ABREOS BIOSCIENCES

The Need for Precision Dosing of Biologic Therapeutics

October 13, 2016

Bradley Messmer, PhD

Founder & CEO, Abreos Biosciences

Faculty, Moores UCSD Cancer Center

Company Introduction

2013
Founded

Dr. Bradley Messmer, founder and CEO of Abreos, invented the core technology while on the faculty at UCSD.

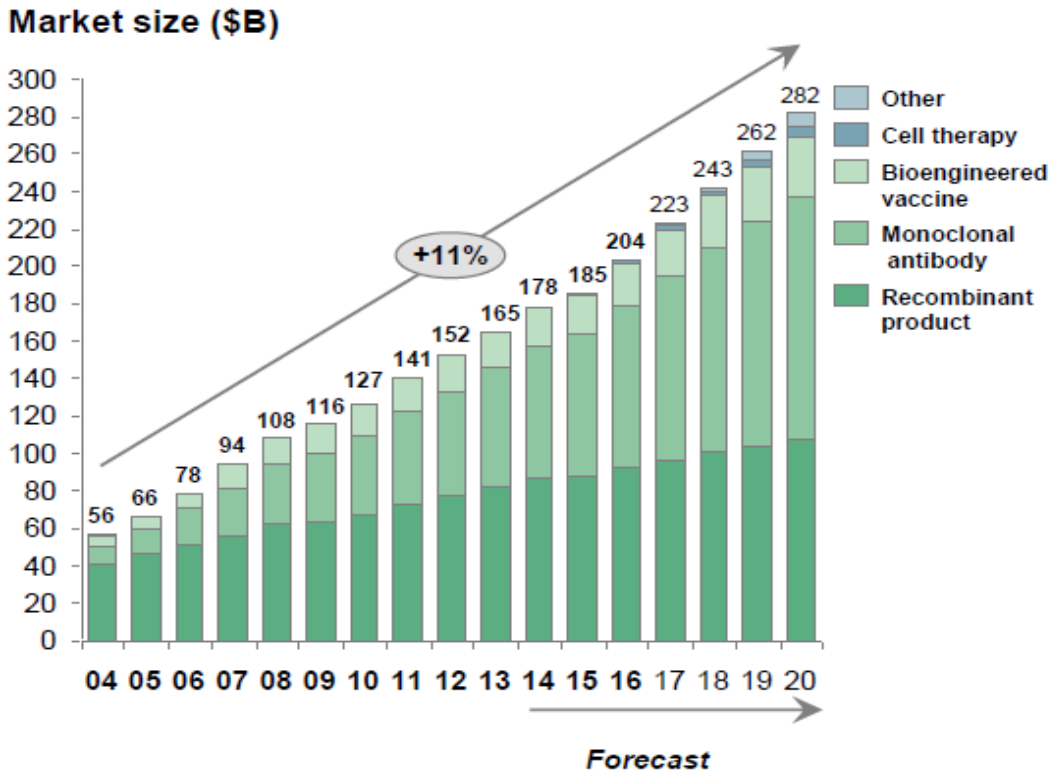
6
Employees

Abreos has 4 PhDs on team and extensive experience in both academic and industry settings.

Clinical
Current Stage

Abreos is finalizing the design of its first POC device and has recently launched its first laboratory test.

Success of Biologic Therapies

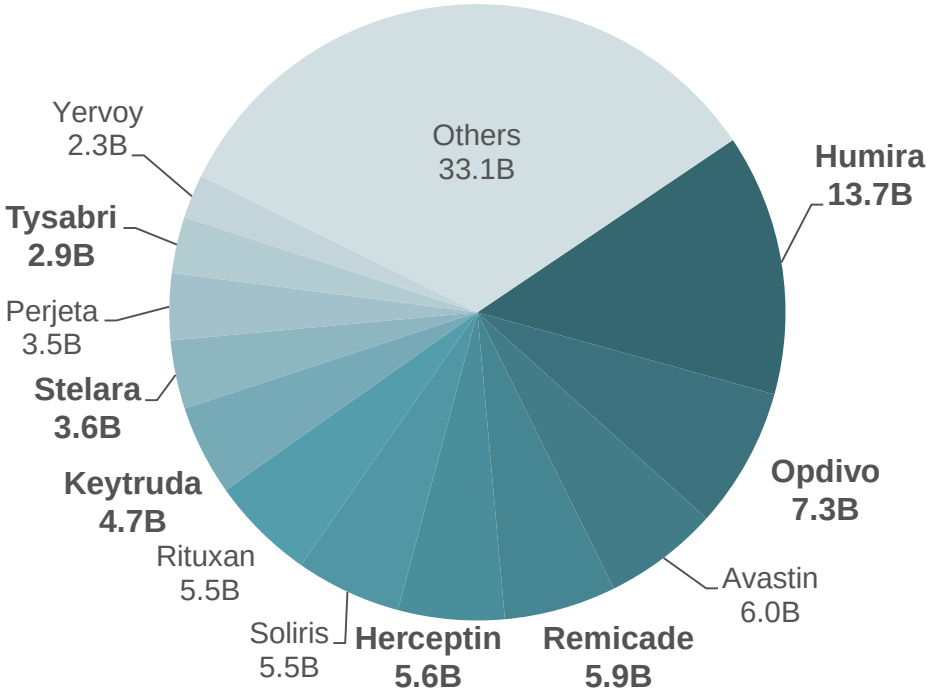


- Biologic therapeutics represent one of the deepest penetrations of biotechnology into the therapeutic field
- Biologics are expected to outpace overall pharma spending growth and represent 19-20% of the total market value by 2017
- Growth is driven by monoclonal antibodies (mAbs) and human insulin, with four out of the top five biologics in 2012 being mAbs

Source: Evaluate Pharma 2015, BCG Analysis, IMS Health The Global Use of Medicines: Outlook Through 2017

