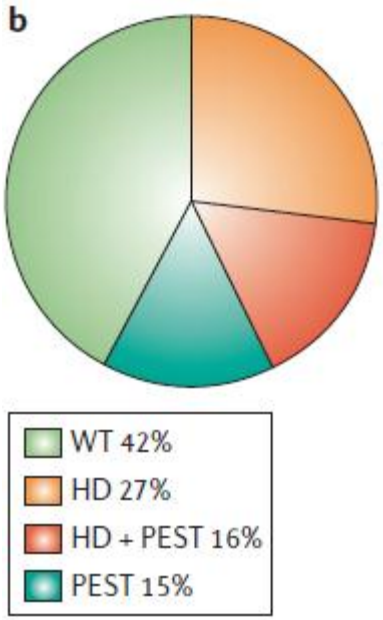
- Although a large number of patients will be required to have a better assessment, Notch1 mutations were observed in 8.3% (10/120) of chronic lymphocytic leukemia (CLL) patients at the time of diagnosis, and significantly higher during disease progression toward Richter transformation (31%, 18/58) and in chemo refractory patients (20.8%, 10/48)*.

- Whole-genome sequencing identified Notch1 as one of the four genes that are recurrently mutated in CLL. Mutations in Notch1 are mainly detected in patients with unmutated immunoglobulins. Overall frequency of mutation is 12% with a CT dinucleotide deletion (P2515Rfs*4) as the main mutation (29/255). Two additional mutations (Q2503*, F2482Ffs*2) were also found in the same region**.

*Source: *Fabbri et al., JEM (2011) 208:1389-1401; ** Puente et al., Nature 2011,* doi:10.1038

# Notch1 Mutations Have Been Identified in Majority of the T-ALL Patients




- T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive blood cancer. The chromosome translocation t(7:9) that juxtaposes a truncated activated form of Notch 1 (TAN1) with the T-cell receptor-β (TCRB) locus occurs in less than 1% of all T-ALL cases.
- Notch1 somatic activating mutations have been found in more than 50% of all T-ALL cases and in all T-ALL subtypes. Note, 42% of 201 cases of pediatric T-ALL shown in the figure were wild type.
- One set of mutations (27% + 16%) destabilizes the Notch heterodimerization domain (HD), likely through facilitating ligand-independent pathway activation. The other set of mutations (15% + 16%) disrupt the intracellular PEST (polypeptide enriched in proline, glutamate, serine and threonine) domain, and might function by increasing the half-life of transcription active intracellular Notch1 (ICN1).

*Source: *Grabher et al., Nature Rev Cancer (2006) 6:347-359*

# Notch2 Mutations Have Been Identified in Diffused Large B-cell Lymphoma (DLBCL)

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- Notch2 is another member of the Notch gene family that is preferentially expressed in mature B cells and is responsible for generating marginal zone B-cell.
- Screening of 63 samples identified Notch 2 mutations in 5 patients (~8%). The mutations are partial or complete deletion of the PEST (proline, glutamic acid, serine and threonine rich) domain or a single amino acid substitution at the C-terminus of Notch 2 protein. Increased copy number of mutated Notch2 allele has also been identified in some DLBCL patients. In vitro studies suggest that these mutations are the driver mutations for DLBCL.

**Table 1. *Notch2* mutational status in five patients with diffuse large B-cell lymphoma**

| Sample | Nucleic acid change | Amino acid change | Copy number |
|---|---|---|---|
| W109539 | 7454 C/T | 2400 Stop | Multiple |
| W121672 | 7454 C/T | 2400 Stop | 3 |
| L8 | 7454 C/T | 2400 Stop | 2† |
| L2 | 7120 Del A | 2288PLKGSTStop | NA |
| W117336 | 7614 G/A | 2453 R/Q | 2 |

†Uniparental disomy for the mutated *Notch2* allele is indicated. NA, information not available.

*Source: Lee et al., Cancer Science (2009) 100:920-926*

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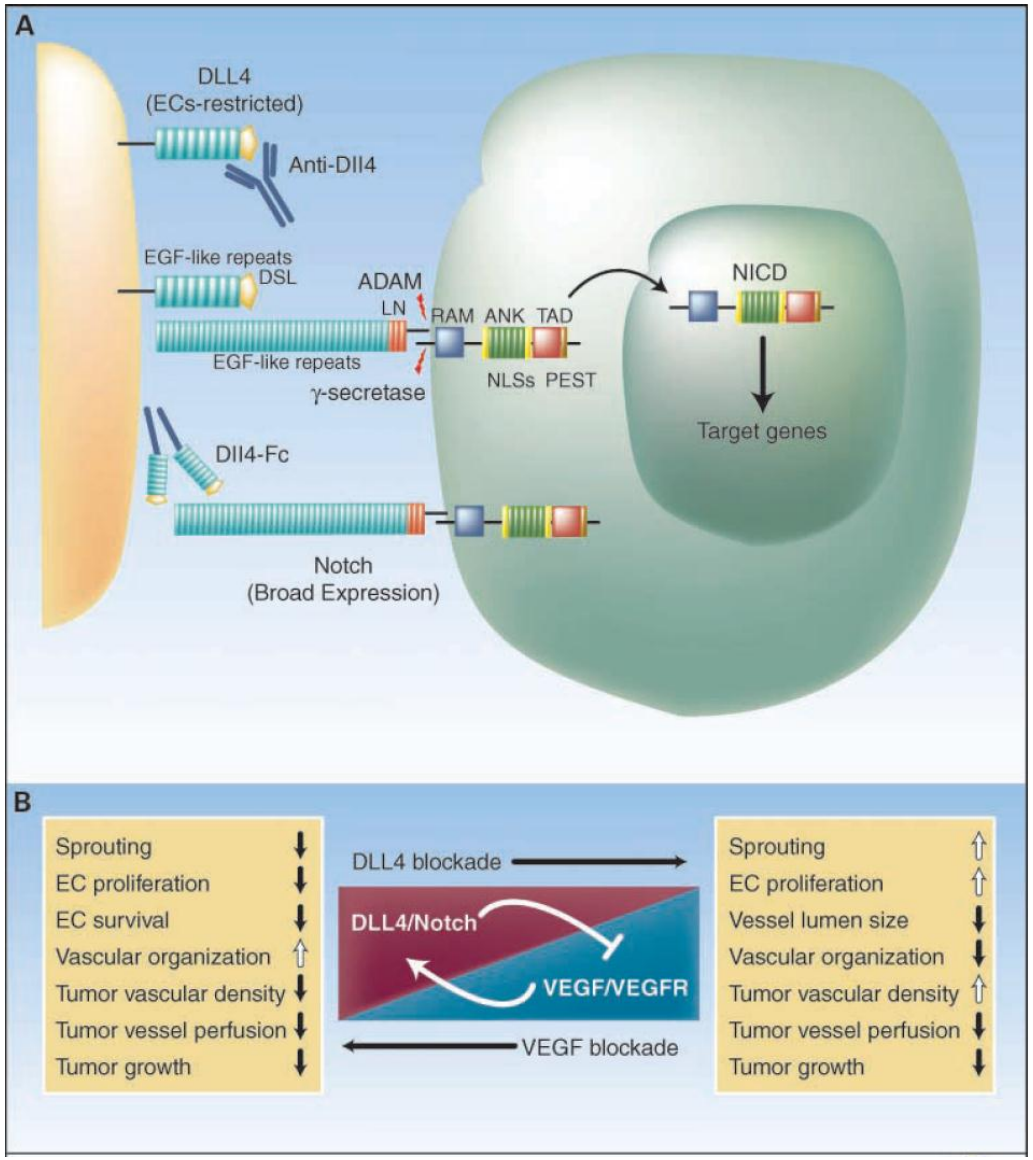
# DEMCIZUMAB – FIRST AGENT AGAINST NOTCH PATHWAY TO ENTER CLINICAL DEVELOPMENT

# DLL4 Is a Notch Ligand, and Acts Downstream of VEGF




- DLL4 is an endothelium specific Notch ligand. Dll4-deficient mouse embryos showed several vascular defects including impaired arteriogeneiss and lack of well-defined major arteries, disrupted vascular hierarchy and enhanced vascular density with reduced vessel caliber.
- DLL4 acts downstream of VEGF and there is a negative feedback. Blocking of Dll4/Notch signaling up-regulated VEGF receptor 2.
- Both DLL4-selective neutralizing antibody and a soluble Dll4 fusion protein showed robust antitumor activity in a variety of human and rodent tumor models.

*Source: Yan et al., Clin Cancer Res (2007) 13:7243-7246*

# Demcizumab Is a Monoclonal Antibody Against DLL4

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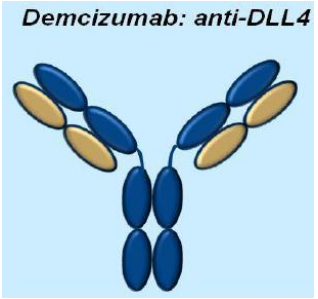
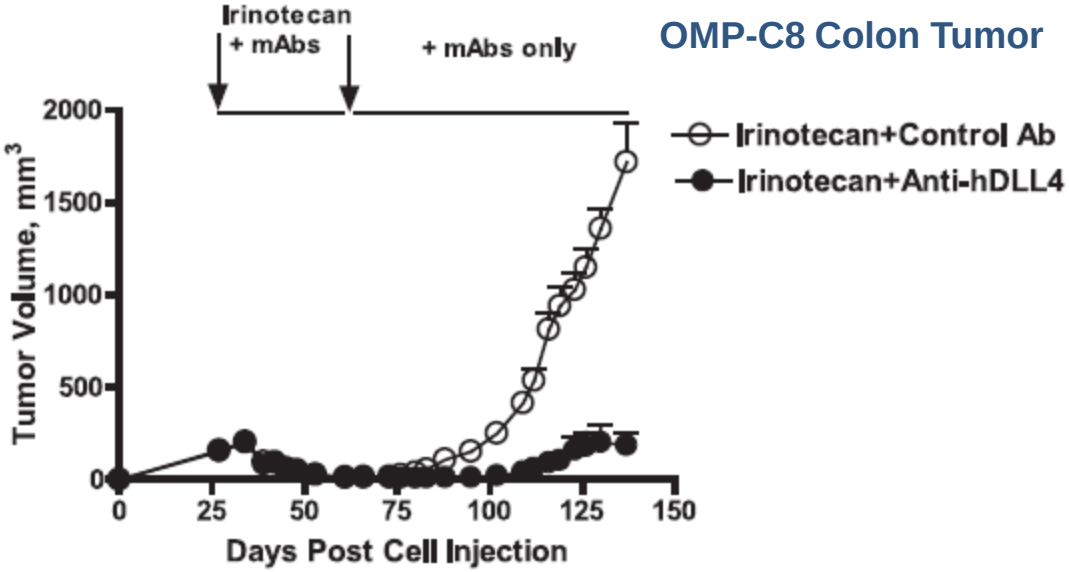
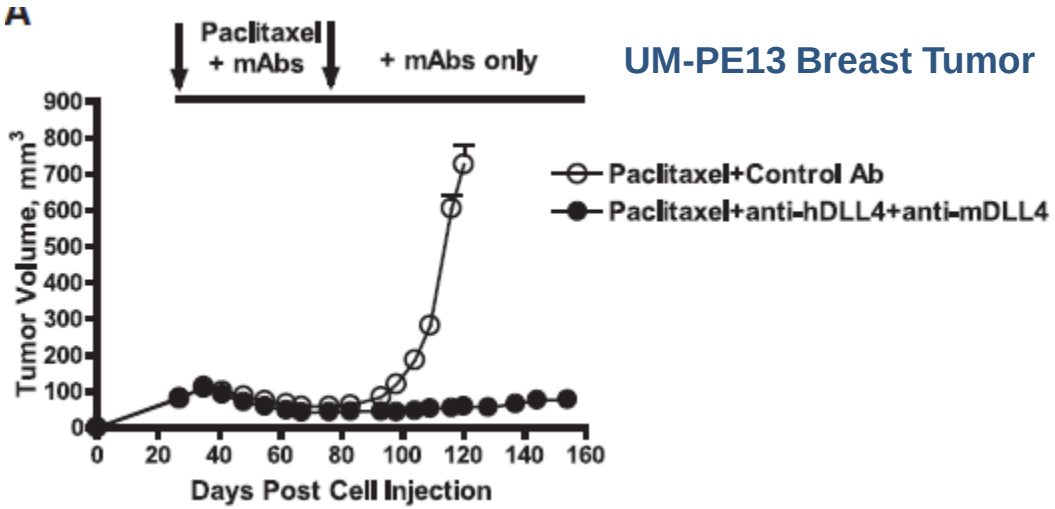



- Treated 114 patients as of May 15, 2013.
- Showed single-agent activity in advanced solid tumor
- Two Phase Ib trials in combination with chemotherapy
  - In combination with SOC carboplatin and pemetrexed (Alimta) in front-line NSCLC
  - In combination with SOC gemcitabine in front-line advanced pancreatic cancers
  - Updated Phase Ib with gemcitabine and Abraxane based on MPACT data
- Phase Ib/II in recurrent ovarian cancer
  - Combination with Taxol to be initiated at MDACC in 2H:13.

