

Transforming the future of cancer treatment

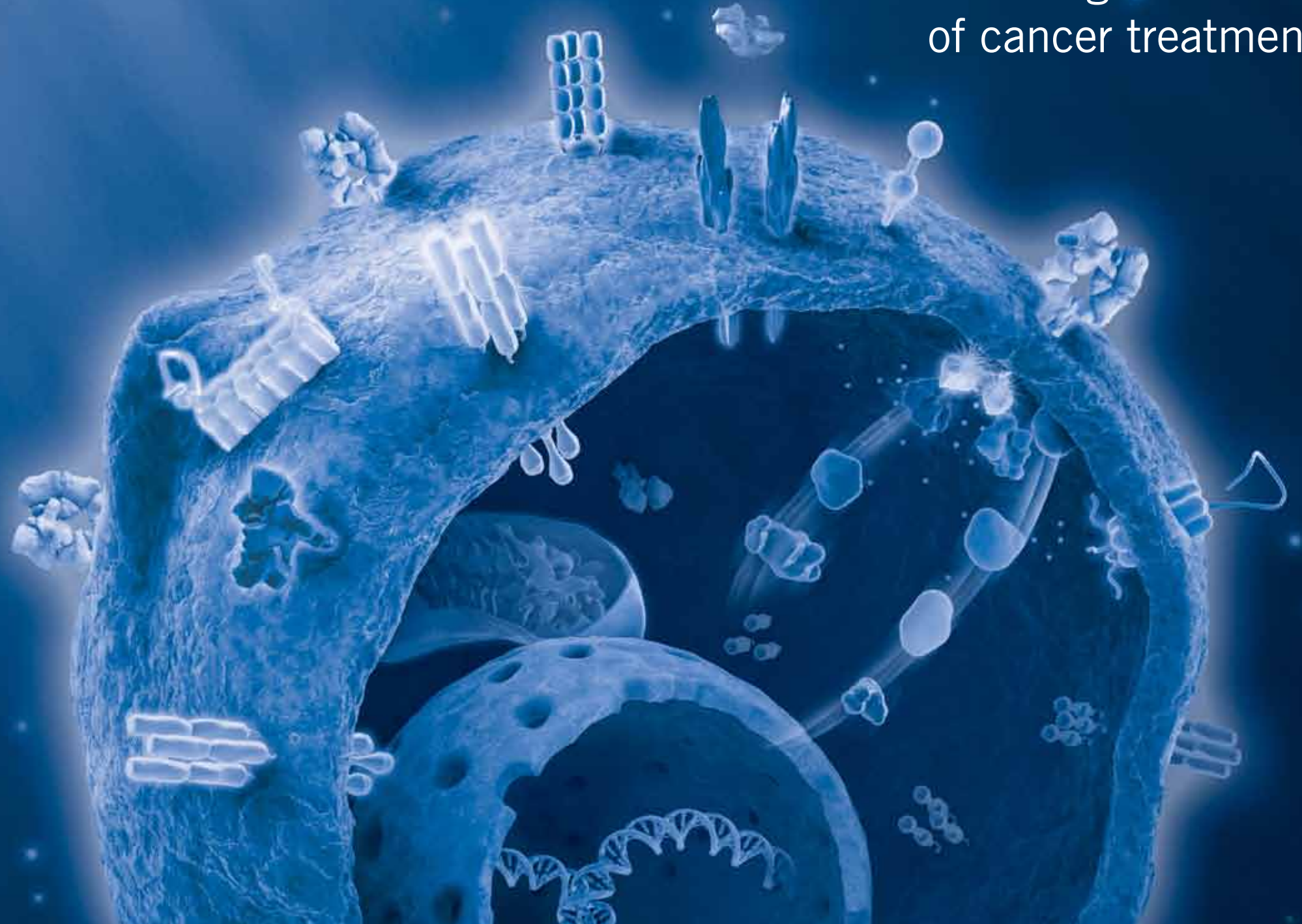


Table of contents

Introduction	3
Our new organizational structure	4
Areas of focus	
Antibody-drug conjugates (ADCs)	6
Angiogenic signaling	8
Anti-EGFL7 MAb (MEGF0444A, RG7414)	9
Anti-NRP1 MAb (MNRP1685, RG7347)	9
Anti-PIGF MAb (TB-403, RG7334)	9
Apoptosis	10
Navitoclax (Bcl-2/Bcl-X _L inhibitor, ABT-263, RG7433)	11
MDM2 antagonist (RG7112)	11
Dulanermin (rhApo2L/TRAIL, RG3639)	11
B-cell surface proteins	12
GA101 (anti-CD20 MAb, RO5072759, RG7159)	13
Hedgehog signaling	14
Hedgehog pathway inhibitor (GDC-0449, RG3616)	15
HER signaling	16
T-DM1 (HER2-targeted antibody-drug conjugate, HER2 ADC, RG3502) ..	17
Pertuzumab (HER2 dimerization inhibitor MAb, RG1273)	17
Anti-EGFR huMAb (GA201, RG7160)	17
MAPK signaling	18
BRAF inhibitor (PLX4032, RG7204)	19
MEK inhibitor (GDC-0973, RG7420)	19
MEK inhibitor, CIF (RG7167)	19
MEK inhibitor, CKI27 (RG7304)	19
MET signaling	20
MetMAb (RG3638)	21
PI3K signaling	22
PI3 kinase inhibitor (GDC-0941, RG7321)	23
PI3 kinase/mTOR inhibitor (GDC-0980, RG7422)	23
Notch signaling	24
Gamma secretase inhibitor (RG4733)	24
References	24
NMEs in oncology	28
Contact information	29

Contact information

Corporate Web sites

www.roche.com

www.gene.com

Clinical trials

- For inquiries about clinical trials in the US, please call the Trial Information Support Line at (888) 662-6728 or e-mail genentechclinicaltrials@druginfo.com
- Roche Clinical Trial Protocol Registry: www.roche-trials.com
- For clinical trials outside the US, contact your local affiliate through the “Roche Worldwide” link at www.roche.com
- National Institutes of Health Web site: www.clinicaltrials.gov

Early development programs

- Genentech Early Development (gRED): earlydevelopment@gene.com
- Pharma Early Development (pRED): global.pred@roche.com

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Introduction

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotechnology company, with truly differentiated medicines in oncology, virology, inflammation, metabolism, and CNS. Roche is also the world leader in in vitro diagnostics, tissue-based cancer diagnostics, and a pioneer in diabetes management. Roche's personalized healthcare strategy aims to provide medicines and diagnostic tools that enable tangible improvements in the health, quality of life, and survival of patients.

In March 2009, Genentech became a wholly owned member of the Roche Group. The new organization leverages the combined strength of both companies while maintaining the diversity of approaches essential for successful innovation.

Our oncology pipeline has 23 new molecular entities (NMEs) under investigation, including 5 NMEs in late-stage development. With the potential to develop into first- and best-in-class medicines, our industry-leading pipeline is poised to deliver a new generation of targeted therapeutics for cancer patients.

For more information about Roche and Genentech, visit www.roche.com and www.gene.com. Additional contact information can be found on page 29.

Our new organizational structure

The Roche Group ensures continued research innovation by maintaining a diversity of approaches and combining the cutting-edge research of Roche and Genentech, as well as Chugai Pharmaceuticals (Japan).

As part of the merger agreement, Genentech's Research and Early Development (Phase I and Phase II) organizations were reformed as a single independent center for discovery research and early clinical development. Genentech Research and Early Development (**gRED**) is focused on continuing the pioneering biotechnology work and tradition established more than 30 years ago and includes therapeutic antibodies, antibody-drug conjugates, and small molecules.

In parallel, Pharma Research and Early Development (**pRED**) combines the global early development and research organizations that existed within Roche, with a focus on creating value from a deep understanding of life sciences. pRED is dedicated to the translation and understanding of disease biology in the clinical setting, and providing novel therapeutics to the specific patient populations in 5 disease areas.

Maintaining these distinct and independent centers for research and early development provides the diversity of approaches essential for successful innovation. Drug candidates from both gRED and pRED that have progressed to Lifecycle (pivotal studies and beyond) are managed by the late-stage development group, Pharma Medicines (**pMED**). The Roche Group has a vast array of novel approaches for treating cancer and is at the forefront of cancer research.

