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Imprime PGG – A novel Innate Immune Modulator

Update to Cancer Research UK
November 2014

Clinical Development Update and Outlook

- Immunotherapy in the Treatment of Cancer
  - Approaches and Status Update
- Imprime PGG
  - Technology Overview and Potential
  - Recent Clinical Results in NSCLC
  - Recent Clinical Results in CLL
- Potential Areas of Scientific Interest

Immunotherapy and Cancer Medicine in 2014

Cancer remains an unbeaten disease

- 2.5 million new cases annually, resulting in over 1 million deaths in EU alone
- 1 in 3 cancer patients today will not survive more than 5 years
- finding a cure remains elusive for most cancers
- **key problem** is that the body does not recognize cancer as bad

Immunological approaches to fight cancer hold great potential

- most promising therapy approach in oncology to date
- expected to become a cornerstone of cancer therapy

Local Therapy		Systemic Therapy			
Surgery	Radiation therapy	Cancer-directed therapy		Immuno-therapy	Supportive therapy
		Chemo-therapy	Hormone therapy	Innate	e.g. bone, blood
		Biological therapy	Combi-nations	Adaptive	

Activating the Immune System to Fight Cancer

Innate

- 1st line of defense
- Non-specific
- Rapid response
- No memory

Components:
- Complement
- White blood cells:
  - Macrophages
  - Neutrophils
  - Natural Killer cells

Adaptive

- Slower response
- Specific
- Memory

Components:
- Antibodies
- B cells
  - Helper T cells
  - Killer T cells
  - Dendritic cells

Key considerations when targeting the innate immune system in cancer

- Need to activate complement in or around the cancer, introducing specificity of immune response against cancer } cancer-targeted antibody
- Need sufficient neutrophils, monocytes/ macrophages
- Need continued dosing

Innate Immune Cell Activation

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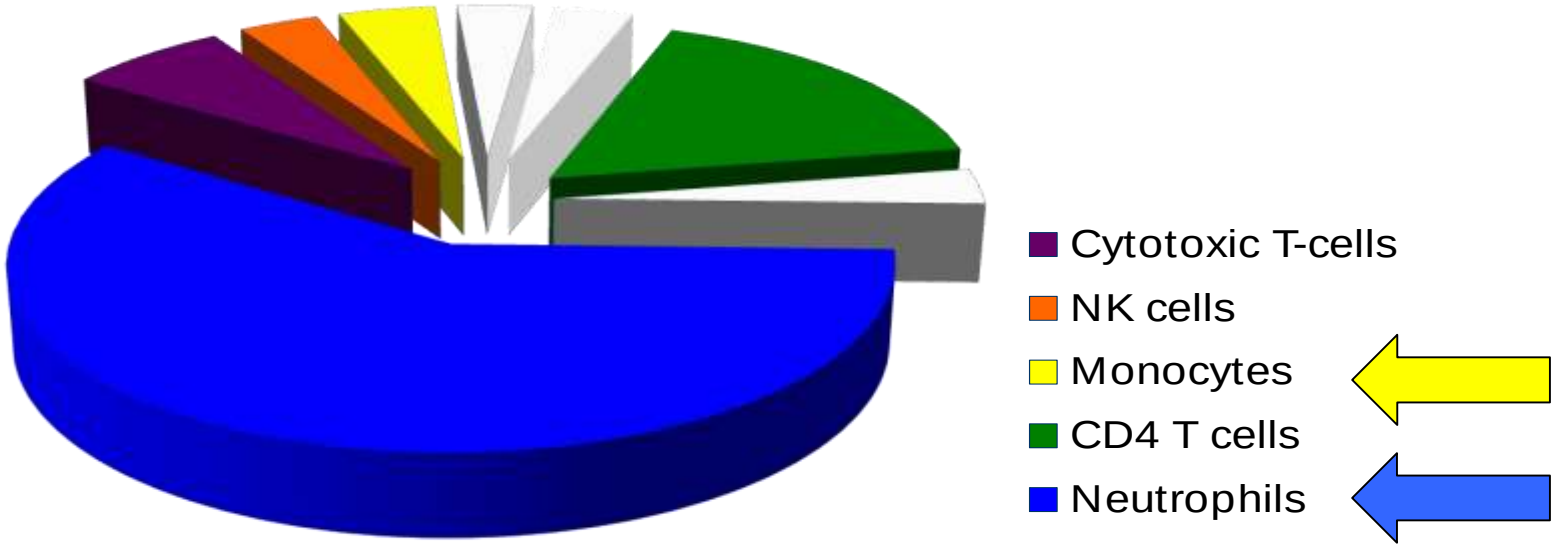
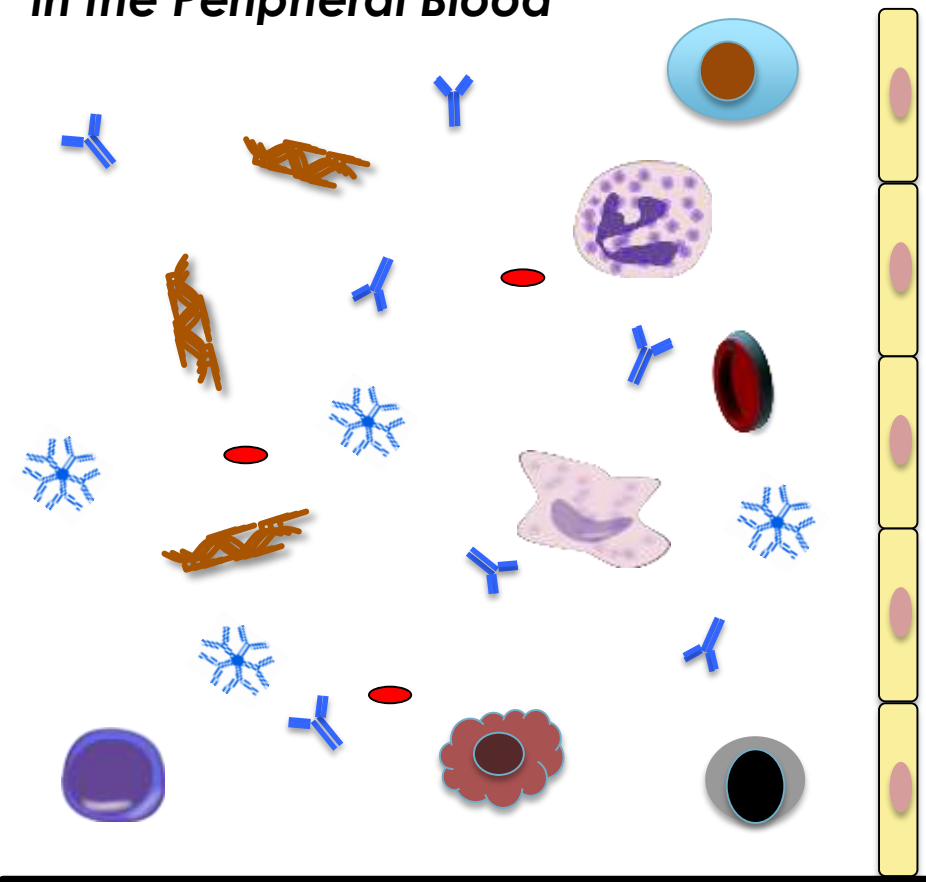
Imprime PGG targets innate immune effector cells, neutrophils and monocytes, that represent ~65% of the body's 26 trillion immune cells



Proposed Mechanism of Action of Imprime PGG

Upstream Initiator Mechanisms in the Peripheral Blood



1. **Imprime PGG is administered via IV infusion to a cancer patient.**

Imprime PGG | Neutrophil | Red Blood Cell | Complement | MDSC

ABA IgG, IgM | Monocytes | B Cell | T cell | NK Cell

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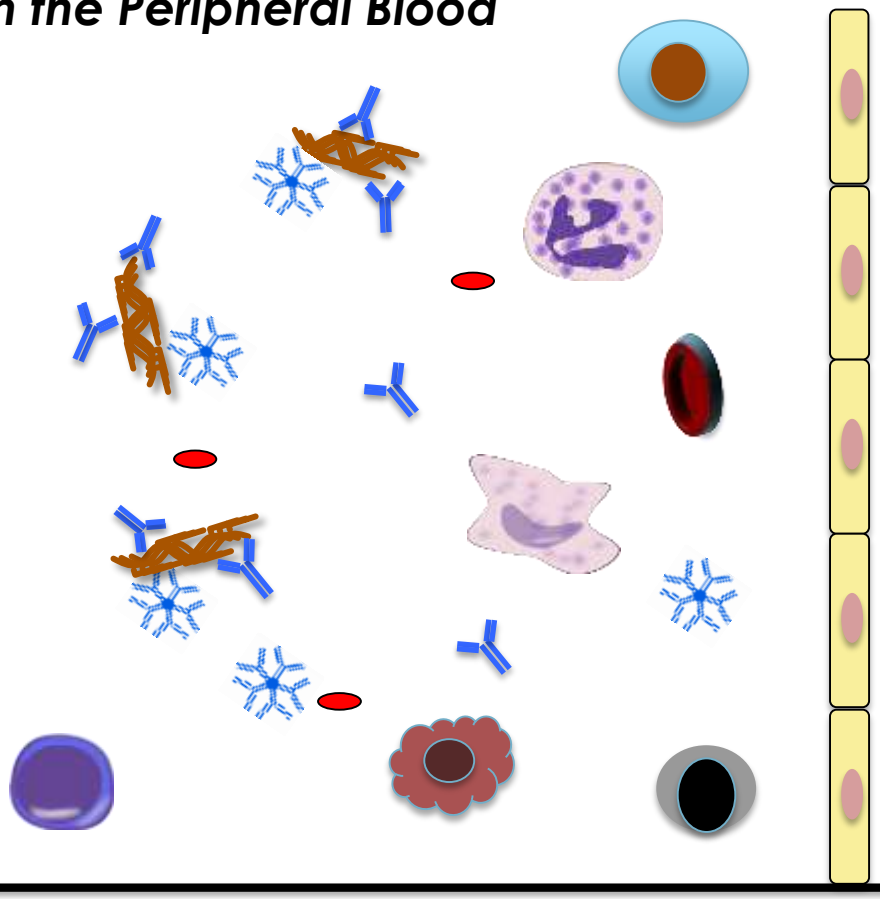

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2. **Endogenous anti-β-glucan antibodies (ABA) bind to Imprime PGG.[17]**

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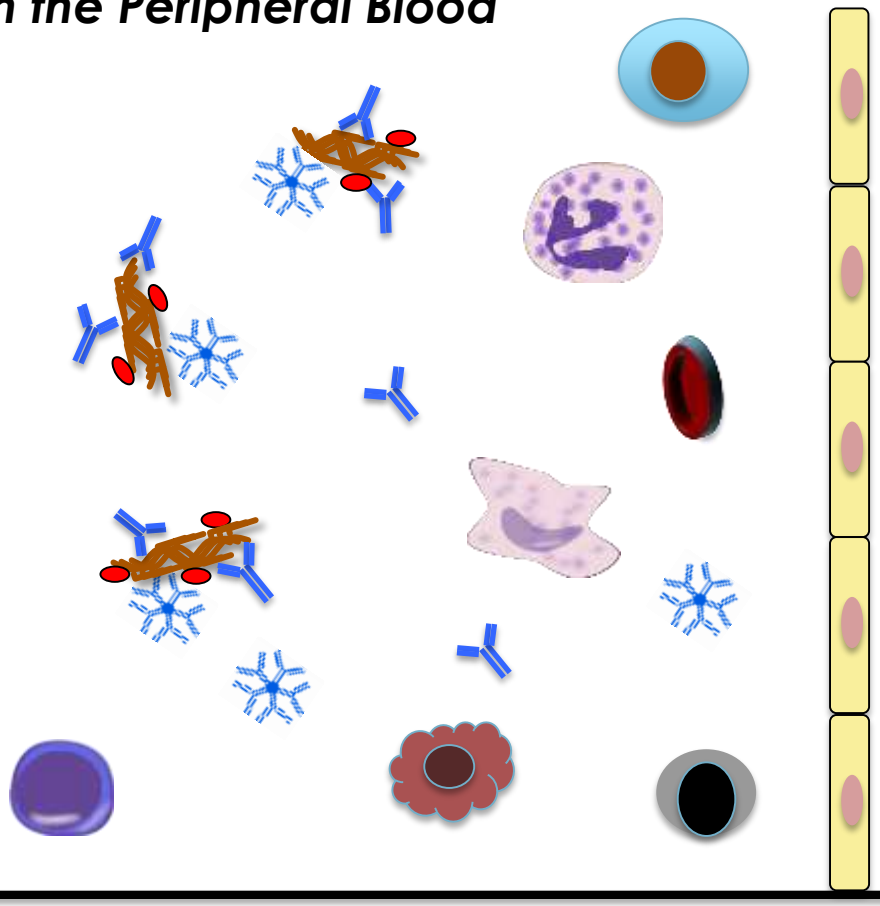

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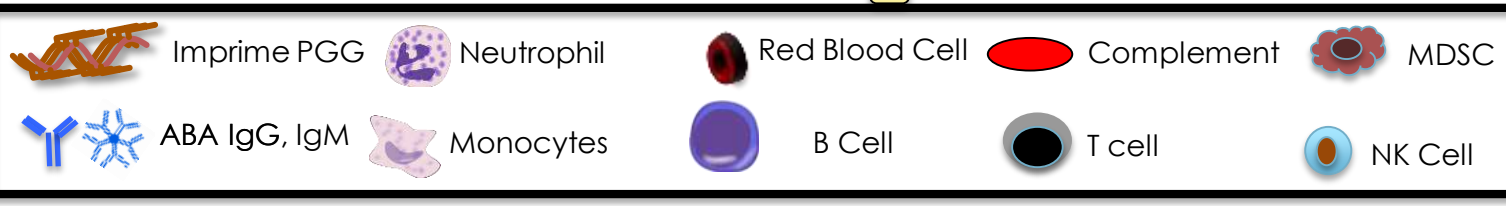

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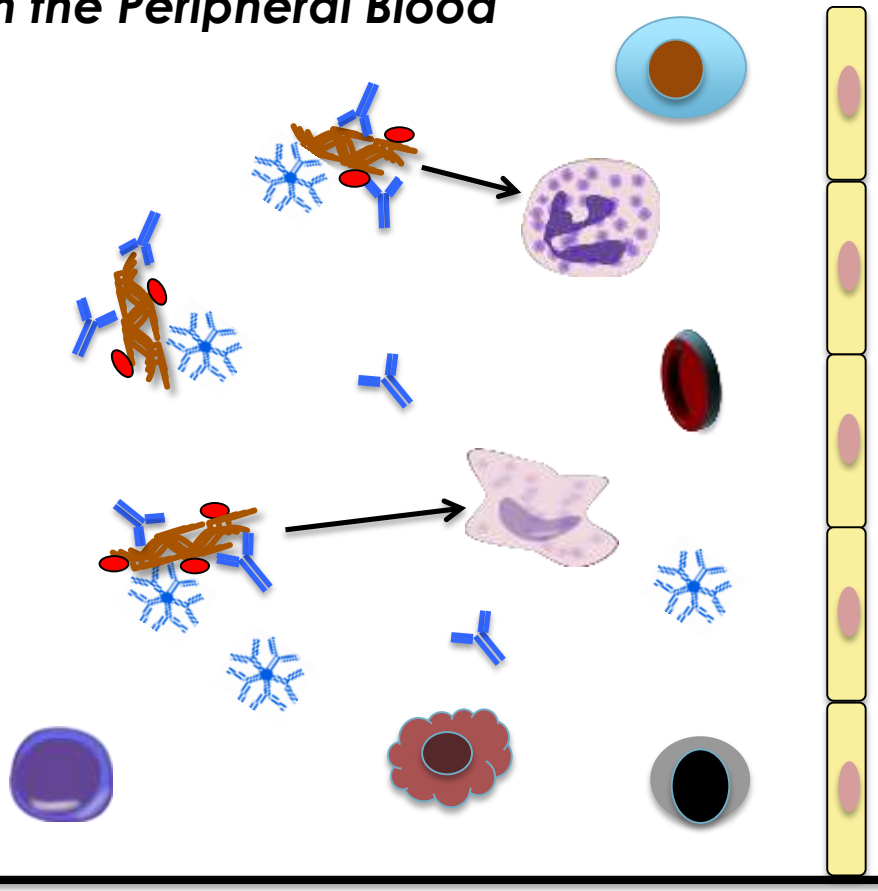

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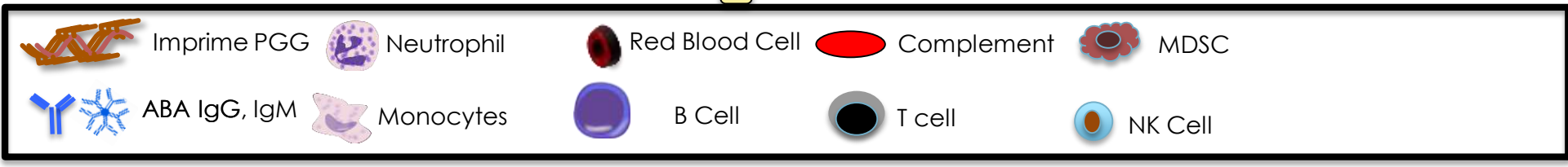

