

Genentech **FACT SHEET**

BIOONCOLOGY™

Media Contact: Charlotte Arnold (650) 467-7694
Investor Contact: Kathee Littrell (650) 225-1034
Advocacy Contact: Kristin Reed (650) 467-9831

Pipeline: Insight and Innovation from Genentech BioOncology

As a result of our commitment to basic research, Genentech BioOncology has a robust product pipeline, with innovative compounds designed to target cancer via specific molecular processes. We believe that studying the biological pathways involved in cancer development, progression and metastasis holds the key to identifying promising molecular targets.

Genentech BioOncology also supports the development of clinical diagnostics to identify patients most likely to benefit from treatment with our medicines. Scientists at Genentech are investigating potential diagnostic markers, including HER receptors, that may aid selection of the patients most likely to benefit from our targeted therapies.

Through our current research focus, including anti-angiogenesis, cell signaling (HER signaling, apoptosis and B-cell signaling) and arming antibodies, we approach cancer research from multiple pathways, helping us to unravel the complexity of cancer treatment and positively impact the lives of patients.

Genentech BioOncology's pipeline includes both new molecular entities and the development of existing products in new therapeutic areas. While we are studying Avastin® (bevacizumab), Herceptin® (Trastuzumab), Rituxan® (Rituximab) and Tarceva® (erlotinib) in numerous tumor types, as well as conducting combination trials, we are also investigating several new molecules as cancer therapies, including:

- Apomab*
- Dulanerim (recombinant human Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand), in collaboration with Amgen
- ABT-263, in collaboration with Abbott Laboratories
- GDC-0449**, in collaboration with Curis, Inc.
- Dacetuzumab, in collaboration with Seattle Genetics
- Pertuzumab
- Trastuzumab-DM1 (T-DM1)
- ABT-869, in collaboration with Abbott Laboratories

Apomab*, Dulanerim and ABT-263: Cell Signaling/Apoptosis

Apoptosis, or “programmed cell death,” is a process by which cells in the body, both normal and abnormal, self-destruct. Under normal conditions, apoptosis eliminates damaged or unneeded cells.¹ However, many cancer cells evade apoptosis, allowing tumors to survive and grow.² Therefore, developing therapies that can activate – or induce – apoptosis may have the potential for treating a variety of cancers.³

Apomab*

Apomab is a fully human antibody discovered by Genentech scientists that is designed to specifically bind to and activate an important receptor, called pro-apoptotic Death Receptor (DR) 5, which is found on the surface of various types of cancer cells.⁴

Binding of Apomab to DR5 may directly activate the extrinsic apoptosis pathway, may also indirectly induce the intrinsic apoptosis pathway in cancer cells.⁵ In preclinical models, Apomab selectively induced apoptosis in cancer cells.^{5,6}

Genentech scientists are currently studying Apomab in early-stage clinical trials in a variety of solid tumors and blood cancers. In April 2007, Genentech announced the initiation of two Apomab Phase II clinical studies – one in non-small cell lung cancer (NSCLC) and the other in non-Hodgkin’s lymphoma (NHL).

Dulanerim

Dulanerim (Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand) is a recombinant (engineered) human protein designed to activate two pro-apoptotic receptors, DR4 and DR5.⁴

Binding of dulanerim to DR4 and DR5 may directly activate the extrinsic apoptosis pathway may also indirectly induce the intrinsic apoptosis pathway in cancer cells.⁷⁻⁹ In preclinical models, dulanerim selectively induced apoptosis in cancer cells, while sparing normal cells.⁸

Genentech BioOncology, in collaboration with Amgen, Inc. and Immunex, a wholly owned subsidiary of Amgen, Inc. is studying dulanerim, the first dual pro-apoptotic receptor agonist, in early-stage clinical trials in a variety of solid tumors and blood cancers, including Phase II studies in NSCLC and NHL.

ABT-263

ABT-263 is a small-molecule agent designed to restore apoptosis in cancer cells. ABT-263 inhibits members of a group of related proteins called the Bcl-2 family of proteins.¹⁰ Bcl-2 family proteins are expressed at high levels in many tumors and play a central role in regulating apoptosis and, consequently, tumor formation and growth. Some of these proteins promote apoptosis and some promote survival by acting as “stop signs” to intrinsic apoptotic signals.¹¹ ABT-263 blocks the activity of pro-survival Bcl-2 family proteins.¹⁰

Genentech BioOncology, in collaboration with Abbott Laboratories, is studying ABT-263 in Phase I/II clinical trials as a single agent for relapsed or refractory chronic lymphocytic leukemia, relapsed or refractory lymphoid malignancies and advanced small cell lung cancer.