Genentech Research and Early Development (**gRED**)

Genentech Research and Early Development (gRED) comprises the combined Research and Early Clinical Development components of Genentech, all located as before, in South San Francisco. Operating as an independent entity, gRED aspires to make fundamental scientific discoveries and to develop these discoveries globally into first- and best-in-class therapeutics that provide unique benefits to patients. Interfacing with the other key members of the Roche family, gRED is responsible for the development of drug candidates and predictive markers that result from Genentech Research, specifically from early development "Go" to "pivotal-trial ready." gPartnering, comprised of Business Development and Alliance Management, focuses on establishing strategic alliances to support gRED's mission, working closely with Genentech's Research and Early Development groups. By leveraging a unique understanding of disease mechanisms, a diversity of approaches to the treatment of cancer, and collaborative partnering, gRED remains focused on bringing promising drug candidates to patients, and the means to identify the patients who may benefit the most. In addition to activities in oncology, gRED focuses on Immunology, Infectious Diseases, and Neuroscience.

Pharma Research and Early Development (**pRED**)

Pharma Research and Early Development (pRED) combines the former Roche Research and Early Development groups as well as several support functions. Uniting more than 3500 colleagues globally, pRED is committed to driving and delivering world-class science through discovery groups that operate across a diversity of therapeutic modalities and translational and diagnostic capabilities. pRED is focused on bringing new, medically significant therapies to patients in need through the implementation of Roche's Personalized Healthcare strategy. In collaboration with Roche Partnering, pRED is exploring external innovation and emerging technologies to create sustainable, value-adding industry partnerships. pRED relies on the global footprint of its numerous sites as well as on a number of external Translational Medicine Hubs with the academic community to expand its access to innovation.

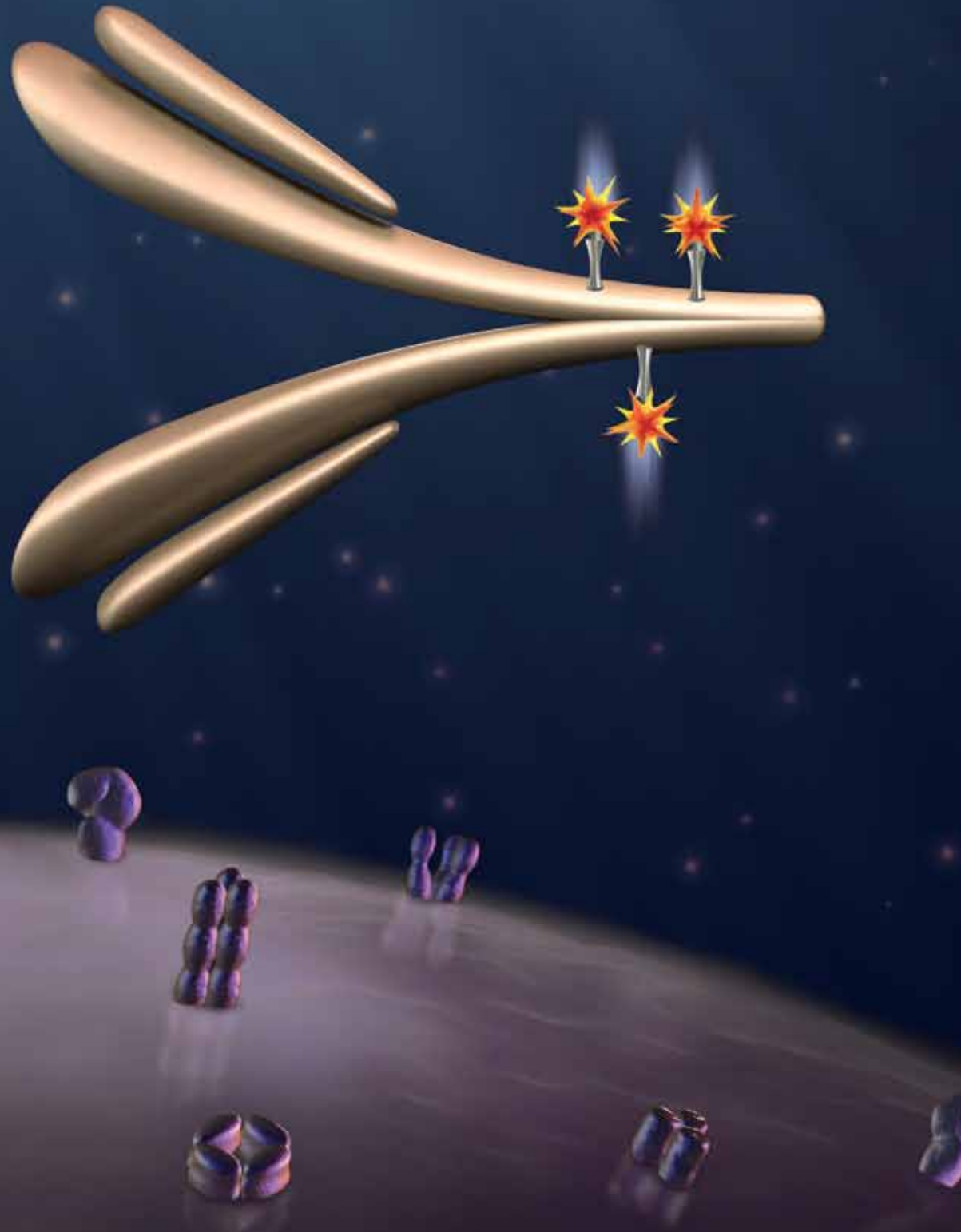
Roche Molecular Diagnostics

Roche's Diagnostics Division is a leading supplier of in vitro diagnostics (IVDs)—products used to test body fluids and tissue samples to obtain information to diagnose, treat, and manage disease. In oncology, an integrated approach combines specific anticancer drugs with molecular diagnostic tests, improving treatment outcome by selecting suitable patients and monitoring the progress of therapy. Once the relationship between a biomarker and a drug treatment has been established, a standardized molecular diagnostic test can be developed during clinical registration trials and prepared for regulatory approval alongside the drug. By combining drug and diagnostic test development expertise under the Roche global biomarker program umbrella, we are uniquely positioned to deliver on individual patient needs through the implementation of targeted treatments.

Contact information for gRED, gPartnering, pRED, and Roche Partnering can be found on page 29 of this brochure.

Antibody-drug conjugates (ADCs)

An ADC is a unique combination of a targeted monoclonal antibody (MAb), a stable linker, and a potent cytotoxic and is designed to selectively kill cancer cells while minimizing effects on normal tissue.¹⁻⁴



ADCs

gRED

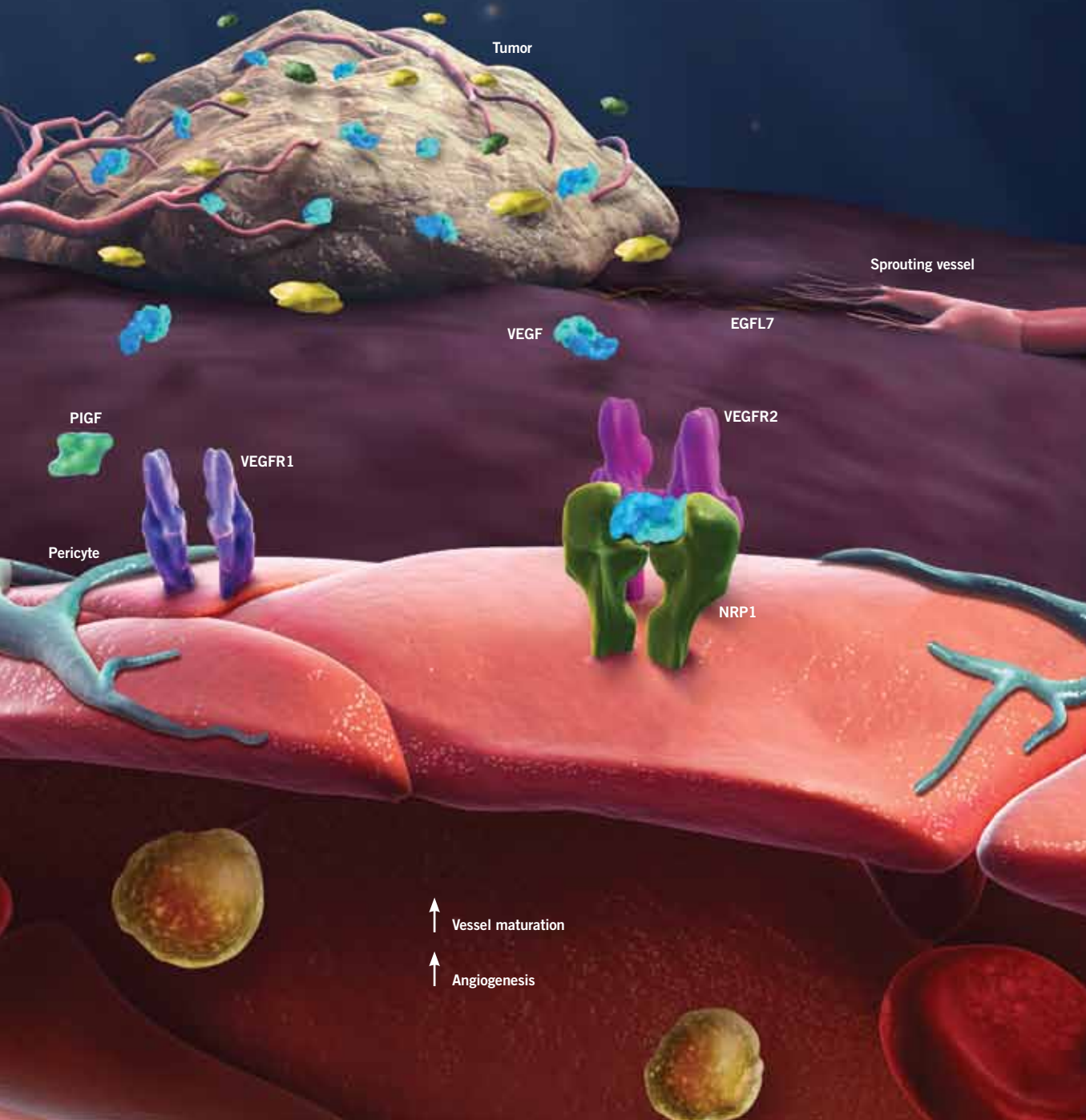
ADC technology is an intensive area of focus at gRED. The concept of conjugating potent cytotoxics to MAbs in order to specifically target tumor cells has been investigated for over 20 years, yet until recently, success had been limited.^{1,5,6} Inappropriate choices of target antigens, insufficient linker stabilities, and inadequate cytotoxic activity resulted in the suboptimal performance of early ADCs.¹

