Disclosures

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Advisory Boards:

Sandoz Novartis, Celtrion, Roche, Janssen, Acerta, Abbvie, Gilead, TG Therapeutics, Takeda, Verastem Oncology

Research Funding:

Celgene, Abbvie, Gilead, TgTherapeutics, Janssen, Acerta, Merck, Beigene, Pharmacyclics, Pfizer, Roche, Sandoz – Novartis, Takeda, Teva, Servier, Eisai, Celtrione, Dova Pharmaceuticals

Biosimilar Rituximab:
better acceptance through better understanding

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Polish Lymphoma Research Group

Number of oncology drugs available has grown rapidly in recent years

In the past 10 years, **>60% increase** in oncology drugs in development

In the past 5 years, **70 new treatments** have launched for >20 cancers

By 2020, it is estimated there may be **>100 new cancer drugs**

- Late phase oncology pipeline includes **270 biological agents**

16 gene therapies

86 new monoclonal antibodies

15 biosimilars of existing monoclonal antibodies

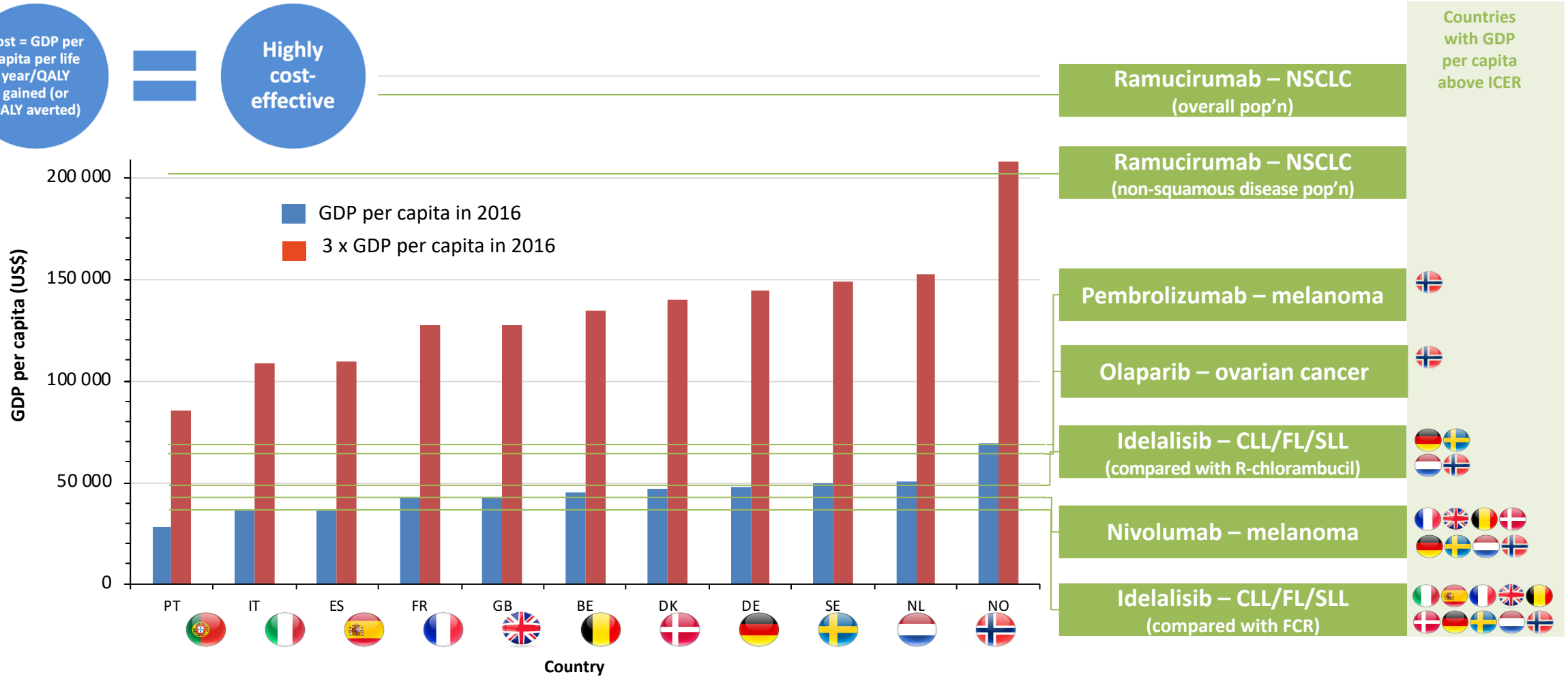
IMS Institute for Healthcare Informatics. 2016.

