### Clinical Trial News on the Treatment of Waldenstrom's Macroglobulinemia

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# OBJECTIVES

### To review current and soon to be opened trials for Waldenstrom's Macroglobulinemia



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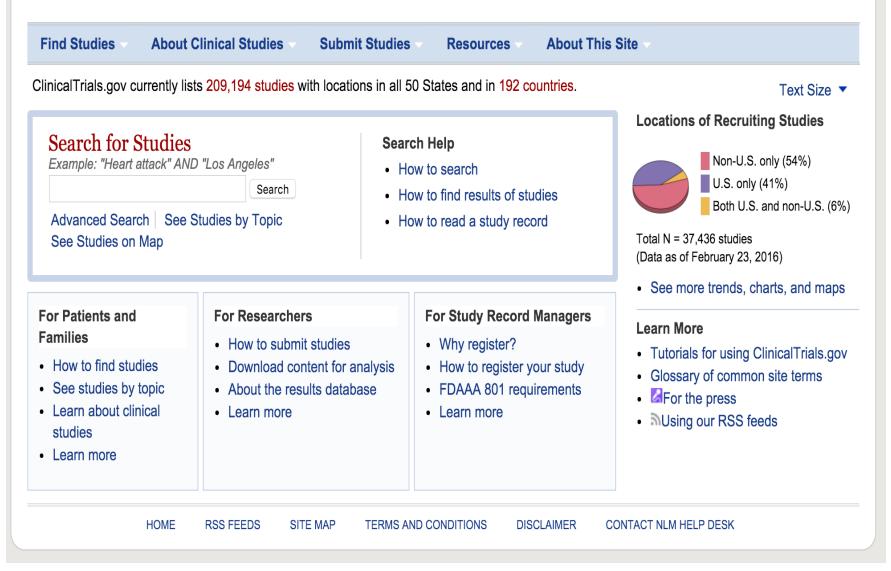
# Hype or Hope ?

- Not just hope
- Through incredible scientific work in the laboratory dreams are becoming reality
- Example
- Ibrutinib truly a breakthrough medicine that has changed the outcomes and expectations of the WM community

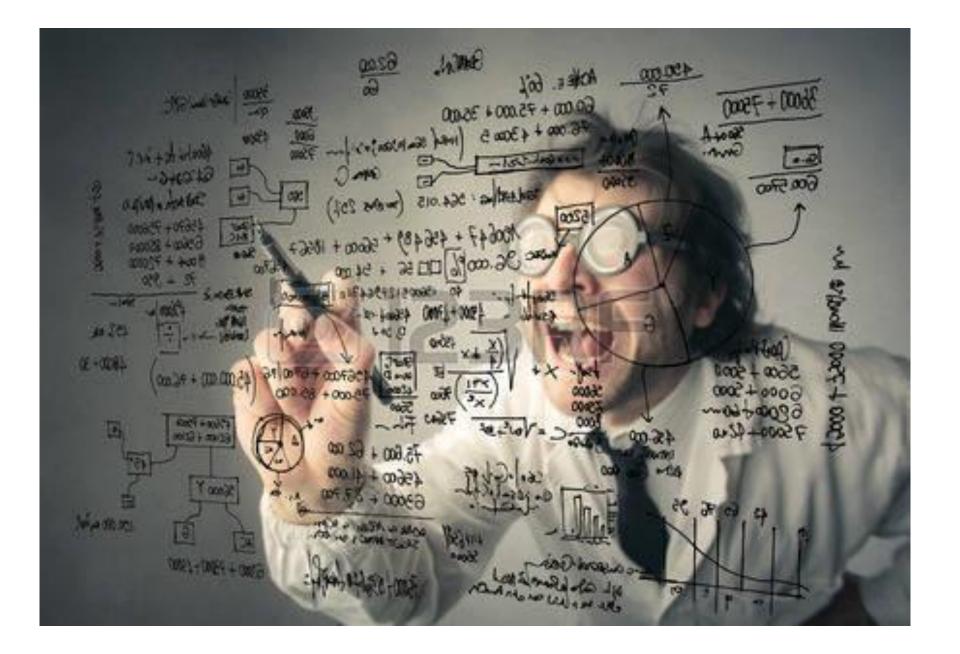
#### ClinicalTrials.gov

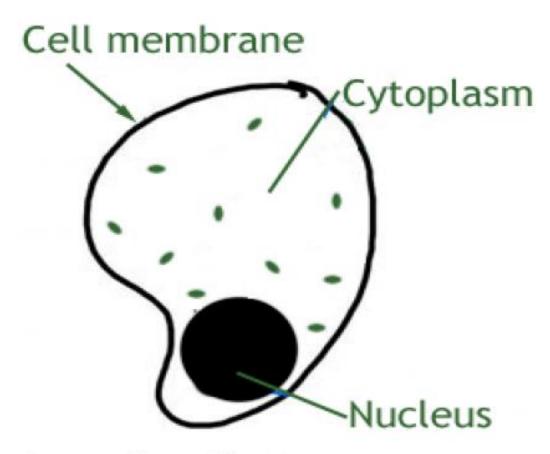
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ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more <u>about</u> clinical studies and about this site, including relevant history, policies, and laws.