Recent advances in antibody technologies, target selection, and cytotoxic potency, coupled with intensive investigation of linkers have resulted in the capacity to create a new generation of ADCs.⁶ We are dedicated to aggressively researching ADCs because we believe these agents may have the potential to treat cancer and improve patients' lives.²

Angiogenic signaling

Angiogenesis is a vital process that facilitates tumor growth and survival.¹⁻³ Tumor angiogenesis refers to the ability of a tumor to stimulate new blood vessel formation.^{1,2} This critical step in development enables tumor expansion, local invasion, and dissemination through the following¹⁻³:

- Delivery of oxygen, nutrients, and survival factors
- Production of growth factors that benefit tumor cells
- Formation of a route for tumor cell egress



Anti-EGFL7 MAb (MEGF0444A, RG7414)

gRED

New vessels and their surrounding cells lay down extracellular matrix with important growth-promoting and survival factors, including EGF-like domain-containing protein 7 (EGFL7).⁴⁻⁸ The anti-EGFL7 MAb RG7414 is designed to block endothelial cell adhesion to the EGFL7 protein.⁹ This antibody may disrupt vascular tube formation⁷ and increase stress-induced endothelial cell apoptosis,^{8,9} thereby inhibiting angiogenesis. In multiple preclinical tumor models, RG7414 was shown to enhance the inhibition of tumor vascularization by vascular endothelial growth factor (VEGF) blockage.⁹

Anti-NRP1 MAb (MNRP1685, RG7347)

gRED

Neuropilin-1 (NRP1) is a growth factor receptor that is important for promoting vascular growth and maturation.¹⁰⁻¹³ The anti-NRP1 MAb RG7347 is designed to target NRP1 and inhibit angiogenesis and the subsequent vascular maturation that is necessary to form the functional vasculature that supports tumor growth. RG7347 has been shown to reduce tumor growth in preclinical models, both alone and in combination with VEGF inhibition. Furthermore, RG7347 may complement and potentiate the antitumor effects of VEGF inhibition.^{12,14}

Anti-PIGF MAb (TB-403, RG7334)

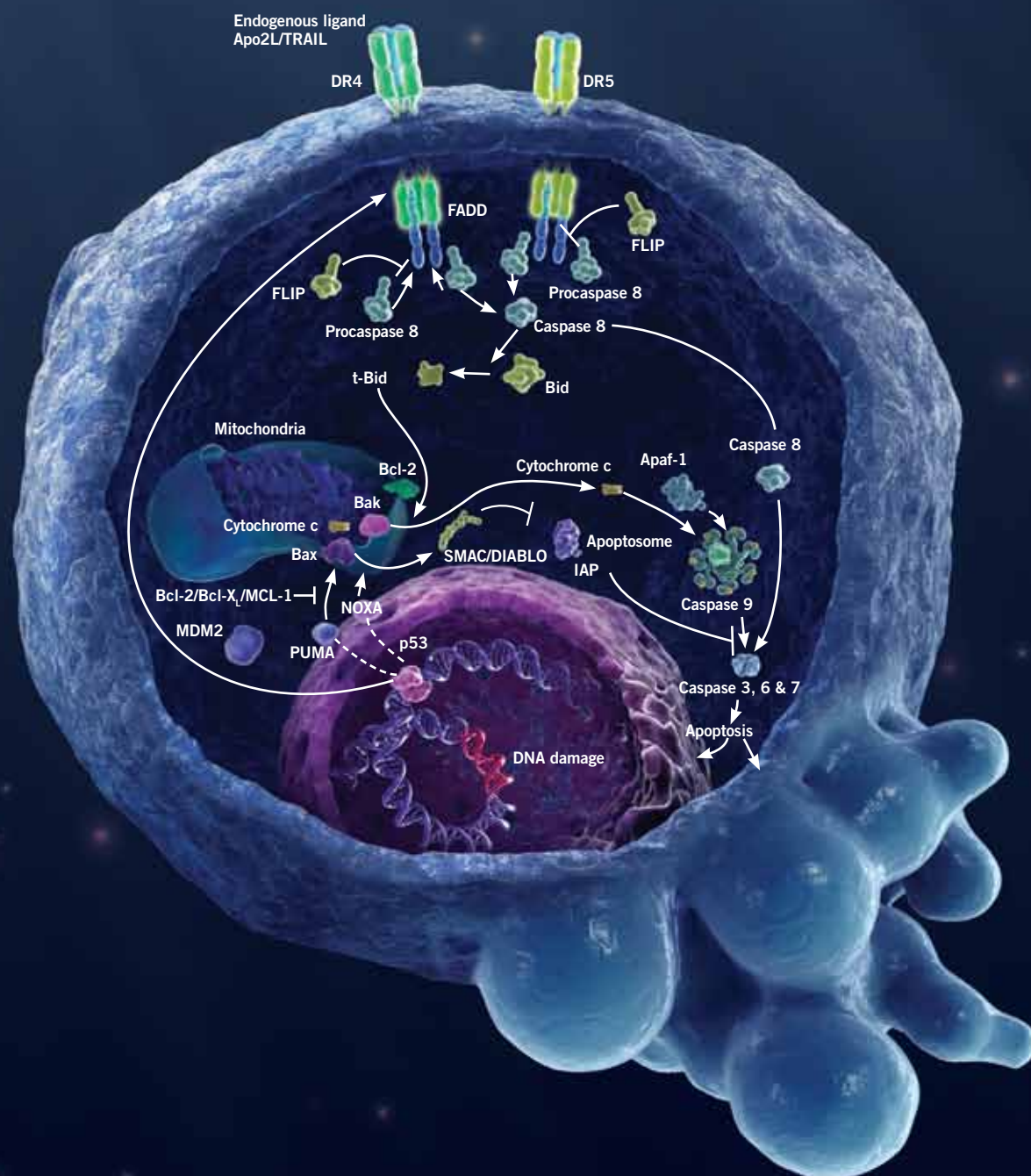
pRED

Placental growth factor (PIGF), VEGF-A, and VEGF-B are ligands for VEGF receptor-1 (VEGFR-1), which is expressed on endothelial cells as well as monocytes/macrophages, and some tumor cells.^{3,15} The humanized anti-PIGF MAb RG7334 is directed against PIGF.¹⁶ Antitumor activity has been demonstrated with RG7334 in human tumor xenograft models of renal cell carcinoma and hepatocellular carcinoma.¹⁶ The mechanism of action of RG7334 is currently under investigation; preclinical studies suggest its effects may include blocking tumor angiogenesis and primary tumor growth as well as inhibition of metastasis.^{15,16} In addition, PIGF inhibition may complement and potentiate the antitumor effects of VEGF inhibition, in part by inhibiting macrophage recruitment.¹⁵⁻¹⁷

Apoptosis

Dysregulation of apoptosis (programmed cell death) is a key process in cancer development and progression.^{1,2} The ability of cancer cells to avoid apoptosis and continue to proliferate is one of the fundamental hallmarks of cancer and is a major focus of cancer therapy development.² Developing novel molecules that promote apoptosis by targeting both the intrinsic and extrinsic apoptotic pathways advances our understanding of the mechanisms behind tumor cell proliferation, which may also lead to the development of effective cancer therapies. Apoptosis is triggered through 2 main signaling pathways^{1,3,4}:

- The extrinsic pathway may be activated in response to multiple external pro-apoptotic signals, including endogenous Apo2L/TRAIL and other pro-apoptotic receptor agonists (PARAs)
- The intrinsic pathway is initiated by cellular developmental cues or as a result of severe cellular stress (eg, DNA damage)



Navitoclax (Bcl-2/Bcl-X_L inhibitor, ABT-263, RG7433)

gRED

Overexpression of the prosurvival Bcl-2 family members (eg, Bcl-2, Bcl-X_L) is associated with tumor progression. The Bcl-2 family members inhibit the intrinsic apoptotic pathway by sequestering and neutralizing pro-apoptotic proteins. Navitoclax is a small-molecule inhibitor that targets anti-apoptotic Bcl-2 family proteins such as Bcl-2 and Bcl-X_L, and thus may cause cells to undergo programmed cell death.⁵

MDM2 antagonist (RG7112)

pRED

The p53 tumor suppressor is a potent growth suppressive and pro-apoptotic molecule that is frequently inhibited in cancer cells by overproduction of its negative regulator, MDM2.⁶⁻⁸ Inhibitors of the p53-MDM2 interaction can release p53 from negative control and restore its antitumor activity.⁶⁻⁸ RG7112 is a first-in-class, potent and selective MDM2 antagonist that activates the p53 pathway in cancer cells where p53 is not mutated, leading to cell cycle arrest and apoptosis.⁸ RG7112 has demonstrated preclinical antitumor activity against a variety of tumor types expressing wild-type p53 both in vitro and in vivo.⁸

Dulanermin (rhApo2L/TRAIL, RG3639)

gRED

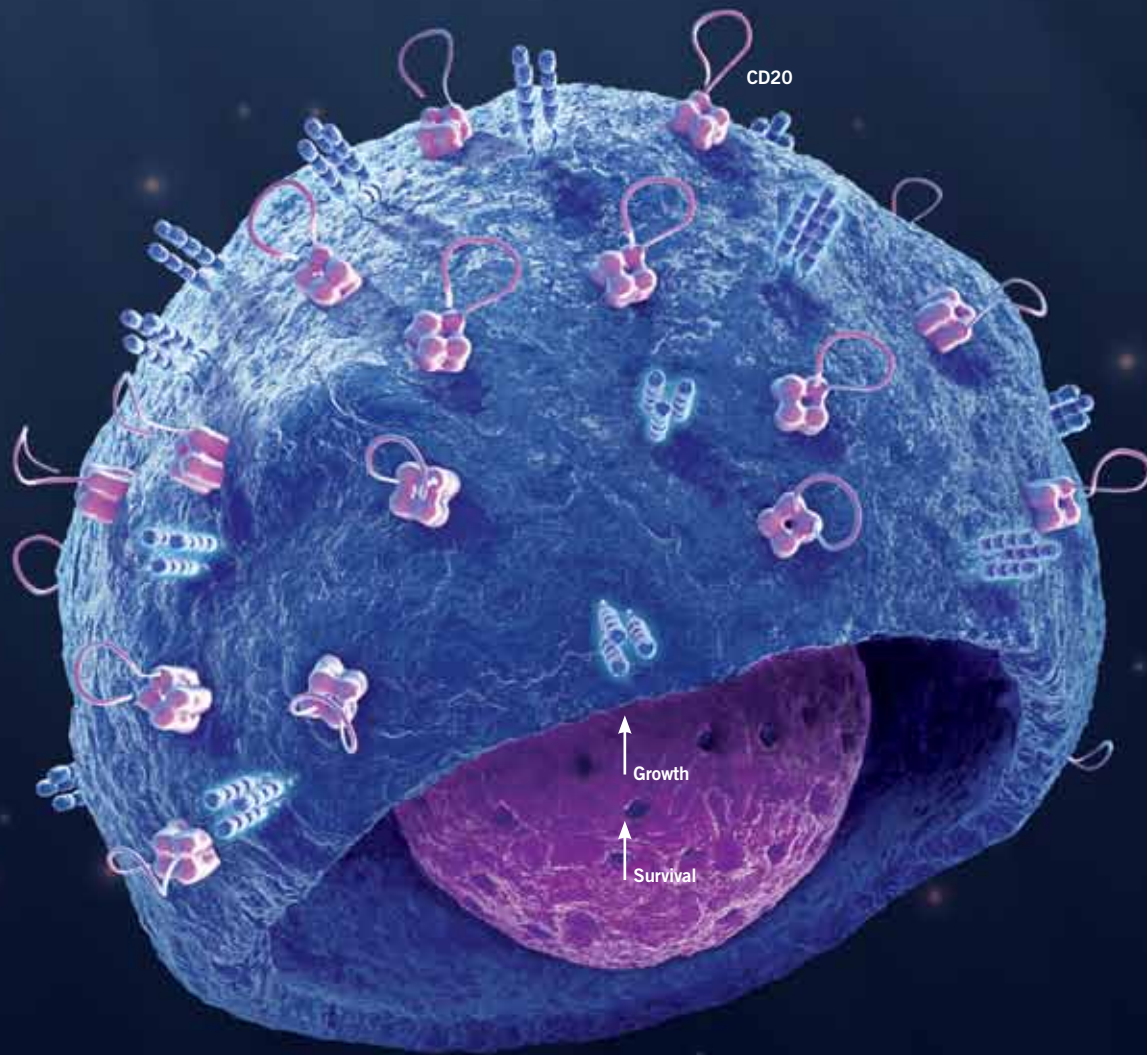
Dulanermin is a pro-apoptotic soluble protein based on naturally occurring Apo2L/TRAIL. Dulanermin is the first dual PARA that directly activates the extrinsic apoptotic pathway via the pro-apoptotic death receptors DR4 and DR5.^{1,9-11} Acting independently of p53, a tumor-suppressor protein that is inactivated in many cancers, dulanermin has the potential to induce the death of tumor cells that may otherwise be resistant to standard chemotherapy agents.¹¹

Dulanermin may also activate the intrinsic apoptotic pathway through the mitochondrial amplification loop.¹¹ Binding of dulanermin selectively induces apoptosis in cancer cells while sparing normal cells.⁹

B-cell surface proteins

B cells are a fundamental component of the body's immune system. However, like most cells in the body, B cells can become cancerous—leading to diseases such as non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Targeting B-cell surface antigens that are highly expressed in B-cell malignancies with monoclonal antibodies may lead to 1 or more of the following mechanisms¹⁻³:

- Apoptosis or direct cell death of cancer cells
- Identification and destruction of the cancer cells by immune effector cells in a process called antibody-dependent cellular cytotoxicity (ADCC)
- Facilitation of the binding of the complement system—proteins that destroy the cell membrane integrity—in a process called complement-dependent cytotoxicity (CDC)



GA101 (anti-CD20 MAb, RO5072759, RG7159)