*Source: Company Reports*

# Demcizumab Reduced Colon and Breast Tumors in Xenograft Mouse Models




- Treatment initiated for colon tumor when tumors were ~200mm$^3$. DEM+irinotecan was stopped at day 60 while DEM treatment continued.
- Treatment initiated for breast tumor when tumors were ~100mm$^3$. DEM+paclitaxel was stopped at day 75 while DEM treatment continued.

**Administration of DEM delayed tumor re-growth after stopping chemotherapy.**

*Source: Hoey et al., Cell Stem Cell (2009) 5:168-177; DEM - demcizumab*

# Demcizumab Showed Single-agent Activity in a Dose-escalation Phase I Study

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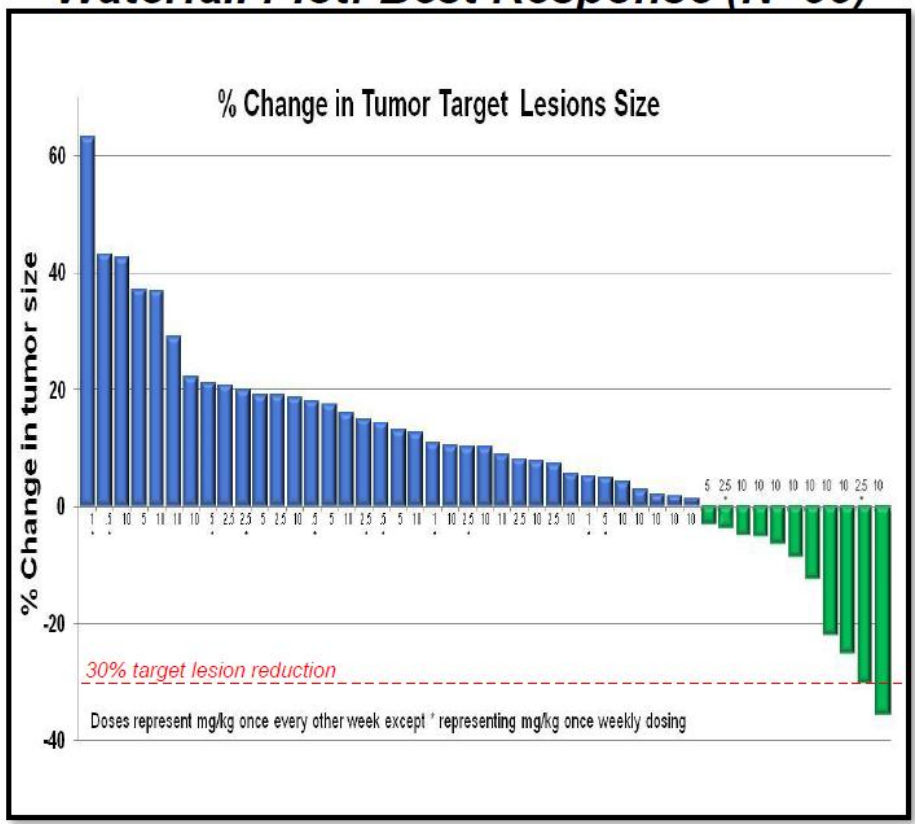
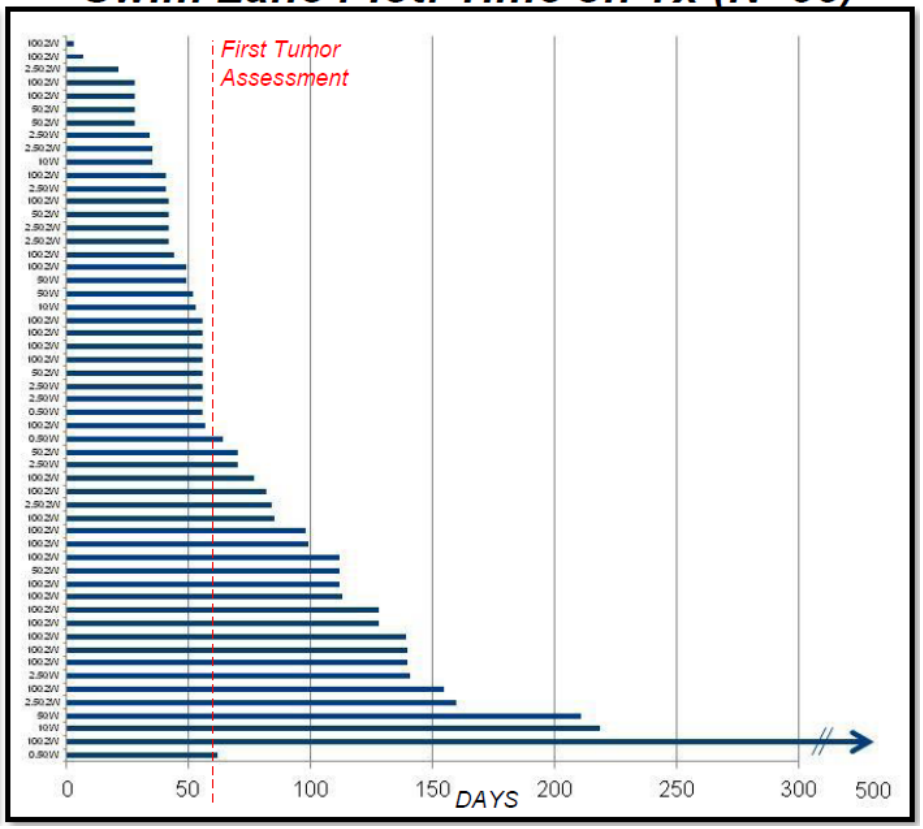
## Waterfall Plot: Best Response (N=55)



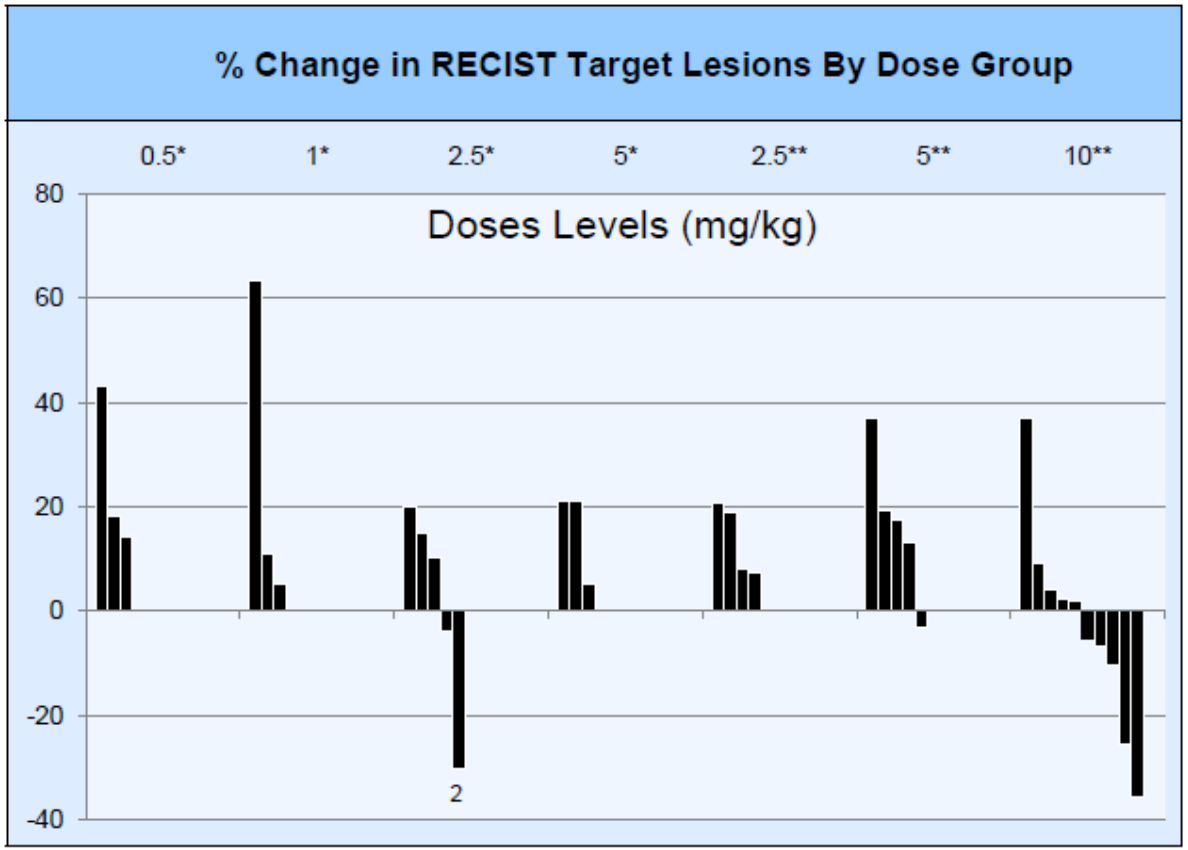

## Swim Lane Plot: Time on Tx (N=55)




- One PR (2%) in recurrent pancreatic adenocarcinoma
- 17/55 (31%) with stable disease (SD) for at least 3 months

*Source: Company Reports*

# At 10 mg/kg, Demcizumab's Activity Appears Encouraging




[2] Progressive disease due to a new 0.6 cm lesion

- The maximal tolerated dose was not reached at 10 mg/kg once every other week.
- Eight of 12 subjects (67%) treated at 10 mg/kg every other week had stable disease or a partial response (pancreatic cancer).

*Source: Smith et al EORTC-NCI-AACR 2010 poster presentation*

# Initial Reported Tolerability Profile of Demcizumab Appears Encouraging

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| Adverse Events (All Grades) Occurring in ≥ 15% of Patients by Dose Level (mg/kg) (N = 39) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Event | 0.5* | 1* | 2.5* | 5* | 2.5** | 5** | 10** | Total |
| N | 3 | 3 | 6 | 3 | 6 | 6 | 12 | 39 |
| Fatigue/Asthenia | 3 | 2 | 2 | 2 | 4 | 3 | 2 | 18 (46%) |
| Nausea | 2 | 2 | 3 | 2 | 3 | 3 | 1 | 16 (41%) |
| Diarrhea | 1 | 1 | 3 | 1 | 4 | 3 | 3 | 16 (41%) |
| Hypertension | 1 | 1 | 2 | 0 | 3 | 1 | 7 | 15 (38%) |
| Headache | 0 | 0 | 2 | 0 | 2 | 3 | 5 | 12 (31%) |
| Abdominal Pain | 0 | 1 | 3 | 1 | 2 | 3 | 1 | 11 (28% |
| Constipation | 0 | 2 | 1 | 1 | 3 | 2 | 0 | 9 (23%) |
| Dyspnea | 0 | 0 | 4 | 1 | 0 | 2 | 1 | 8 (21%) |
| Decreased Appetite | 0 | 0 | 2 | 1 | 2 | 2 | 0 | 7 (18%) |
| Peripheral Edema | 0 | 1 | 4 | 1 | 0 | 1 | 0 | 7 (18%) |
| Cough | 0 | 0 | 2 | 1 | 1 | 1 | 1 | 6 (15%) |
| ALT Increased | 1 | 2 | 2 | 0 | 0 | 0 | 1 | 6 (15%) |
| Pyrexia | 0 | 0 | 2 | 1 | 1 | 0 | 2 | 6 (15%) |
| Anorexia | 1 | 0 | 1 | 2 | 1 | 0 | 1 | 6 (15%) |

* Once weekly dosing for 9 doses, then every other week
** Once every other week dosing

- The most common drug-related toxicity was asymptomatic hypertension, which was successfully managed with oral anti-hypertensives.
- There were several cardiopulmonary events, however (described later).