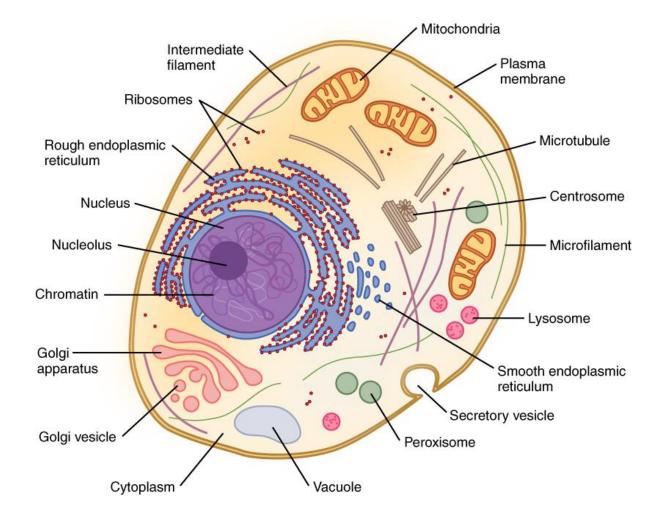
Rank	Status	Study		
1	Recruiting	An Open-Label, Randomized, Phase 3 Trial of Nivolumab Versus Investigator's Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer (CheckMate 026)		
		Condition:	Stage IV or Recurrent Non-Small Cell Lung Cancer	
		Interventions:	Biological: Nivolumab; Drug: Gemcitabine; Drug: Cisplatin; Drug: Carboplatin; Drug: Paclitaxel; Drug: Pemetrexed	
2	Recruiting	Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Head and Neck Carcinoma		
		(CheckMate 141)		
		Condition:	Squamous Cell Carcinoma of the Head and Neck	
		Interventions:	Drug: Nivolumab; Drug: Cetuximab; Drug: Methotrexate; Drug: Docetaxel	
3	Recruiting	Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Rena		
		Cell Carcinoma (CheckMa	ate 214)	
		Conditions:	Advanced Renal Cell Carcinoma; Metastatic Renal Cell Carcinoma	
		Interventions:	Biological: Nivolumab; Biological: Ipilimumab; Drug: Sunitinib	
4	Recruiting	Efficacy Study of Nivolumab Compared to Ipilimumab in Prevention of Recurrence of Melanoma After Comple Resection of Stage IIIb/c or Stage IV Melanoma (CheckMate 238)		
		Condition:	Melanoma	
		Interventions:	Drug: Ipilimumab; Drug: Nivolumab; Other: Placebo matching Ipilimumab; Other: Placebo matching Nivolumab	
5	Recruiting	Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab in Subjects With Advanced Liver		
	-	-	nti-Programmed-Death-1 Hepatocellular Carcinoma)	
		Condition:	Hepatocellular Carcinoma	
		Intervention:	Biological: Nivolumab	
6	Recruiting	Study of ONO-4538 in Unresectable Advanced or Recurrent Gastric Cancer		
		Condition:	Gastric Cancer	
		Interventions:	Drug: ONO-4538; Drug: Placebo	
7	Recruiting	Study of Combination Therapy With Mogamulizumab (KW-0761) and Nivolumab (ONO-4538/BMS-936558) in		
		Subjects With Advanced Solid Tumors		
		Condition:	Solid Tumor	
		Intervention:	Biological: Mogamulizumab: KW-0761, Nivolumab: (ONO-4538/BMS-936558)	



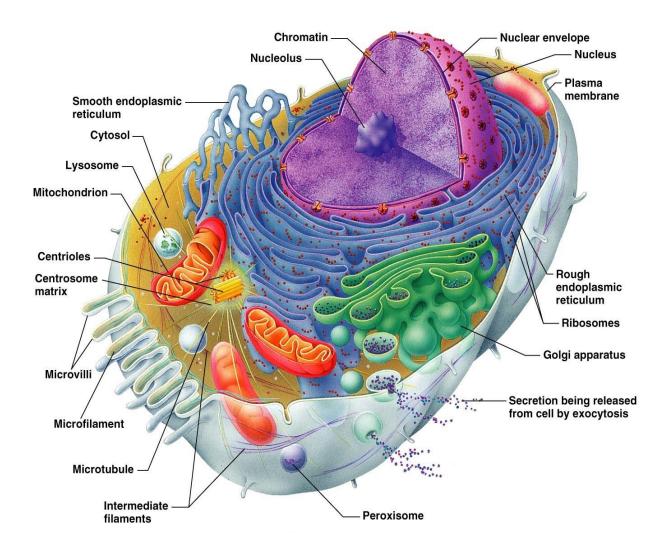


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# Two dimensional picture of cell



## 3D picture of cell



#### Research Studies of new Treatments for WM

- Subcutaneous rituximab
- Ixazomib (Ninlaro) -Velcade in pill form
- Oprozomib carfilzomib in pill form
- Ublituximab (TG-1101)
- obinutuzumab (Gazyva)
- Bruton Kinase inhibitors: ibrutinib, BDB-3111, acalabrutinib(ACP-196)
- CXCR4 inhibitors

- BCL-2 inhibitors: Venetoclax
- Idelalisib
- Aurora Kinase inhibitors
- Checkpoint inhibitors
- Daratumumab ?