mAb Market

2020 Market = $100B



TYSABRI (natalizumab)
$5,200/dose

HUMIRA adalimumab
$1,300/dose

Stelara (ustekinumab)
$8,200/dose

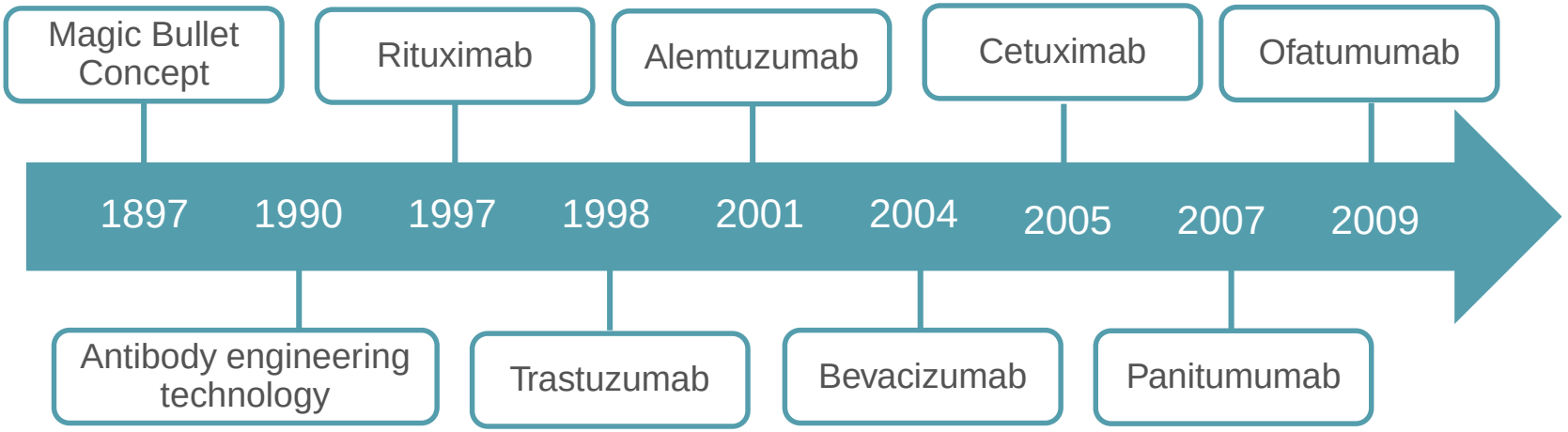
OPDIVO (nivolumab)
$4,400/dose

KEYTRUDA (pembrolizumab) Injection 100 mg
$5,100/dose

Herceptin trastuzumab
$3,800/dose

Remicade INFLIXIMAB
$1,000/dose

mAbs: Forefront of Targeted Therapies



Drug	Diagnostic Target	Diagnostic
Herceptin® trastuzumab	HER2 overexpression Her-2 gene amplification	Companion HER2 IHC, Her-2/Neu FISH or CISH (Dako, Ventana, Abbott, Biogenex, Life Tech, Leica)
KEYTRUDA® (pembrolizumab) Injection 100 mg	PD-L1 expression	Companion PD-L1 IHC (Dako)
OPDIVO® (nivolumab)	PD-L1 expression	Complementary PD-L1 IHC (Dako)
ERBITUX® CETUXIMAB	KRAS mutation EGFR expression	Companion KRAS PCR & EGFR IHC (Roche, Qiagen, Dako)

Source: FDA, Public information available on company websites

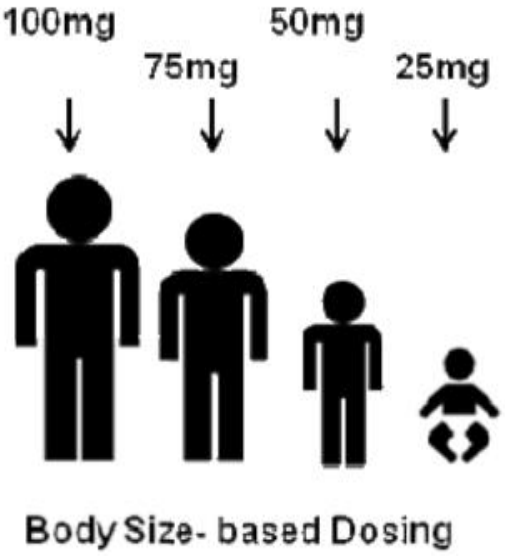
Biologic Dosing

Biologic dosing follows one of two methods

One-Dose-Fits-All

Many mAbs, like Tysabri and Gazyva, are prescribed in a one-dose-fits-all regimen

Body Mass/Surface Area Adjusted

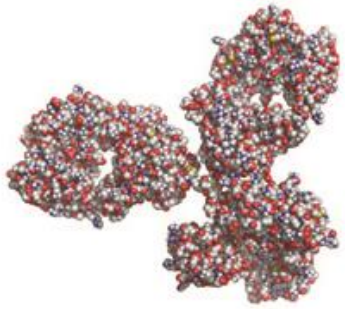


Body Size- based Dosing

Even those that are body mass or surface area adjusted ignore enormous inter-individual PK variability

Biologic PK Advantages

Biologic Drugs

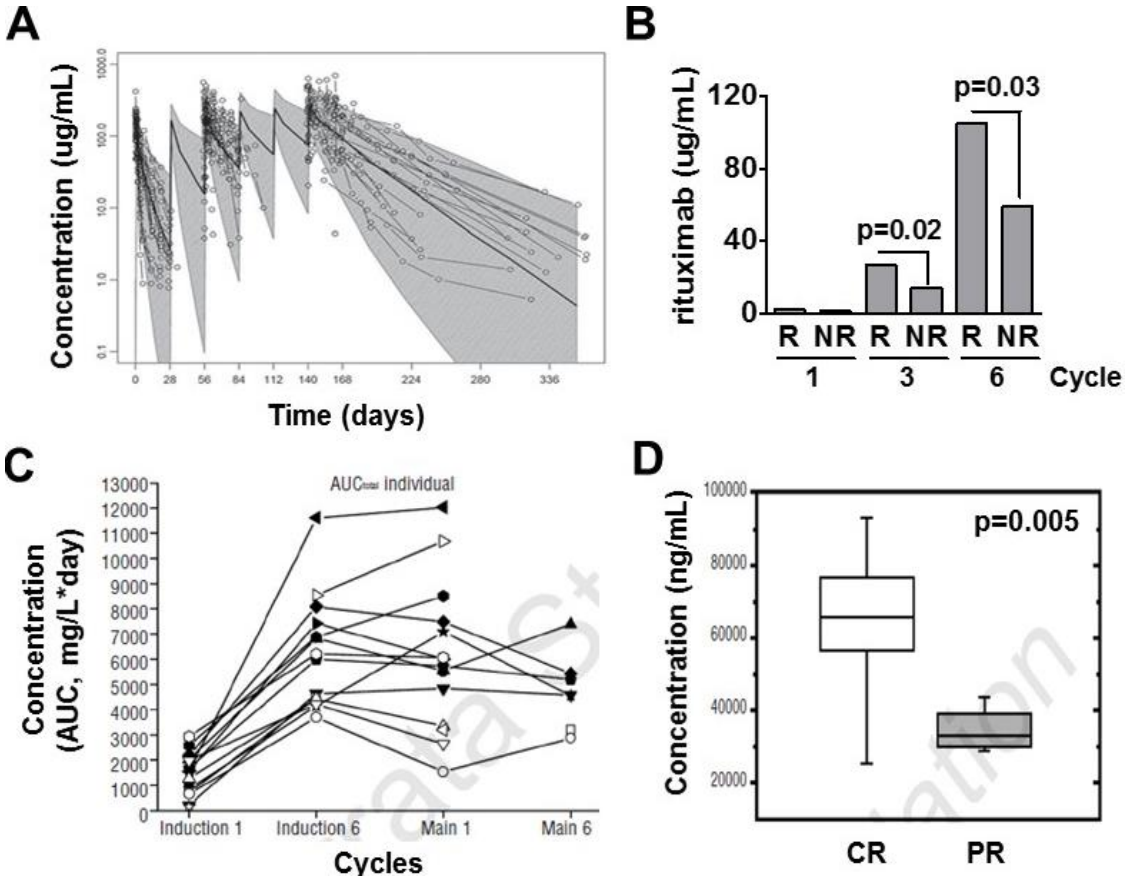


VS

Small Molecules

1. Directly injected or infused
2. Complete bioavailability that usually supersaturates target
3. Long half-lives
4. Rarely have acute dose limiting toxicity