*Source: Smith et al., EORTC-NCI-AACR 2010 poster presentation*

# Demcizumab Combination with Gemcitabine in Front-line Pancreatic Cancer

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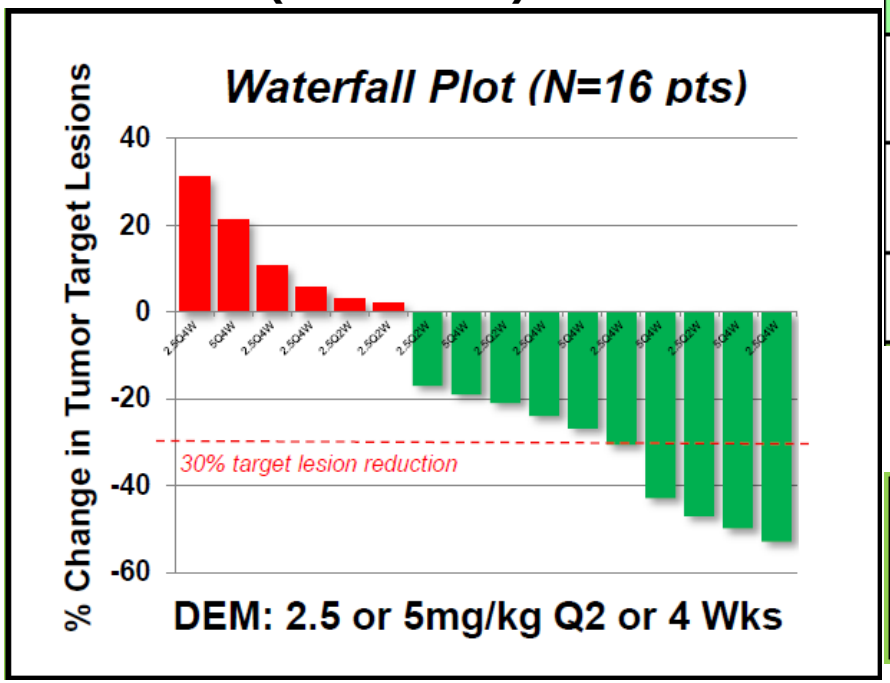
## Gemcitabine + Demcizumab (GEM/DEM)




| | GEM + DEM (N=16) | GEM (Package Insert) |
|---|---|---|
| Partial Response (PR) | 4 (25%) | 7% |
| Stable Disease (SD) | 7 (44%) | 44% |
| PR + SD | 11 (69%) | 51% |

***Median PFS by DEM Dose (Kaplan-Meier)***

- *GEM (MPACT Trial*): 103d*
- *GEM+DEM (mg/kg): 2.5Q4W: 50d 2.5Q2W: 101d 5Q4W: 143d*

- Although cross-trial comparisons are difficult, preliminary findings of efficacy and combinability are encouraging. Limited PFS data appear to point to improved efficacy data at higher doses.

*PFS: progression-free survival*

*Source: Company Reports*

# Demcizumab Combination with Chemotherapy in Front-line NSCLC

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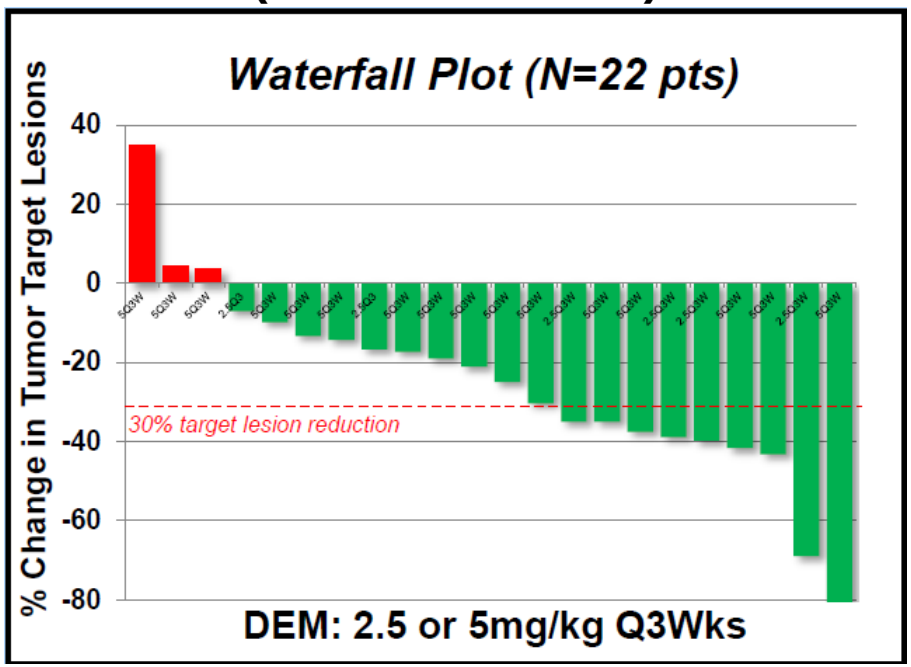
## Carboplatin/Pemetrexed/Demcizumab (Carbo/PEM/DEM)




| | Carbo/PEM + DEM (N=22) | Carbo/PEM (Package Insert) |
|---|---|---|
| Partial Response (PR) | 9 (41%) | 27% |
| Stable Disease (SD) | 10 (45%) | |
| PR + SD | 19 (86%) | |

***Median PFS by DEM Dose (Kaplan-Meier)***

- ***Platinum/PEM (PEM PI): 139d***
- ***Carbo/PEM + DEM: 2.5Q3W: 129d 5Q3W: 160d***

*PFS: progression-free survival*

*Source: Company Reports*

# Activity of Demcizumab is Corroborated by Data on Another Anti-DLL4 Antibody

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- Three anti-DLL4 antibodies are in clinical development – demcizumab from OMED (Phase Ib, entered clinic in 2008), enoticumab (REGN421, SAR153192) from REGN/SNY (Phase Ia, entered clinic in 2009), MEDI0639 from AZN/MedImmune (Phase Ia, entered clinic in 2012).
- Demcizumab dose-escalation study showed 1/55 (2%) PR (in pancreatic cancer) and 17/55 (31%) SD for at least 3 months.
- Enoticumab dose-escalation study showed 2/53 (4%) PR (in ovarian and NSCLC) and 3/53 (6%) SD for over 6 months.

*PR – partial response; SD – stable disease*

*Source: Yan and Plowman, Clin Cancer Res (2007) 13:7243-7246.*

# Enoticumab (REGN421, Anti-Dll4) Showed Single-agent Activity in Preclinical Studies

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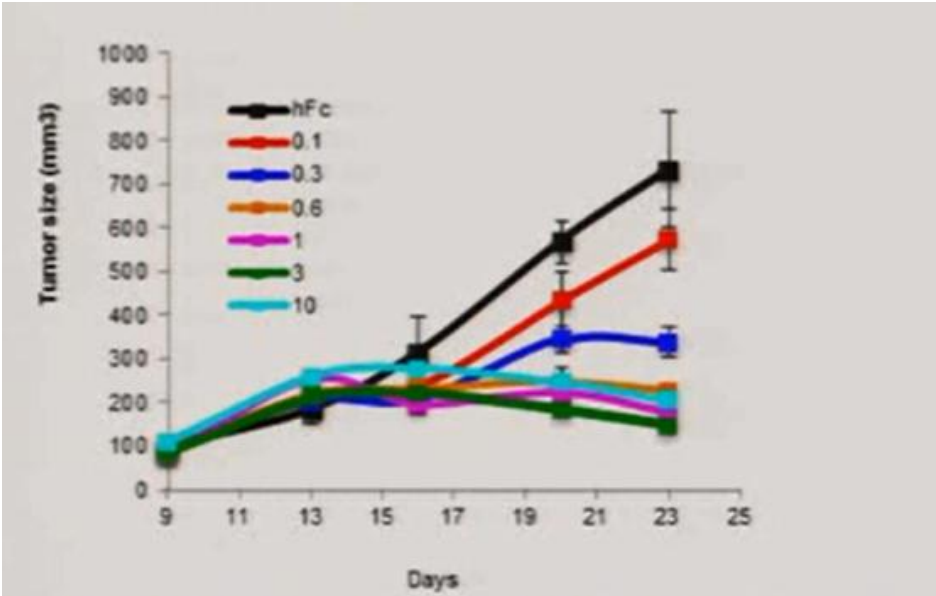
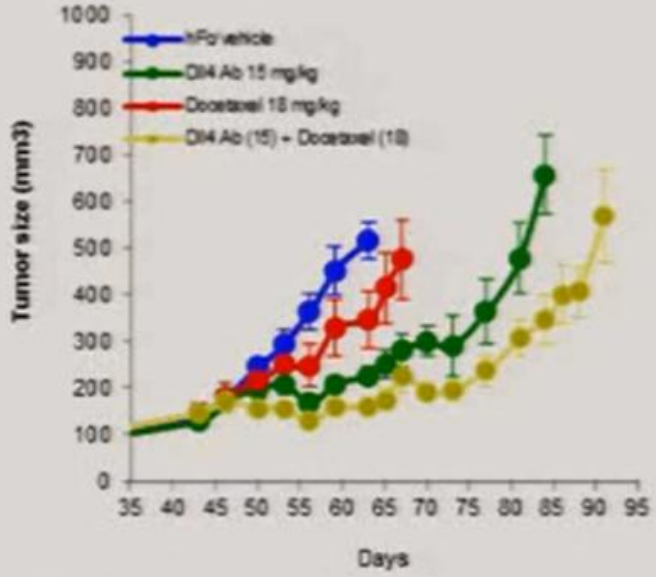
- Enoticumab is a humanized IgG1 antibody against Dll4.
- Showed single-agent activity in preclinical tumor models including models resistant to VEGF blockade.
- Enhanced activity in combination with chemotherapy.