#### Subcutaneous Rituximab: A new twist on an "old" therapy

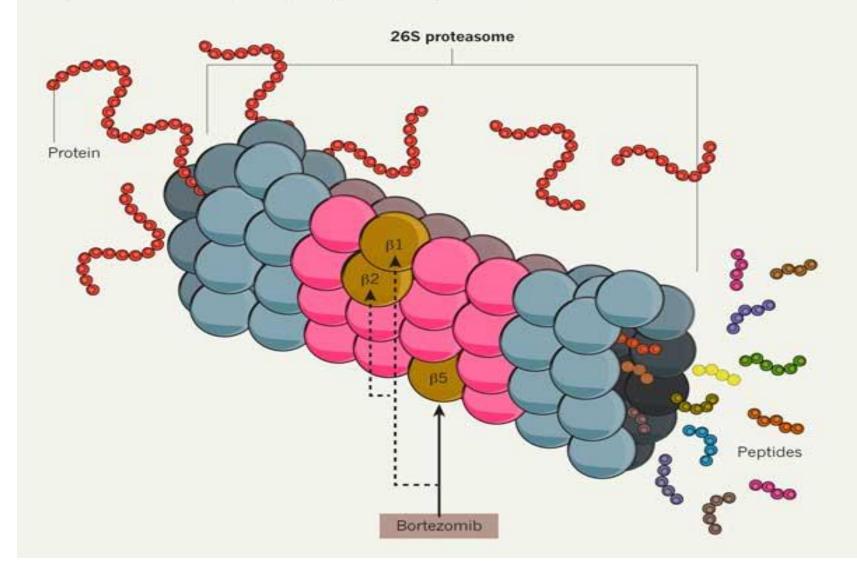
- Numerous studies of subcutaneous rituximab in a many different diseases
- 2000+ patients studied
- On March 29,2017 the FDA Advisory Committee
   Unanimously Recommended Approval of Genentech's
   Subcutaneous Rituximab for Certain Blood Cancers
- Final approval decision is expected from the FDA by June 26, 2017

#### Subcutaneous Rituximab: A twist on an "old" therapy

- Proposed indications for subQ Rituximab include follicular lymphoma, diffuse large B-cell lymphoma, low grade and chronic lymphocytic leukemia
- WM is a low grade lymphoma
- Use of SubQ rituximab will probably rapidly be expanded to most/all CD20+ blood cancers including WM
- 5-7 minutes to administer subQ versus more than 1½ hours for IV Rituximab

#### **DISRUPTING A PROTEIN DISPOSAL OPERATION**

Proteasome inhibitors such as bortezomib turn off the machinery that disposes of damaged proteins, causing myeloma cells to suffocate in their own waste. The drug targets the  $\beta$ 5 (chymotrypsin-like) enzyme but also hits the  $\beta$ 1 and  $\beta$ 2 enzymes, causing side effects.



### Oral proteasome inhibitors for WM

- Both Velcade(bortezomib) and Kyprolis (carfilzomib) are highly effective treatments for WM
- Inconvenient though.....either subQ or IV injections
- Can these drugs be developed into a pill form ?
- YES !

#### Oral proteasome inhibitors for WM

- Ninlaro (oral Velcade) is approved for multiple myeloma
- One Ninlaro pill per week !
- Two studies, one currently open
- Ixazomib( Ninlaro) and Rituximab for indolent b-cell NHL (Seattle).ClinicalTrials.gov Identifier: NCT02339922