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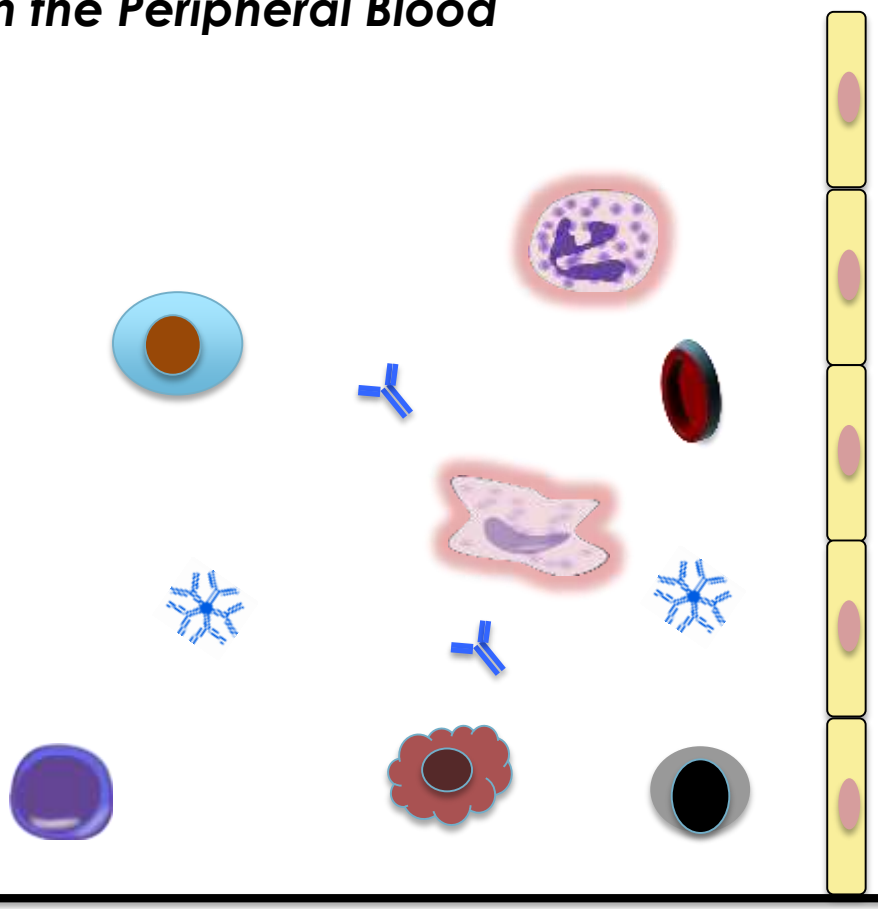

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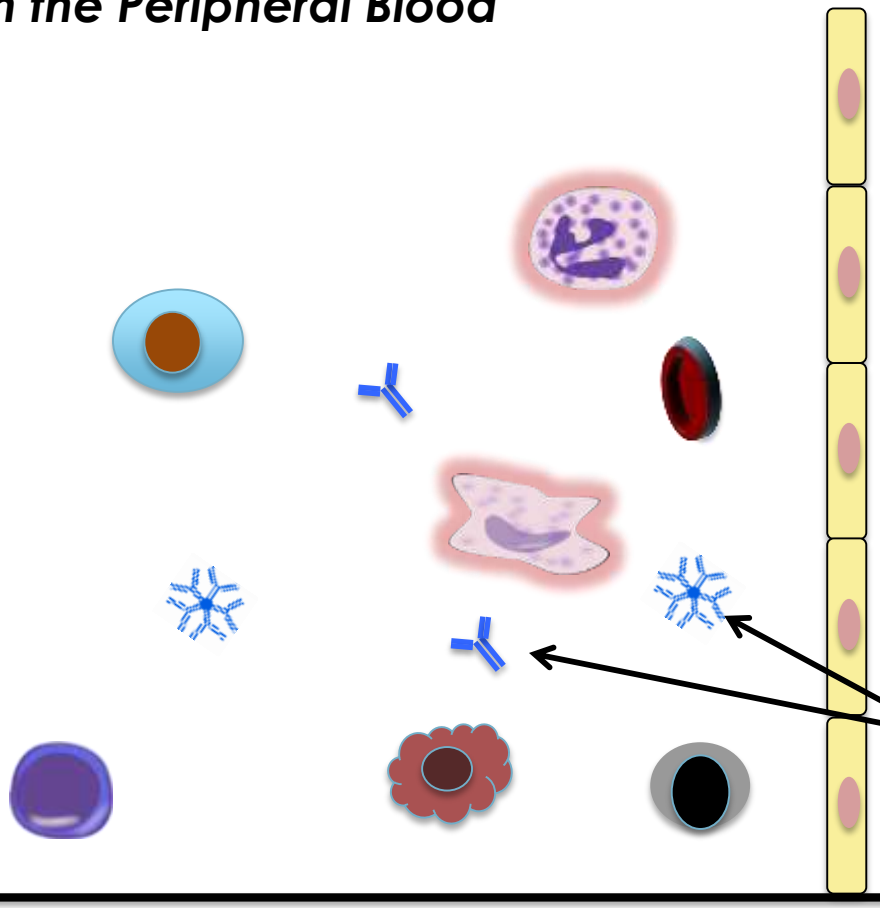

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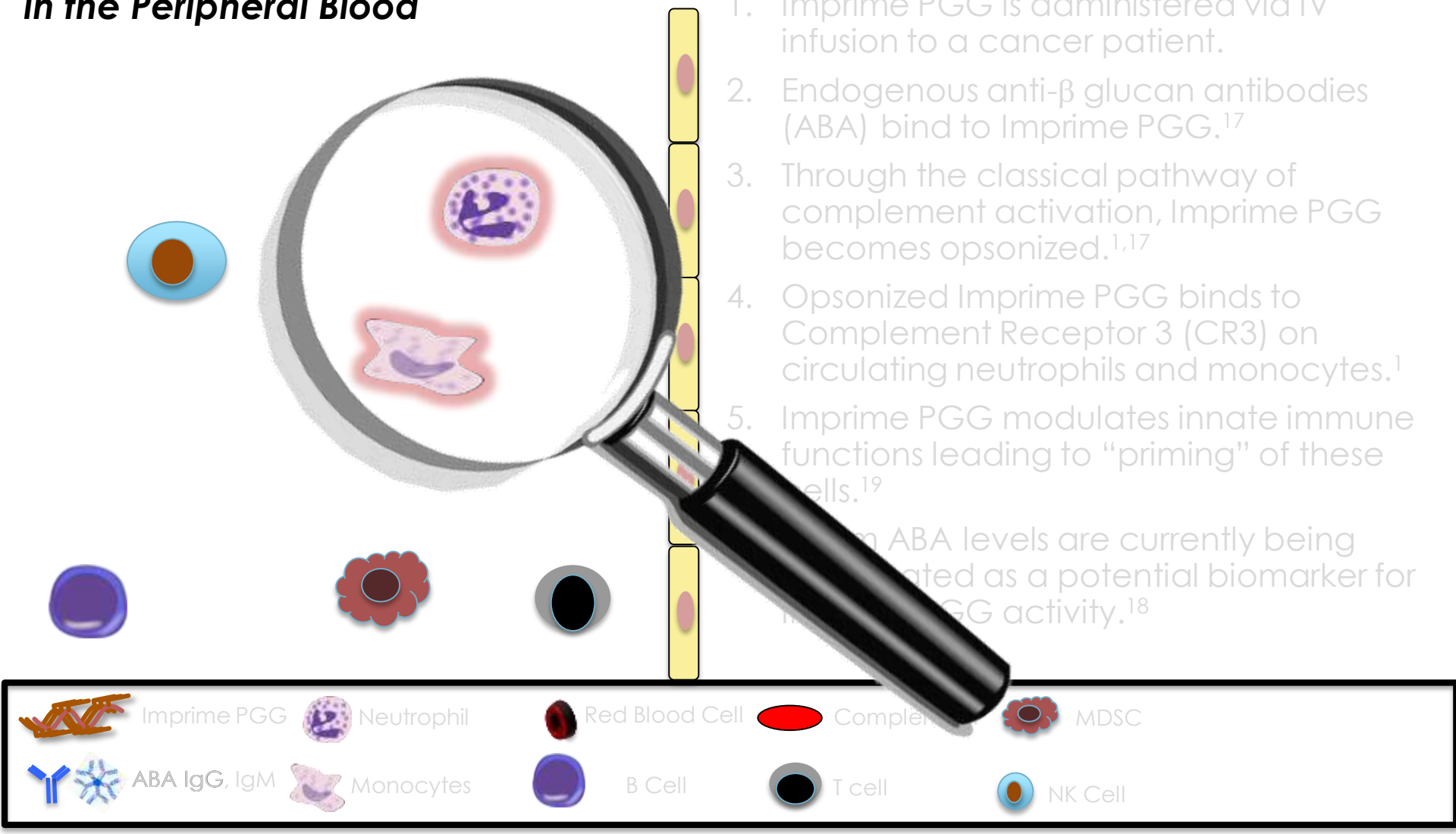

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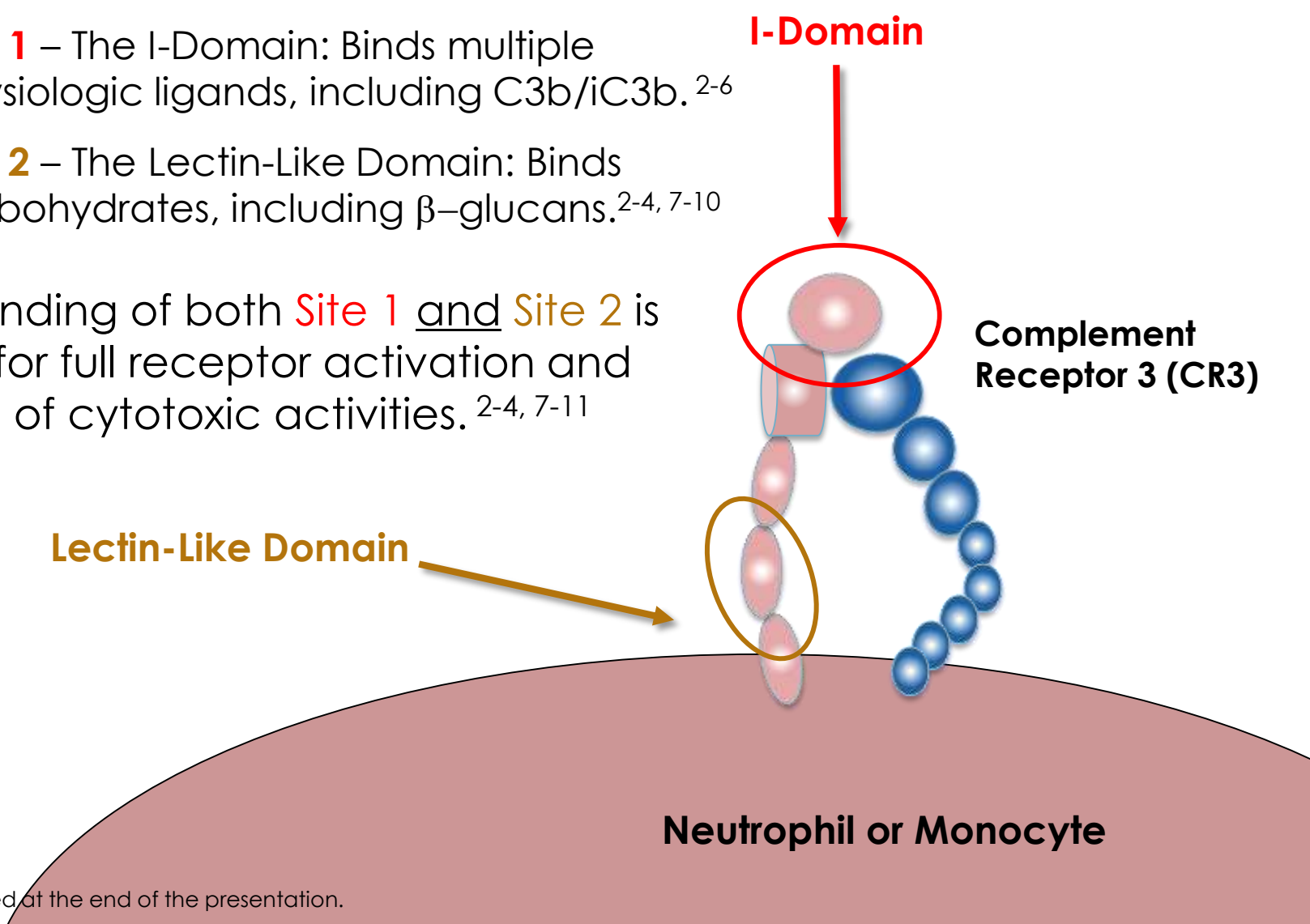
Proposed Mechanism of Action of Imprime PGG

CR3 is a dual-occupancy receptor[2-4]

- **Site 1** – The I-Domain: Binds multiple physiologic ligands, including C3b/iC3b.[2-6]
- **Site 2** – The Lectin-Like Domain: Binds carbohydrates, including β–glucans.[2-4, 7-10]

Ligand binding of both Site 1 and Site 2 is required for full receptor activation and induction of cytotoxic activities.[2-4, 7-11]



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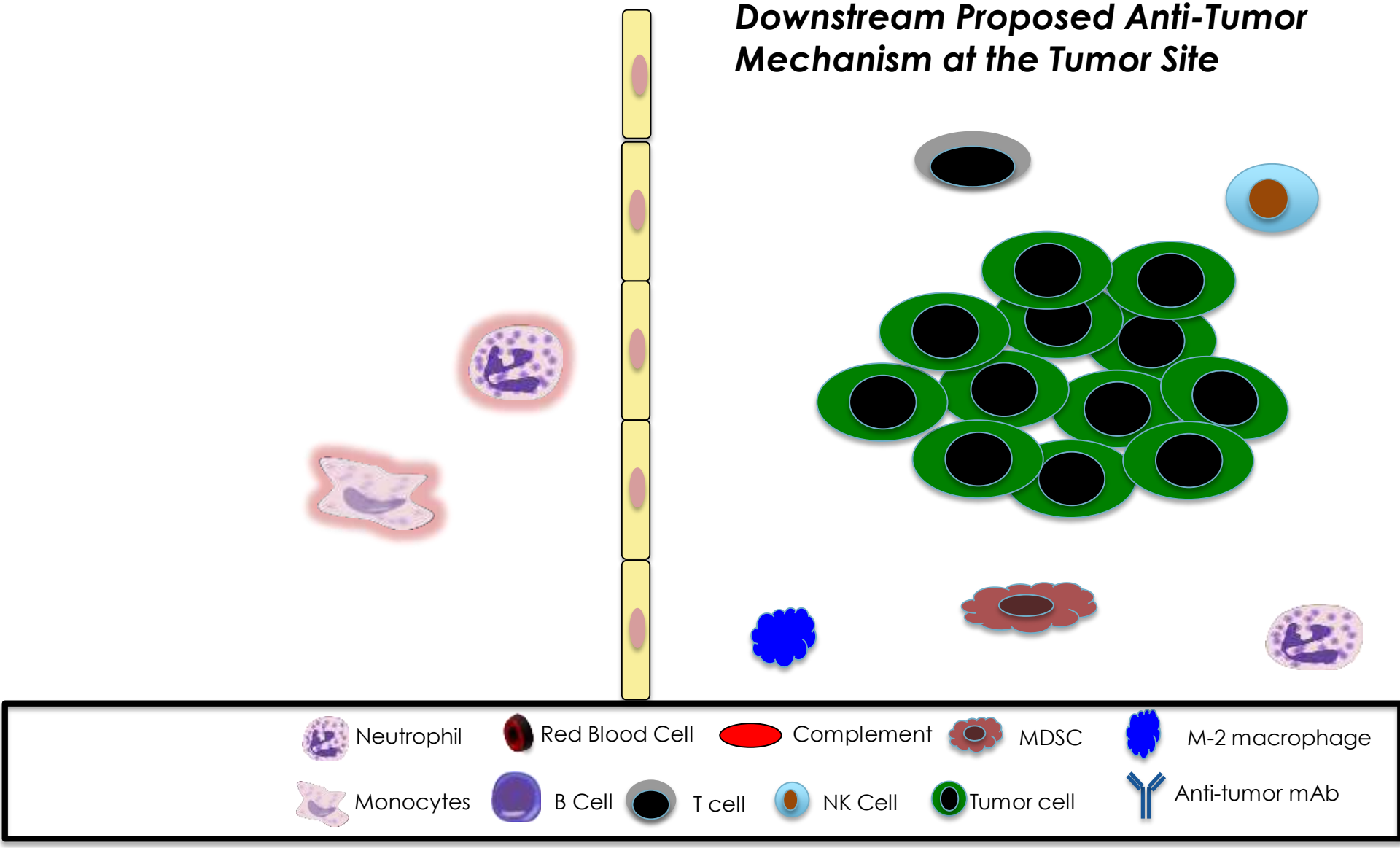

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Proposed Mechanism of Action of Imprime PGG