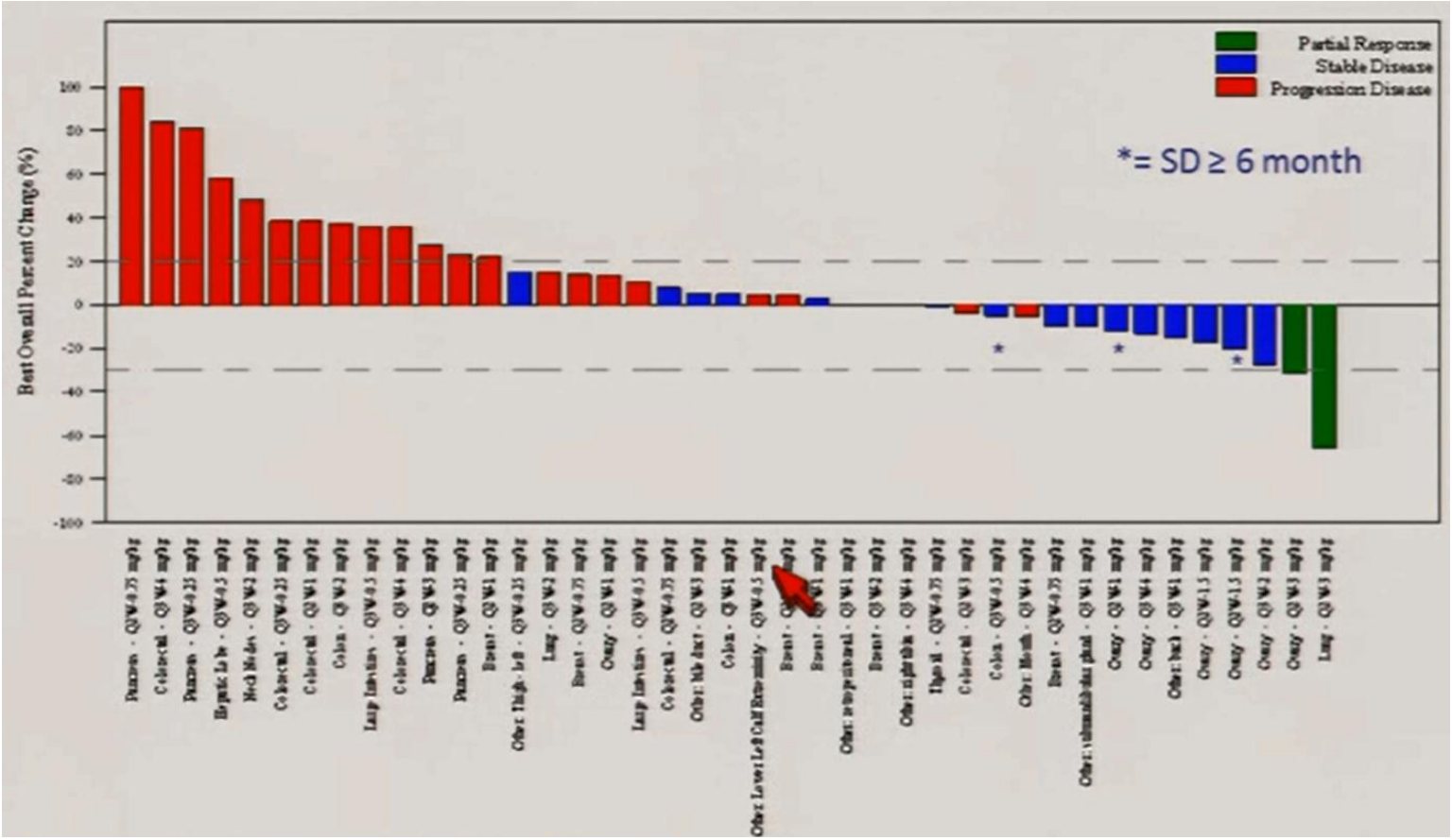

Anti-Dll4 Inhibits the Growth of Established Human HT1080 Tumor Xenografts in Dose-Dependent Manner




Combinations of Anti-Dll4 with Chemotherapy Result in Enhanced MDA-MB-231 Tumor Growth Inhibition

*Source: Jimeno et al., ASCO 2013, #2502*

# Enoticumab (REGN421, Anti-Dll4) Phase I Showed Overall Similar Efficacy vs. Demcizumab




**Two patients (2/53, 4%) had PR (ovarian cancer and NSCLC). Three patients (3/53, 6%) had SD for over 6 months.**

*PR – partial response; SD – stable disease*

*Source: Jimeno et al., ASCO 2013, #2502*

# Cardiopulmonary Toxicity Has Been Observed in Demcizumab-treated Patients

LEERINK SWANN

- Demcizumab was evaluated in three Phase I trials. From these three trials, hypertension was one of  common adverse events (36-45% all Grades and ~20% Grade 3-5).
- Three cases of drug-related pulmonary hypertension and heart failure have occurred among all three trials in patients dosed with demcizumab for over 125 days. CV toxicity was all reversible.

**Drug-Related Grade 3-5 AEs from Phase Ib in Front-line NSCLC**

| Related Grade 3-5 Adverse Events ≥ 10% by Dose Cohort (mg/kg) (N = 20) | | | | |
|---|---|---|---|---|
| **Dose Level – mg/kg** | 5 Prior to Risk Mitigation | 2.5 After Risk Mitigation | 5 After Risk Mitigation | Total |
| N | 6 | 6 | 8 | 20 |
| Hypertension | 2 | 4 | 3 | 4 (20%) |
| Neutropenia | 2 | 1 | 4 | 3 (15%) |
| Alanine Aminotransferse increased | 3 | 0 | 0 | 2 (10%) |

*Source: Company Reports*

# Cardiac Adverse Events Also Seen in Enoticumab (REGN421), Another Dll4 Inhibitor in Development

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**In Phase I dose-escalation study, 3 patients had over Grade 3 cardiac adverse events.**

| Cardiac Adverse Events | Total (N=53) | |
|---|---|---|
| | All G N (%) | ≥G3 N (%) |
| Number of patient with cardiac TEAE | 12 (22.6) | 3 (5.7) |
| Number of cardiac events | 24 | 6 |
| BNP increased | 3 | 0 |
| Pulmonary hypertension | 3 | 2 |
| Right Ventricular dysfunction | 3 | 2 |
| Ejection fraction decreased (Left ventricular) | 2 | 0 |
| Left Ventricular dysfunction | 2 | 1 |
| Tachycardia | 2 | 0 |
| Atrial fibrillation | 1 | 0 |
| Bradycardia | 1 | 0 |
| Pericardial effusion | 1 | 0 |
| Pulmonary valve disease | 1 | 0 |
| Troponin I increased | 1 | 1 |
| Ventricular dysfunction (Bi-ventricular) | 1 | 0 |
| Ventricular extrasystoles | 1 | 0 |

*Source: Jimeno et al,. ASCO 2013, #2502*

# Enoticumab (REGN421, Anti-Dll4) – Five Treatment-related G3 SAEs in 3 Patients

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| Serious Adverse Event | Q3W | | Q2W | | Total | |
|---|---|---|---|---|---|---|
| | All Grade | G3 | All Grade | G3 | All Grade | G3 |
| Pulmonary HTN | 0 | 0 | 2 | 2 | 2 | 2 |
| RV dysfunction | 0 | 0 | 1 | 1 | 1 | 1 |
| LV dysfunction | 0 | 0 | 1 | 1 | 1 | 1 |
| Elevated troponin I | 1 | 1 | 0 | 0 | 1 | 1 |

All SAEs either improved or resolved upon discontinuation of therapy

**The Phase II dose was 4mg/kg for q3w schedule and 3mg/kg for q2w schedule.**

*Source: Jimeno et al., ASCO 2013, #2502*

# Cardiovascular Toxicity Likely a Class Toxicity

- Both Dll4 inhibitors showed similar level of cardiovascular (CV) toxicity, suggesting this is a class-related toxicity.
- In vitro studies on the underlying mechanism indicate a negative feedback loop where blocking Dll4-mediated Notch signaling up-regulates VEGF receptor 2, which may explain increased cardiovascular toxicity seen in Dll4 inhibitors*.

*Source: *Yan and Plowman, Clin Cancer Res (2007) 13:7243-7246.*

# Cardiovascular Toxicity May Be Managed by Truncated Dosing

LEERINK SWANN

- The FDA had put a partial clinical hold on demcizumab due to findings of cardiopulmonary toxicity.
- OMED implemented a risk-mitigation plan in its Phase Ib studies outside the US that included intermittent dosing and cardiac monitoring using B-type natriuretic peptide (BNP) testing and echocardiography. In addition, a cardioprotective medication (i.e., an angiotensin-converting enzyme inhibitor or carvedilol) was administered to patients with rising BNPs.
- After findings of CV toxicity in patients dosed over 125 days, OMED is exploring truncated dosing where demcizumab dosing is stopped after 75 days before the occurrence of CV toxicity.
  - Although there is no immediate plan, in our view, re-challenging the dose could potentially provide sustainable activity while bypassing CV toxicity.

*Source: McKeage, EORTC 2012*

# Experience with Gamma Secretase Inhibitors Sustains Interest in Exploration of Anti-DLL4 Agents

LEERINK SWANN

- Gamma secretase acts downstream of Notch ligands and receptors. Gamma secretase inhibitors (GSIs) are in development for both Alzheimer's disease and cancer.
- Preclinical models would predict that GSIs may be associated with gastrointestinal (GI) toxicity due to indiscriminate blockade of all NOTCH receptors. On the other hand, blocking DLL4 would primarily interfere with NOTCH1 signaling and is not predicted to result in severe GI toxicity.
- Early data on a daily schedule of MK-0752, a GSI from MRK, do show severe limiting toxicities of diarrhea, fatigue and cough. Modified schedules are still associated with diarrhea, nausea, vomiting and fatigue. Of 59 evaluable patients in Phase I, there were 1 objective complete response and an additional 10 patients with stable disease longer than 4 months among patients with high-grade gliomas.
- For Roche's RO4929097, dose cannot be escalated due to metabolic issues, and the drug appeared well tolerated at the doses given. Tumor responses included 1 partial response in a patient with colorectal adenocarcinoma with neuroendocrine features, 1 mixed response (stable disease) in a patient with sarcoma, and 1 nearly complete FDG-PET response in a patient with melanoma.

*Source: Yan, Vascular Cell 2011; Gounder and Schwartz, JCO 2012; Krop, JCO 2012; Tolcher, JCO 2012*

# Demcizumab Combination Therapy May Lead the Road for Dll4 Targeted Therapy

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- Among three clinical-stage agents targeting Dll4, demcizumab is in the most advanced development stage. Demcizumab has been evaluated in three Phase I studies.
  - Phase Ib dose escalation study
  - Demcizumab/gemcitabine in front-line advanced pancreatic cancer
  - Demcizumab/carboplatin/pemetrexed in front-line NSCLC
- As a result of the lifting of partial clinical hold, a Phase Ib/II trial of demcizumab in combination with paclitaxel in platinum-resistant ovarian cancer patients is expected to start in 2H:13 at MD Anderson Cancer Center.

*PR – partial response; SD – stable disease*

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# BI-SPECIFIC DLL4/VEGF ANTIBODY COULD BE AN INTERESTING NEXT STEP FOR DLL4 BLOCKADE

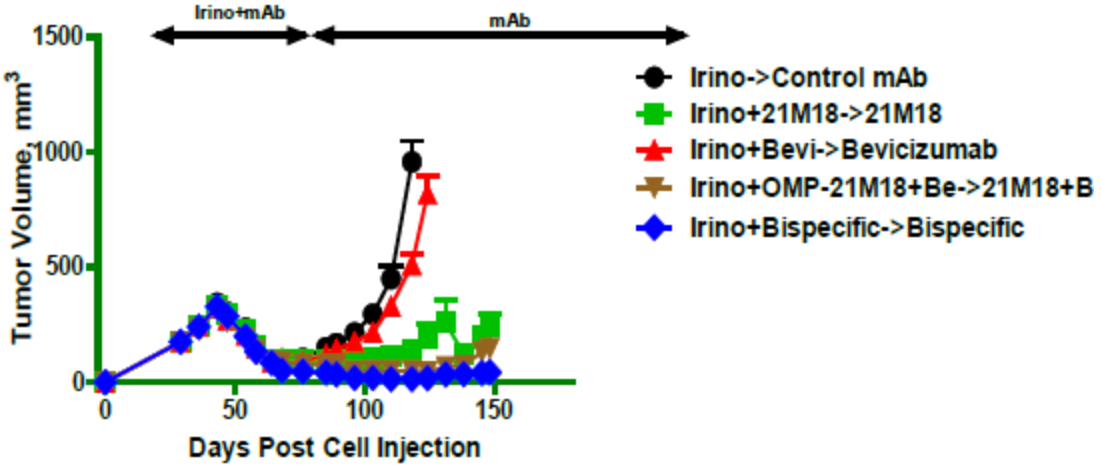
# Bi-specific Dll4/VEGF Antibody Appears to Have Enhanced activity – It May Also Have a Different Toxicity Profile

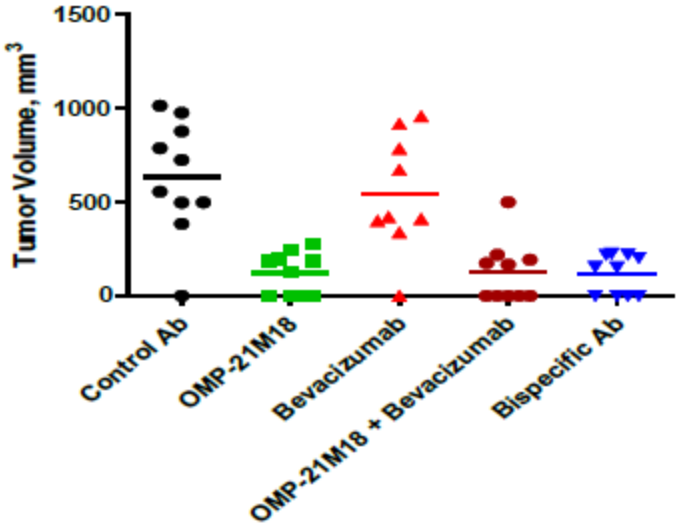
LEERINK SWANN

- From a mechanistic point of view, OMED's wholly owned bi-specific Dll4/VEGF could be a promising second-generation Dll4 inhibitor after demcizumab. It's expected to enter clinic in 1H:14.
- Although Dll4 inhibition demonstrated robust antitumor activity in a variety of human and rodent tumor models with some initial clinical evidence, treated tumor showed increased vascular density – consistent with the negative feedback loop mechanism. However, intravascular tracer labeling suggested these blood vessels were poorly perfused*.
- Although the mechanism of anti-tumor activity for Dll4 inhibitor is not fully understood, dual-target against Dll4 and VEGF could potentially have a different toxicity profile, and more importantly, provide enhanced activity against tumor.