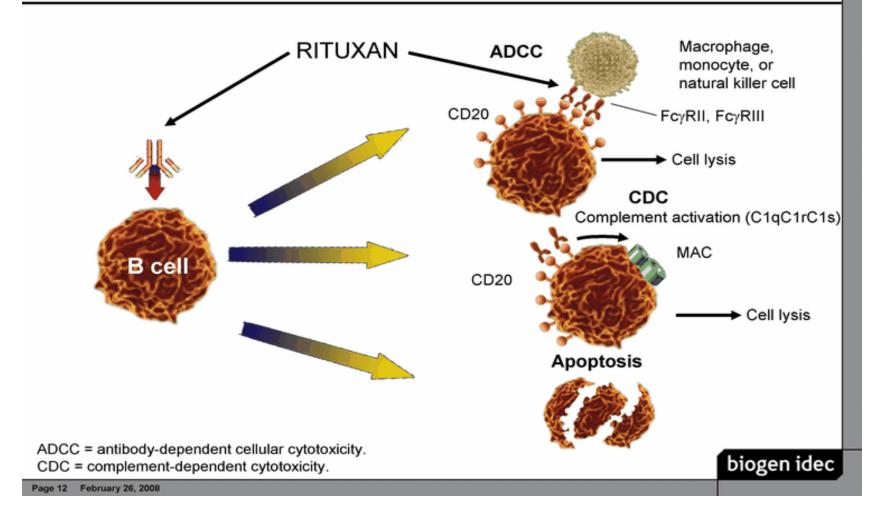
#### Ninlaro + Rituximab + dexamethasone: NCT02400437

- Dana Farber study of 26 patients presented at ASH 2016
- Overall response rate was 88% (VGPR 6%, PR 44%, MR 38%)
- Major response rate of 50%
- Major responses (VGPR + PR) were observed in 47% of patients with CXCR4 mutations versus 64% in those who were wild-type CXCR4 (p=0.32)
- Rapid response 8 weeks

# Oprozomib

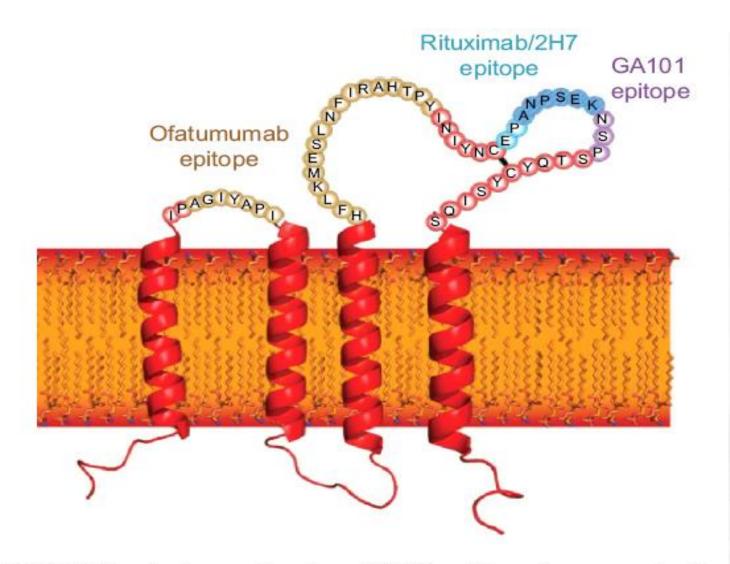
- Oral form of carfilzomib (Kyprolis)
- Still early in development
- New Phase 1 study for patients with multiple myeloma has recently opened
- In an earlier study diarrhea, nausea, and vomiting were a significant issue
- Drug has been re-formulated to decrease the gastrointestinal side effects

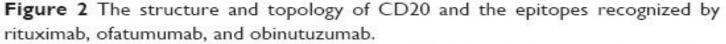
#### **RITUXAN** Mechanism of Action



# New anti-CD20 agents: Ublituximab (TG-1101) and obinutuzumab (Gazyva or GA101)

- Can we improve on the original anti CD20 agent Rituximab ?
- These new drugs are monoclonal antibodies that target a unique epitope on the B-lymphocyte CD20 antigen
- They are bioengineered to potentially deliver better results
- Ublituximab has been bioengineered for enhanced biological activity with an increased ability to trigger an immune response, delivering superior killing of lymphoma cells

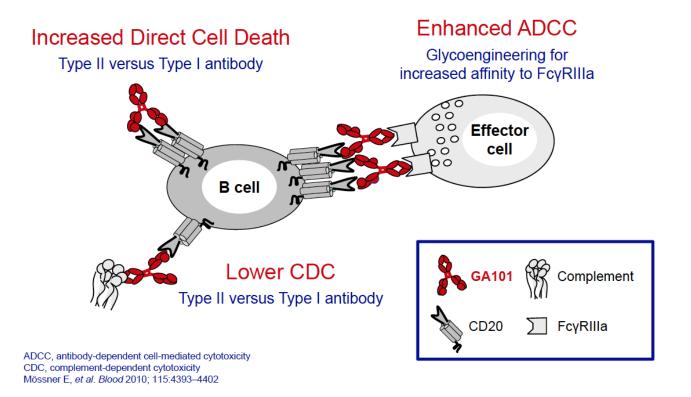




**Note:** Adapted from Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *MABs*. 2013;5(1):22–31.<sup>20</sup>

## **Obinutuzumab (GA101)**

#### **GA101: Mechanisms of action**



# Studies

- Efficacity of Idelalisib and Obinutuzumab in Patient With Relapsed Refractory Waldenstrom's Macroglobulinemia (RemodelWM3) – France
- Entospletinib and Obinutuzumab in Treating Patients With Relapsed Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Non-Hodgkin Lymphoma ClinicalTrials.gov Identifier: NCT03010358