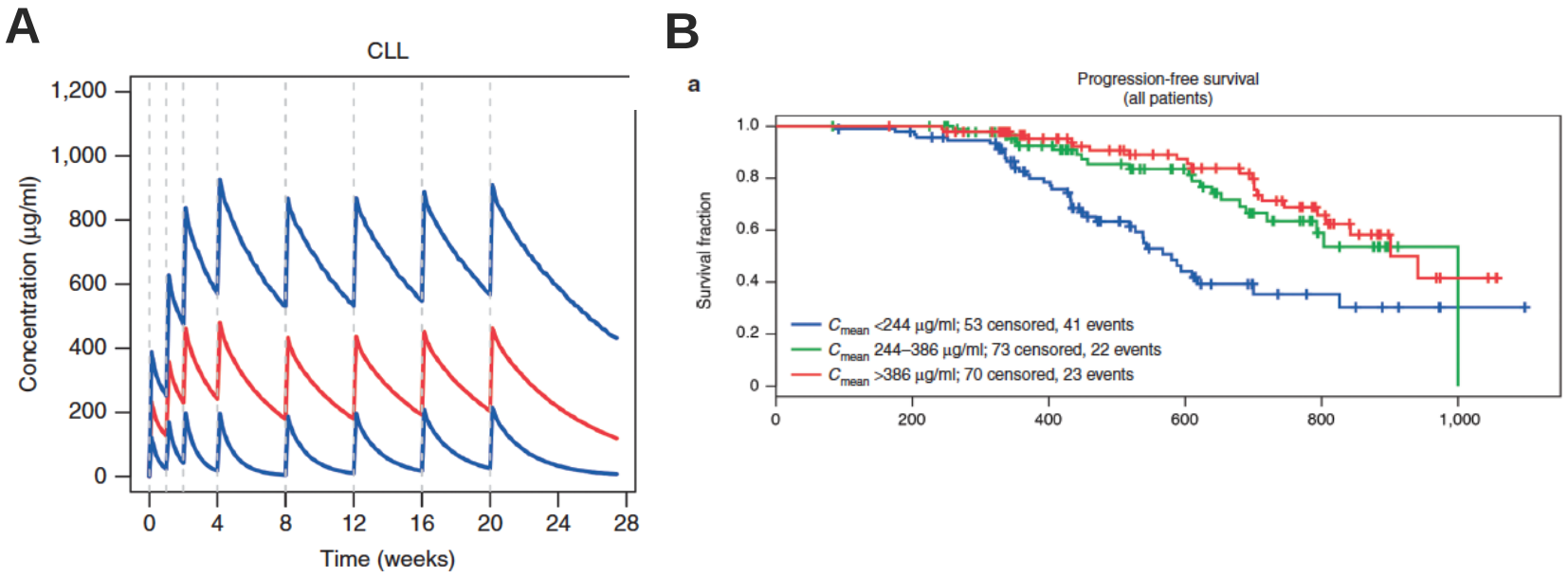
Rituxan in CLL/NHL



- Significant inter-individual variability in rituximab blood levels has been observed in both CLL and NHL patients
- Lower drug levels or exposure over time are associated with poorer clinical outcomes

Source: Li et al. J Clin Pharmacol (2012), Jager et al. Haematologica (2012)

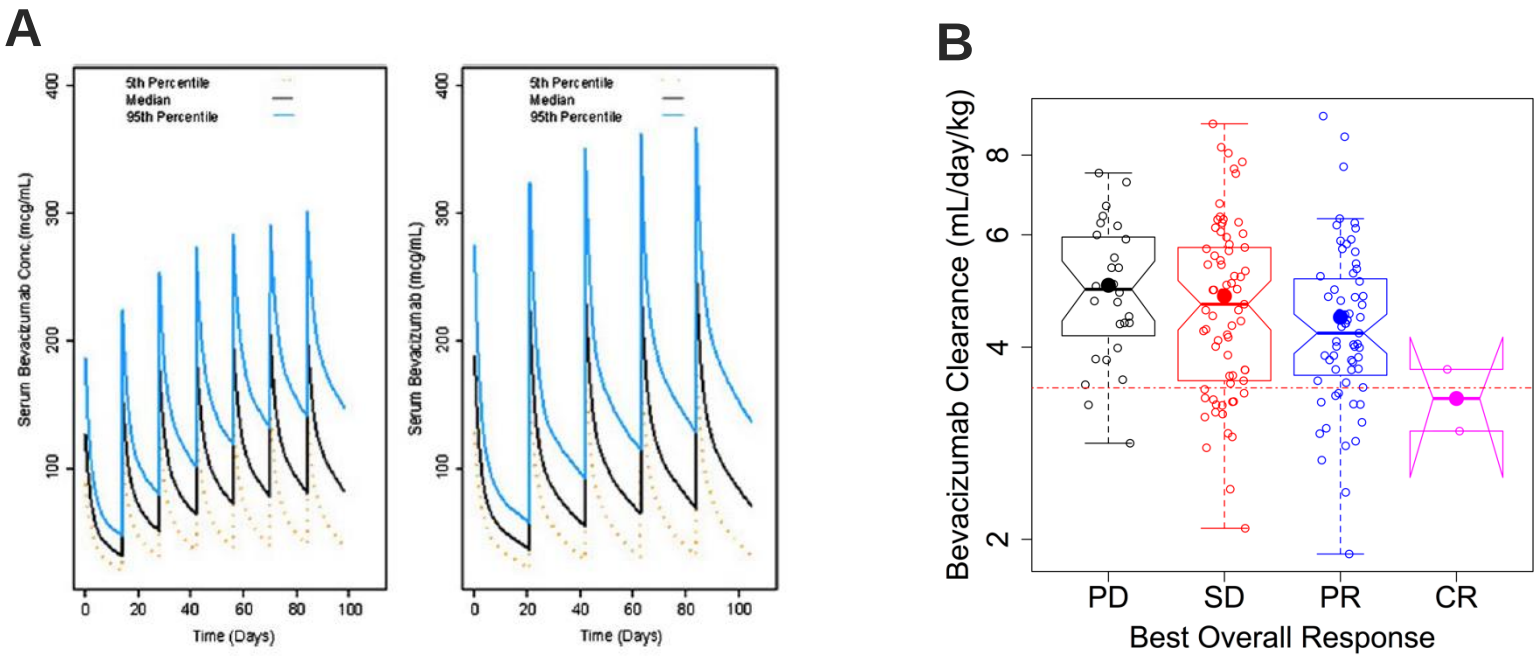
Gazyva in CLL



- Predicted serum levels of obinutuzumab (Gazyva), new anti-CD20 mAb, vary by orders of magnitude in CLL patients
- Progression-free survival is the shortest for CLL patients with the lowest blood levels of obinutuzumab (blue) compared to intermediate (green) and high levels (red)