*Source: *Yan and Plowman, Clin Cancer Res (2007) 13:7243-7246.*

# In Preclinical Models, Bi-specific Dll4/VEGF Antibody Appears to Have Enhanced Activity Compared to Demcizumab or Avastin




*Source: Beviglia et al ., AACR 2013 poster presentation.*

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# PARTNERED AGENTS ROUND OUT PORTFOLIO TARGETING NOTCH

# OMP-59R5 (Anti-Notch 2/3) – Partnered Program with GSK on Notch Signaling Pathway

LEERINK SWANN

- OMP-59R5 is a humanized monoclonal antibody targeting the Notch signaling pathway. It binds Notch2 and Notch3 receptor and blocks ligand dependent signaling.
- Preclinical studies demonstrated reduction of tumorigenicity and delay of tumor recurrence in patient-derived pancreatic adenocarcinoma.
- Phase I dose-escalation study showed the drug is generally well tolerated, with diarrhea as the main adverse event, which is dose dependent. Stable disease for over 60 days was seen in triple negative breast cancer (TNBC), liposarcoma, adenoid cystic carcinoma, Karposi sarcoma and rectal cancer.
- Two Phase Ib/II trials are ongoing including: 1) the ALPHINE trial evaluating ’59R5/gemcitabine/Abraxane in front-line pancreatic cancer, and 2) the PINNACLE trial evaluating ’59R5/etoposide/cisplatin in front-line SCLC.
- GSK has options through Phase II trials.

*Source: Company Reports, TNBC – triple negative breast cancer*

# OMP-59R5 (Anti-Notch 2/3) – Reduces Tumor Recurrence and Tumorigenicity in Patient-Derived Pancreatic Adenocarcinoma Preclinical Studies

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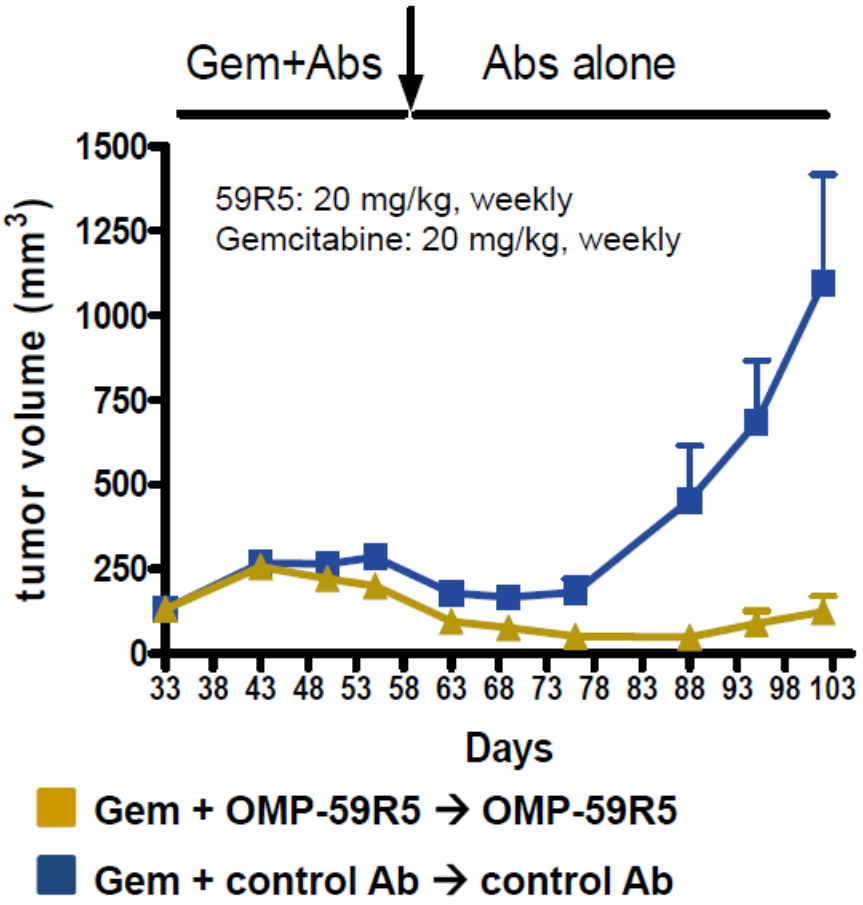
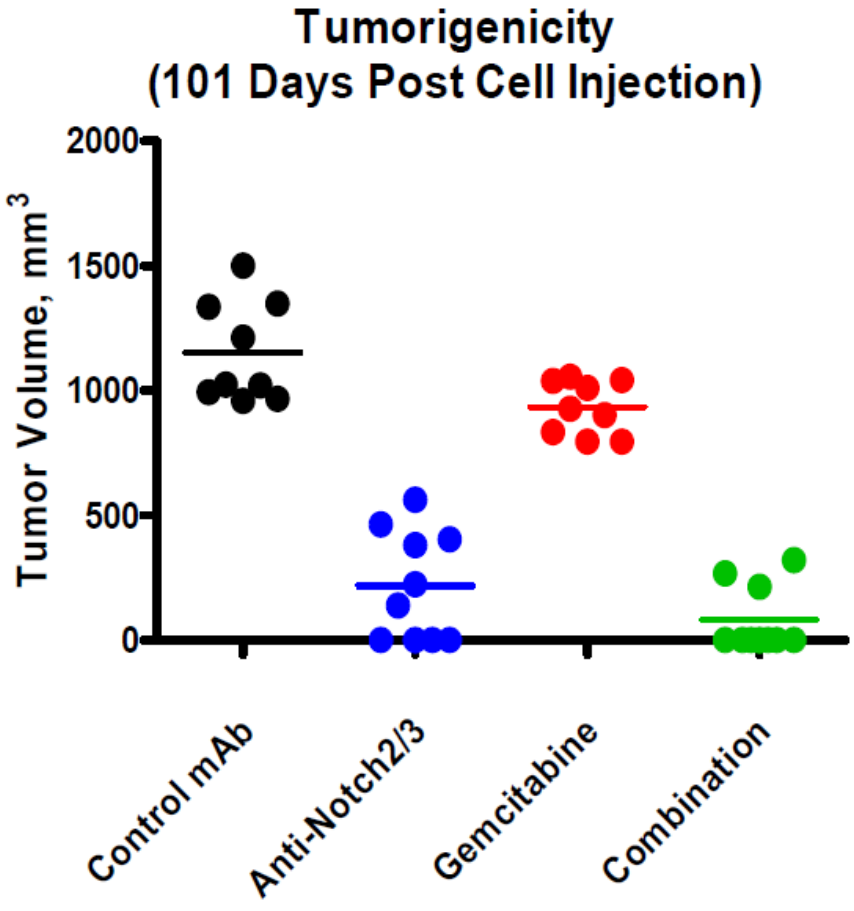
***Anti-Notch2/3 Delays Tumor Recurrence After Gemcitabine Treatment in PN8 Tumors***




***Anti-Notch 2/3 Decreases Tumorigenicity Of CD44+; PROCR+ Cells in NOD/SCID mice***




*Source: Company Reports*

# OMP-59R5 (Anti-Notch 2/3) – Prolonged SD Seen in Several Tumor Types in Phase I Trial

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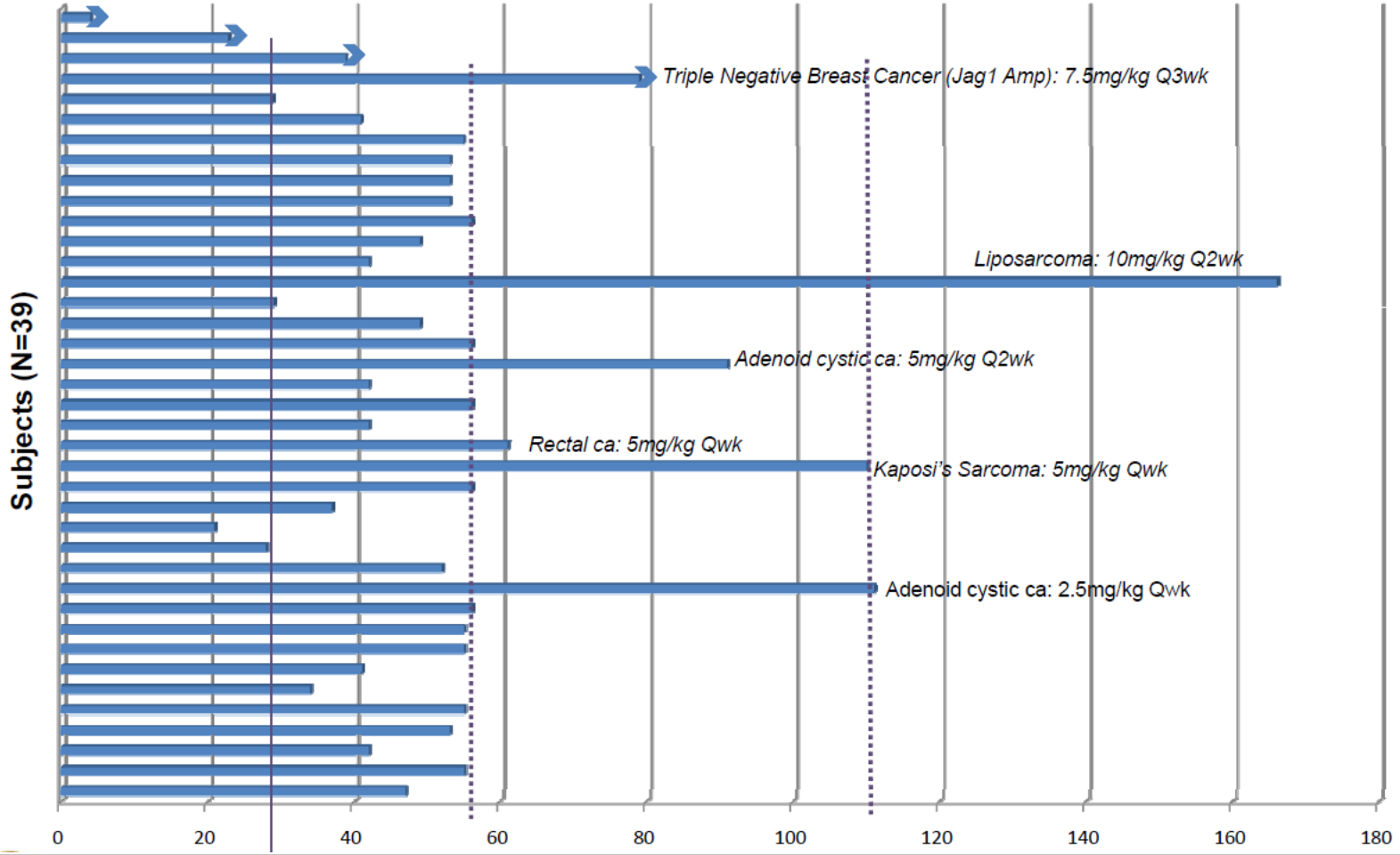
- Stable disease for over 60 days was seen in triple negative breast cancer (TNBC), liposarcoma, adenoid cystic carcinoma, Karposi sarcoma and rectal cancer.