Cost-effectiveness does not equate to affordability

Some recently approved cancer drugs are not affordable in Europe

Cost < 3 x GDP per capita per life year/QALY gained (or DALY averted) = Cost-effective

Cost = GDP per capita per life year/QALY gained (or DALY averted) = Highly cost-effective



DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; GDP, gross domestic product; QALY, quality-adjusted life year; WHO, World Health Organization.

1. Simoens S. *Front Pharmacol*, 2010;1:115; 2. WHO. 2001.

More affordable medicines: generics and biosimilars

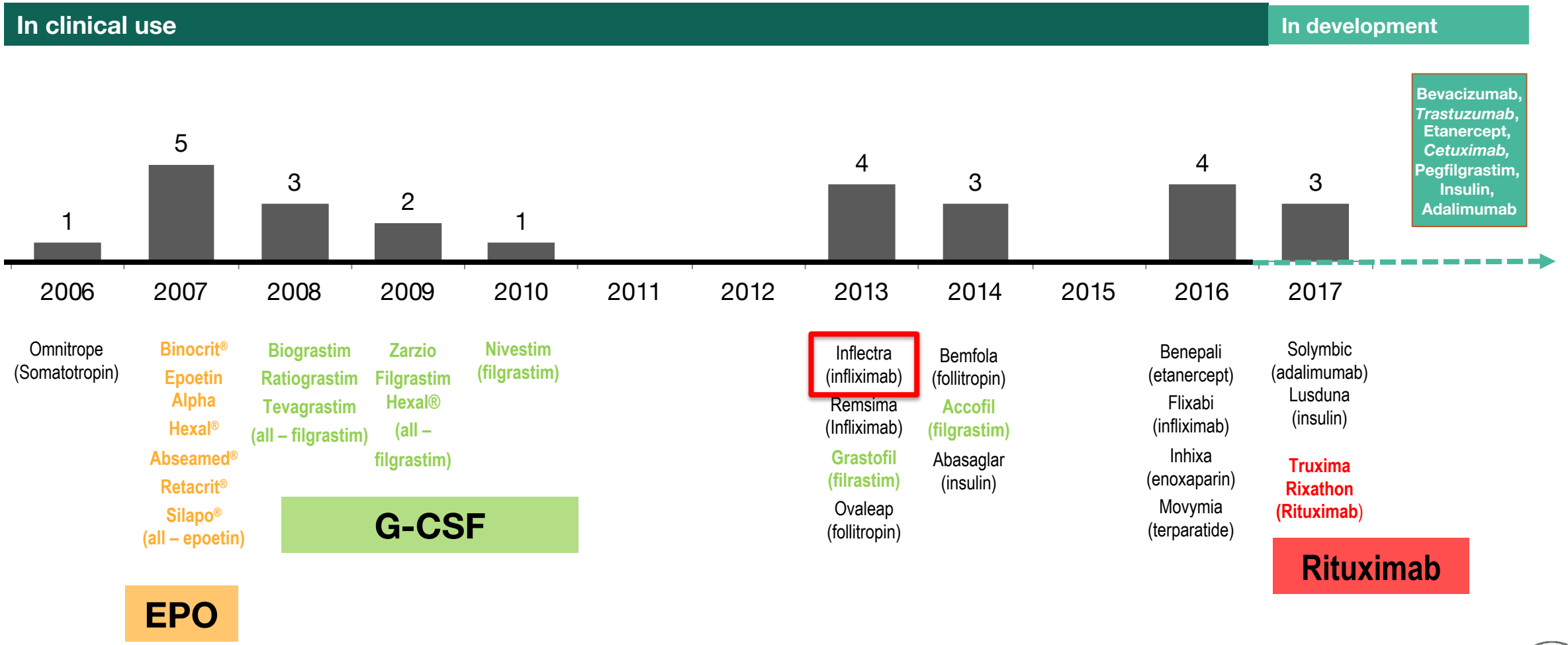
	Generic	Biosimilar
Molecular weight	Low	High
Structure	Simple, low potential for variation	Complex, high potential for variation
Synthesis	Chemical method producing identical molecules	Biological method producing highly similar proteins
Matches reference medicine in terms of	All attributes	Efficacy, PK/PD, safety and immunogenicity, as demonstrated by comprehensive preclinical and clinical comparability programme