Source: Gibiansky et al. Pharmacometrics & Systems Pharmacology (2014)

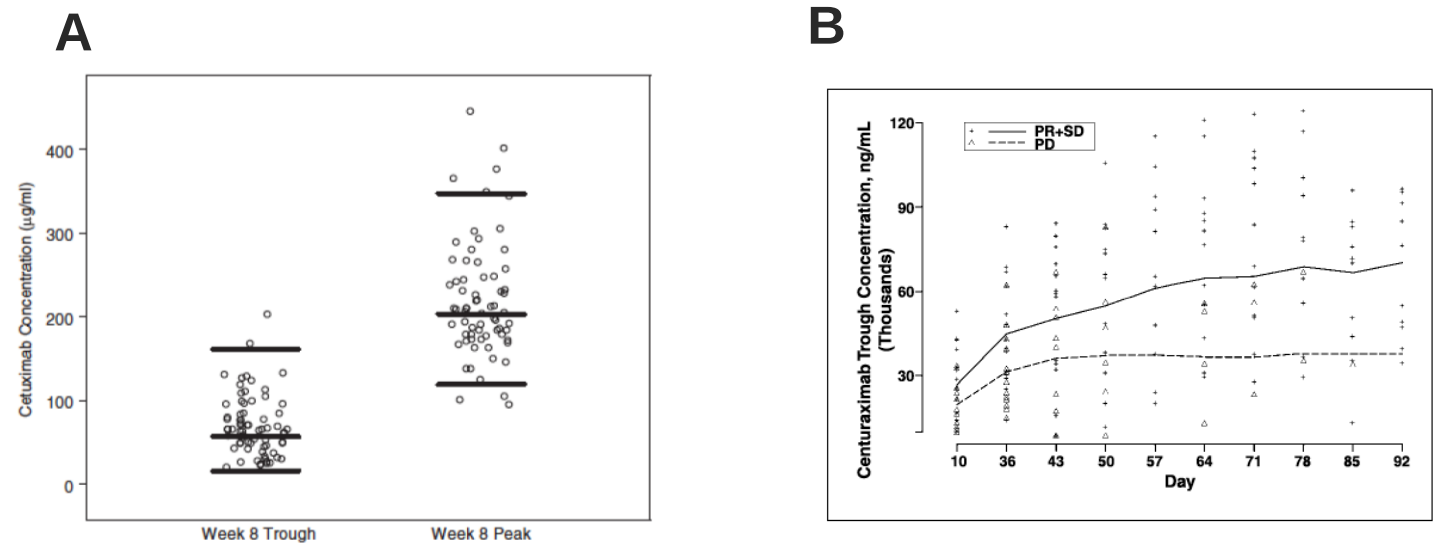
Avastin in solid tumors



- Model predicted steady-state concentrations of bevacizumab (Avastin) in in patients with solid tumors also highly variable
- Gastric cancer patients with the slowest bevacizumab clearance rate, i.e. highest drug levels, have better outcomes

Source: Lu et al. Cancer Chemotherapy and Pharmacology (2008), Han et al. The AAPS Journal (2014).

Erbitux in epithelial malignancies



- Widespread variation in observed and simulated trough and peak levels of cetuximab (Erbitux) levels in squamous cell head and neck cancer patients
- For epithelial malignancies, cetuximab trough levels are lower in non-responders (lower dash line, progressive disease (PD)), as opposed to responders (upper line partial response (PR) + stable disease (SD))

Source: Dirks et al. Journal of Clinical Pharmacology (2008), Fracasso et al. Clinical Cancer Research (2007).

Pharmacogenomics?

~~Pharmacogenomics~~

Pharmacoimmunogenomics?

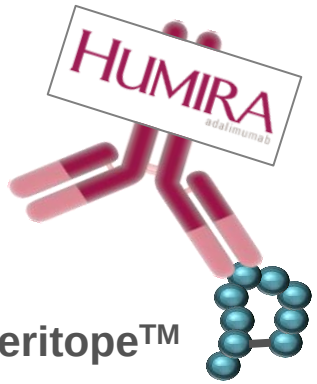
Methods of detecting mAb in biological samples

Technique	Detection	Feasibility	Expense	Speed	Activity
Anti-Id ELISA	Specific mAb	Clinical Lab	Low	Hours	No
Anti-antigen ELISA	Specific mAb	Clinical Lab	Low	Hours	Yes
Label free LBA	Specific mAb	Research lab	High	Hours	Yes
Mass Spec	Specific mAb	Research lab	High	Hours	No
Flow cytometry	Specific mAb	Clinical Lab	Medium	Hours	Yes
Abreos Veritope ELISA	Specific mAb	Clinical Lab	Low	Hours	Yes
Abreos Veritope LFA	Specific mAb	Point-of-Care	Minimal	Minutes	Yes

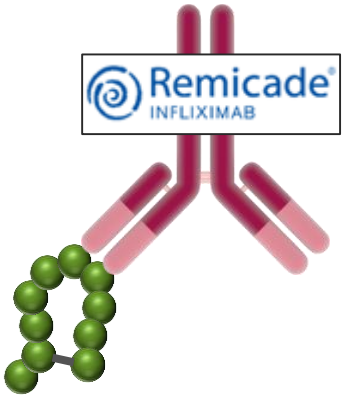
LBA: ligand binding assay such as surface plasmon resonance

Simple, rapid, and affordable tools for dose monitoring are now available

Core Technology: Veritope™

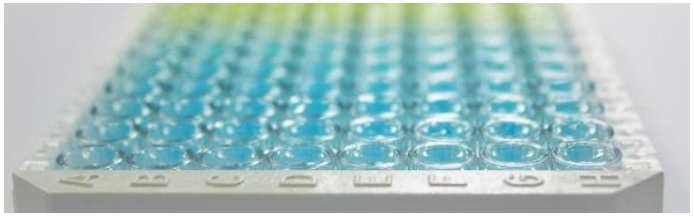


Veritope™

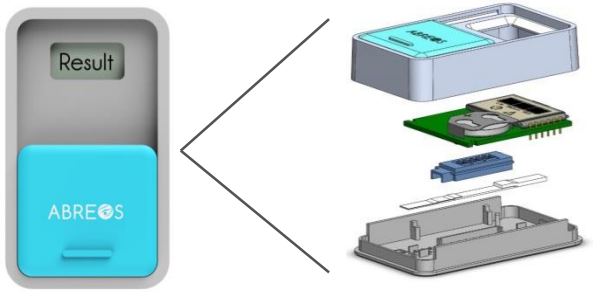


Veritopes™ are peptides that specifically detect a given biological drug (novel or biosimilar)