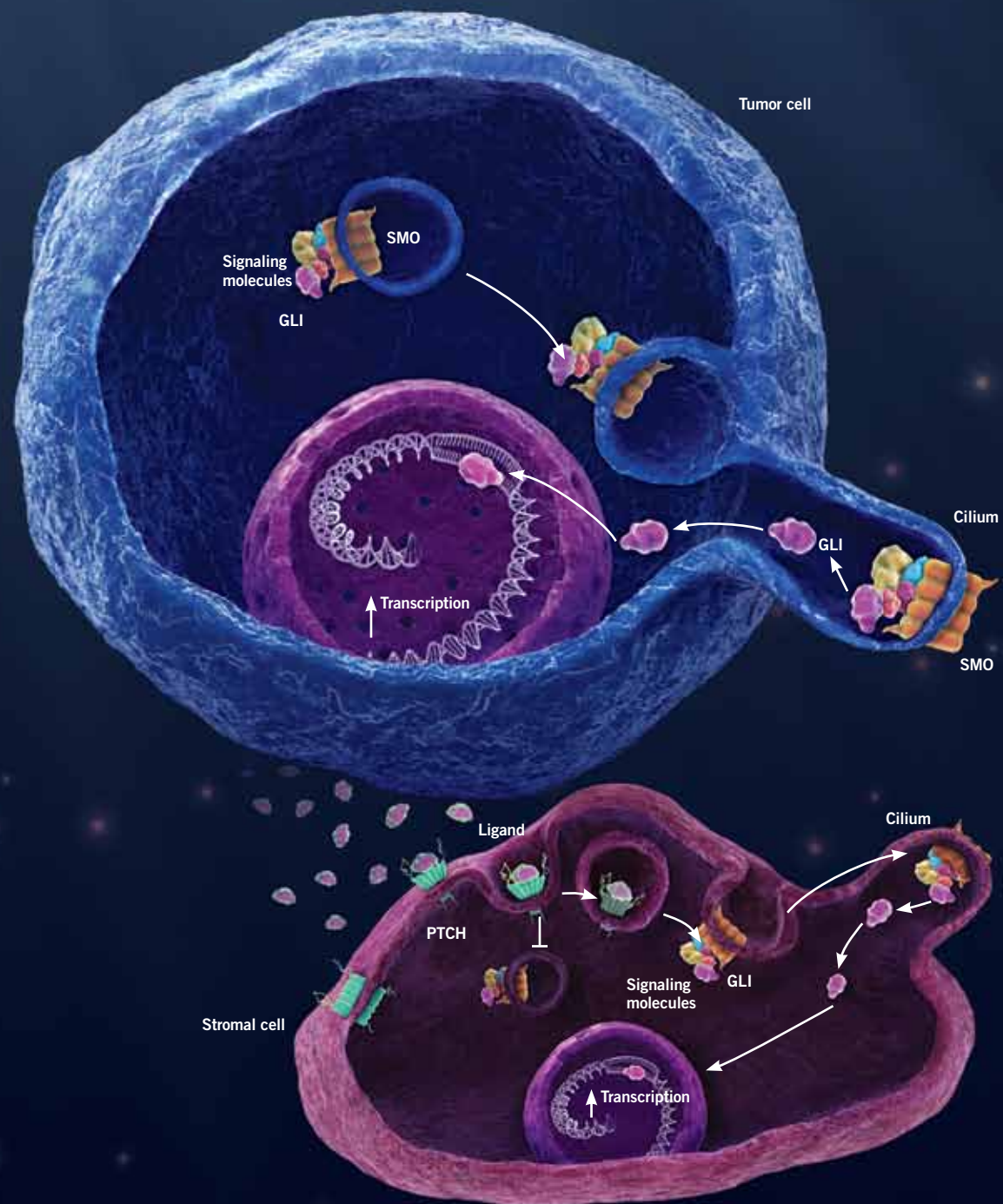
pMED

CD20 is a B-cell surface protein that is expressed on malignancies of B-cell precursors and mature B cells, including NHL and CLL.^{2,4,5} GA101 is a type II, glycoengineered, humanized anti-CD20 MAb designed to enhance direct cell death and ADCC mechanisms when binding to CD20-positive malignant B cells.⁶

By virtue of its type II antibody characteristics, GA101 causes higher direct cell death induction of cancer cells and lower complement recruitment compared with type I anti-CD20 antibodies. Afucosylation of the Fc region of GA101 (GlycoMAb™ technology) has resulted in stronger FcγRIIIa binding, which translates to enhanced ADCC. Preclinical studies demonstrate that GA101 induces greater B-cell depletion in peripheral blood as well as in lymphoid tissue compared with other available monoclonal antibodies. It also mediates high antitumor activity in NHL xenograft models.⁶

Hedgehog signaling

The Hedgehog (Hh) signaling pathway plays a crucial role in human embryogenesis, but is largely inactive in adult tissues under normal conditions.^{1,2} The Hh signal is relayed by a number of key proteins, including Patched (PTCH) and Smoothened (SMO), at the cell surface. In the absence of Hh ligand, PTCH acts as a suppressor of SMO.^{1,3} Upon ligand binding to PTCH, SMO is translocated to the primary cilium, where the transcription factor GLI is activated, translocates to the nucleus, and leads to the expression of Hh target genes.^{1,3} GLI mediates the expression of genes involved in cell growth and differentiation.¹



Hedgehog pathway inhibitor (GDC-0449, RG3616)

pMED

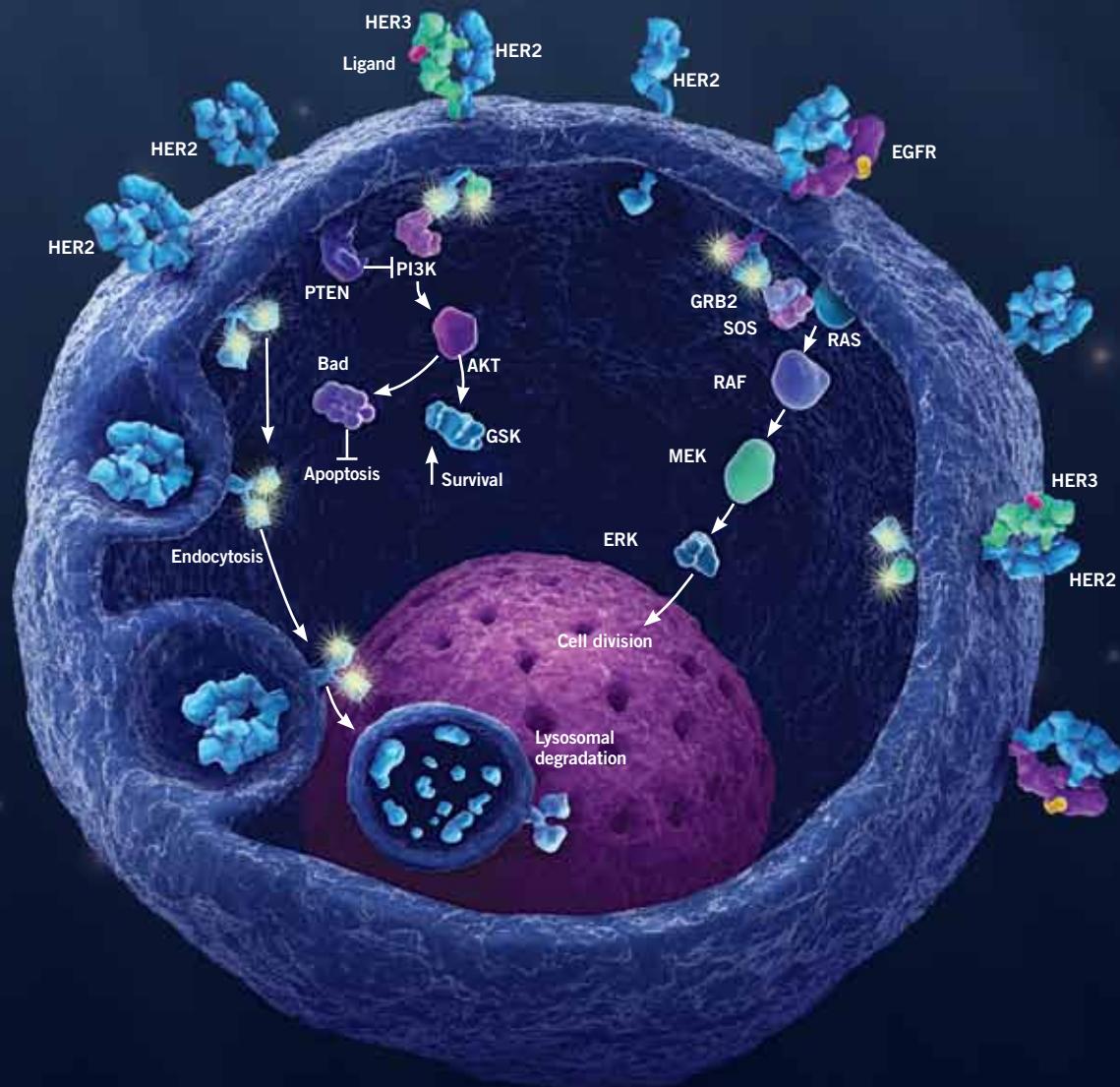
Overactive Hh signaling may occur in cancer by 2 distinct mechanisms: ligand-dependent and mutation-driven (ligand-independent) signaling.^{3,4} Aberrant activation of the Hh signaling pathway has been implicated in the development of many types of cancer.^{1,5}

Emerging preclinical evidence suggests that tumor growth occurring in mutation-driven models and in ligand overexpression models can be inhibited by blocking key components of the pathway, such as SMO.^{4,6-8} RG3616 is a small-molecule inhibitor designed to specifically inhibit SMO.^{1,6,8} In preclinical models, RG3616 inhibits overactive SMO signaling and tumor growth driven by mutations or by elevated levels of Hh ligands, offering the potential for broad application.^{1,6,7} Inhibition of SMO signaling renders the transcription factor GLI inactive, preventing the expression of genes that mediate the role of Hh on tumor growth.¹

HER signaling

Human epidermal growth factor receptor (HER) pathways play a critical role in cancer biology. Dysregulation of HER-mediated signaling pathways results in the growth and spread of cancer cells.¹ The HER family consists of 4 structurally related receptors: HER1 (EGFR), HER2, HER3, and HER4.^{1,2} Inappropriate signaling may occur as a result of receptor overexpression or dysregulation of receptor activation, which may lead to the following³⁻⁵:

- Increased/uncontrolled cell proliferation
- Resistance to apoptosis (programmed cell death)
- Enhanced cancer cell motility
- Angiogenesis



T-DM1 (HER2-targeted antibody-drug conjugate, HER2 ADC, RG3502)

pMED

Trastuzumab-DM1 (T-DM1) is an antibody-drug conjugate (ADC) composed of trastuzumab, a unique stable linker, and the potent cytotoxic agent DM1. It is designed to bind to the HER2 receptor on the surface of cancer cells and selectively kill cancer cells while minimizing cytotoxic effects on normal tissue.⁶

T-DM1 has multiple mechanisms of action. Preclinical studies show that the potent monoclonal antibody-mediated antitumor effects include antibody-dependent cellular cytotoxicity (ADCC), inhibition of cell signaling, and induction of cell cycle arrest.⁶ After internalization, the potent cytotoxic agent DM1 causes cell death by inhibiting the polymerization of microtubules.⁷ In preclinical animal models of HER2-overexpressing cancer, T-DM1 demonstrated activity against both trastuzumab-sensitive and trastuzumab-insensitive tumors.^{6,8}

Pertuzumab (HER2 dimerization inhibitor MAb, RG1273)

pMED

Pertuzumab is the first in a new class of targeted anticancer therapeutic agents known as HER2 dimerization inhibitors (HDIs) and is designed to block the dimerization of HER2 with other members of the HER family.^{9,10} Inhibition of HER2 dimerization may prevent abnormal activation of HER-mediated intracellular signaling cascades in cancer cells.⁹ Preclinical studies have identified HER dimerization as a key step in the ability of cells to independently proliferate, regardless of whether HER2 is overexpressed.⁹ These preclinical studies suggest that pertuzumab may be an effective anticancer strategy in tumors with either normal or elevated expression of HER2.⁹

Anti-EGFR huMAb (GA201, RG7160)

pRED

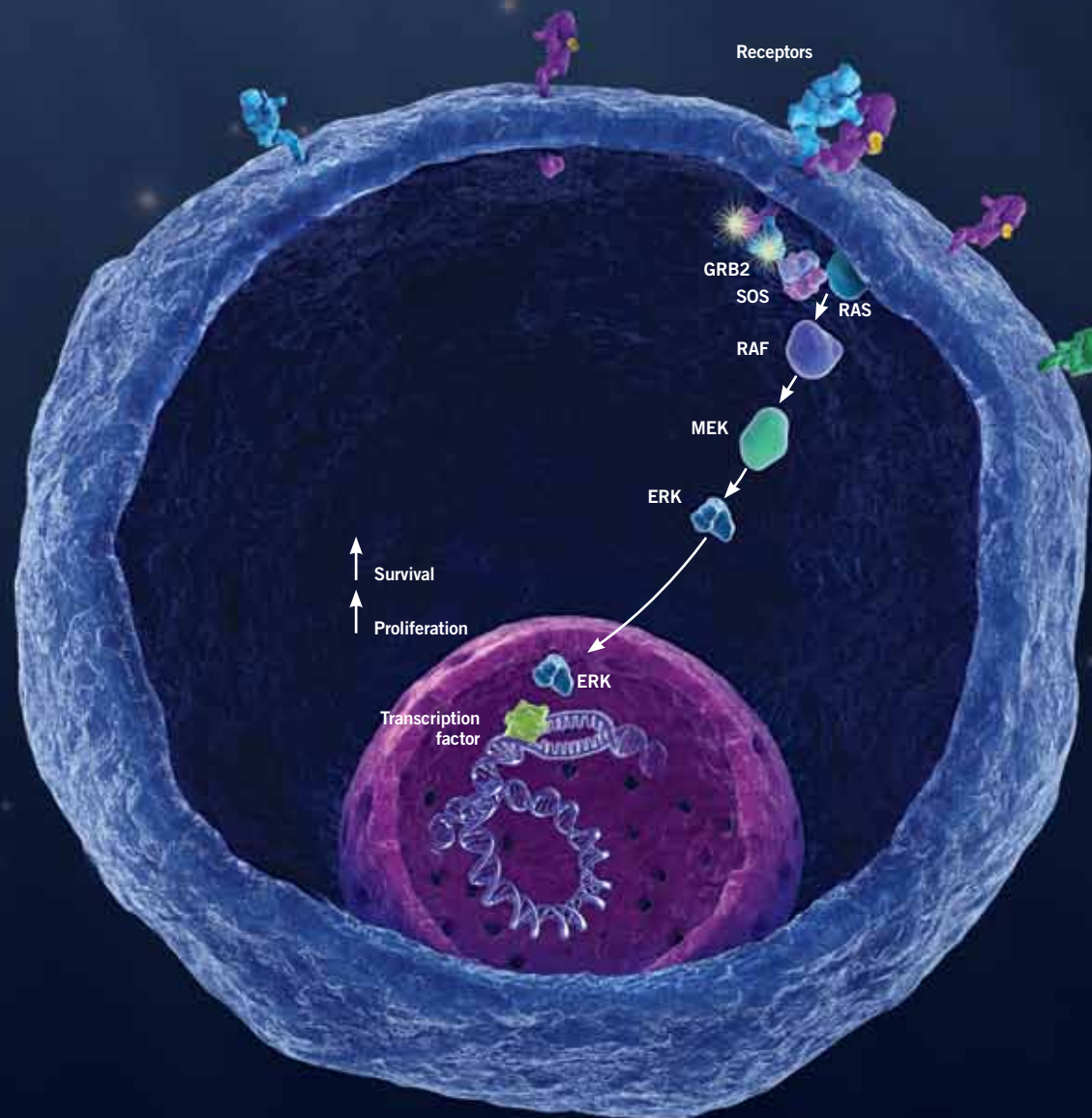
The anti-EGFR MAb GA201 is a recombinant, humanized, and glycoengineered MAb of the immunoglobulin G1 (IgG1) subclass directed against EGFR/HER1.¹¹ GA201 has demonstrated high-affinity binding to EGFR with inhibition of EGF ligand binding, EGFR/HER2 heterodimerization, EGFR downstream signaling and cell proliferation, and induction of cell death.¹¹ In addition, GA201 was engineered for high ADCC potency.¹¹ In preclinical models, GA201 has demonstrated greater activity than other anti-EGFR antibodies.¹¹

MAPK signaling

The MAPK signaling pathway plays a key role in the regulation of gene expression, cellular growth, and survival.^{1,2} MAPK signaling is initiated by receptor tyrosine kinases upon their activation by growth factors in the extracellular space.³ Adaptor molecules that interact directly with the intracellular portion of the receptor mediate the recruitment and activation of signaling molecules of this pathway, which include Ras, Raf, MEK, and ERK, also known as MAPK.^{1,2}

Dysregulated MAPK signaling is implicated in a wide range of cancers and occurs via multiple mechanisms, including abnormal expression or activating mutations in receptors and activating K-Ras and B-Raf mutations.¹⁻³ Abnormal MAPK signaling may lead to the following^{1,2}:

- Increased/uncontrolled cell proliferation
- Resistance to apoptosis (programmed cell death)
- Resistance to chemotherapy, radiotherapy, and targeted therapies



BRAF inhibitor (PLX4032, RG7204)

pMED

The V600E mutation in the *BRAF* gene results in constitutively active oncogenic BRAF^{V600E} protein and leads to excessive cell proliferation and survival, regardless of the presence of growth factors.¹ The BRAF inhibitor RG7204 is a potential first-in-class therapeutic small molecule designed to selectively inhibit mutated V600 BRAF, a key driver of cellular transformation. In preclinical models, RG7204 was shown to bind oncogenic BRAF and inhibit its activity as reflected by the inhibition of downstream molecules MEK and ERK. The inhibition of oncogenic BRAF leads to a block in tumor cell proliferation and the induction of apoptosis. In preclinical studies, RG7204 has been shown to cause significant growth delay or regression in tumors harboring this mutation.^{4,5}

MEK inhibitor (GDC-0973, RG7420)

gRED

The inhibition of MAPK signaling with agents targeted toward critical proteins in the pathway, such as MEK, has the potential to inhibit growth in a variety of tumor types.⁶ The MEK inhibitor GDC-0973 is a potent, selective, orally bioavailable small-molecule inhibitor of MEK that is designed to bind to MEK in a site adjacent to the ATP-binding site, resulting in high specificity.^{6,7} Inhibiting MEK may overcome activating mutations that occur upstream in the MAPK cascade. In multiple preclinical studies, GDC-0973 has been shown to inhibit cell growth and induce tumor regression.⁷

MEK inhibitor, CIF (RG7167)

pRED

RG7167 is a potent, orally bioavailable, highly selective MEK inhibitor. It potently inhibits the MAPK signaling pathway activation and tumor cell growth. Single-agent oral administration resulted in complete tumor regression in xenograft models.⁸