#### International Workshops on WALDENSTRÖM'S MACROGLOBULINEMIA

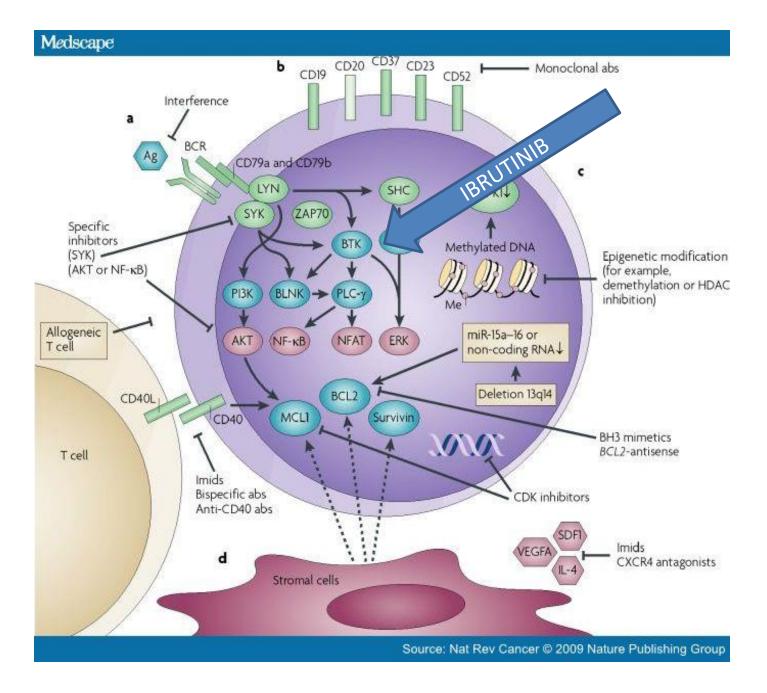


ORIGINAL ARTICLE

#### Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S.,
Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D.,
Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

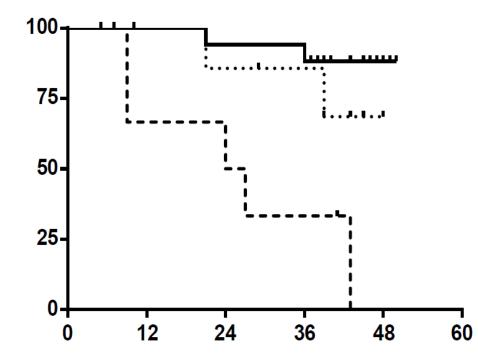
NEJM 372;15. April 9, 2015



# Resistance to Ibrutinib

- **CXCR4<sup>WHIM</sup>** mutations are common Waldenstrom's Macroglobulinemia (WM), and are associated with clinical resistance to ibrutinib
- WHIM = Warts, Hypogammaglobulinemia, Infections and Myelokathexis
- Approximately 90–95% of WM patients have mutations in MYD88 and 30% in CXCR4(WHIM)
- Major response rate was 77% for patients without WHIM mutation versus 30% in those with WHIM mutations
- Decreases in serum IgM and IgM M-spike as well as improvements in hemoglobin were greater in patients with wild-type CXCR4

# Progression free survival according to MYD88 and CXCR4 mutation status



- MYD88<sup>Mut/WT</sup>CXCR4<sup>WT</sup>
- MYD88<sup>Mut/Mut</sup>
- --- MYD88<sup>Mut/WT</sup>CXCR4<sup>Mut</sup>

# Treatment of Resistant WM with CXCR4 inhibitors

 Dana Farber - Phase II clinical trial of plerixafor with ibrutinib in WM patients and to evaluate their outcome based on CXCR4 mutation status (future)

ALDENSTRÖM'S MACROGLOBULINEMIA

• This slide is placed later in the syllabus\*

International Workshops on

#### Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- New second-generation small-molecule oral BTK inhibitor
- Blocks signaling that leads to growth inhibition and cell death in malignant B-cells
- Potentially better safety and tolerability, inhibition of BTK
- Potentially has less off target inhibition of other kinases, including EGFR, ITK, JAK3, HER2 and TEC, which may be associated with ibrutinib side effects
- Potential for more complete and sustainable inhibition of BTK and better quality of response
- Other BTK inhibitors (CT-1530) are coming as well

Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- Results: 24 patients treated
- Median age was 66 years
- 96% were previously treated with a median 2 lines of therapies
- BGB-3111 well tolerated with 71% reporting no drug related AE>Gr 1 severity within the first 12 weeks of therapy

ldenström's Macroglobulinemia

International Workshops on

# Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- 2 SAEs assessed as possibly related to BGB-3111 (Gr 2 atrial fibrillation, Gr 3 cryptococcal meningitis); in both cases, BGB-3111 was temporarily held but safely resumed
- 2 pts developed AF
- No serious hemorrhage (>Gr 3 or CNS hemorrhage of any grade) was reported
- Most frequent AEs (≥20%) of any attribution (all Gr 1/2) were upper respiratory infection (25%), diarrhea (25%),and nausea (21%)