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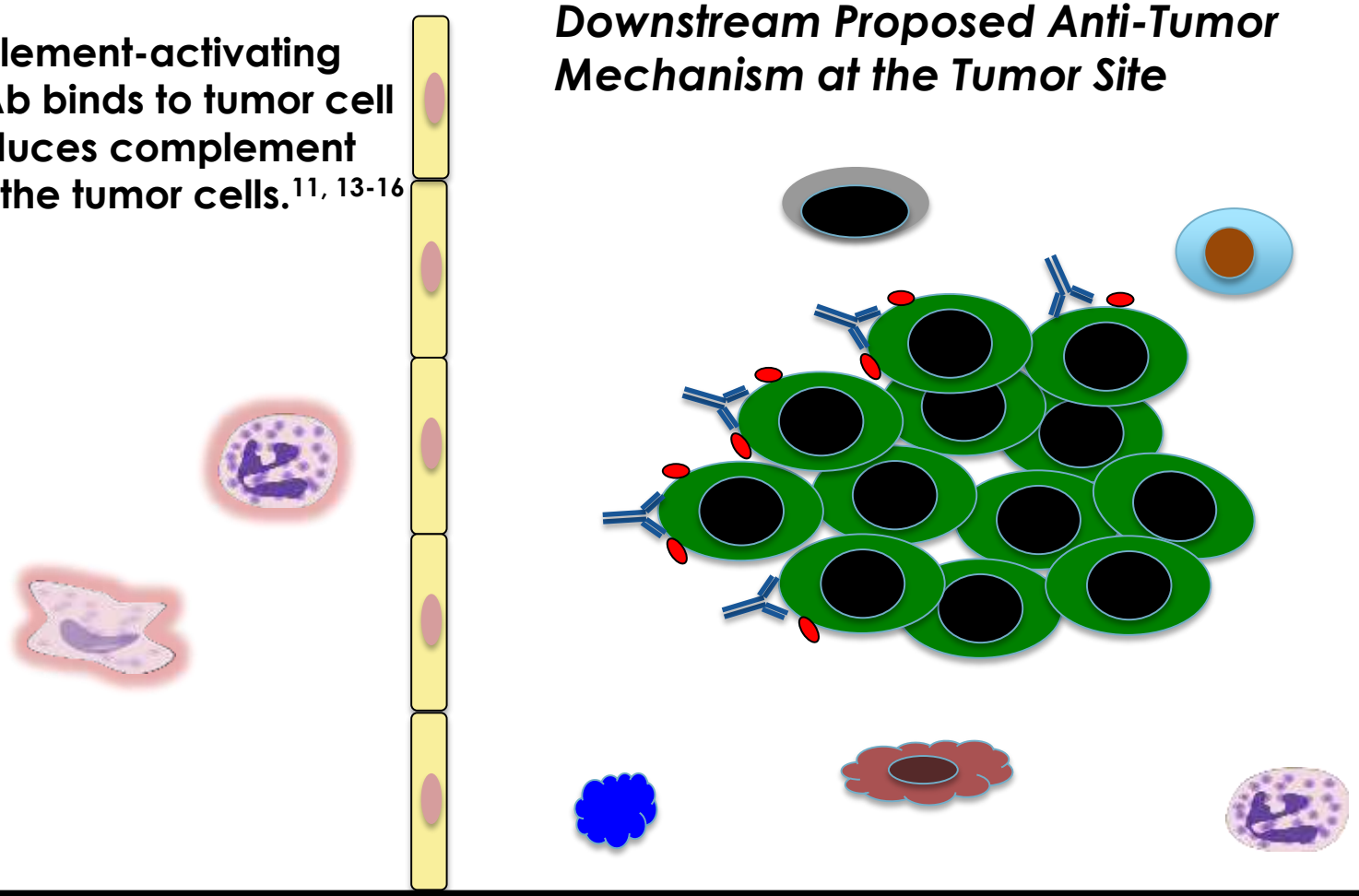
Downstream Proposed Anti-Tumor Mechanism at the Tumor Site



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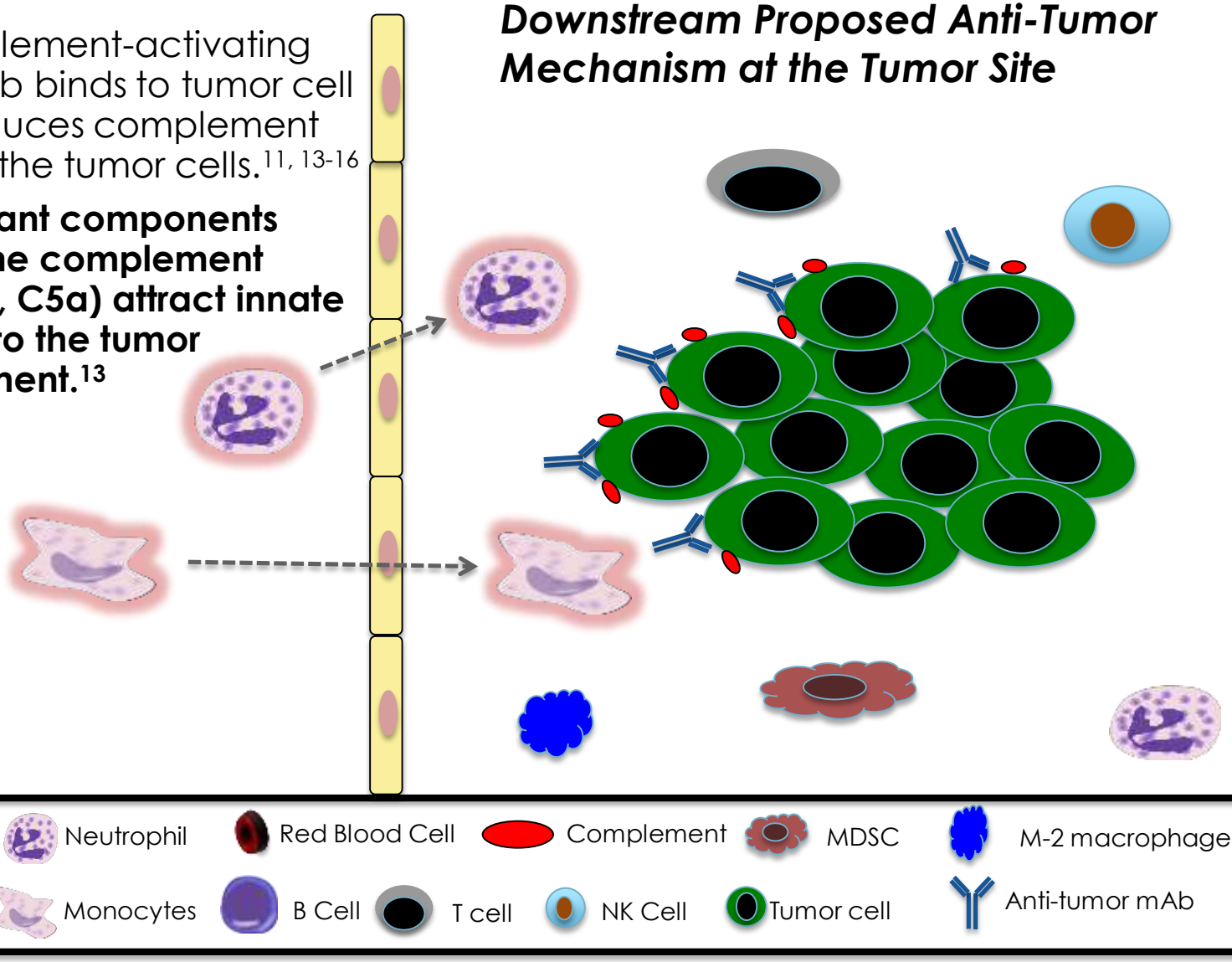

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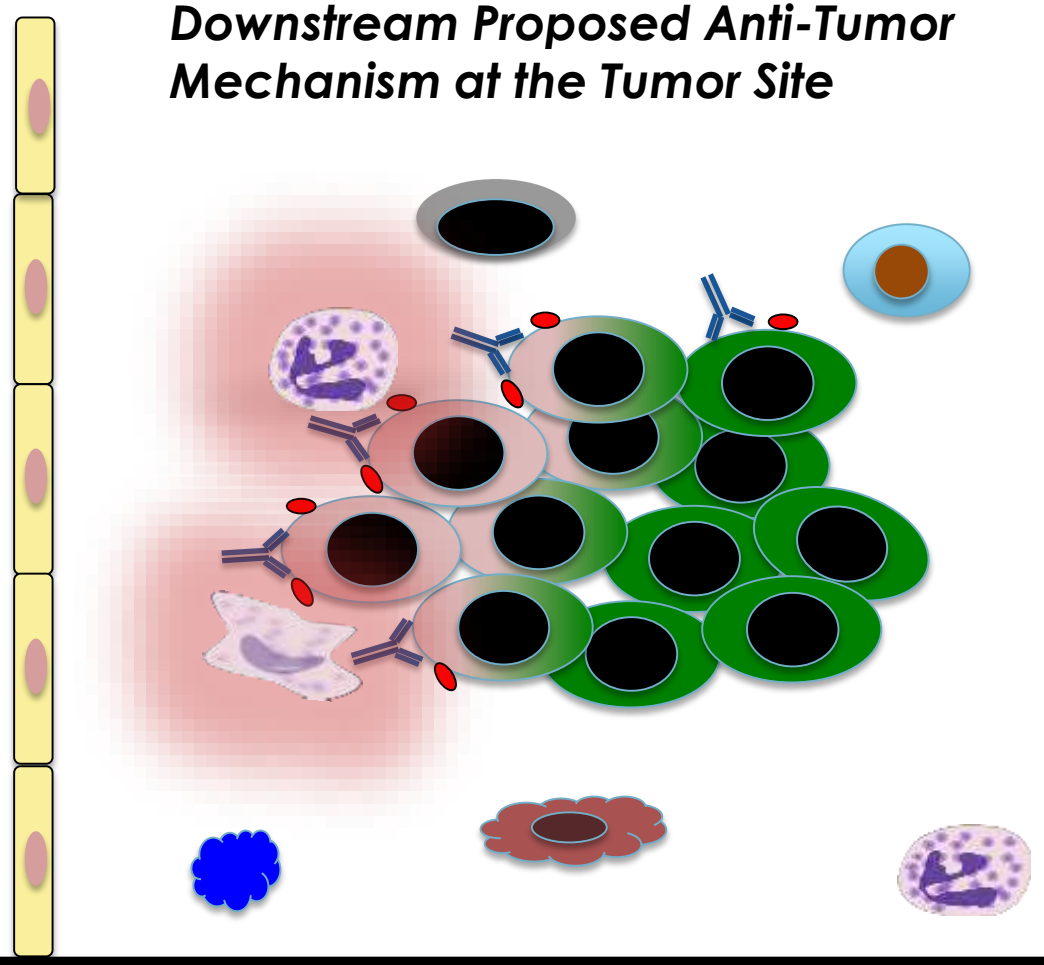

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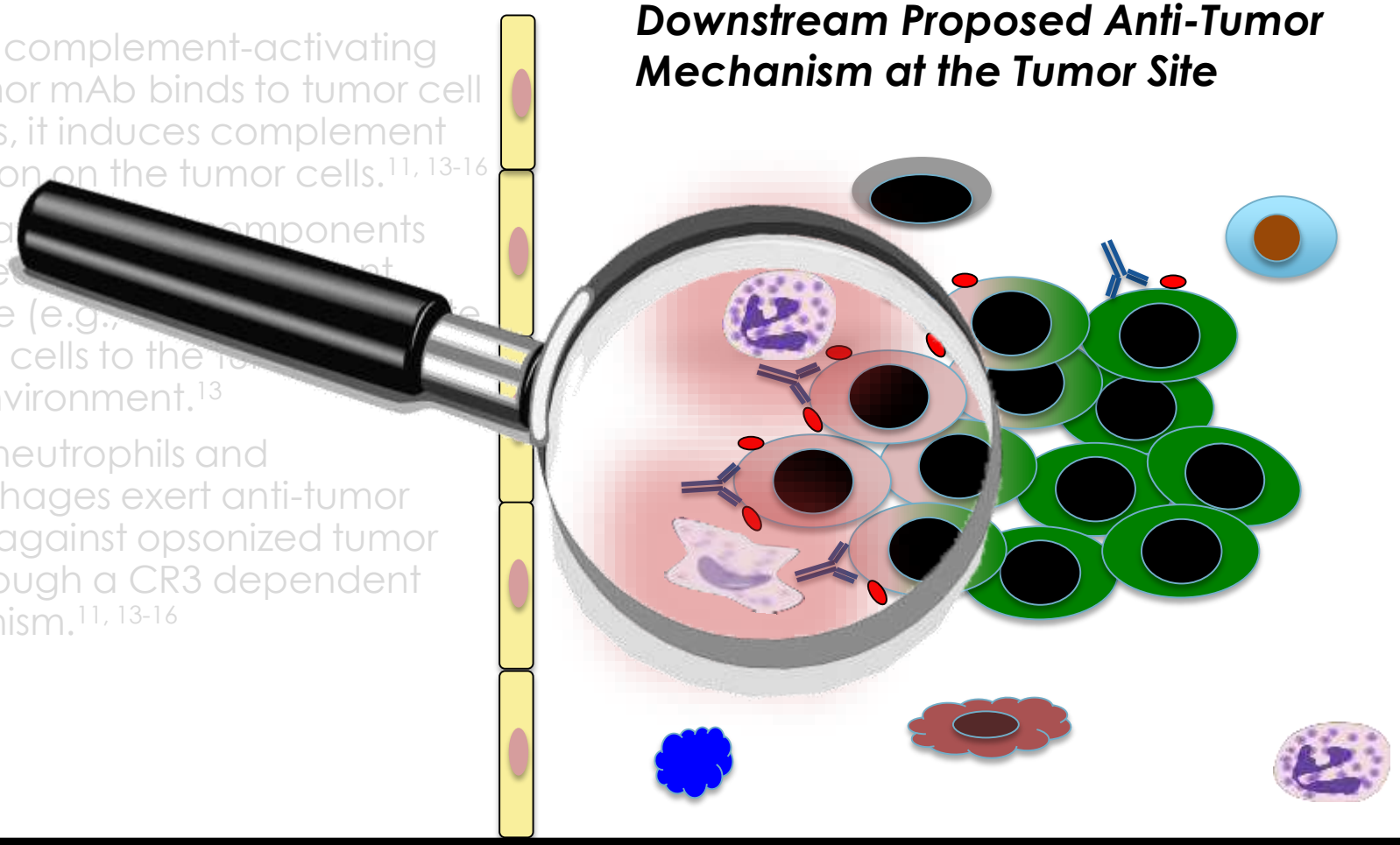

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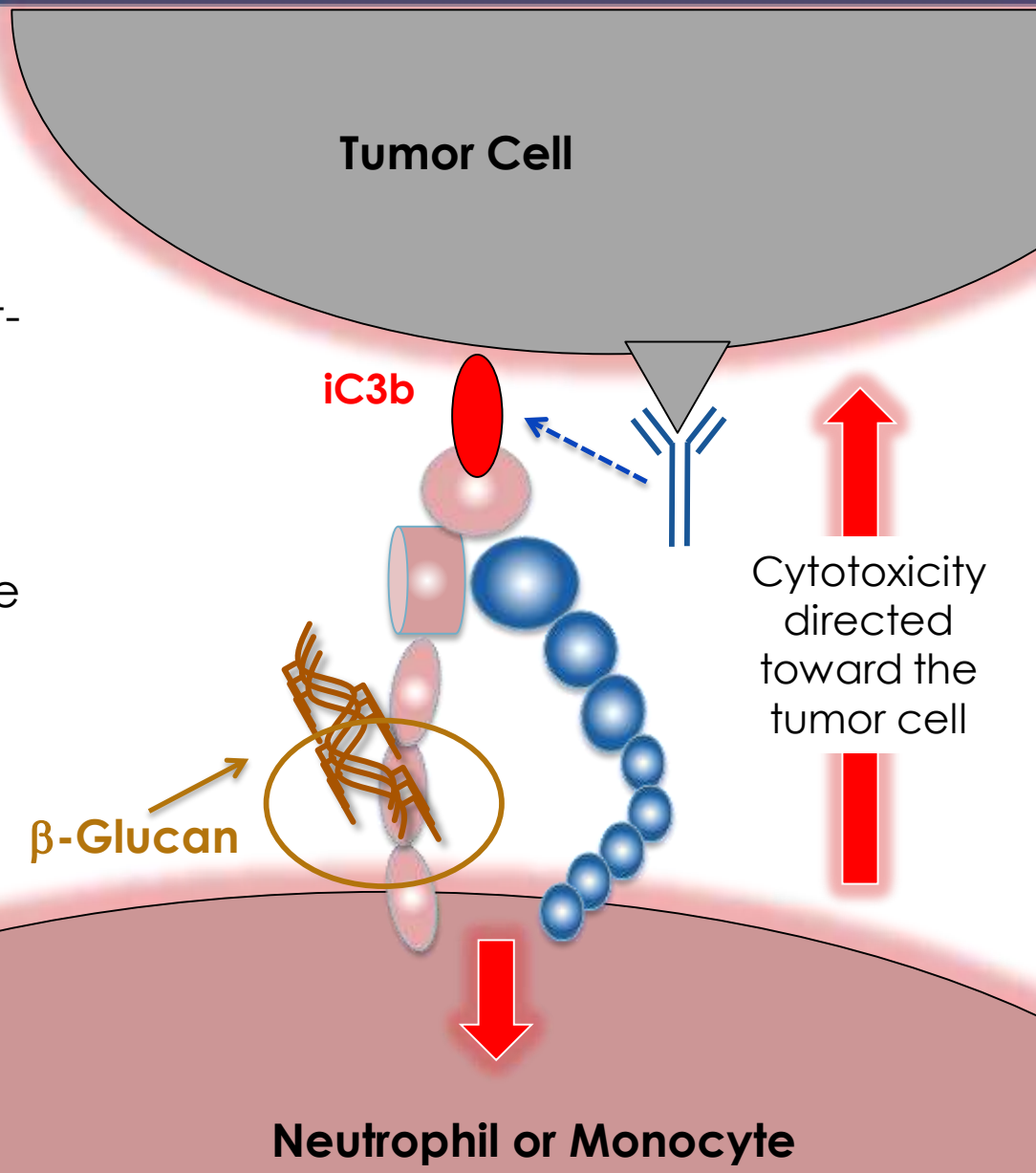
Proposed Mechanism of Action of Imprime PGG