Laboratory Developed Test
Lab-based ELISA



Point of Care Device
Disposable, cloud enabled system



Case #1: Herceptin Clinical Trials in Gastric Cancer

2010: FDA approved

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang, Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†*

2013: Dosing questioned

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

Jun Yang PhD, Hong Zhao PhD, Christine Garnett PharmD, Atiqur Rahman PhD, Jogarao V. Gobburu PhD, William Pierce PharmD, Genevieve Schechter MD, Jeffery Summers MD, Patricia Keegan MD, Brian Booth PhD, Yaning Wang PhD

Case #1: Herceptin Clinical Trials in Gastric Cancer

Population pharmacokinetics and exposure–response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer

Table 2 Percentage of patients in each category of best overall tumor response by quartile of C_{min} at steady state

Category of C_{min} at steady state	Percentage of patients by category of best overall tumor response			
	CR	PR	SD	PD
<17.3 µg/mL	5.6	40.7	22.2	31.5
≥17.3 and <27.6 µg/mL	5.5	49.1	36.4	9.1
≥27.6 and <36.9 µg/mL	5.5	49.1	36.4	9.1
≥36.9 µg/mL	8.5	55.9	27.1	8.5

C_{min} minimum concentration, *CR* complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

Source: Cosson et al. Cancer Chemotherapy and Pharmacology (2014)

Same as chemo alone – no benefit

Case #1: Herceptin Clinical Trials in Gastric Cancer

Simulated **Observed**

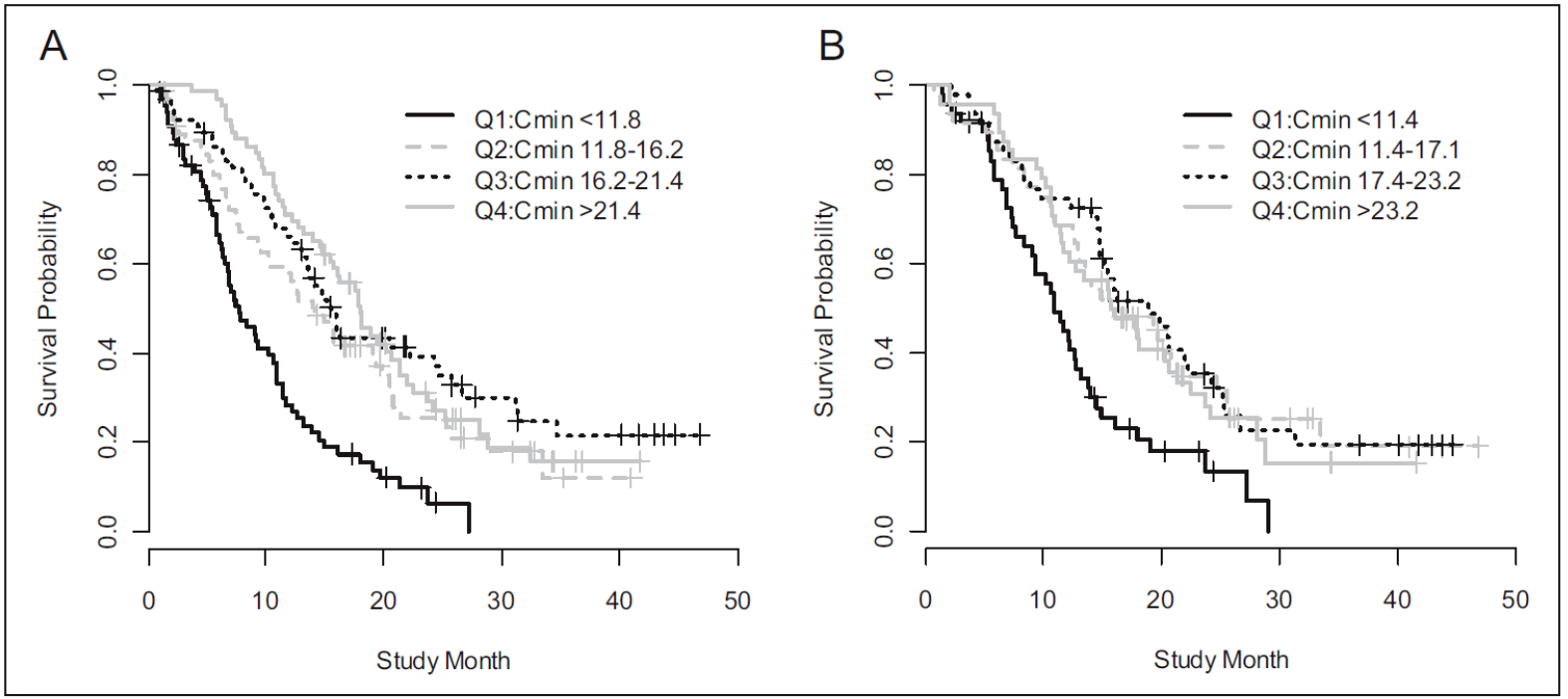


Figure 1. Kaplan-Meier curves in patients divided into groups according to quartile of trough trastuzumab concentrations in cycle 1 (A: simulated, n = 266; B: observed, n = 193). Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Survival probability is influenced by trough drug levels: lowest drug levels (darkest line) are associated with shortest survival

Source: Yang et al. The Journal of Clinical Pharmacology (2012)

Case #1: Herceptin Clinical Trials in Gastric Cancer

- 2015 Herceptin sales for gastric cancer: **$566M**
- Standard dosing has necessitated a new phase IIIb trial