- Use of these drugs may help to:[3]
  - **Combat the substantially increasing** costs of cancer drugs
  - **Increase access** to cancer treatment

PK/PD, pharmacokinetics/pharmacodynamics.

1. IMS Institute for Healthcare Informatics. 2016; 2. Rugo HS, et al. *Cancer Treat Rev*, 2016;46:73–9; 3. Leung LK, et al. *Chin J Cancer* 2016;35:91.

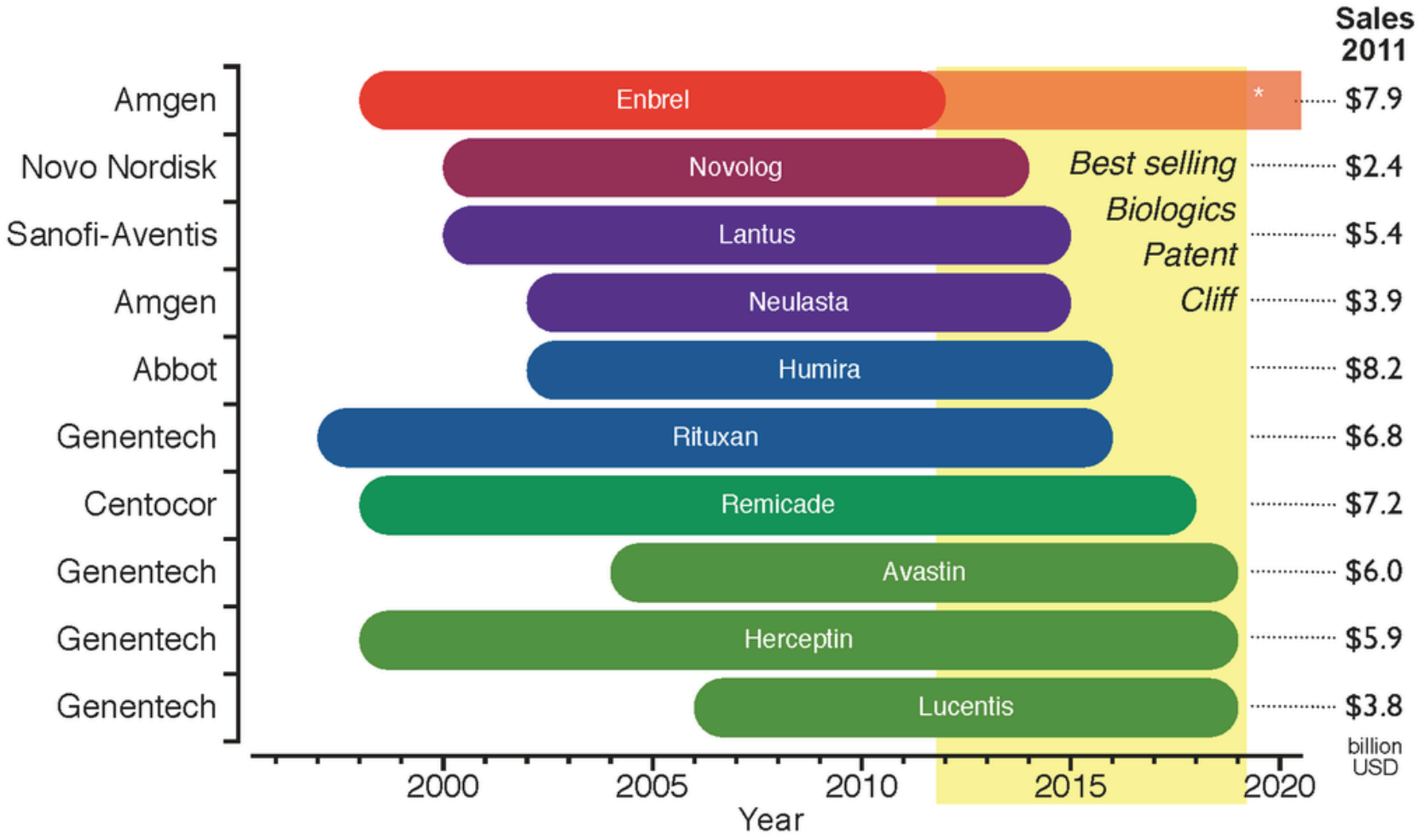
Biosimilars Approved by EMA



G-CSF: Granulocyte-colony stimulating factor; EMA: European Medicines Agency; EPO: epoetin.

EMA website. http://www.ema.europa.eu/ema/. Accessed 7 June 2017