- **Site1** engagement by iC3b on the tumor cell (following administration of a tumor-antigen-targeted, complement-activating antibody)
- **Site 2** engagement by administration of beta glucan

may result in neutrophil/monocyte killing of tumor cells [13-16]



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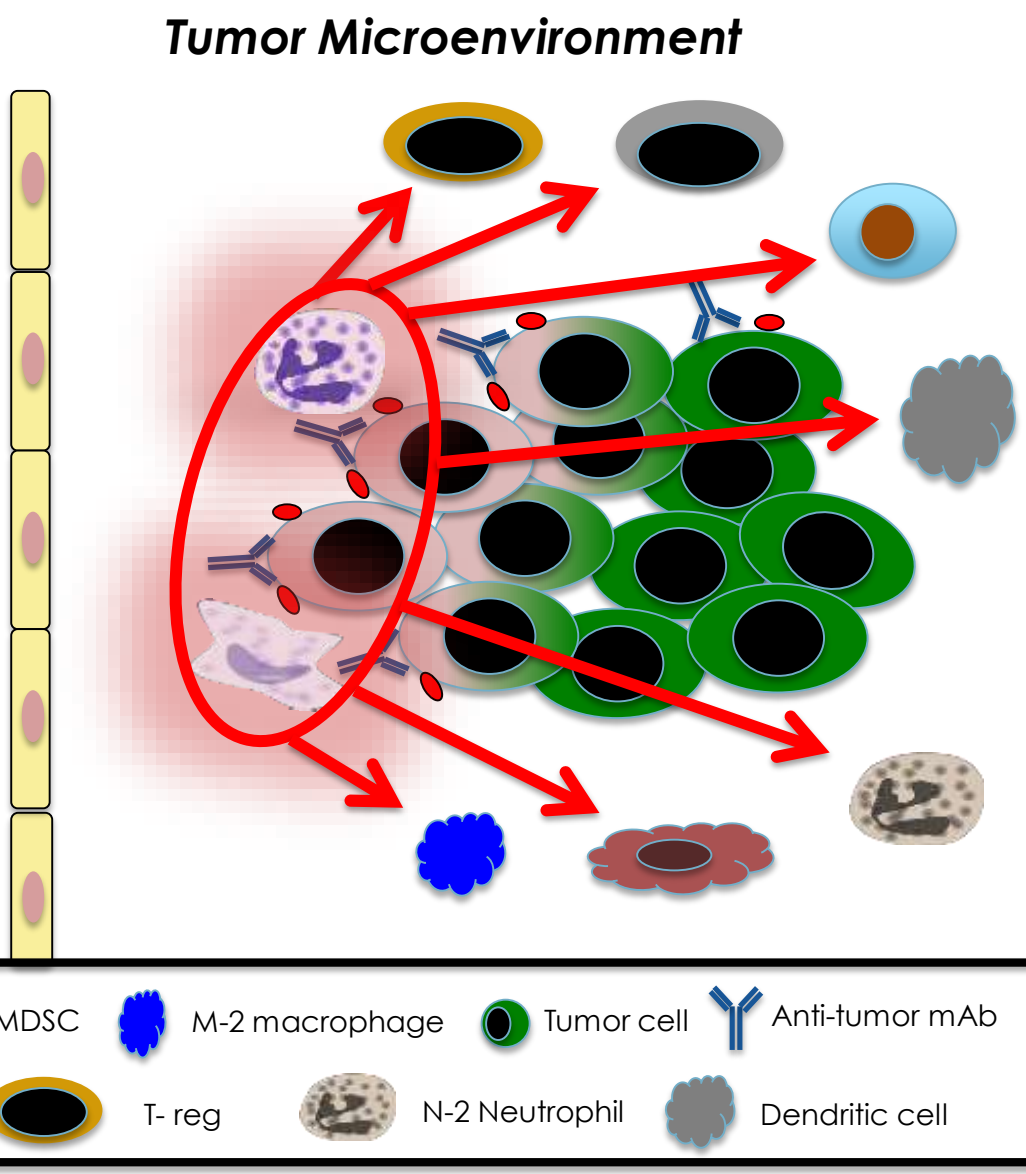
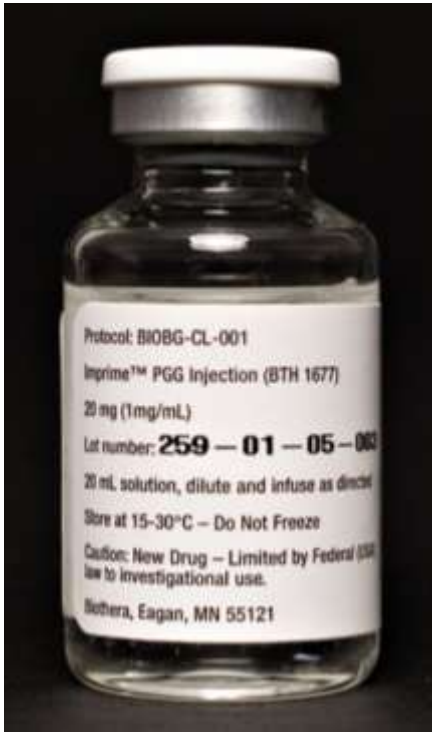
3. Primed neutrophils and macrophages can exert anti-tumor activity against opsonized tumor cells through a CR3 dependent mechanism.[11, 13-16]
4. **Primed neutrophils and macrophages can also modulate responses of other cells in the tumor environment (Bystander Effect)**



Imprime PGG Value Proposition

An **innate immune cell activator** in phase 3 clinical development in **combination with therapeutic antibodies** for the treatment of **cancer**



- **Novel Mechanism of Action**
  - Activates innate immune effector cells to kill antibody-targeted, complement opsonized cancer cells
- **Favorable Safety Profile**
  - Based on > 20 preclinical toxicology studies, and Phase 1 and Phase 2 clinical trials
  - Over 360 subjects dosed to date
- **Compelling Preliminary Efficacy Results**
  - Multiple Phase 2 studies performed in a range of cancers
- **Potential for Patient Selection**
  - Potential for a serum biomarker-led clinical program
  - Substantially increases chances of technical success
- **Broad Potential Indication Spectrum**
  - Combination with any complement-activating antibody

Imprime PGG Potential Indication Spectrum [a]

Indication	Treatment Setting	Combination Antibody	Geographic Region (US, EU)
Oncology			
Breast Cancer	Neoadjuvant	Pertuzumab, Trastuzumab	US [b]
	Metastatic	Trastuzumab	US, EU
		Bevacizumab	EU
Cervical Cancer	Metastatic	Bevacizumab	US
Colorectal Cancer	Metastatic	Bevacizumab	US, EU
		Cetuximab	US, EU
Gastric Cancer	Metastatic	Trastuzumab	US, EU
		Ramucirumab	US
Head and Neck (HNSCC)	Metastatic	Cetuximab	US, EU
Non-Small Cell Lung Cancer	Metastatic	Bevacizumab	US, EU
		Ramucirumab	*Pending*
Ovarian Cancer	Metastatic	Bevacizumab	US, EU
Renal Cell Cancer	Metastatic	Bevacizumab	US, EU
Hematology			
B-Cell Malignancies (CD20+)		Rituximab	US, EU
		Obinutuzumab	US, EU
		Ofatumumab	US, EU

[a] incomplete representation; indications subject to change; [b] accelerated approval only

Imprime PGG Has Demonstrated Synergistic Anti-Tumor Activity in Multiple Tumor Models with Multiple Antibodies

Syngeneic	Xenogeneic
T-Cell Lymphoma: • RMAS-MUC1/anti-MUC1 Mab[1] - Wild-type mice • RMAS-MUC1/anti-MUC1 MAb[2] - CR3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - C3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - Neutrophil-deficient mice	**Non-Small Cell Lung Carcinoma (KRAS mutant):** • NCI-H23/Cetuximab[4] **Non-Small Cell Lung Carcinoma:** • PC14PE6/Bevacizumab (orthotopic)[3] • PC14PE6/Bevacizumab[3] **Ovarian Carcinoma:** • SKOV3/Bevacizumab[5]

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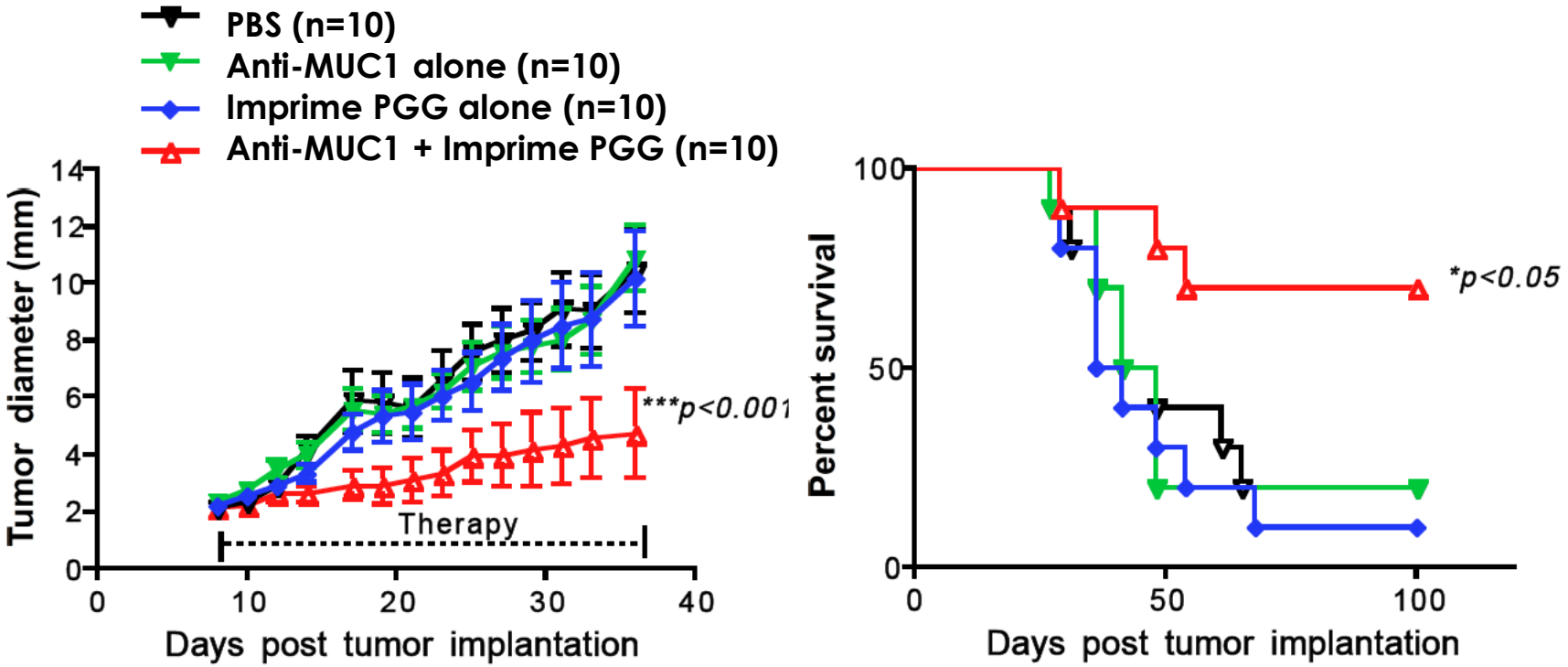
Anti-Tumor and Survival Enhancing Activity of Imprime PGG plus Anti-MUC1 Antibody in T-Cell Lymphoma Model



Mice: C57Bl/6
Tumor: Murine lymphoma w/ human MUC-1 (Mouse RMA-S-Muc1 T-cell lymphoma) implanted subcutaneously
MAb: BCP8 (mouse IgG2a anti-human MUC-1)
Treatment Regimen: Imprime PGG (1200 µg/mouse) and BCP8 (200 µg/mouse) injected intravenously twice per week
Qi, C. et al., Blood, 117: 6825-6836, 2011

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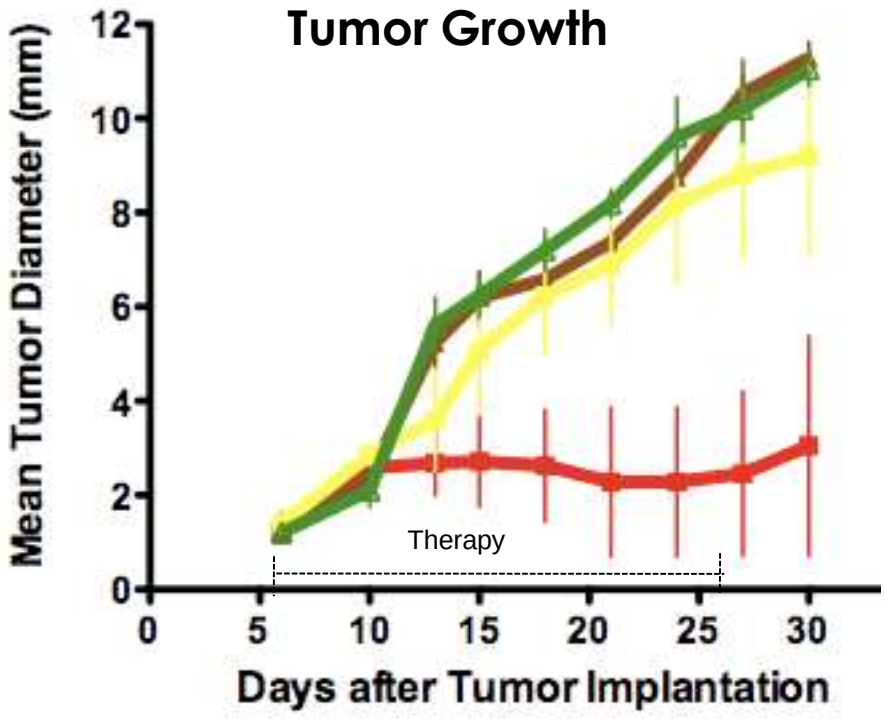
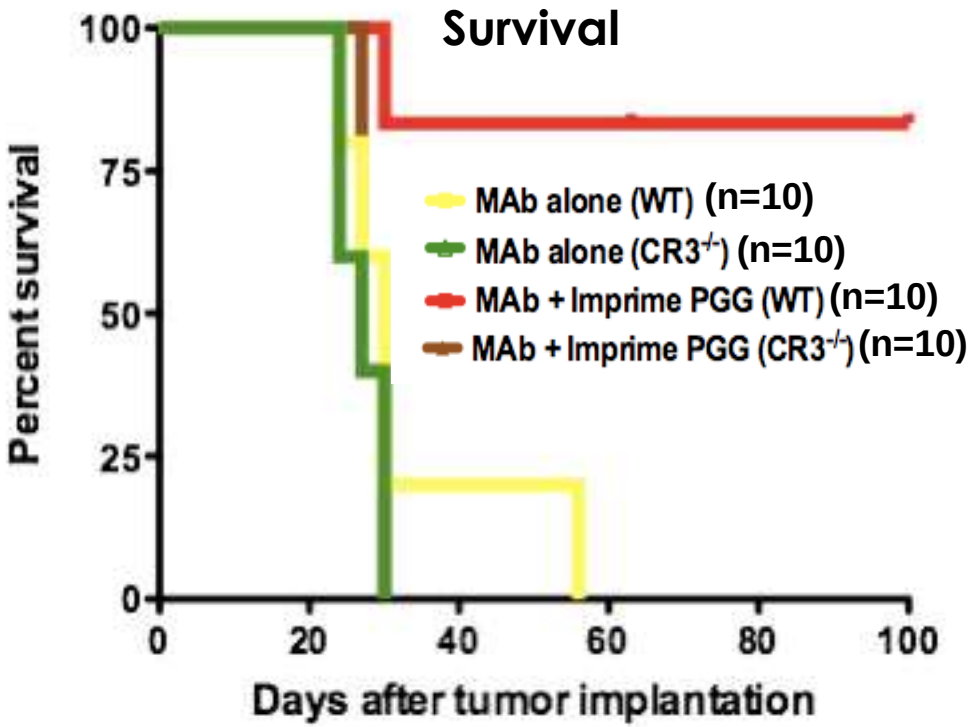
Imprime PGG Mechanism of Action is Complement Receptor 3 (CR3) Dependent

Inhibition of tumor growth and prolonged survival is seen in wild type mice (red) but not in CR3 deficient mice (brown).