Pertuzumab: Cell-Signaling/HER Pathway

Pertuzumab, a humanized monoclonal antibody, represents the first in a new class of investigational agents known as HER (human epidermal growth factor receptor) dimerization inhibitors (HDIs).¹²

Pertuzumab is designed to bind to the HER2 receptor – a protein found on the surface of epithelial cells – and inhibits the ability of HER2 to interact with other HER family members (HER1/EGFR, HER2, HER3 and HER4).^{13,14} HER dimerization (receptor pairing) is believed to play an important role in the growth and formation of several different cancer types.¹²

Pertuzumab binds to a different part of the HER2 receptor than other approved products, known as the dimerization domain.

Based on results from Phase II trials of pertuzumab and Herceptin, Genentech BioOncology and Roche have initiated a Phase III clinical trial (CLEOPATRA) investigating pertuzumab in combination with Herceptin for the treatment of first-line, HER2-positive metastatic breast cancer.

Phase II clinical trials are ongoing or planned evaluating pertuzumab in combination with Herceptin for neoadjuvant HER2-positive breast cancer, second-line HER2-positive metastatic breast cancer, and in combination with Tarceva for second-line metastatic non-small cell lung cancer.

GDC-0449: Cell-Signaling/Hedgehog Pathway**

Genentech BioOncology, under a collaboration agreement with Curis, Inc., is currently investigating GDC-0449, a novel small molecule antagonist of the Hedgehog signaling pathway. Abnormal activation of the Hedgehog signaling pathway appears to be an important mechanism for tumors to survive and grow and has been implicated in the development of basal cell carcinoma (BCC), as well as in the progression of several solid tumor cancers.¹⁵

Genentech BioOncology has initiated a Phase II study evaluating GDC-0449 in first-line metastatic colorectal cancer and is planning to initiate two additional Phase II studies in the second half of 2008 in advanced BCC and an advanced epithelial tumor.

Dacetuzumab (Anti-CD40): Cell-Signaling/B-Cell Signaling

Genentech BioOncology, in collaboration with Seattle Genetics, is currently investigating dacetuzumab, a humanized monoclonal antibody that targets the

CD40 antigen. CD40 is highly expressed on most B cell blood cancers.¹⁶

Several Phase I and II clinical trials evaluating dacetuzumab as single agent or in combination with standard therapies, including Rituxan, for relapsed multiple myeloma, relapsed follicular non-Hodgkin's lymphoma, and diffuse large B-cell lymphoma.

Trastuzumab-DM1 (T-DM1): Armed Antibody

T-DM1 is an investigational HER2 antibody drug conjugate that builds on the science of Herceptin by combining two therapeutic strategies for HER2-positive breast cancer: Herceptin (trastuzumab) biologic activity and targeted intracellular delivery of a potent anti-microtubule (cancer killing) agent. T-DM1 is being developed in collaboration with Roche and Immunogen, Inc.

T-DM1 is currently being evaluated in Phase II and Phase III clinical trials in patients with locally advanced or metastatic HER2-positive breast cancer who have progressed on a chemotherapy regimen containing Herceptin.

ABT-869: Anti-Angiogenesis

Genentech is building upon the scientific breakthroughs of Avastin by co-developing ABT-869, a small molecule inhibitor of angiogenesis, with Abbott Laboratories. ABT-869 is designed to selectively inhibit vascular endothelial growth factor (VEGF) receptors.

ABT-869 is currently being evaluated in Phase II clinical trials for metastatic non-small cell lung cancer, metastatic breast cancer and metastatic colorectal cancer,

For the full prescribing information and Boxed Warnings for Avastin, Rituxan, Herceptin and Tarceva please visit <http://www.gene.com>.

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* APOMAB® is an internationally registered trademark of Medvet Science Pty Ltd. Genentech's antibody is not affiliated, connected or associated with Medvet Science Pty Ltd.

** GDC-0449 was discovered by Genentech and was jointly validated through a series of preclinical studies performed under a collaborations agreement between Genentech and Curis, Inc.

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