*Source: Company Reports*

# OMP-59R5 (Anti-Notch 2/3) Is Generally Well Tolerated, Diarrhea Was the Main Adverse Event

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- Maximum tolerate dose (MTD) was reached at 2.5mg/kg for q1w, 7.5mg/kg for q2w and q3w dosing. Dose-limiting toxicity is diarrhea.
- Drug-related adverse events were mostly diarrhea with 21/36 (58%) for all Grades and 5/36 (14%) for Grade 3.

| **Drug-Related AEs** | **OMP-59R5 dose level (mg/kg) (N=36)**** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **All Grades Related AEs (≥5%) (All G3, no G4/5)** | 0.5QW (N=3) | 1QW (N=3) | 2.5QW (N=6) | 5QW (N=9) | 5QoW (N=6) | 10QoW (N=3) | 7.5Q3W (N=6) | ALL (%) |
| Diarrhea | - | - | - | 2 | - | 3 | - | 5 (14%) |
| Anemia | - | - | 1 | 1 | - | - | - | 2 (3%) |
| Fatigue | - | - | - | - | 1 | - | - | 1 (3%) |
| Increased ALT | - | - | 1 | - | - | - | - | 1 (3%) |
| Hypokalemia | - | - | - | 1 | - | - | - | 1 (3%) |

*Source: Company Reports*

# OMP-52M51 (Anti-Notch1) – Partnered Program with GSK

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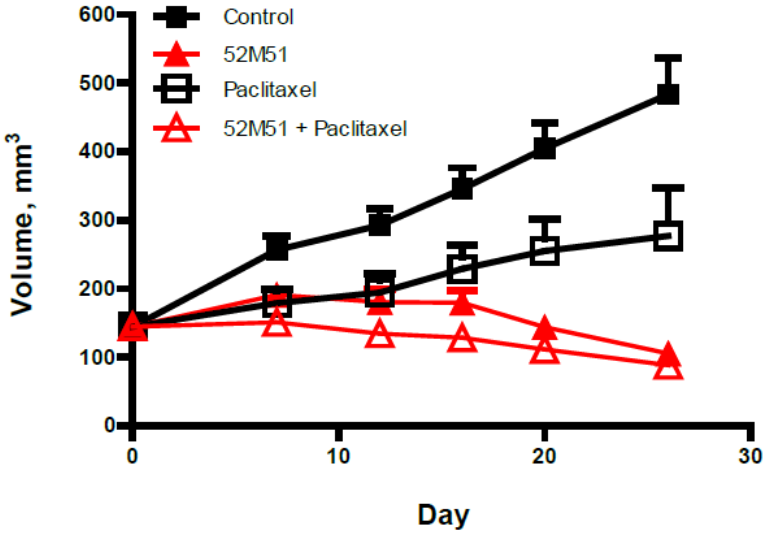
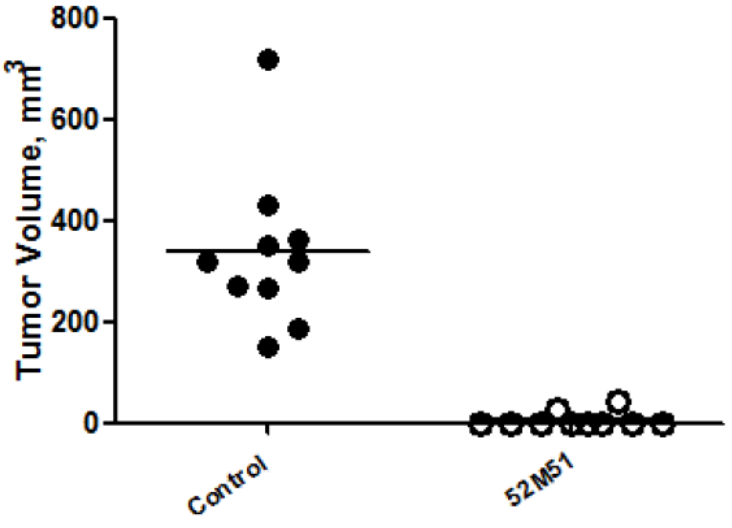
- OMP-52M51 is a monoclonal antibody targeting Notch1 receptor. Notch 1 mutation is associated with reduced survival in chronic lymphocytic leukemia (CLL)*.
- Preclinical data showed anti-tumor activity and reduction in tumorigenicity in triple negative breast cancer (TNBC) xenograft model.
- Two Phase Ia clinical trials are ongoing in hematologic or solid tumors. There may be a strong predictive biomarker for both hematologic anD solid tumors.

**Anti-tumor activity in TNBC Xenograft model**




**Reduction in tumorigenicity**




*Source: *Fabbri et al., J Exp Med (2011) 208:1380-1401; Cancilla et al., AACR 2013, #3728*

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# ONCOMED HAS ESTABLISHED A LEADERSHIP POSITION IN TARGETING THE WNT PATHWAY

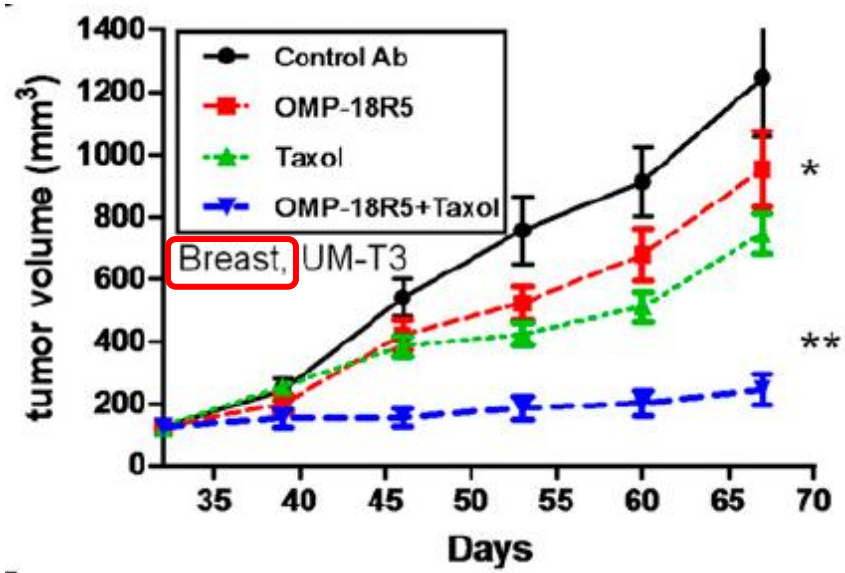
# Vantictumab (OMP-18R5, anti-Fzd7) – Partnered Program with Bayer on Wnt Signaling Pathway

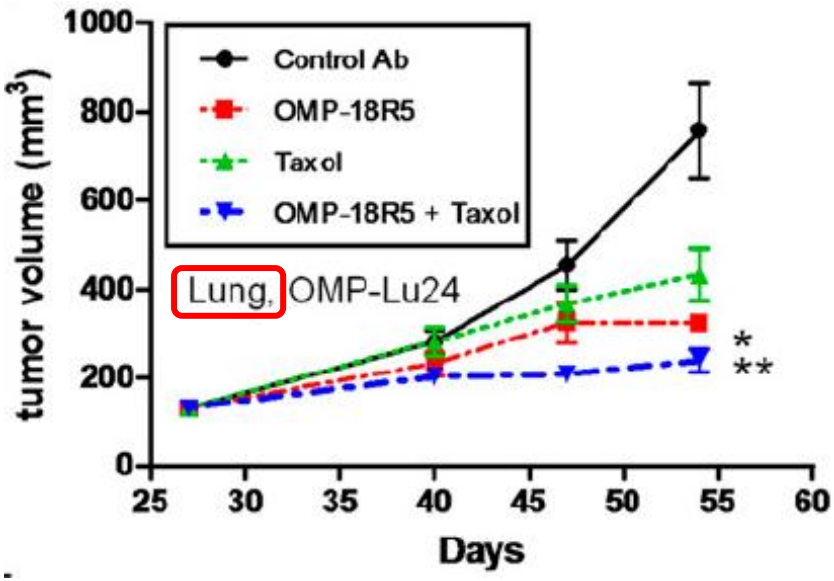
LEERINK SWANN

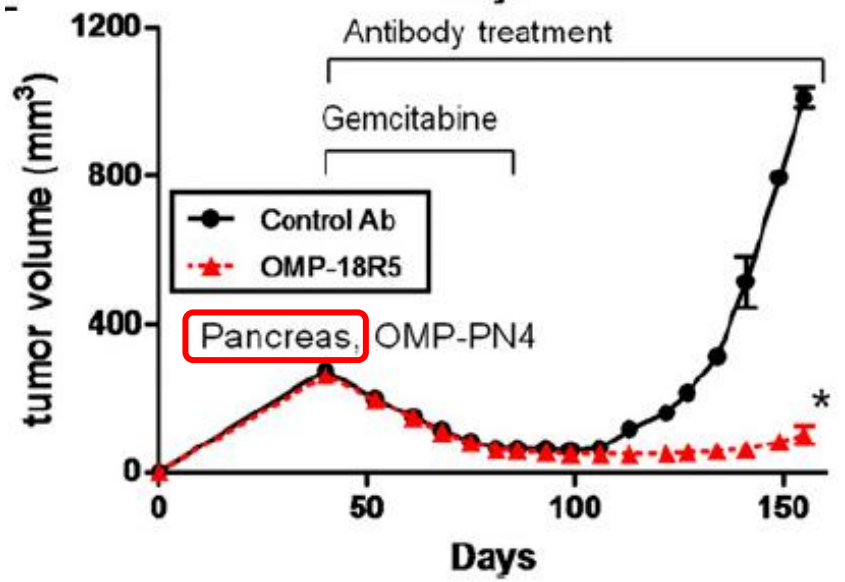
- Vantictumab is a humanized monoclonal antibody targeting Frizzled7 receptor (Fzd7). It binds a conserved epitope of 5 Frizzled receptors and inhibits the Wnt signaling pathway.
- A preclinical study showed reduction of growth and tumorigenicity in several tumor cells with vantictumab. Combination of vantictumab with standard of care (SOC) chemotherapy showed the synergistic effect of anti-tumor activity.
- Phase I trial in advanced solid tumor showed single-agent activity in neuroendocrine tumors (NETs). The drug is generally well tolerated with one report of bone turnover -- however, manageable.
- OMED plans to initiate 3 Phase Ib trials in 2H:13 in combination with SOC in 3 solid tumor indications.
- Bayer has options through Phase I trials.