Mice: C57Bl/6 - wild-type (WT) and complement receptor 3 deficient (CR3 -/-)
Tumor: Murine lymphoma w/ human MUC-1 (Mouse RMA-S-Muc1 T-cell lymphoma) implanted subcutaneously
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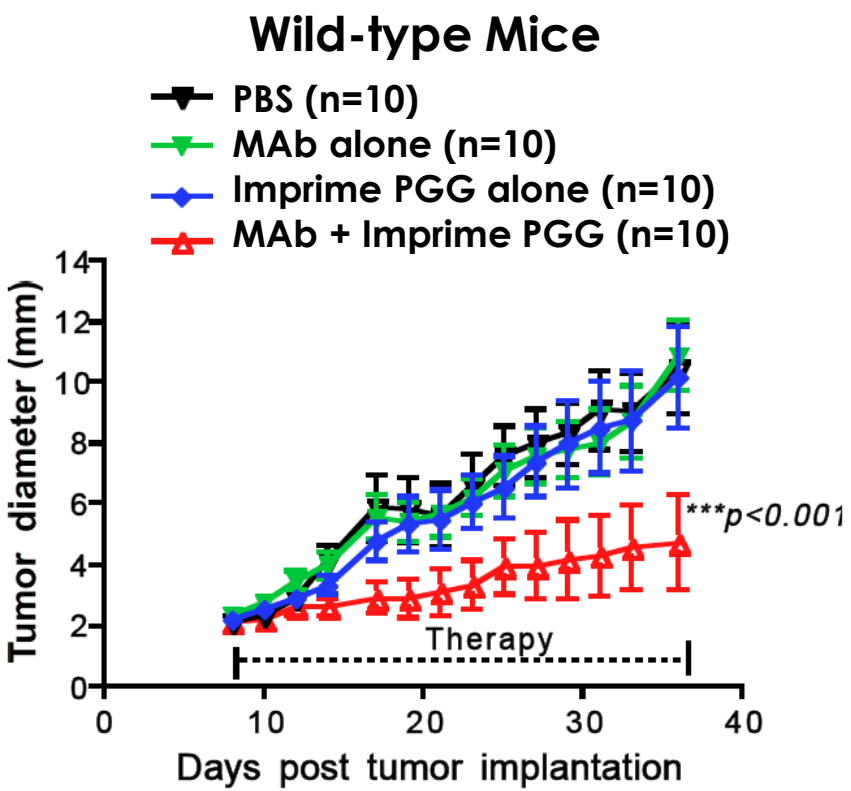
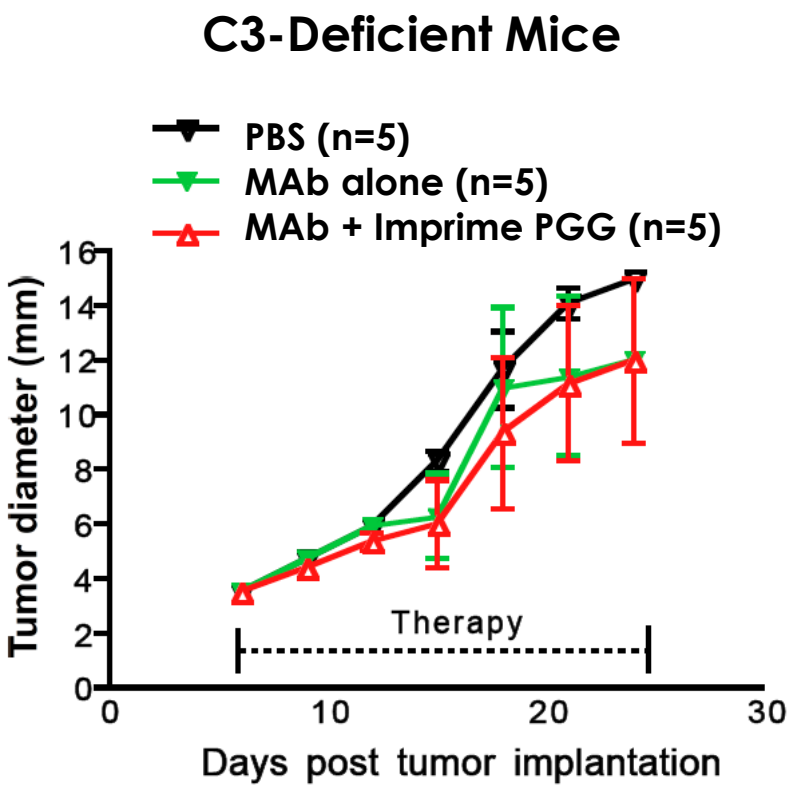
Imprime PGG Mechanism of Action is Complement Dependent

Inhibition of tumor growth and prolonged survival is seen in wild type mice (left) but not in complement deficient mice (right).





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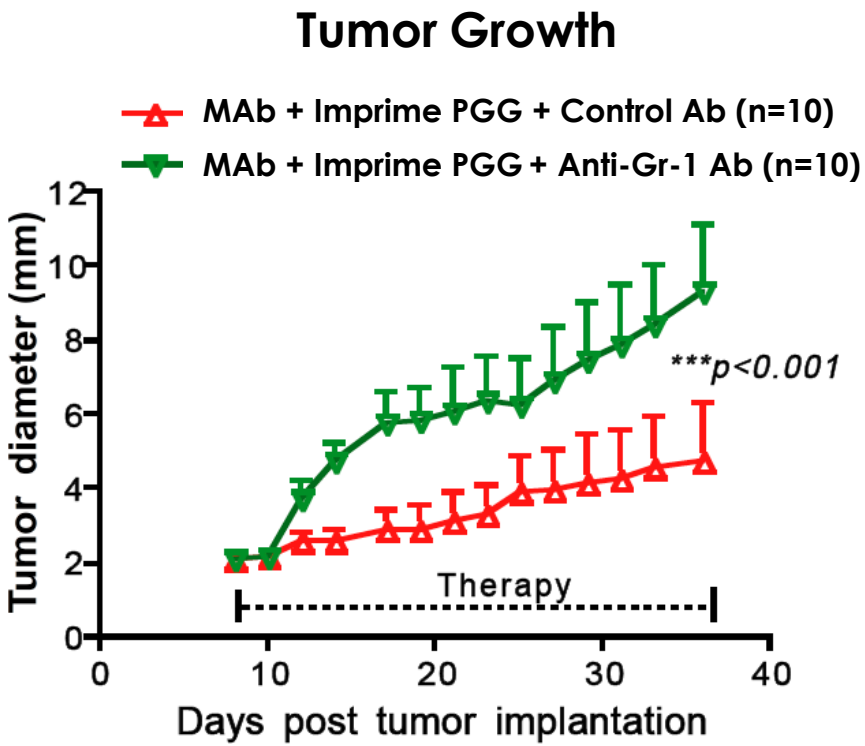
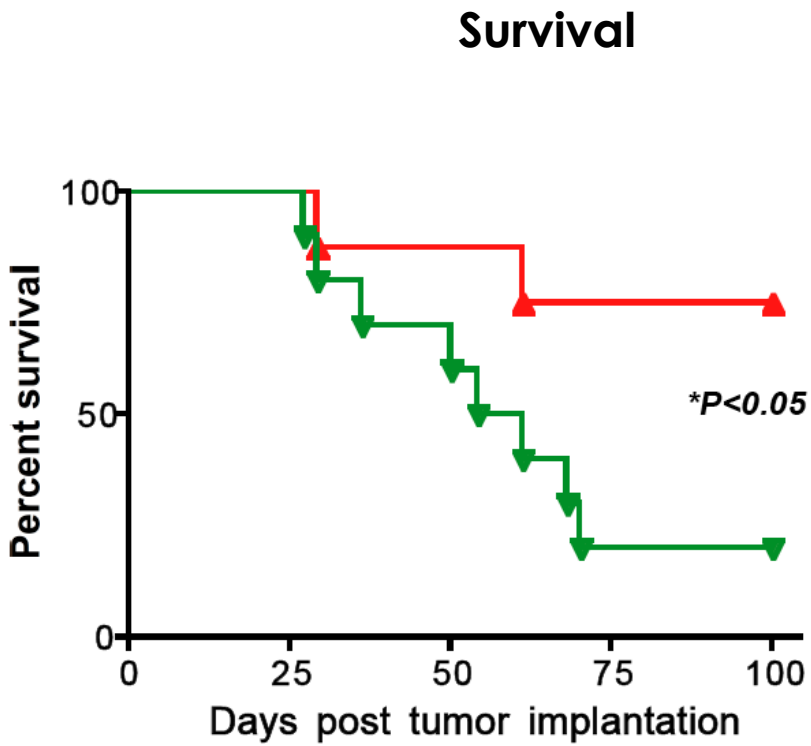
Imprime PGG Mechanism of Action is Neutrophil Mediated

Inhibition of tumor growth and prolonged survival is seen in non-neutrophil depleted mice (red) but not in neutrophil depleted mice (green).





Mice: C57Bl/6
Anti-Gr-1 antibody administered to deplete neutrophils (controls were administered an isotype control antibody)
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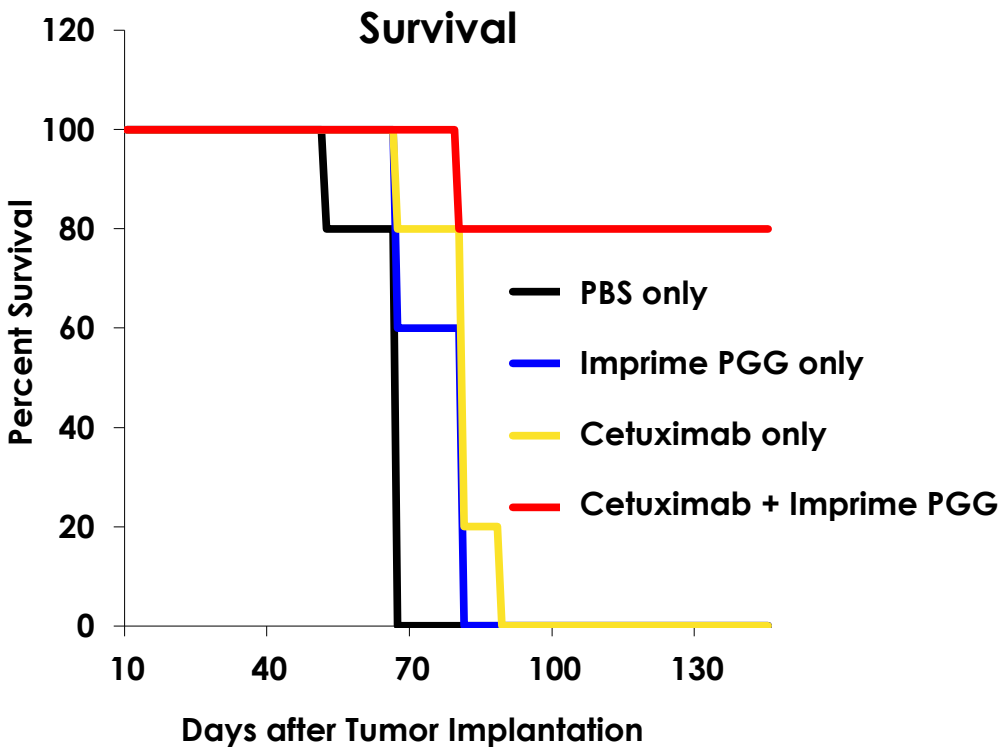
Anti-Tumor Activity of Imprime PGG Has Also Been Shown With Clinically Used Monoclonal Antibodies: Cetuximab

Imprime PGG administered in combination with cetuximab prolongs survival even in a *KRAS*-mutant lung cancer xenograft model.



Mice: Fox Chase Institute for Cancer Research (ICR) severe combined immune deficient (SCID)
Tumor: Human NCI-H23 non-small-cell lung carcinoma (**contains KRAS mutation, G12C**)
Antibody: Cetuximab (Erbitux®; chimeric IgG1 anti-EGFR)
Treatment Regimen: Imprime PGG (1200 µg/mouse) and cetuximab (150 µg/mouse) injected intravenously twice per week for four weeks beginning on Day 10
N = 8 – 9 mice per treatment group
Li et al., Cancer Research, 67:7421-7430, 2007.

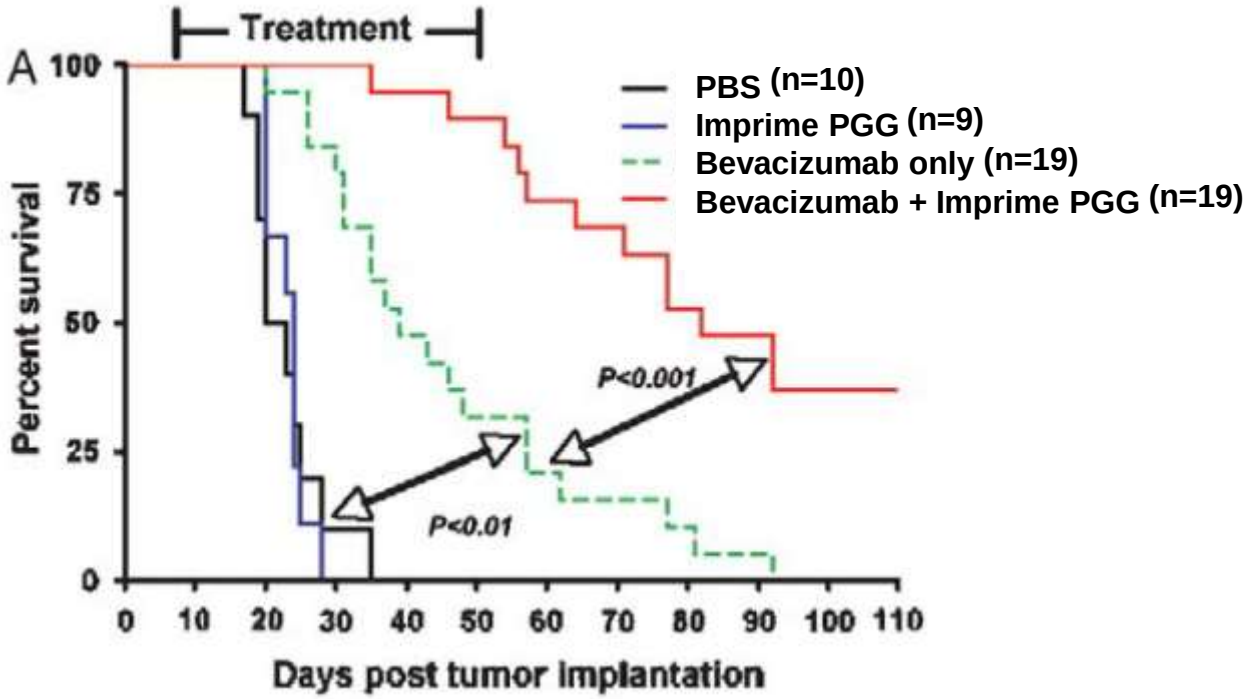
Imprime PGG Has Demonstrated Synergistic Anti-Tumor Activity in Multiple Tumor Models with Multiple Antibodies

Syngeneic	Xenogeneic
T-Cell Lymphoma: • RMAS-MUC1/anti-MUC1 Mab[1] - Wild-type mice • RMAS-MUC1/anti-MUC1 MAb[2] - CR3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - C3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - Neutrophil-deficient mice	**Non-Small Cell Lung Carcinoma (KRAS mutant):** • NCI-H23/Cetuximab[4] **Non-Small Cell Lung Carcinoma:** • PC14PE6/Bevacizumab (orthotopic)[3] • PC14PE6/Bevacizumab[3] **Ovarian Carcinoma:** • SKOV3/Bevacizumab[5]

[1]Qi, et al., Blood, 117: 6825-6836 (2011); [2]Li, et al., Journal of Immunology, 177:1661-1669 (2006); [3]Zhong, et al.. Journal of Immunotherapy 32: 703-712 (2009); [4]Li, et al., Cancer Research, 67:7421-7430 (2007); [5]Salvador, et al., Clinical Cancer Research, 14:1239-1247 (2008)

Anti-Tumor Activity of Imprime PGG Has Also Been Shown With Clinically Used Monoclonal Antibodies: Bevacizumab

Imprime PGG administered in combination with bevacizumab prolongs survival in a PC14PE6 orthotopic lung cancer xenograft model.



Note: Flow cytometric analysis demonstrated that PC14PE6 cells express cell-surface VEGF.