HELOISE Study: A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer

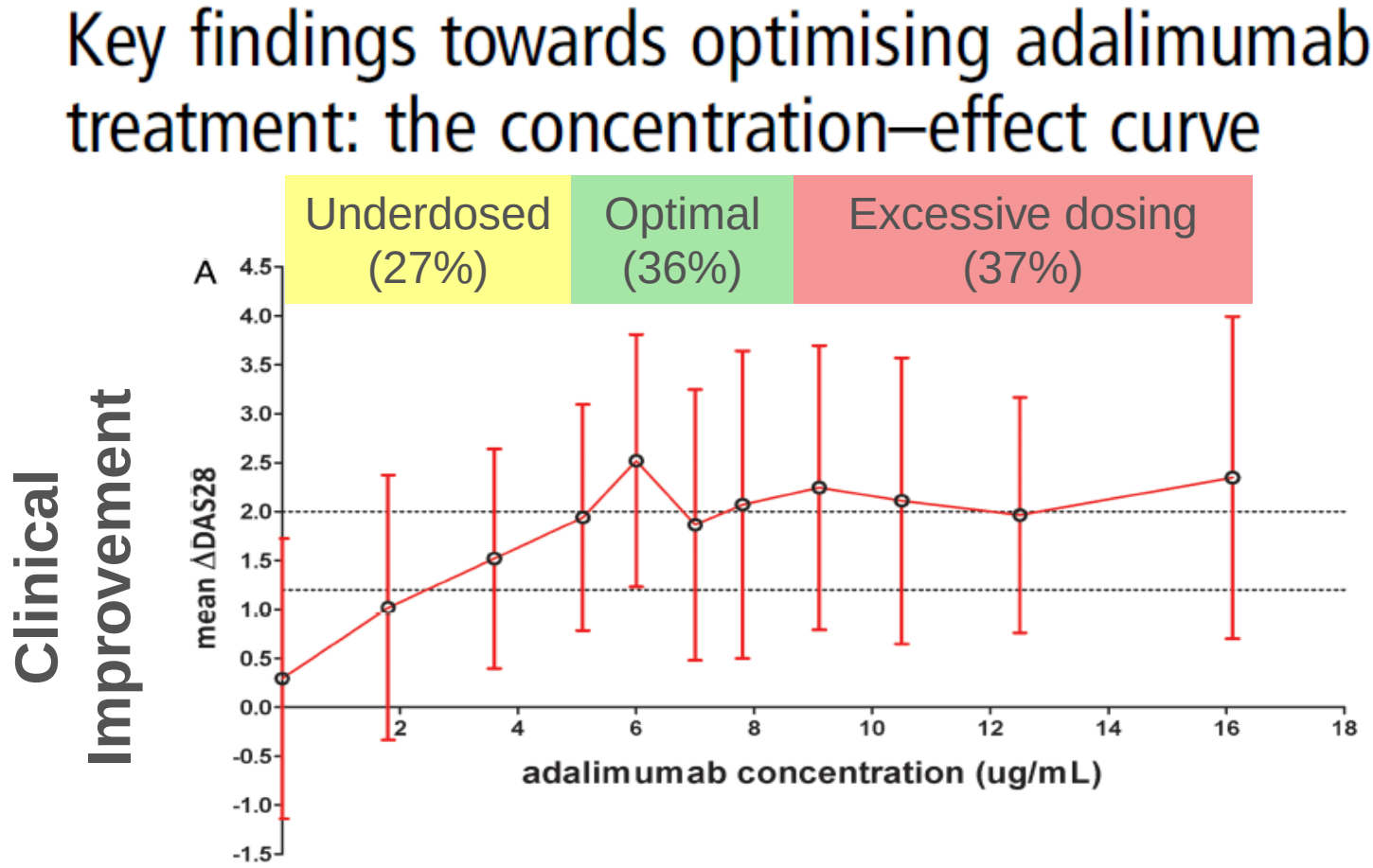
- Even if successful, the trial will result in excessive dosing of 75% of patients and increase cost of therapy

Precision dosing would eliminate excess cost and improve cost effectiveness

Case #2: Humira

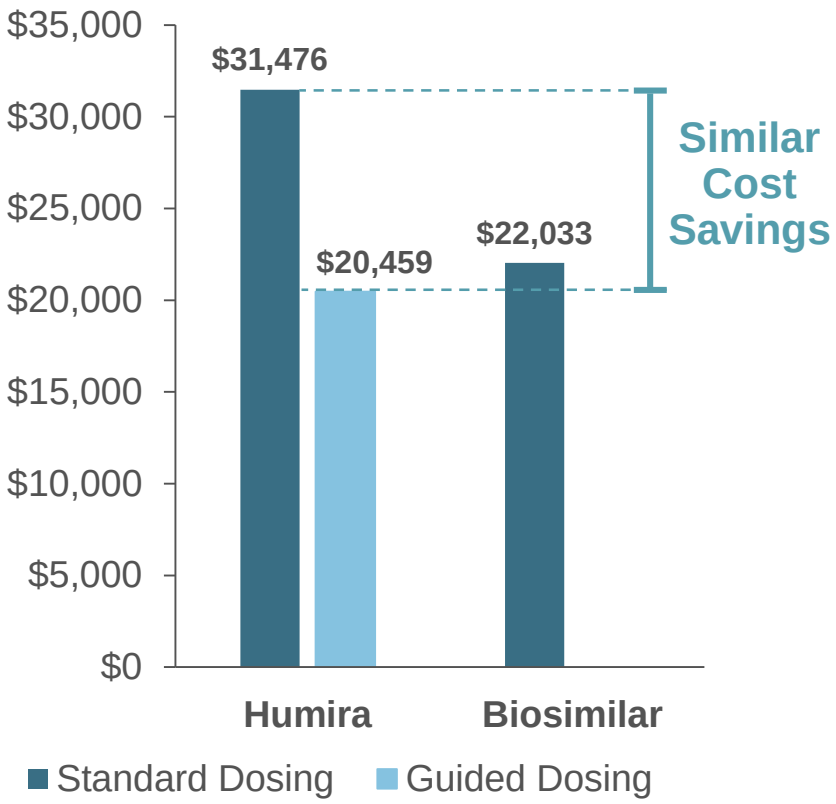
- Top selling biologic: $14B/year
- Each dose costs $1,300
- Self administered every two weeks
- Cost per patient per year = **$31,476**

Case #2: Humira



Source: Pouw et al., Ann Rheum Dis (2015)