**ALDENSTRÖM'S MACROGLOBULINEMIA** 

# Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- At median follow-up of 7.6 months the response rate was 92% (22/24)
- Major response rate was 83% (20/24)
- VGPR (>90% reduction in IgM and reduction in extramedullary disease) in 33% (8/24)
- PR (50-90% reduction in IgM and reduction in extramedullary disease) in 50% (12/24) pts
- Median time to initial response and major response were 29 days and 34 days
- IgM decreased from median of 29.9g/l at baseline to 3.0g/L
- Hemoglobin increased from a median of 10.1g/dL at baseline to 13.5g/L

**WALDENSTRÖM'S MACROGLOBULINEMIA** 

International Workshops on

# Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- Only one patient discontinued BGB-3111, due to exacerbation of pre-existing bronchiectasis while in VGPR
- There have been no cases of disease progression
- Analysis of response by genomic characteristics (including MYD88 and CXCR4 mutational status) is ongoing.

**Conclusions:**BGB-3111 is well-tolerated and highly active in WM. The depth and quality of responses, as reflected by the VGPR rate of 33%,warrant a randomized comparison against ibrutinib in pts with WM.

DENSTRÖM'S MACROGLOBULINEMIA

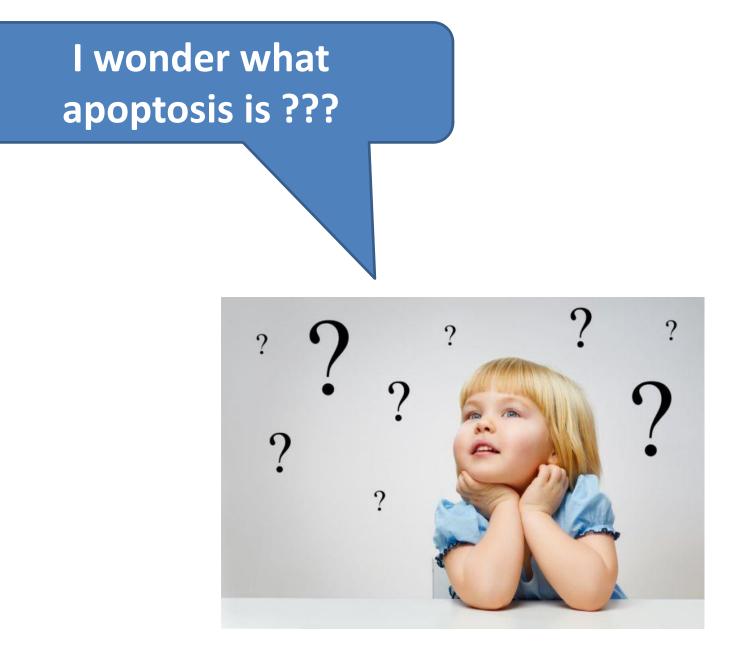
International Workshops on

#### Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

- Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with WM
- ClinicalTrials.gov Identifier: NCT03053440
- Newly diagnosed or previously treated WM (167 patients)
- Opening around the world
- Primary study question is the percentage of study patients achieving either CR or very good partial response (VGPR)

### **Other BTK inhibitors studying WM**

- ACP-196 (Acalabrutinib) in Combination With Pembrolizumab, for Treatment of Hematologic Malignancies (KEYNOTE145) ClinicalTrials.gov Identifier: NCT02362035
- SNS 062: Safety, PK, PD, and Antitumor Activity of SNS-062 in B Lymphoid Cancers. NCT03037645
- CT 1530: Study of Safety, Efficacy and Pharmacokinetics of CT-1530 in Patients With Relapsed or Refractory B Cell Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, and Waldenstrom's Macroglobulinemia. NCT02981745