Mice: Fox Chase Institute for Cancer Research (ICR) severe combined immune deficient (SCID
Tumor: PC14PE6 (human lung cell line)
MAb: Bevacizumab (Avastin®; human IgG1 anti-VEGF)
Treatment Regimen: Imprime PGG (1200 µg/mouse) and bevacizumab (100 µg/mouse) injected intravenously twice per week for three weeks beginning on Day 7;
Zhong, W. et al. J. Immunotherapy 32: 703-712 (2009)

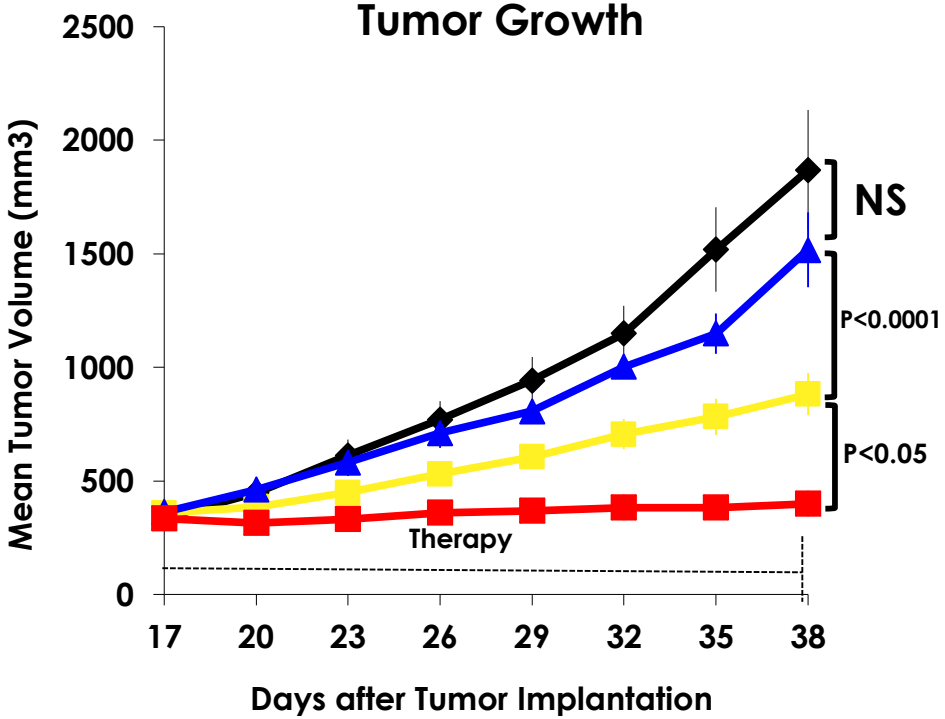
Imprime PGG Has Demonstrated Synergistic Anti-Tumor Activity in Multiple Tumor Models with Multiple Antibodies

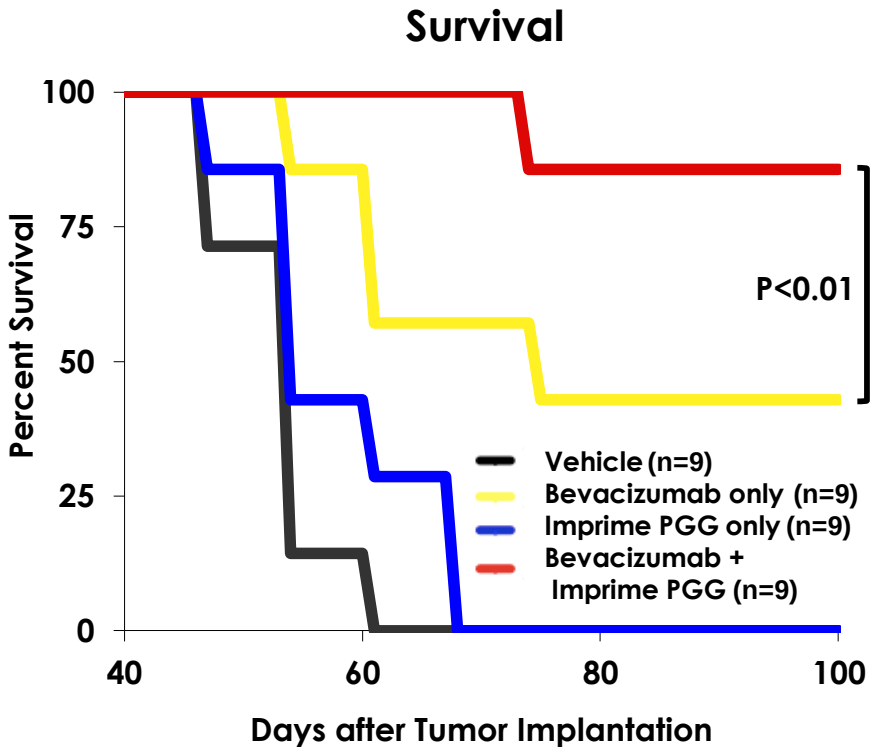
Syngeneic	Xenogeneic
T-Cell Lymphoma: • RMAS-MUC1/anti-MUC1 Mab[1] - Wild-type mice • RMAS-MUC1/anti-MUC1 MAb[2] - CR3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - C3-deficient mice • RMAS-MUC1/anti-MUC1 MAb[1] - Neutrophil-deficient mice	**Non-Small Cell Lung Carcinoma (KRAS mutant):** • NCI-H23/Cetuximab[4] **Non-Small Cell Lung Carcinoma:** • PC14PE6/Bevacizumab (orthotopic)[3] • PC14PE6/Bevacizumab[3] **Ovarian Carcinoma:** • SKOV3/Bevacizumab[5]

[1]Qi, et al., Blood, 117: 6825-6836 (2011); [2]Li, et al., Journal of Immunology, 177:1661-1669 (2006); [3]Zhong, et al.. Journal of Immunotherapy 32: 703-712 (2009); [4]Li, et al., Cancer Research, 67:7421-7430 (2007); [5]Salvador, et al., Clinical Cancer Research, 14:1239-1247 (2008)

Anti-Tumor Activity of Imprime PGG Has Also Been Shown With Clinically Used Monoclonal Antibodies: Bevacizumab

Imprime PGG administered in combination with bevacizumab inhibits tumor growth and prolongs survival in a SK-OV-3 ovarian cancer xenograft model.





Mice: Fox Chase Institute for Cancer Research (ICR) severe combined immune deficient (SCID)
Tumor: Human SK-OV-3 ovarian carcinoma
Antibody: Bevacizumab (Avastin®; human IgG1 anti-VEGF)
Treatment Regimen: Imprime PGG (1200 µg/mouse) and bevacizumab (100 µg/mouse) injected intravenously twice per week for three weeks beginning on Day 17;
Salvador et al., Clinical Cancer Research, 14:1239-1247, 2008.

Note: Flow cytometric analysis demonstrated that SK-OV-3 cells express cell-surface VEGF.

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Summary: Proof of Activity / Mechanism of Action

- Imprime PGG's novel mechanism redirects the cytotoxic abilities of innate immune cells to kill monoclonal antibody targeted tumor cells, with an **absolute requirement** for:
  - **CR3**
  - **Complement**
  - **Innate immune cells (neutrophils and monocytes)**

- Imprime PGG is thought to enable innate immune cells to recognize and kill tumor cells **'flagged' by monoclonal antibodies (MAb)**
  - Imprime PGG's mechanism does not require the normal function of the MAb to elicit anti-tumor activity (e.g., signal blockade, CDC, ADCC).
  - However, Imprime PGG does not interfere with these MAb functions.

- *In vivo*, Imprime PGG **inhibits tumor growth and prolongs overall survival** in **multiple tumor models** using **different** tumor-targeted monoclonal **antibodies**

Biothera's Clinical Program Is Guided by Expert Advisors

Leonard Saltz, M.D.
Member of Memorial Sloan-Kettering Cancer Center and Attending Physician at Memorial Hospital for Cancer and Allied Diseases, New York, NY

Eric Van Cutsem M.D., Ph.D.
Professor of Internal Medicine at the University of Leuven, and head of division of Digestive Oncology at the University Hospital Gasthuisberg in Leuven, Belgium

Arkadiusz Dudek, M.D., Ph.D.
Professor and Medical Director, Oncology Clinical Trials at University of Illinois, Chicago, IL. Previously, Associate Professor of Medicine and Director of Clinical Trials Office, Hematology/Oncology and Transplantation Division at University of Minnesota

Roy Herbst, M.D., Ph.D.
Chief of Medical Oncology and Associate Director for Translational Research at Yale Cancer Center, New Haven, CT

Fred Hirsch, M.D., Ph.D.
Professor of Medicine and Pathology at University of Colorado School of Medicine, Aurora, CO. Chief Executive Officer of International Association for the Study of Lung Cancer (IASLC)

Jerome Ritz, M.D.
Professor of Medicine, Harvard Medical School, Dana-Farber Cancer Institute in Boston, MA. Director for Clinical Trial Cores, Cancer Vaccine Center; Executive Director, Cell Manipulation Core Facility

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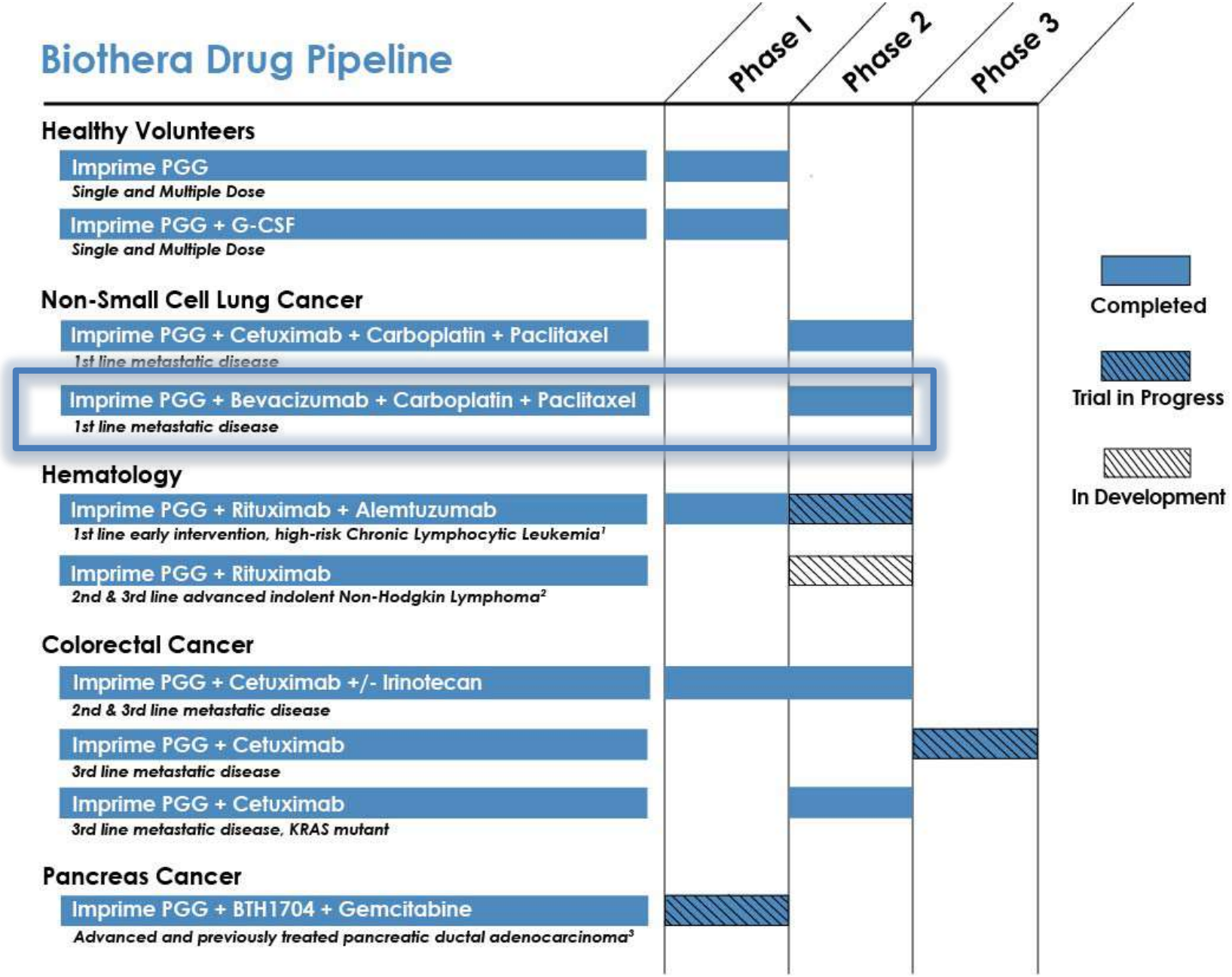
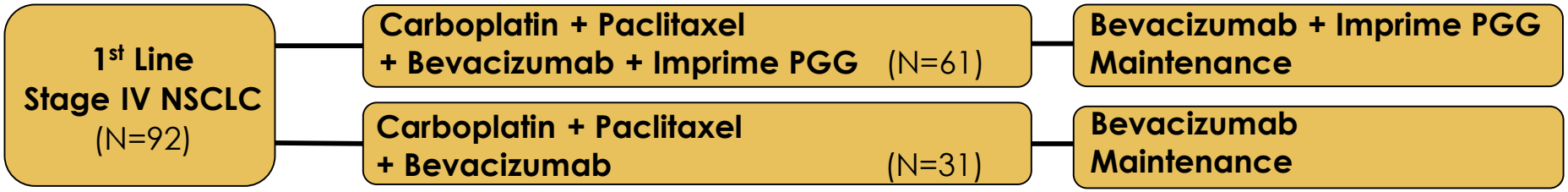
Biothera Drug Pipeline



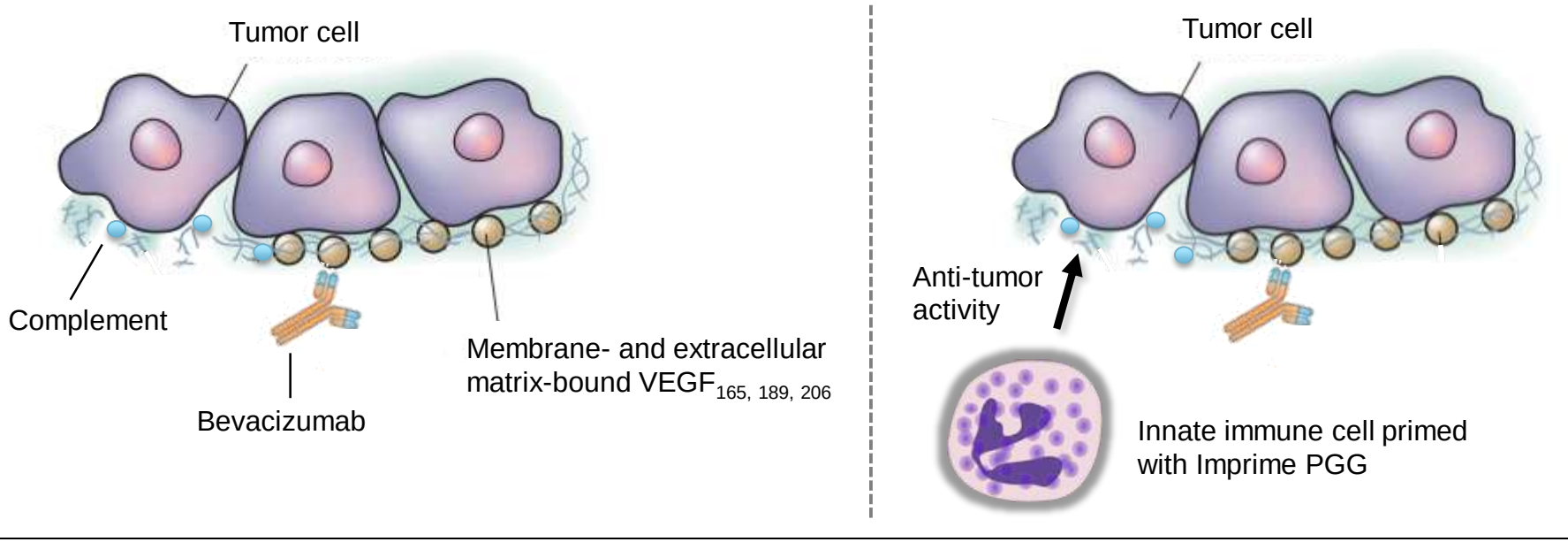
1) Investigator-initiated trial, Mayo Clinic
2) Investigator-initiated trial, Dana-Farber Cancer Institute
3) Investigator-initiated trial, University of Illinois Cancer Center

Non-Small Cell Lung Cancer (NSCLC) Open-Label, Randomized Phase 2 Study (LCA0821)



- **Primary Endpoint**
  - Objective Response Rate (modified RECIST v1.0)
- **Secondary Endpoints**
  - Disease Control Rate (CR, PR, SD)
  - Duration of Response
  - Time to Progression
  - Overall Survival
  - Safety
  - Pharmacokinetics
- **Treatment**
  - Imprime PGG (4 mg/kg IV) Days 1, 8 and 15 of each 3-week treatment cycle
  - Bevacizumab (15 mg/kg IV) Day 1 of each cycle
  - Carboplatin (AUC 6), Paclitaxel (200 mg/m^2) Day 2 of each cycle (for 4 to 6 cycles)
- **Imaging Assessments**
  - CT chest, abdomen (every 6 weeks)
- **Simon 2-Stage Design**
  - 90% power to detect ORR improvement from ≤ 30 to ≥ 50%

Rationale for Combining Imprime PGG with Bevacizumab



VEGF (vascular endothelial growth factor) is overexpressed by many human cancers, including NSCLC.[20,21]

Although VEGF is secreted, a significant fraction remains bound to the cell surface and the extracellular matrix by virtue of its heparin-binding affinity, and its bioavailability is regulated by proteolytic cleavage.[22-25]

Bevacizumab is a humanized IgG1 antibody that binds to all human VEGF-A isoforms and bioactive proteolytic cleavage fragments.[25] Bevacizumab has been shown to accumulate in the tumor microenvironment due to local accretion of cell- and matrix-associated VEGF.[26-31]

Binding of bevacizumab to surface-retained VEGF can induce complement (C3) deposition (opsonization),[32,33] but does not result in cell- or complement-mediated cytotoxicity.[33]