MEK inhibitor, CKI27 (RG7304)

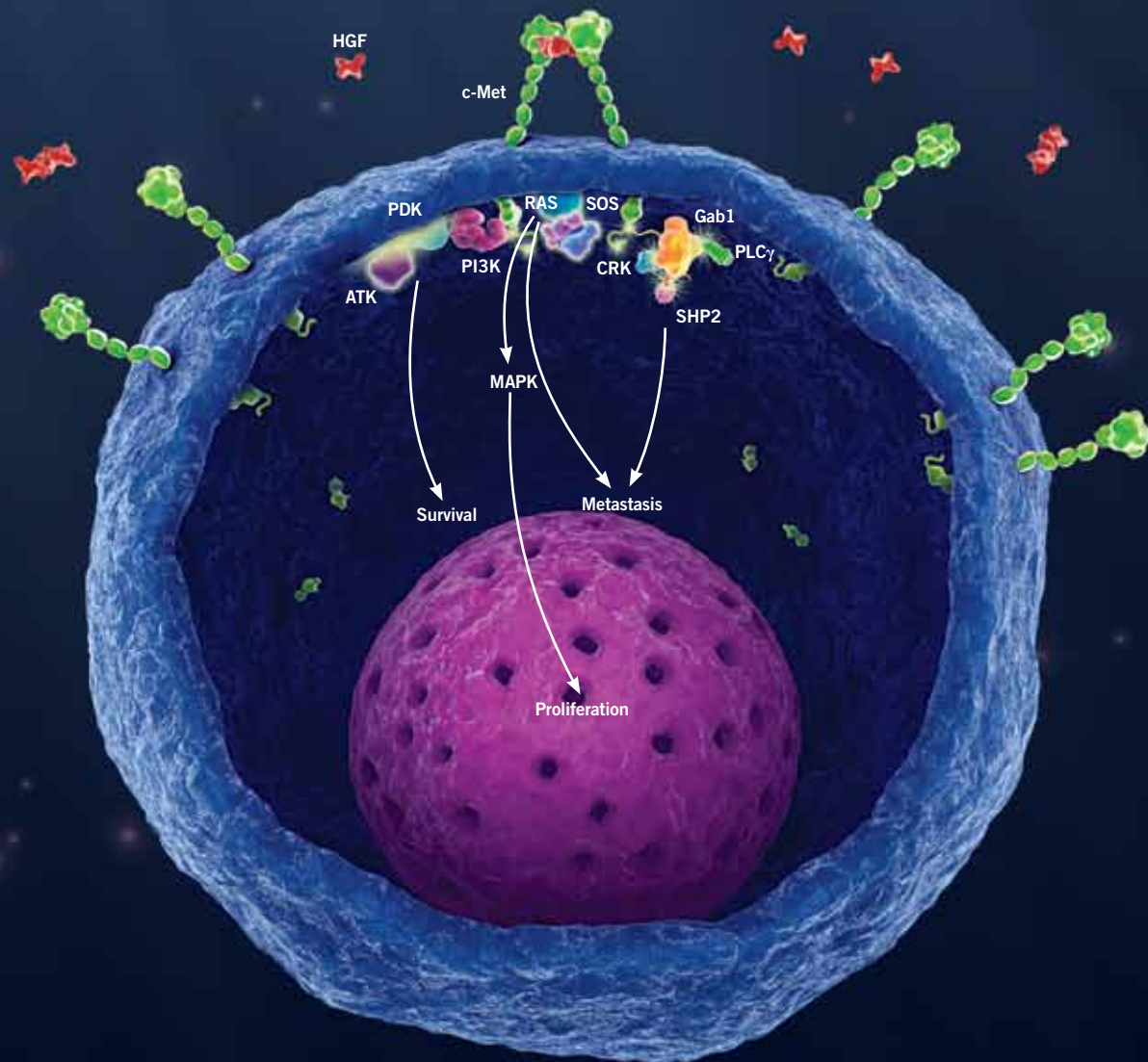
pRED

RG7304 is a selective dual Raf and MEK inhibitor under investigation for cancers with hyperactive MAPK signaling. It is designed to selectively inhibit Raf1 (C-Raf), B-Raf, mutant B-Raf (V600E), and MEK1. The inhibition of MAPK signaling with agents targeting critical proteins in the pathway has the potential to inhibit growth in a variety of cancers.⁶

MET signaling

Met activates signaling pathways leading to invasive cancer growth. Met expression has been correlated with a poorer prognosis in a variety of tumor types.^{1,2} Met activation occurs following binding of its ligand, hepatocyte growth factor (HGF), also known as scatter factor (SF).³ Once activated, the intracellular domains of Met recruit a variety of signaling proteins, such as PI3K, a kinase that drives tumor cell survival signals, and the signaling adaptors Gab1 and Grb2 that further amplify and transmit signals leading to cellular proliferation and migration in preclinical models.^{4,5} Met signaling in tumor cells may lead to the following⁶⁻⁸:

- Increased/uncontrolled cell proliferation
- Angiogenesis
- Metastasis
- Resistance to
 - Apoptosis (programmed cell death)
 - Chemotherapy, radiotherapy, and targeted therapies



MetMAb (RG3638)

gRED

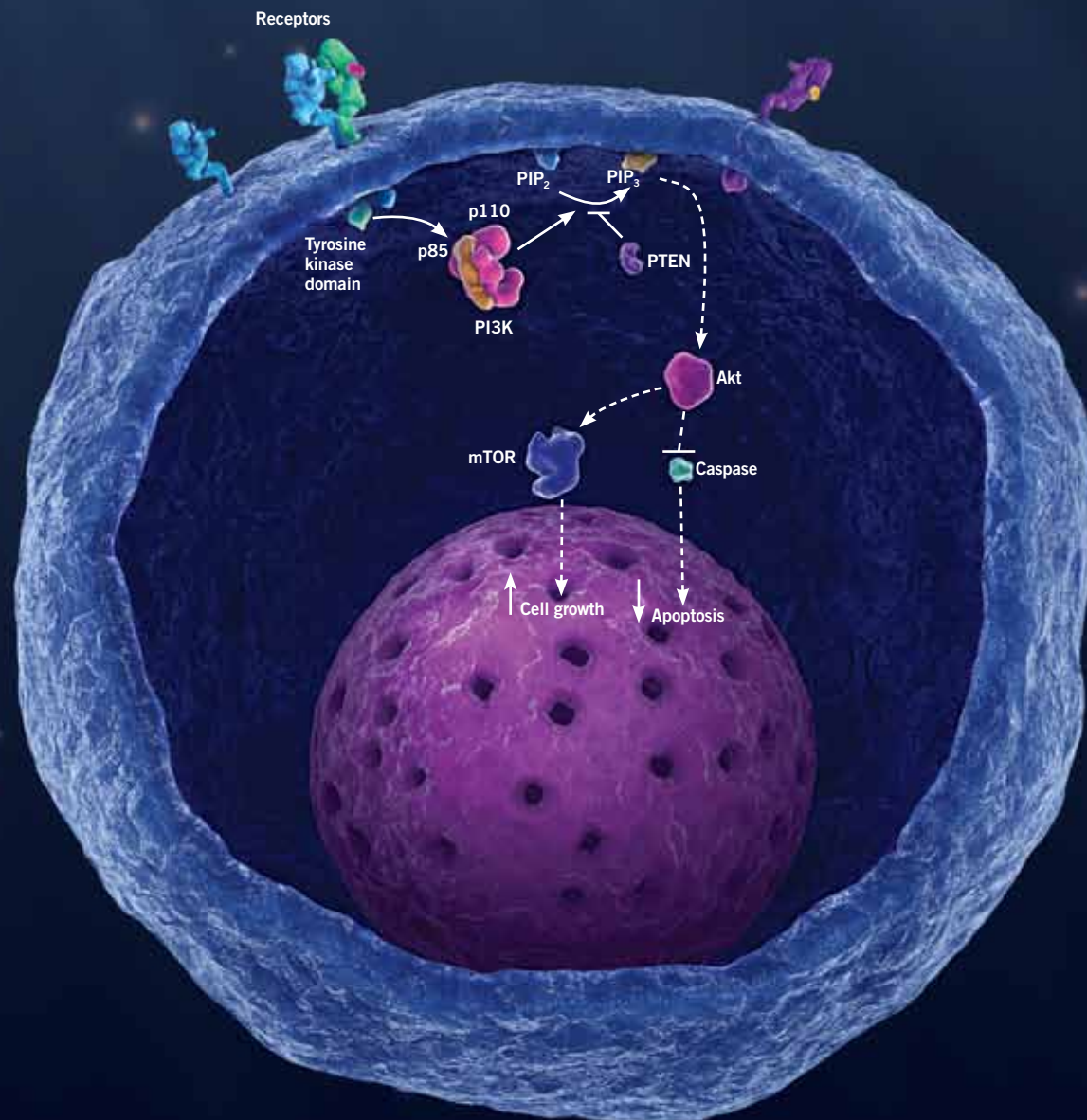
Enhanced Met signaling in tumors can result from increased levels of HGF provided by the tumor cells and/or supporting cells, activating mutations within Met, and/or receptor overexpression with or without gene amplification.^{6,7} Activation of Met via its ligand, HGF, is the predominant mechanism by which Met becomes activated. Inhibition of ligand binding by targeting the extracellular region of Met can block Met-induced tumor cell growth and survival, as well as metastasis of ligand-dependent tumor cells.^{4,5,9,10}