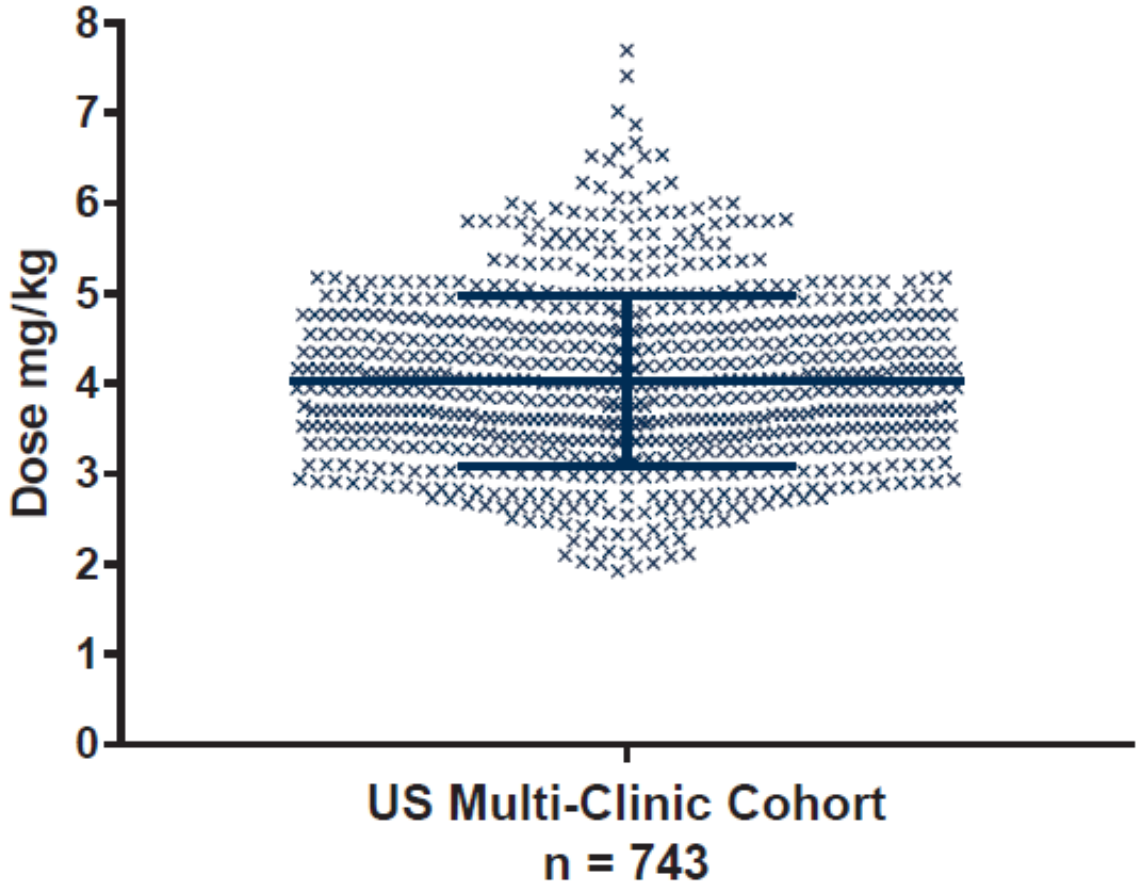
Case #2: Humira



- Syringe preloaded with a standard dose administered biweekly
- Average annual cost per patient is **$31,476**
- Guided dosing could reduce annual per patient cost by **25%-35%**
- Biosimilars are predicted to be ~30% cheaper than reference drug

Guided dosing of reference drug eliminates economic advantage of biosimilars

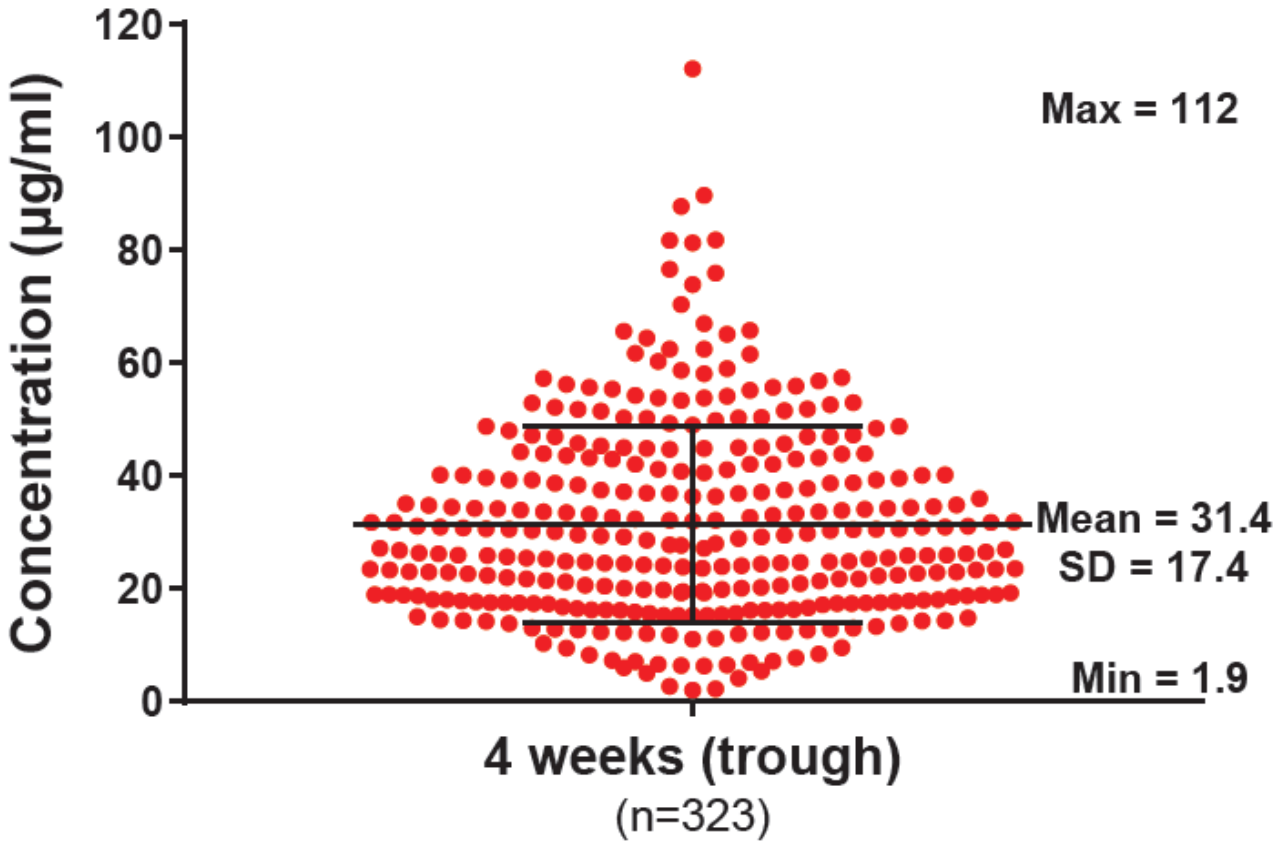
Case #3: Tysabri Variation & PML Risk



Large inter-patient variability in actual amount of Tysabri administered when expressed relative to patient's weight

Source: J. Foley et al., American Academy of Neurology Meeting (2016)

Case #3: Tysabri Variation & PML Risk



Serum trough drug levels are highly variable with standard dosing of 300mg every 4 weeks

Source: J. Foley et al., American Academy of Neurology Meeting (2016)