Imprime PGG is a novel innate immune cell modulator that primes neutrophils, monocytes and macrophages through a complement receptor 3 (CR3)-dependent mechanism to exert anti-tumor activity against complement opsonized tumor cells.[11,13-16]

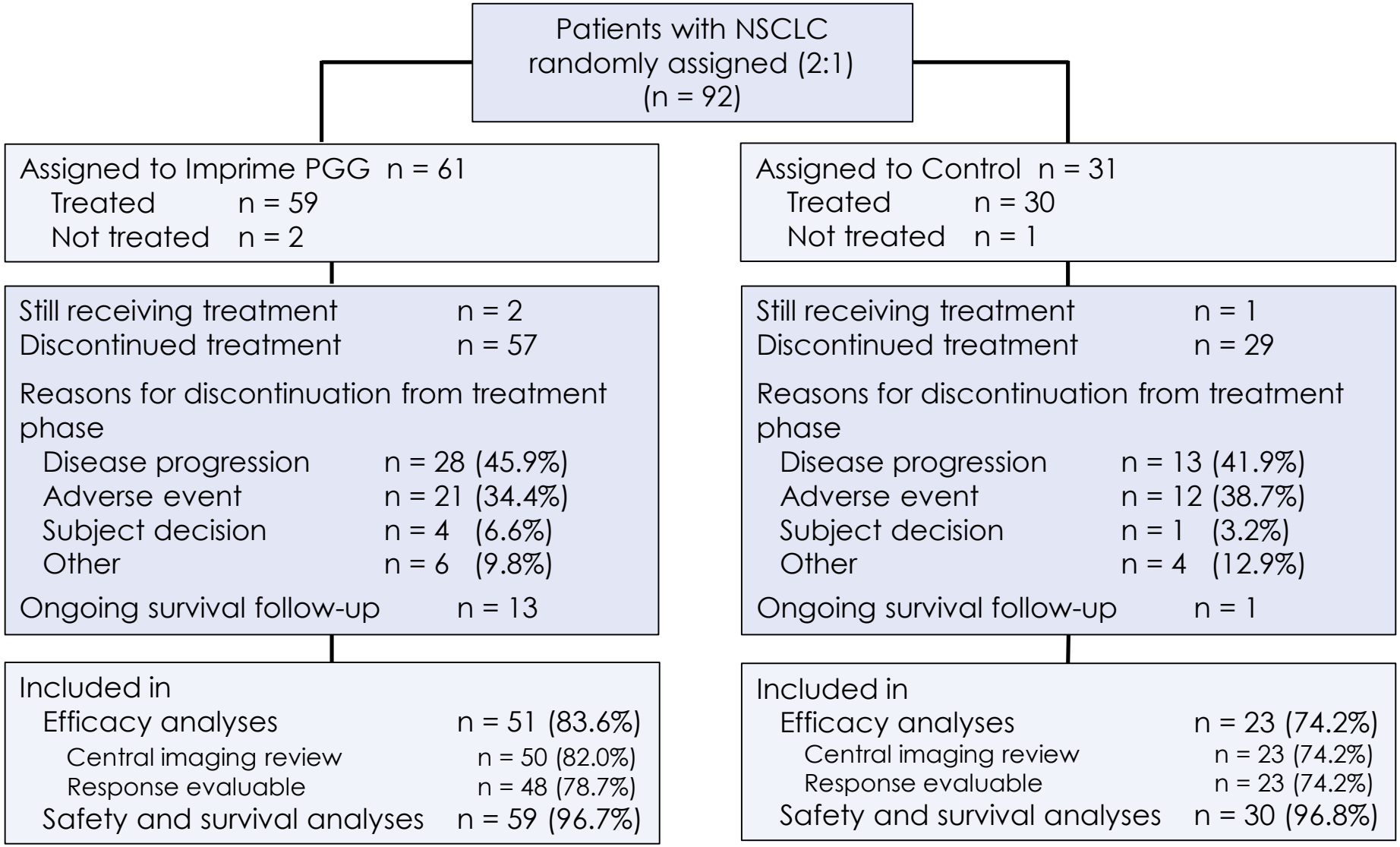
Image components adapted from Ferrara N et al, The biology of VEGF and its receptors, Nature Medicine 2003 [21]

Analysis Populations (LCA0821)

- Primary Efficacy Population (PEP):
  - All subjects with an evaluable baseline CT scan and at least one evaluable post-baseline CT scan

- Safety Population:
  - All subjects receiving any drug treatment

Patient Disposition (LCA0821)



Baseline Demographics and Disease Characteristics

(LCA0821)

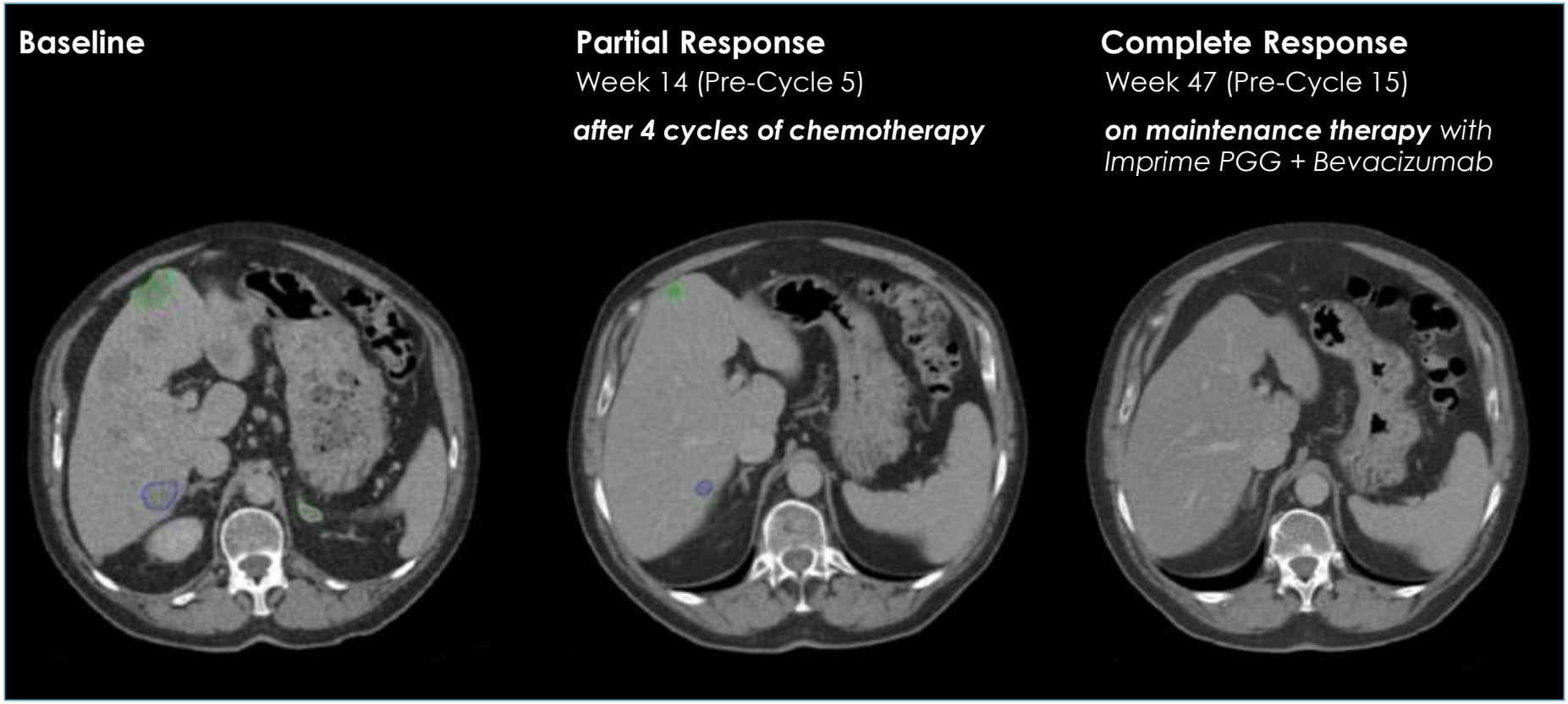
Demographic or Disease Characteristic	**Imprime PGG** (n = 59)	**Control** (n = 30)
Age, years median (range)	 59 (43, 76)	 58 (28, 75)
Gender, n (%) Female Male	 33 (55.9%) 26 (44.1%)	 16 (53.3%) 14 (46.7%)
Race / Ethnicity, n (%) White Asian or Pacific Islander Black	 57 (96.6%) 1 (1.7%) 1 (1.7%)	 30 (100%) 0 (0%) 0 (0%)
ECOG performance status, n (%) 0 1	 31 (52.5%) 28 (47.5%)	 20 (66.7%) 10 (33.3%)
Time from diagnosis of Stage IV NSCLC to randomization, median (range) days	18.0 (1, 168)	17.5 (7, 77)
Time from initial diagnosis of NSCLC to randomization, median (range) days	20.0 (1, 3171)	17.5 (7, 77)
Prior treatment for NSCLC, n (%) Surgery Radiotherapy*	 8 (13.6) 2 (3.4)	 2 (6.7) 0 (0.0)

* excludes palliative radiation to the skeleton

Efficacy Results – Primary Endpoint (LCA0821)

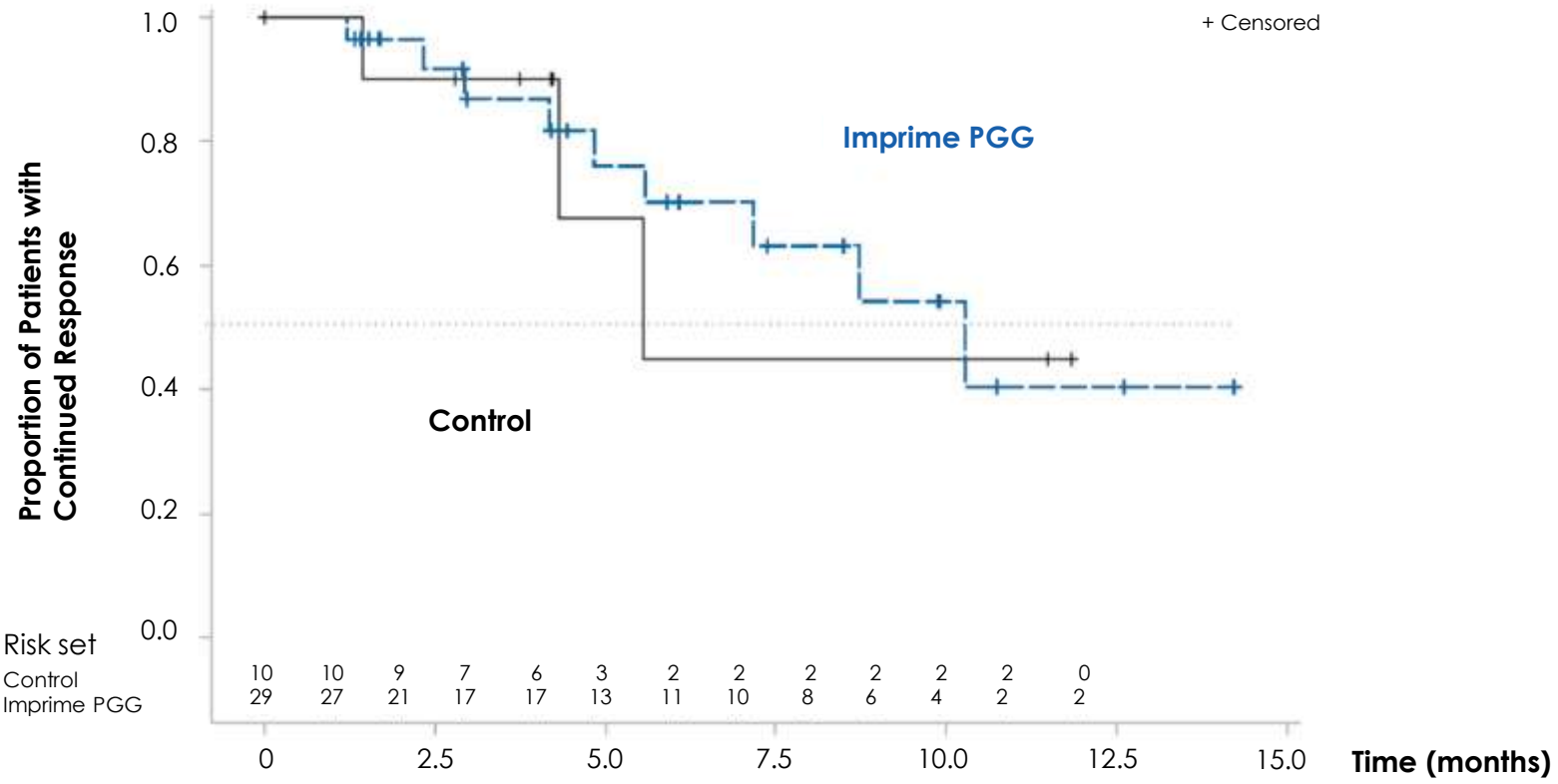
Objective Tumor Response (Based on Central Radiology Review)	**Imprime PGG** (N=48)			**Control** (N=23)			P-value
	n	%	(95% CI)	n	%	(95% CI)	
Objective Response Rate	29	**60.4**	(45.3, 74.2)	10	**43.5**	(23.2, 65.5)	0.2096
Complete Response	1	2.1		0	0.0		
Partial Response	28	58.3		10	43.5		
Stable Disease	16	33.3		11	47.8		
Progressive Disease	3	6.3		2	8.7		

Continued Regression of Lesions on Maintenance (LCA0821)



- *Target lesion locations at baseline included left hilum, mediastinal lymph nodes, adrenals, liver*
- *The patient remained on study and in CR at the time of the primary analysis (19 weeks later)*

Duration of Response (LCA0821)



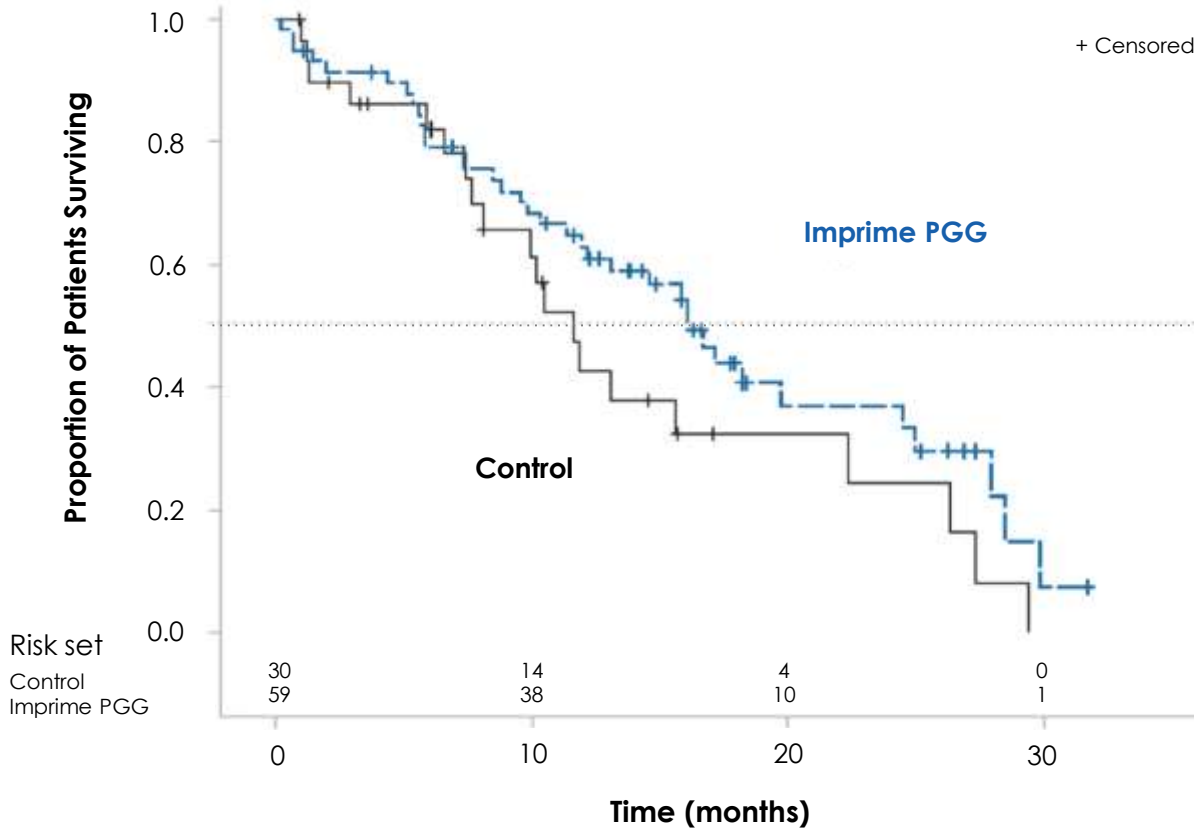
Duration of Response (months)	Median	(Q1, Q3)	P-value
Imprime PGG (N=29)	**10.3**	(5.6, NE)	0.9040
Control (N=10)	**5.6**	(4.3, NE)	

NE, not estimable

Progression-Related Time to Event Endpoints (LCA0821)