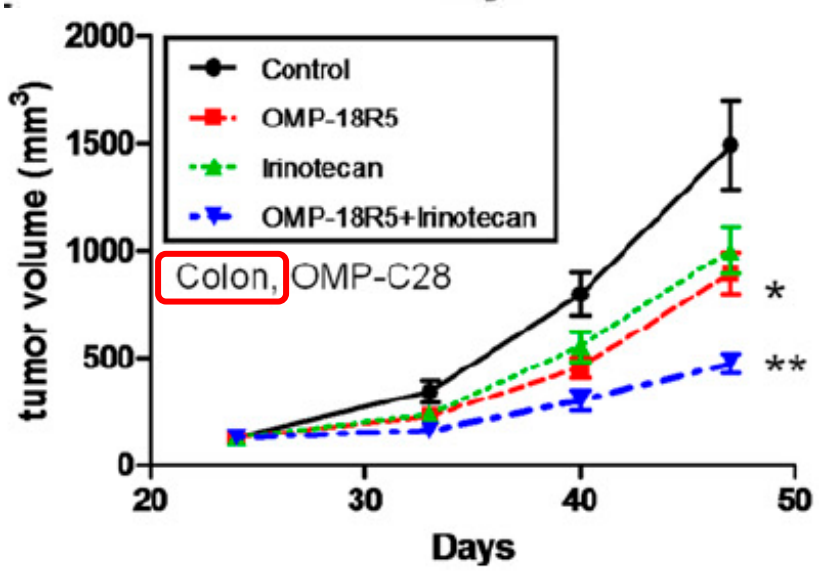
*Source: Company Reports*

# Vantictumab Treatment Resulted in Growth Inhibition in Several Tumor Cell Types; Synergistic Effect Was Seen for Vantictumab/SOC Chemotherapy




*Source: Gurney et al., PNAS (2012) 109:11717-22; Statistical significance p<0.02 (* vs. control Ab, ** vs. chemo alone)*

# Vantictumab Treatment Resulted in Tumorigenicity Reduction in Pancreatic and Breast Tumor Cells

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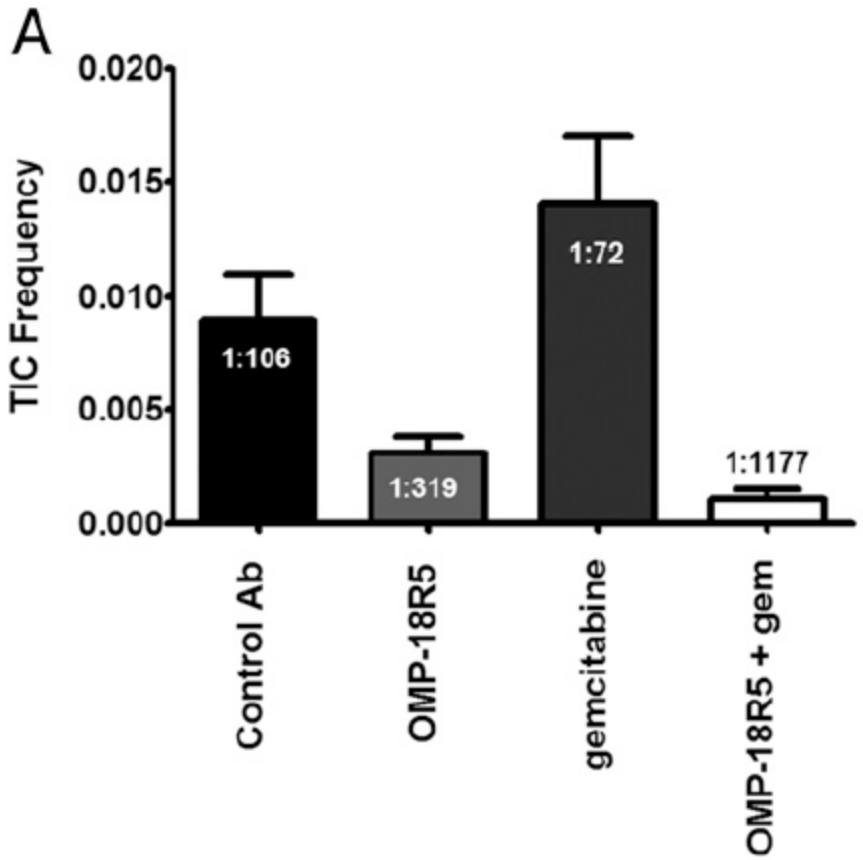
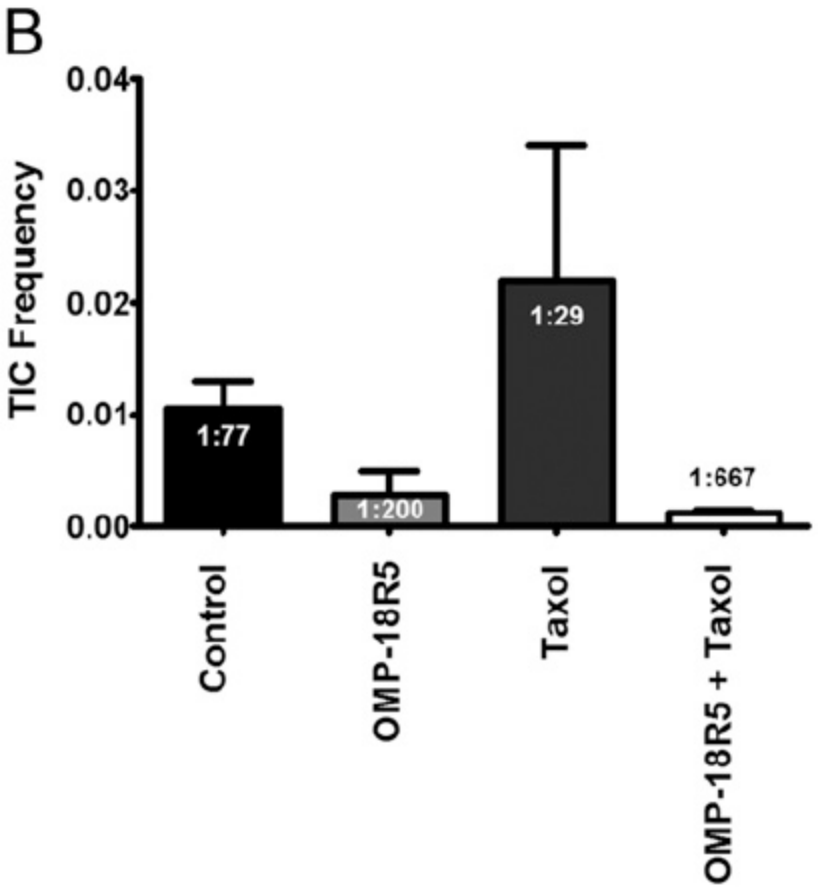
## Pancreatic PN4 Tumor




## Breast PE13 Tumor




*Source: Gurney et al., PNAS (2012) 109:11717-22*

# Vantictumab Phase I Data Showed Single-agent Activity in Neuroendocrine Tumor (NET) Patients

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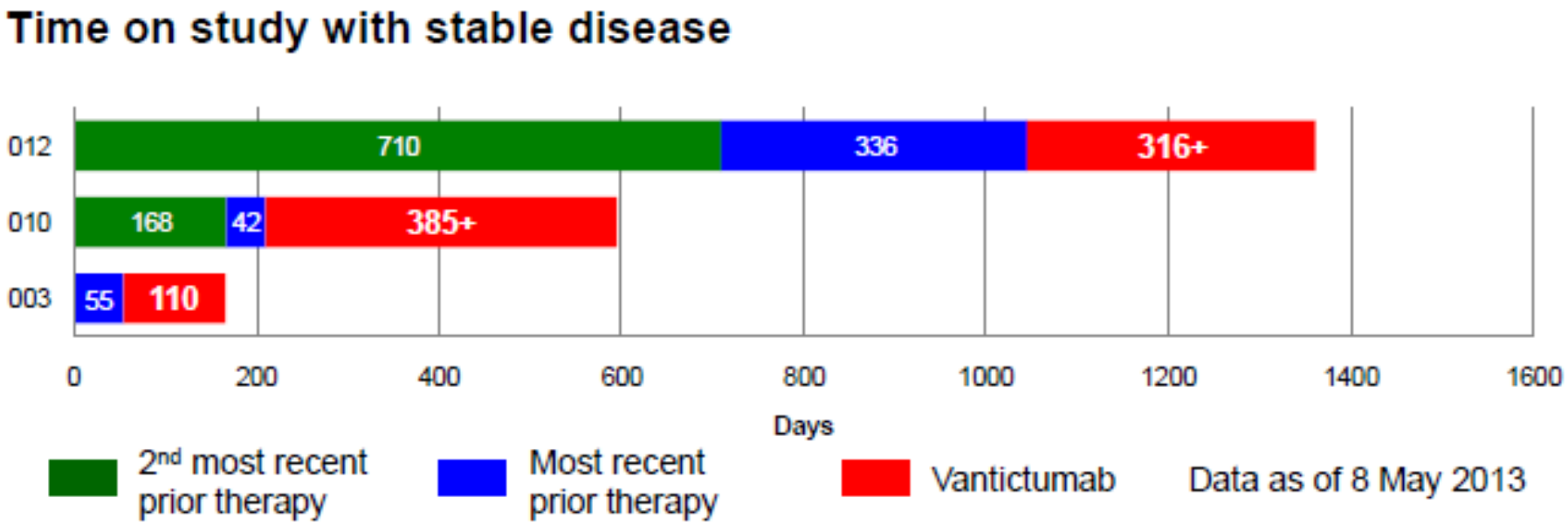
- In Phase I dose-escalation study (n=24), 3/3 NET patients (2 with carcinoid, 1 [patient 010] with pancreatic NET) had prolonged SD at dose of 0.5mg/kg q1w, 0.5mg/kg q2w, and 1mg/kg q3w, suggesting single-agent activity.
- Although NET can be slow growing, 2 recent Phase III trials showed median progression-free survival of 5.4-5.5 months in advanced pancreatic NET patients on placebo who were progressing or progressed within last 12 months (Yao et al., NEJM, 2011; Raymond et al., NEJM, 2011).




*Source: Smith et al., ASCO 2013, #2540*

# Vantictumab Is Generally Well Tolerated, Bone Turnover Side Effect Manageable

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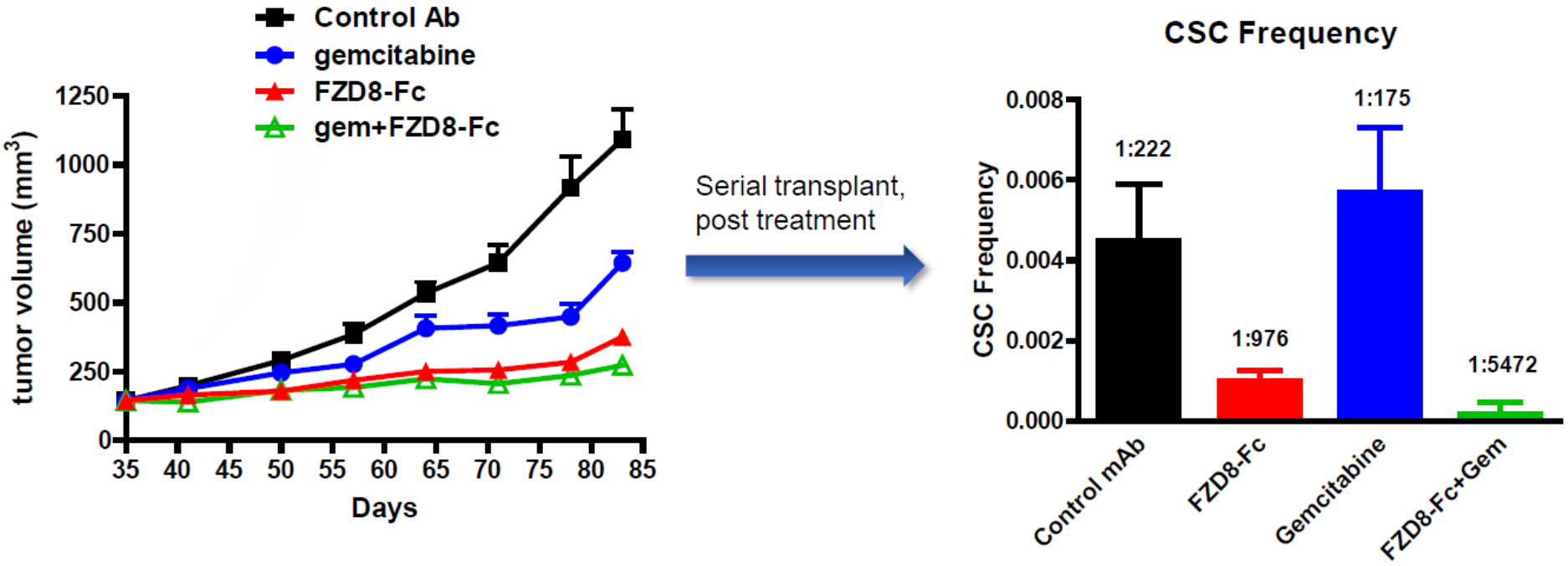
- Maximum tolerate dose (MTD) is not reached yet. Dosing escalation continues. Drug-related adverse events were mostly Grade 1/2 fatigue, nausea and vomiting.
- Patient 004 experienced Grade 3 vomiting and diarrhea, which was the only Grade 3 AEs and were considered as dose-limiting toxicity.
- Patient 003 who were dosed at 0.5mg/kg q1w experienced Grade 2 compression fracture after minor fall on Day 110. The program was revised to manage bone toxicity.
  - More stringent exclusion criteria such as chronic glucocorticoid use, high beta c-terminal telopeptide (beta-CTX) and known insufficient fracture.
  - Prophylactic Vitamin D and calcium carbonate.
  - Less frequent dosing.
  - Zoledronic acid treatment if doubling beta-CTX, or T-score decline to <-2.5 as measured by DEXA.