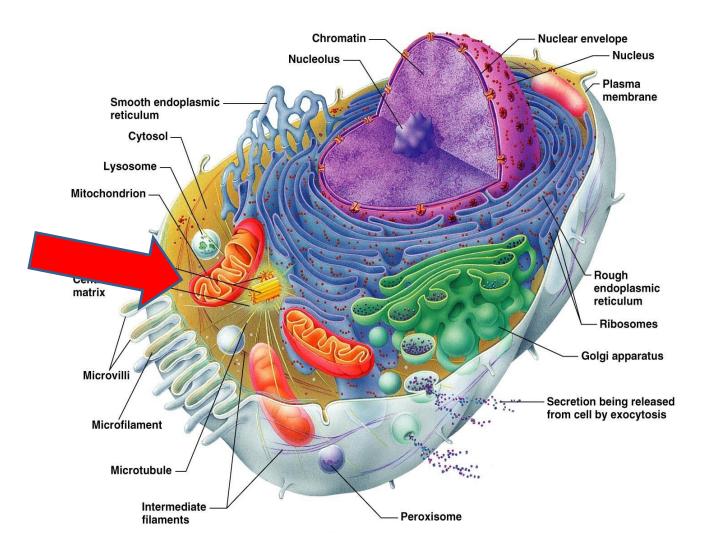


## I am done with my role here. It's time for me to die now.

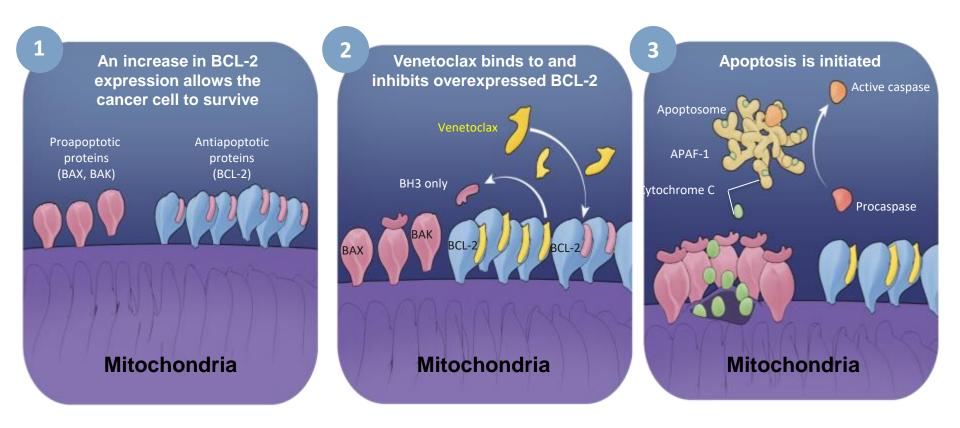
I will miss you my altruistic brother.

Cells have predefined suicidal pathways, that are activated in case of cellular damage, or after accomplishment of a particular role.

# 3D picture of cell



# Venetoclax: Mechanism of Action



Kumar S, et al. ASCO 2015. Abstract 8576. Reproduced with permission.

# Novel Therapeutic approaches for WM: antiBCL-2

- Dysregulation of anti-apoptotic(anti-death) protein BCL-2 is key factor causing of many types of non-Hodgkin lymphoma
- Oral BCL-2 antagonist venetoclax has high efficacy in patients with high risk relapsed or refractory chronic lymphocytic leukemia, leading to FDA approval in this patient population
- Promising suggestions of activity seen in the first few patients with WM treated with venetoclax
- New studies of venetoclax monotherapy in WM and novel agent combination regimens in NHL and WM that hold promise to achieve deeper and more durable remissions

**VALDENSTRÖM'S MACROGLOBULINEMIA** 

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# Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

- 106 patients but only 4 with WM
- Grade 3 to 4 side effects reported in 59 patients (56%), primarily low blood counts
- Response rate varied by disease type (44% MCL, 75%; FL, 38%; DLBCL, 18%)
- For the 4 Waldenstrom's patients the ORR was 100% (no complete remissions)
- DOR for the four patients with WM was 11.1, 12.4, 38.2, and 41.5 months

## Phase 2 Study of Venetoclax (ABT-199) In Patients With Relapsed Or Refractory Waldenström Macroglobulinemia

- ClinicalTrials.gov Identifier: NCT02677324
- Non randomized
- Primary Outcome Measures: The Overall Response Rate (ORR) Of ABT-199 In Symptomatic WM Patients Study Time Frame: 2 years
- Centers: Bing Center-Dana Farber Boston Massachusetts, Weill Cornell Medical College- New York City, City of Hope Duarte California, Stanford-San Francisco



# YOU ARE LEAVING<br/>THE AMERICAN SECTOR<br/>BЫ BЫE3ЖАЕТЕ ИЗ<br/>АМЕРИКАНСКОГО СЕКТОРАVOUS SORTEZ<br/>DU SECTEUR AMÉRICAINSIE VERLASSEN DEN AMERIKANISCHEN SEKTOR<br/>US AMY

## Novel therapeutic approaches in WM: Checkpoint inhibitors Stephen Ansell Mayo Clinic

- Interactions between programmed death 1 (PD-1) and its ligands (PD-L1 and PD-L2) have been shown to be an important checkpoint in immune regulation
- Role of PD-1/PD-1 ligand interactions in WM is not really known
- PD-L1 and PD-L2 expression is increased in some studies of WM samples