Time to Event Endpoints Efficacy Analysis Set	**Imprime PGG** (n=50)		**Control** (n=23)		Hazard Ratio (95% CI)	P-value
	median	(Q1, Q3)	median	(Q1, Q3)		
Time to Progression (months)	**11.6**	(6.2, 14.5)	**9.6**	(7.3, NE)	**1.31** (0.54, 3.65)	0.5639
Progression-free Survival (months)	**11.9**	(6.1, 24.5)	**10.2**	(7.1, 22.3)	**0.86** (0.49, 1.54)	0.5901

Overall Survival (LCA0821)



Overall Survival (months)	Median	(Q1, Q3)	Hazard Ratio (95% CI)	P-value
Imprime PGG (N=59)	**16.1**	(8.5, 27.9)	**0.66** (0.38, 1.16)	0.1345
Control (N=30)	**11.6**	(7.4, 22.3)		

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Safety Results (LCA0821)

Adverse Events (AEs)	Imprime PGG (N=59)		Control (N=30)	
	All Events		All Events	
	n	%	n	%
Any AEs	58	98.3	30	100.0
CTCAE Grade 3 or 4 AEs	55	93.2	20	66.7
Serious AEs	24	40.7	13	43.3
AEs leading to treatment discontinuation*	22	37.3	13	43.3
Fatal AEs**	7	11.9	1	3.3

* disease progression was reported as AE leading to treatment discontinuation for 1 subject in each group

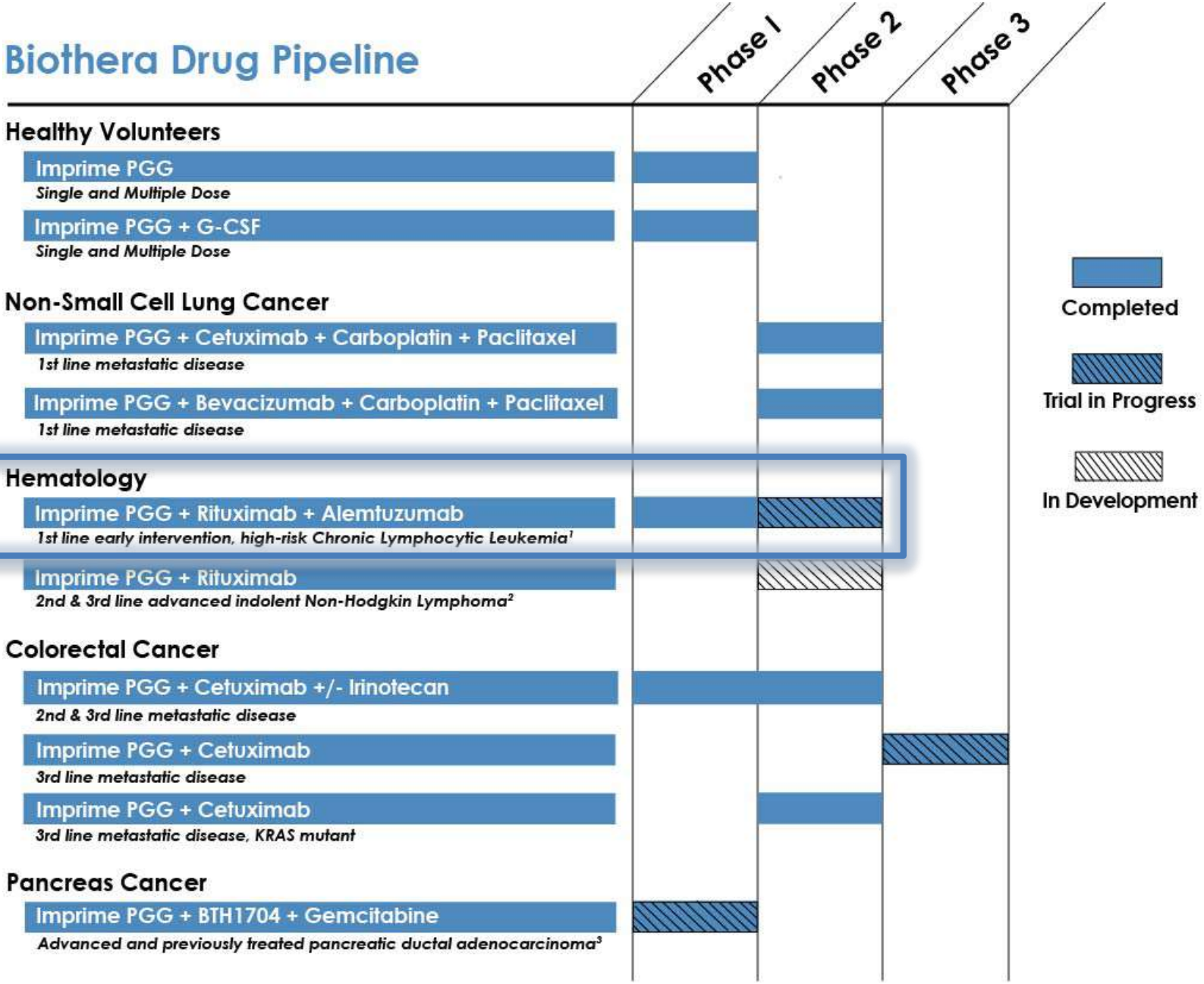
** included general physical health deterioration (n=3), disease progression, pneumonia, pneumothorax, hemorrhage intracranial (n=1 each) in the Imprime PGG group; and pneumonia (n=1) in the control group. All fatal AEs were deemed to be unrelated to Imprime PGG by the investigator

CTCAE, Common Terminology Criteria of Adverse Events

Conclusions (LCA0821)

- Imprime PGG in combination with carboplatin, paclitaxel and bevacizumab therapy resulted in **substantial increases in objective response rate** and **duration of response** in patients with non-squamous non-small cell lung cancer
- Although the study was not powered for survival, treatment with Imprime PGG was associated with a **4.5-month median increase in survival**, and a **34% reduction in the risk of death**
- **Overall**, Imprime PGG was **well tolerated**; adverse events mostly reflected expected toxicities with the backbone chemotherapy and bevacizumab or were complications of the patients' lung cancer. Premedication with low-dose corticosteroids and antihistamines is recommended
- Imprime PGG is a novel innate immune modulator that holds **promise** as an **adjunct to antibody-based therapy for** patients with **non-small cell lung cancer**

Biothera Drug Pipeline



1) Investigator-initiated trial, Mayo Clinic
2) Investigator-initiated trial, Dana-Farber Cancer Institute
3) Investigator-initiated trial, University of Illinois Cancer Center

Chronic Lymphocytic Leukemia (CLL)
Open-Label, Sequential Phase 1/2 Study (LS1084)

Sequential Phase 1 / Phase 2 study to assess safety and efficacy of Imprime PGG + Alemtuzumab + Rituximab in the treatment of subjects with early/intermediate stage, high-risk prognosis, chronic lymphocytic leukemia

- Investigator-initiated study at the Mayo Clinic
- Lead Investigator
  - Clive Zent, MD
- Co-Investigators
  - Stephen Ansell (Mayo Clinic)
  - Thomas Witzig (Mayo Clinic)
  - George Weiner (University of Iowa)

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Phase 1/2 CLL Study: Preliminary Phase 1 Response Results[a] (LS1084)

Phase 1 results with Imprime PGG in combination with Alemtuzumab and Rituximb in CLL

	Imprime PGG plus Alemtuzumab and Rituximab
Number of Evaluable Subjects	11
Overall Response (ORR)	11 (100%)
Partial Response (PR)	2 (18%)
Nodular Partial Response (nPR)	1 (9%)
Complete Response (CR)	8 **(73%)**

Phase 2 of the study powered to see an improvement in complete response (CR) from 30% to 50%

[a] Zent et al., Blood 120: Abstract 1792, 2012; Updated data as of 03/06/14 presented here. Responses according to IWCLL NCI-WG96 update (Hallek et al, Blood 111:5446-5456, 2008);

Phase 1/2 CLL Study: Preliminary Phase 1 Response Results by Risk Factor[a] (LS1084)

Subject	Imprime PGG Dose (mg/kg)	High-Risk of Progression Prognostic Factor	Response
LS4827	1.0	UnMut IgH_v & ZAP	**CR**
LS3775	1.0	UnMut IgH_v & ZAP	**CR**
LS4782	1.0	17p-	PR
LS5074	2.0	11q-	**CR**
LS4877	2.0	11q-	nPR
LS5196	2.0	17p-	**CR**
LS-4973	4.0	17p-	**CR**
LS3217	4.0	UnMut IgH_v & ZAP	**CR**
LS5177	4.0	11q-	PR
L55245	4.0	17p-	**CR**
LS4473	4.0	VH 3-21 & ZAP	**CR**

[a] Zent et al., Blood 120: Abstract 1792, 2012; Updated data as of 03/06/14 presented here.
Responses according to IWCLL NCI-WG96 update (Hallek et al, Blood 111:5446-5456, 2008);
CR = complete response; nPR = nodular partial response; PR = partial response;

Phase 1/2 CLL Study: Preliminary Phase 1 Survival Follow-up[a] (LS1084)

Median Follow-up		
Imprime PGG Subjects	**Imprime PGG in 17p$^-$ Subjects**	**Historical 1st Line Treatments in 17p- Subjects**
(N=11) **31.1months** (22.9mo - 37.0 mo)	(N=4) **29.3 months** (24.5mo - 34.4 mo)	**<24 months[b]**

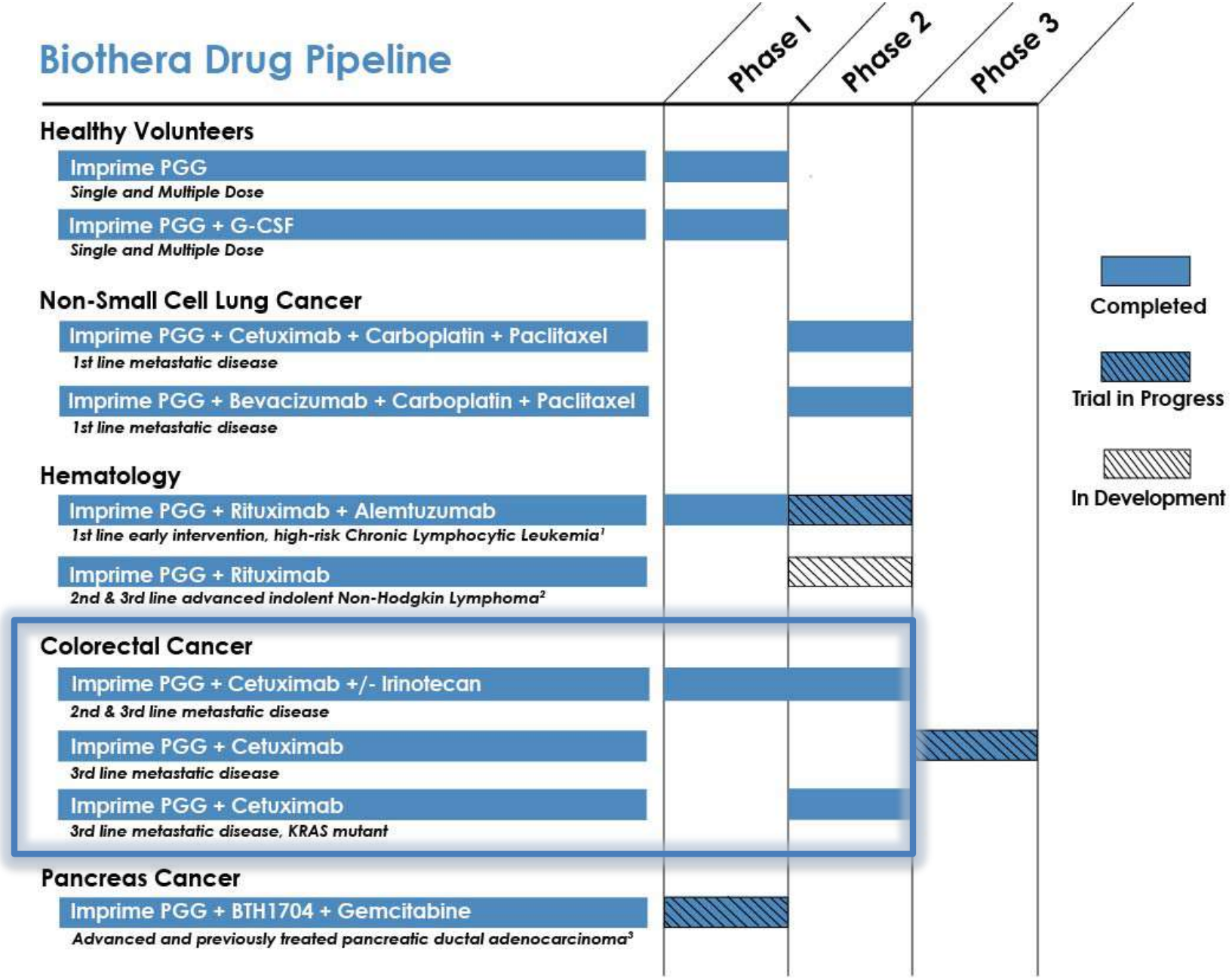
No Deaths Have Occurred to Date

[a] Data as of 03/06/14.
[b] Stilgenbauer and Zenz, ASH Educational Book, 1:481-488, 2010.

Phase 1/2 CLL Study Status

- Phase 1, which is the Imprime PGG dose-escalating portion of the study, is complete:
  - No DLTs observed to-date
  - 4 mg/kg Imprime PGG dose chosen for Phase 2
    - Phase 2 enrollment in progress
  - Early results show a promising CR rate, above that expected from prior reported alemtuzumab/rituximab results, including in subjects with 17p deletion.
- No deaths have occurred to date, with promising interim survival in 17p deletion subjects.
- No safety concerns to date
  - Grade 3 AEs were diarrhea (n=3), increased transaminase levels, dehydration, gastritis, hypertension, hyponatremia, hypertension (each n=1)
  - Grade 4 AEs were neutropenia (n=2) and febrile neutropenia (n=1)

Biothera Drug Pipeline



1) Investigator-initiated trial, Mayo Clinic
2) Investigator-initiated trial, Dana-Farber Cancer Institute
3) Investigator-initiated trial, University of Illinois Cancer Center

Imprime PGG Clinical Response Summary

Indication	Design	Control ORR	Imprime PGG ORR	Percent ORR Improvement
Non-Small Cell Lung Cancer				
Cetuximab (Erbitux®), Carboplatin/Paclitaxel	**Randomized** Controlled	23.1%	47.8%	**107%**
Bevacizumab (Avastin®), Carboplatin/Paclitaxel	**Randomized** Controlled	43.5%	60.4%	**39%**
Colorectal Cancer				
Cetuximab (KRAS mutant)	Single Arm	~1% (0-2%) [a]	6%	**500%**
Cetuximab (not selected for KRAS)	Single Arm	11% [a]	24%	**118%**
(KRAS wild type subset)		17% [a]	45%	**165%**
Cetuximab, Irinotecan (not selected for KRAS)	Single Arm	16% [a]	30%	**88%**
Hematological Malignancies				
Chronic Lymphocytic Leukemia Rituximab, Alemtuzumab [b]	Single Arm	37% [a, b]	73% [b]	**97%**

ORR, Objective Response Rate
[a] Historical reference; [b] interim data; [c] complete responses

Potential Areas of Scientific Interest

1. Novel combinations with approved or advanced stage (phase 3 results available) complement-activating antibodies, in particular in areas of high unmet medical need (hematology or oncology)
    - Clinical safety and preliminary efficacy (e.g. combination with ofatumumab in CLL)
2. Translational research studies elucidating evidence of biological impact in human
    - Clinical and correlative endpoints (e.g. pre-surgical window of opportunity or neo-adjuvant study in breast cancer)
3. Novel combinations in immune modulation
    - Preclinical or clinical research (e.g. PD-L1)

Questions / Discussion

References Cited in Presentation

[1]Bose et al., Frontiers in Immunology, 4:1-13, 2013;

[2] Ross et al., Journal of Immunology, 134:3307-3315, 1985;

[3] Cain et al., Complement, 4:75-86, 1987;

[4] Ross et al., Complement, 4:61-74, 1987;

[5] Diamond et Al., Journal of Cell Biology 120: 1031-1043, 1993;

[6] Ueda et al., PNAS (USA), 91:10680-10684, 1994

[7] Thonrton et al., Journal of Immunology, 156:1235-1246, 1996;

[8] Vetvicka et al., Journal of Clinical Investigation, 98:50-61, 1996;

[9] Xia et al., Journal of Immunology, 162:2281-2290, 1999;

[10] Xia et al., Journal of Immunology, 162:7285-7293, 1999;

[11] Li et al., Journal of Immunology, 177:6661-6669, 2006;

[12] Schenkein et al., Journal of Immunology, 126:7-10, 1981;

[13] Li et al., Cancer Research, 67:7421-7430,2007;

[14] Salvador et al., Clinical Cancer Research, 14:1239-1247, 2008;

[15] Zhong et al., Journal of Immunotherapy, 32:703-712, 2009;

[16] Qi et al., Blood, 117:6825-6836, 2010;

[17] Bose et al., Keystone Symposium, January 27, 2013, Vancouver, BC, Canada, Abstract/program # J4.

[18] Bose et al., Journal of Clinical Oncology, 32 (15S) (Abstract #3045), 2014;

[19] Antonysamy et al., Journal of Immunology 192:73.9 (Abstract), 2014;

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