MetMAb is a monovalent anti-Met MAb consisting of a single Fab region. Its monovalent design enables MetMAb to bind Met and effectively inhibit HGF binding and receptor activation without inducing Met dimerization.^{3,9,10} In preclinical studies, MetMAb demonstrated antiproliferative, anti-angiogenic, and pro-apoptotic effects.^{9,10}

PI3K signaling

The phosphatidylinositol 3-kinase (PI3K) pathway is critical for cell survival and cell growth, and can be activated by growth factors binding to cell surface receptors. It is an intricate signaling cascade that is among the most frequently activated pathways in cancer. PI3K is composed of a catalytic subunit that confers enzyme activity, and a regulatory subunit that binds to both cell surface receptors and to the Ras protein. The p110 alpha catalytic subunit of PI3K as well as the Phosphatase and Tensin homolog tumor suppressor, PTEN, a negative regulator of this pathway, are commonly mutated in a wide range of human tumors. Additionally, many cell surface receptors that activate PI3K are subject to undergoing mutation or amplification in tumors. Because PI3K signaling can affect many cellular processes, dysregulation of the PI3K pathway is a key step in tumorigenesis.¹ Abnormal PI3K signaling may lead to the following¹:

- Abnormal cell growth
- Increased/uncontrolled proliferation
- Increased cell survival
- Enhanced cancer cell motility



PI3 kinase inhibitor (GDC-0941, RG7321)

gRED

Components of the PI3K pathway are frequently mutated or amplified in a broad range of cancers. Developing novel molecules that effectively and specifically block the PI3K pathway may inhibit the proliferation and growth of tumor cells and sensitize them to apoptosis.²

In preclinical studies, the PI3K inhibitor GDC-0941 exhibited selectivity for PI3K over other kinases and inhibited activation of downstream signaling components in the PI3K pathway. GDC-0941 leads to cell cycle arrest and apoptosis in certain human tumor cell lines.

In preclinical studies, when administered as a single agent or in combination therapy with other anticancer agents, GDC-0941 has demonstrated significant antitumor activity.²

PI3 kinase/mTOR inhibitor (GDC-0980, RG7422)

gRED

Inhibition of both PI3 kinase and mTOR may provide a more efficient blockade of the PI3K pathway and may prevent development of resistance as well.^{3,4} In preclinical studies, the PI3K inhibitor GDC-0980 exhibits selectivity for PI3K and mTOR over other kinases and inhibits activation of downstream signaling components of the pathway. GDC-0980 leads to cell cycle arrest and apoptosis in certain human tumor cell lines.⁵

Notch signaling

pRED

Gamma secretase is a key enzyme in the intramembrane proteolytic processing of several signaling receptors, including Notch, a cell surface receptor critical in cell fate signaling.¹

The gamma secretase processing of Notch produces its active form, called intracellular Notch (ICN).^{1,2} This protein translocates to the nucleus and forms part of a large transcription complex that directly alters the expression of key proliferation- and differentiation-specific genes.¹

Notch's role in cell fate determination points to 3 potential drivers of efficacies:

- (1) promotion of cell differentiation,
- (2) reduction of the cancer stem cell tumor subpopulation,
- (3) inhibition of angiogenesis by targeting Notch signaling in tumor endothelial cells.¹

Gamma secretase inhibitor (RG4733)

The gamma secretase inhibitor RG4733 is a potent and selective inhibitor of gamma secretase, inhibiting Notch signaling in tumor cells.¹ Blocking of Notch signaling produces a slower-growing, less-transformed phenotype in preclinical cancer models, resulting in significant inhibition of tumor growth in vivo.^{1,2}

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ADCs

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Angiogenic signaling

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NMEs in oncology*

Phase I	
MDM2 antagonist (RG7112) Solid tumors & hematologic malignancies	PI3 kinase inhibitor (GDC-0941, RG7321) Metastatic breast cancer, metastatic non-small cell lung cancer
Anti-EGFR huMAB (GA201, RG7160) Head and neck squamous cell carcinoma, non-small cell lung cancer, solid tumors	PI3 kinase/mTOR inhibitor (GDC-0980, RG7422) Solid tumors, non-Hodgkin's lymphoma
MEK inhibitor, CKI27 (RG7304) ^a Solid tumors	MEK inhibitor (GDC-0973, RG7420) ^d Solid tumors
MEK inhibitor, CIF (RG7167) ^b Solid tumors	Anti-NRP1 MAb (MNRP1685, RG7347) Solid tumors
Gamma secretase inhibitor (RG4733) Solid tumors	Anti-EGFL7 MAb (MEGF0444A, RG7414) Solid tumors
Anti-PIGF MAb (TB-403, RG7334) ^c Solid tumors	Dulanermin (rhApo2L/TRAIL, RG3639) ^e Colorectal cancer
	Antibody-drug conjugate (ADC) (DCDT2980S) ^f Hematologic malignancies
Phase II	Phase III
Pertuzumab (HER2 dimerization inhibitor MAb, RG1273) ^g Neoadjuvant HER2+ breast cancer, second-line HER2+ metastatic breast cancer	Pertuzumab (HER2 dimerization inhibitor MAb, RG1273) ^g First-line HER2+ metastatic breast cancer
T-DM1 (HER2-targeted antibody-drug conjugate, HER2 ADC, RG3502) ^h First- & third-line HER2+ metastatic breast cancer	T-DM1 (HER2-targeted antibody-drug conjugate, HER2 ADC, RG3502) ^h Second-line HER2+ metastatic breast cancer
GA101 (anti-CD20 MAb, R05072759, RG7159) ⁱ Chronic lymphocytic leukemia, non-Hodgkin's lymphoma	GA101 (anti-CD20 MAb, R05072759, RG7159) ⁱ First-line chronic lymphocytic leukemia
BRAF inhibitor (PLX4032, RG7204) ^j Second- & third-line metastatic melanoma	BRAF inhibitor (PLX4032, RG7204) ^j First-line metastatic melanoma
Hedgehog pathway inhibitor (GDC-0449, RG3616) ^k Advanced basal cell carcinoma, first-line metastatic colorectal cancer, ovarian cancer in second or third complete remission	
MetMab (RG3638) Second- & third-line metastatic non-small cell lung cancer	<ul style="list-style-type: none"> ■ NMEs developed by pRED (Pharma Research and Early Development) ■ NMEs developed by gRED (Genentech Research and Early Development) ■ NMEs developed by pMED (Pharma Medicines, late-stage development)
Navitoclax (Bcl-2/Bcl-X _L inhibitor, ABT-263, RG7433) ^l Relapsed chronic lymphocytic leukemia, relapsed lymphoid malignancies, small-cell lung cancer	

*Products under investigational study have not been approved for the use under investigation. This information is presented only for purposes of providing an overview of clinical trials and should not be construed as a recommendation for use of any product for unapproved uses.

^aRG7304 (CKI27): developed in collaboration with Chugai.

^bRG7167 (CIF): developed in collaboration with Chugai.

^cRG7334 (anti-PIGF): developed in collaboration with ThromboGenics/BioInvent.

^dRG7420 (GDC-0973): developed in collaboration with Exelixis.

^eRG3639 (dulanermin): developed in collaboration with Amgen.

^fDCDT2980S (ADC): developed in collaboration with Seattle Genetics.

^gRG1273 (pertuzumab): developed in collaboration with Chugai.

^hRG3502 (T-DM1): developed in collaboration with ImmunoGen.

ⁱRG7159 (GA101): developed in collaboration with Biogen Idec.

^jRG7204 is an oral agent being developed by Roche and Genentech, in partnership with Plexikon Inc.

^kGDC-0449 was discovered by Genentech and was jointly validated with Curis, Inc. through a series of preclinical studies. Genentech and Roche are responsible for the clinical development and commercialization of GDC-0449.

^lRG7433 (navitoclax): developed in collaboration with Abbott.

Information current as of April 2010.

Safety: 10.5"

Trim: 1"

Bleed: 11.25"