*Source: Smith et al., ASCO 2013, #2540*

# OMP-54F28 (Anti-Fzd8-Fc) – Partnered Program with Bayer

LEERINK SWANN

- OMP-54F28 is an antibody against Fzd8-Fc, a component of Wnt signaling pathway.
- Preclinical data showed anti-tumor activity as a single agent as well as in combination with chemotherapy. '54F28 also showed activity in gemcitabine resistant pancreas tumor in preclinical studies.
- Phase I dose-escalation trial is ongoing.




*Source: Hoey et al., AACR 2013, oral presentation*

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# ONCOMED DISCOVERED RSPO AS A PART OF LGR PATHWAY, WHICH IS EMERGING AS AN IMPORTANT CSC PATHWAY

# OMED's New Development of Antibodies Against RSPO-LGR, an Emerging CSC Pathway

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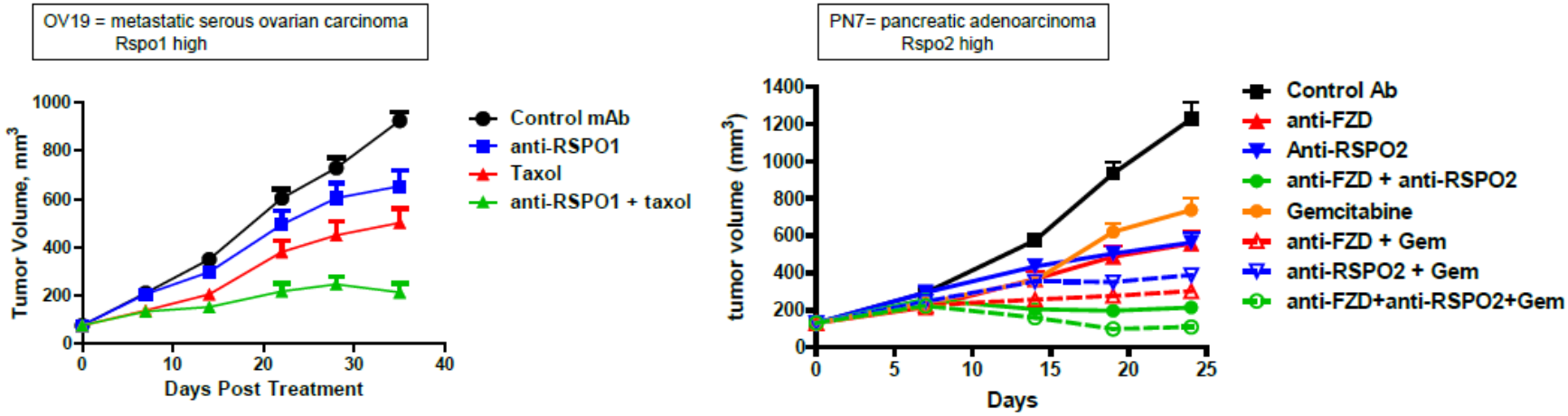
- The R-spondin (RSPO) – LGR signaling is a recently appreciated pathway that promotes β-catenin signaling in normal stem cell populations. RSPOs genes were identified as potent activators of Wnt/β-catenin signaling. Certain LGR receptors are distributed specifically on adult stem cells in mammalian tissues, and LGR-expressing cells have been linked to the development of cancer.
- Specific antibody against RSPO family were developed, and in vitro studies suggested marked inhibition of several tumor types. OMED wholly owns the program and plans to advance it into clinical trials as early as in 2014.

## *In vivo* Efficacy Study Results with Anti-RSPO Antibodies and Paclitaxel in ovarian and pancreatic tumors




*Source: Company Reports*

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# PARTNERSHIPS

# GSK Partnership

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- Formed a strategic alliance with GSK in Dec. 2007
- Targeting the Notch signaling pathway
- $35M upfront for 2 biologic programs
  - OMP-59R5 (anti-Notch2/3)
  - OMP-52M51 (anti-Notch1)
- GSK may exercise an option through completion of Phase II proof-of-concept trials. If GSK does not exercise the options, OMED obtains worldwide rights for these programs.
- OMED leads R&D prior to GSK's exercise of its options
- Up to $345M in milestone for OMP-59R5
- Up to $350M in milestone for OMP-52M51
- Royalties: Low double-digit to high teens (we estimate 12-16%)
- GSK option through Phase II trials
- GSK holds 11.7% equity stake as of 12/31/2012

*Source: Company Reports*

# Bayer Partnership

LEERINK SWANN

- Formed a strategic alliance with Bayer in June 2010
- Focusing on anti-CSC biologic and small molecule therapeutics targeting the Wnt signaling pathway
- $40M upfront and $20M for 2011 IND
- 3 biologic and 2 small molecule programs
  - Up to $388M for each biologic program
  - Up to $112M for each small molecule program
- Royalties: mid-single-digit to high teens for biologics and single-digit for small molecule
  - We estimate 12-17% for the first biologic, 5-12% for the second biologic, and 2-4% for small molecules
- Bayer option through Phase I trials

*Source: Company Reports*

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# INTELLECTUAL PROPERTY

# Intellectual Property

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| Drug | Status | Expiry | Coverage |
|---|---|---|---|
| Demcizumab (OMP-21M18) | Issued | 2028 | The composition of matter and methods of use |
| Anti-Notch2/3 (OMP-59R5) | Issued | 2030 | The composition of matter and methods of use |
| Anti-Notch1 (OMP-52M51) | Issued | 2030 | The composition of matter and methods of use |
| Vantictumab (OMP-18R5) | Issued | 2029 | The composition of matter and methods of use |
| Fzd8-Fc (OMP-54F28) | Pending | 2031 | The composition of matter and methods of use |

*Source: Company Reports*

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# FINANCIALS

# Income Statement

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| OMED Income Statement | 2011A | 2012A | Mar-13A | Jun-13E | Sep-13E | Dec-13E | 2013E | 2014E | 2015E | 2016E | 2017E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Collaboration revenue - related party | 3,365 | 15,970 | 493 | 490 | 490 | 490 | 1,963 | 0 | 0 | | |
| Collaboration revenue | 28,000 | 8,689 | 2,439 | 2,500 | 13,000 | 15,000 | 32,939 | 47,000 | 48,000 | 50,000 | 120,000 |
| Grant revenue | 44 | 22 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| Demcizumab sales | | | | | | | | | | | |
| Royalties | | | | | | | | | | | |
| Total revenue | 31,409 | 24,681 | 2,932 | 2,990 | 13,490 | 15,490 | 34,902 | 47,000 | 48,000 | 50,000 | 120,000 |
| COGS | | | | | | | | | | 0 | 0 |
| *% of revenue* | | | | | | | | | | *8%* | *8%* |
| R&D | 40,058 | 39,893 | 9,576 | 9,863 | 11,836 | 14,203 | 45,478 | 46,843 | 48,248 | 49,695 | 51,186 |
| G&A | 6,591 | 7,157 | 1,985 | 2,045 | 2,249 | 2,474 | 8,752 | 9,015 | 9,285 | 10,214 | 11,235 |
| *% of revenue* | | | | | | | | | | | |
| Total operating expenses | 46,649 | 47,050 | 11,561 | 11,908 | 14,085 | 16,677 | 54,231 | 55,858 | 57,533 | 59,909 | 62,422 |
| Net income (loss) from operations | (15,240) | (22,369) | (8,629) | (8,918) | (595) | (1,187) | (19,329) | (8,858) | (9,533) | (9,909) | 57,578 |
| Interest expenses | (38) | (6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Other income | 244 | 140 | 31 | 0 | 0 | 0 | 31 | 0 | 0 | 0 | |
| Total other income (expenses) | 206 | 134 | 31 | 0 | 0 | 0 | 31 | 0 | 0 | 0 | 0 |
| Net income (loss) before income taxes | (15,034) | (22,235) | (8,598) | (8,918) | (595) | (1,187) | (19,298) | (8,858) | (9,533) | (9,909) | 57,578 |
| Provision (benefit) for income taxes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| *Tax rate* | | | | | | | | | | | |
| Net income (loss) | (15,034) | (22,235) | (8,598) | (8,918) | (595) | (1,187) | (19,298) | (8,858) | (9,533) | (9,909) | 57,578 |
| **Net loss per share** | **(15.40)** | **(21.30)** | **(0.39)** | **(0.40)** | **(0.02)** | **(0.04)** | **(0.74)** | **(0.30)** | **(0.31)** | **(0.31)** | **1.69** |
| Basic shares | 976 | 1,044 | 22,265 | 22,287 | 27,785 | 28,063 | 26,045 | 29,466 | 30,939 | 32,486 | 34,110 |
| Dilutive shares | | | 24,885 | 24,910 | 28,618 | 28,904 | 27,478 | 29,482 | 30,957 | 32,504 | 34,130 |

*Source: Company Reports and Leerink Swann*

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# MANAGEMENT

| Management | Title | Prior Experience |
|---|---|---|
| Paul Hastings | President and CEO | President & CEO of QLT and Axys, President of Chiron, VP, Global Marketing of Genzyme |
| John Lewicki, PhD | EVP and CSO | VP of Research with Scios |
| Jakob Dupont, MD | SVP and CMO | Global Medical Director, Avastin at Genentech, faculty member at MSKCC |
| Sunil Patel | SVP and CBO | VP of Corporate Development and Marketing at BiPar, VP of Corporate Development at Allos, various positions with Connetics, Abgenix, Gilead, Consultant with McKinsey |
| Will Waddill | SVP and CFO | SVP, CFO of Ilypsa, Principal at Square One Finance, Senior Director of Finance and Administration at Exelixis |
| Austin Gurney, PhD | SVP, Molecular & Cellular Biology | Genentech |
| Tim Hoey, PhD | SVP, Cancer Biology | Director, Biology Department at Amgen, Director, Biology Department at Tularik |
| Alicia Hager, JD, PhD | VP, General Counsel | Associate at Morrison & Foerster |

*Source: Company Reports*


## Disclosures Appendix

## Analyst Certification

I, Howard Liang, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

| Distribution of Ratings/Investment Banking Services (IB) as of 06/30/13 | | | | |
|---|---|---|---|---|
| | | | IB Serv./Past 12 Mos. | |
| Rating | Count | Percent | Count | Percent |
| BUY [OP] | 103 | 62.80 | 30 | 29.00 |
| HOLD [MP] | 61 | 37.20 | 2 | 3.00 |
| SELL [UP] | 0 | 0.00 | 0 | 0.00 |

## Explanation of Ratings

**Outperform (Buy):** We expect this stock to outperform its benchmark over the next 12 months.

**Market Perform (Hold/Neutral):** We expect this stock to perform in line with its benchmark over the next 12 months.

**Underperform (Sell):** We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

## Important Disclosures

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For price charts, statements of valuation and risk, as well as the specific disclosures for covered companies, client should refer to https://leerink2.bluematrix.com/bluematrix/Disclosure2 or send a request to Leerink Swann Publishing Department, One Federal Street, 37th Floor, Boston, MA 02110.

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