**ALDENSTRÖM'S MACROGLOBULINEMIA** 

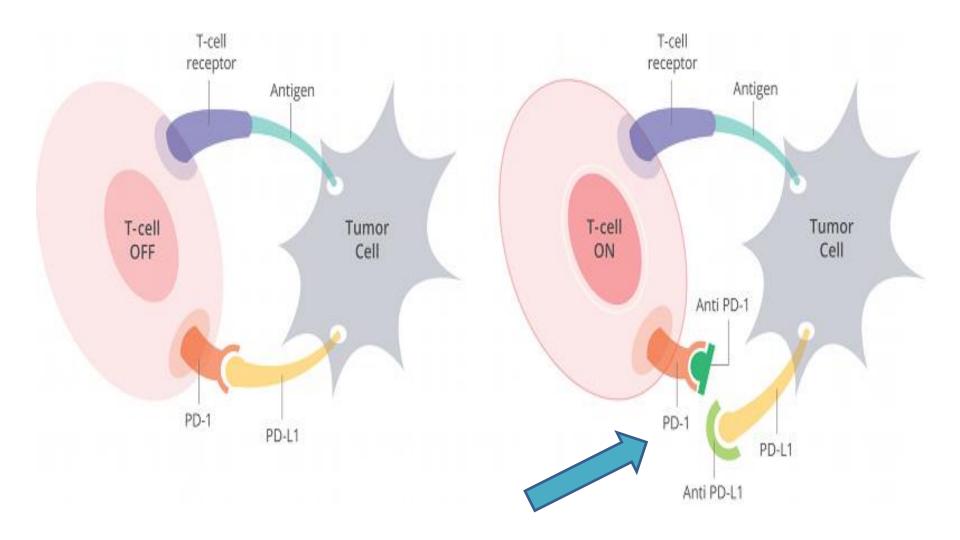
- Blocking PD-1/PD ligand interactions may therefore be a potential therapeutic strategy in patients with WM
- Clinical trials of anti-PD-1 antibodies are in progress

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#### Immune cells (t-cells) fighting cancer cells



#### How do anti PD1 and anti PDL1 antibodies work?



## PD1 or PD-L1 inhibitors / Checkpoint inhibition

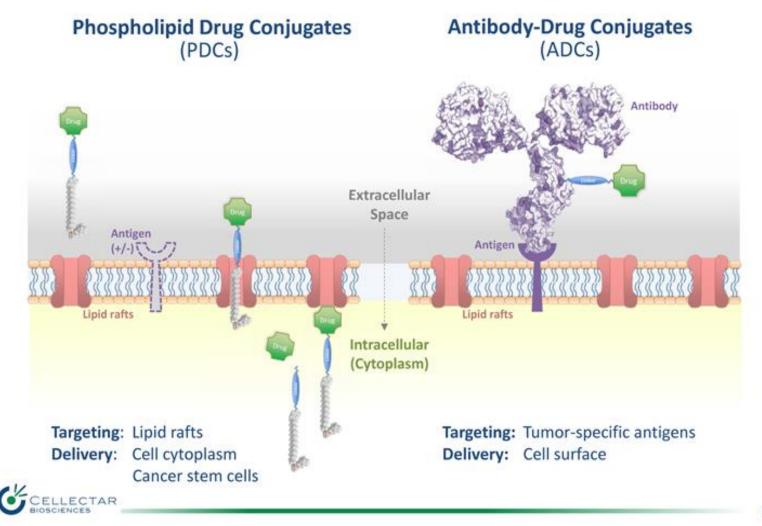
- Pembrolizumab and Ibrutinib in Treating Patients With Relapsed or Refractory Non-Hodgkin Lymphoma **NCT02950220** Ohio State
- Pembrolizumab Alone or With Idelalisib or Ibrutinib in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Other Low-Grade B-Cell Non-Hodgkin Lymphomas NCT02332980 Mayo Clinic
- ACP-196 (Acalabrutinib) in Combination With Pembrolizumab, for Treatment of Hematologic Malignancies (KEYNOTE145) NCT02362035
- Nivolumab and Lenalidomide in Treating Patients With Relapsed or Refractory Non-Hodgkin or Hodgkin Lymphoma ClinicalTrials.gov Identifier: NCT03015896 – Ohio State

# Study of CLR 131 in Relapsed or Refractory Select B-Cell Malignancies

# • NCT02952508

- Antibody radioisotope conjugate
- Many years of scientific data supporting the sensitivity of blood cancers to radiotherapeutics
- Ideally, a cancer-targeted radiopharmaceutical would deliver lethal radiation dose to all tumor cells while sparing critical normal tissues from consequential radiation dose
- CLR 131 is an investigation into this approach by selectively depositing cytotoxic radiation.

#### PDC Cancer-Targeting and Payload Delivery



# CLR-131

- ClinicalTrials.gov Identifier:
- NCT02952508
- Study of CLR 131 in Relapsed or Refractory Select B-Cell Malignancies

Are research studies and development of new drugs really making a difference ?

- YES !
- 5784 WM patients diagnosed between 1991 and 2010
- 1991-2000 compared to 2001-2010
- Median Overall Survival for the 1991–2000 and the 2001–10 cohorts was 6 and 8 years, respectively

Jorge J. Castillo, British Journal of Haematology, 2015, 169, 81–89