Case #3: Tysabri Variation & PML Risk

Multiple sclerosis

RESEARCH PAPER

Extended interval dosing of natalizumab in multiple sclerosis

L Zhovtis Ryerson,[1] T C Frohman,[2] J Foley,[3] I Kister,[1] B Weinstock-Guttman,[4] C Tornatore,[5] K Pandey,[6] S Donnelly,[7] S Pawate,[8] R Bomprezzi,[9] D Smith,[10] C Kolb,[4] S Qureshi,[2] D Okuda,[2] J Kalina,[1] Z Rimler,[1] R Green,[6] N Monson,[2] T Hoyt,[3] M Bradshaw,[8] J Fallon,[1] E Chamot,[11] M Bucello,[4] S Beh,[2] G Cutter,[11] E Major,[12] J Herbert,[1] E M Frohman[2,13,14,15]

- Extended Interval Dosing (EID) has been proposed as potential risk mitigation strategy for natalizumab-induced PML
- Multi-center study in the US compared EID and standard interval dosing (SID) in higher risk patients

Source: Zhovtis Ryerson et al, Journal of Neurology, Neurosurgery, and Psychiatry (2016)

Case #3: Tysabri Variation & PML Risk

US cohort[1]	SID	EID
# PML cases	4	0
Total # patients	1093	905

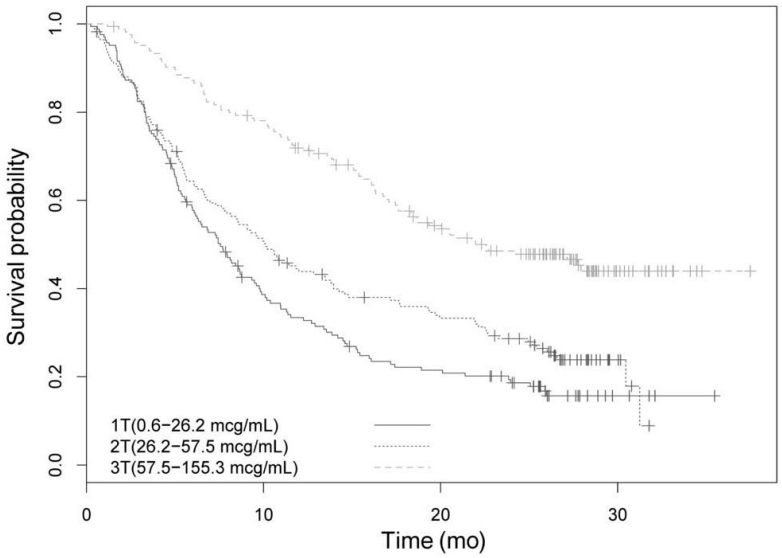
Italian cohort[2]	SID	EID
# PML cases	4	0
Total # patients	34	136

- In two independent clinical trials comparing EID with SID, PML cases were only identified in the SID cohorts

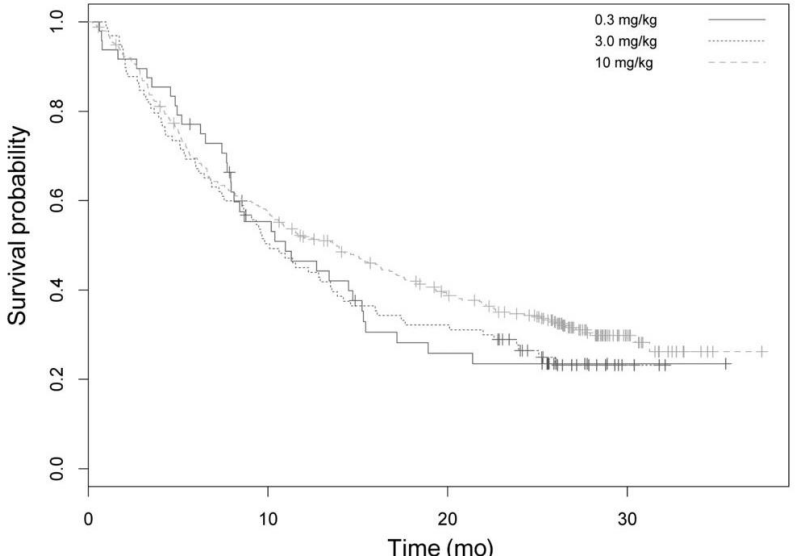
Source: Zhovtis Ryerson et al, Journal of Neurology, Neurosurgery, and Psychiatry (2016); Zhovtis Ryerson et al, ECTRIMS (2016)

Case #4: Yervoy for melanoma

Grouped by free serum concentration (tertiles)



Grouped by dose



- Minimal difference in dosing cohorts, but significant difference when grouped by drug level
- Combination therapy can potentially compound variation

Source: Feng, et al Clin Cancer Res (2013)

Case #5: Aducanumab for Alzheimer's

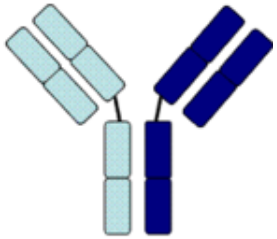
FierceBiotech

UPDATED: In a setback, Biogen's mid-range dose of aducanumab flops in Alzheimer's study

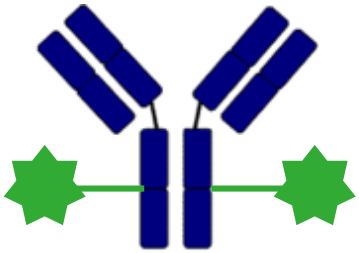
- 6-mg dose of the drug fell short of statistical significance and did worse than the 3-mg arm on the MMSE rating
- Preliminary Phase III results suggest exposure-dependent response in disease modification

Source: FierceBiotech

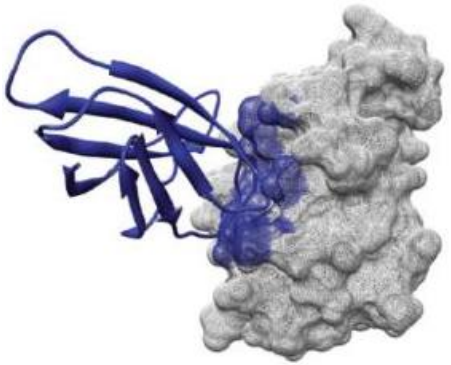
Growing Need for Precision Dosing



Bi-Specific Antibodies



Antibody-drug Conjugates



Engineered Scaffolds

- The need for dose monitoring is only going to grow as next generation biologics such as antibody-drug conjugates (ADC), bispecific antibodies, and engineered scaffolds are developed
- As the therapeutic power, and associated expense, increases, so will the need for precision dosing

Personalized Medicine Requires Precision Dosing

The **Right Drug** for the **Right Patient** at the **Right Dose**

Precision Dosing of Biologics will:

- Enhance disease management & improve clinical outcomes
- Minimize exposure to unnecessary side-effects
- Reduce healthcare costs

Better dosing makes better drugs

ABREOS BIOSCIENCES

For more information please contact:

Bradley Messmer Ph.D.
bmessmer@abreosbio.com
+1 858 -248-9253