Biosimilars which may be potentially developed in the next 10 years



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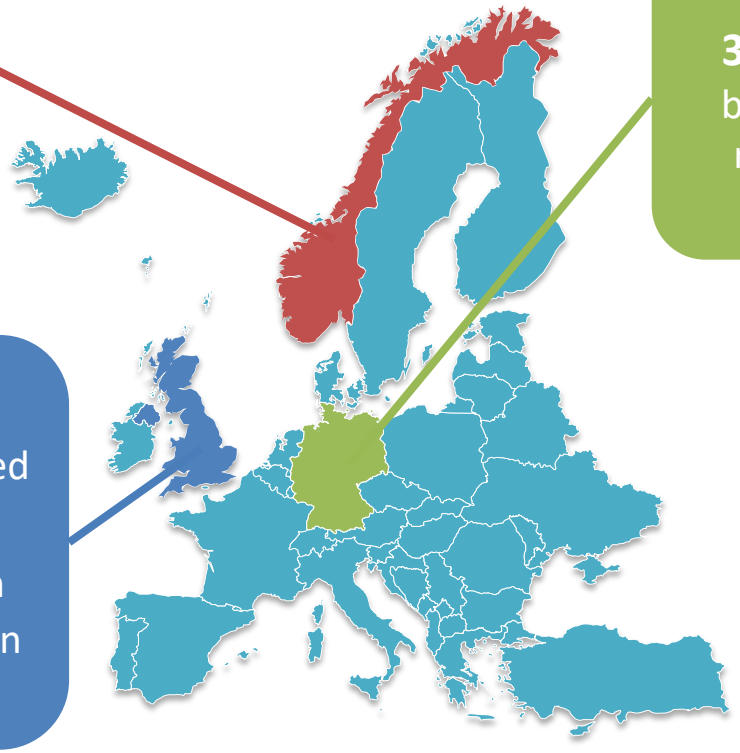
Biosimilars offer the potential to increase patient access to beneficial cancer treatments

Norway

72% price reduction for biosimilar infliximab over reference medicine in 2005

Germany

30% price reduction in biosimilar epoetin over reference medicine in 2008



UK

Filgrastim biosimilar launched in 2008

Overall uptake of filgrastim increased by **104%** between 2008 and 2014[4]

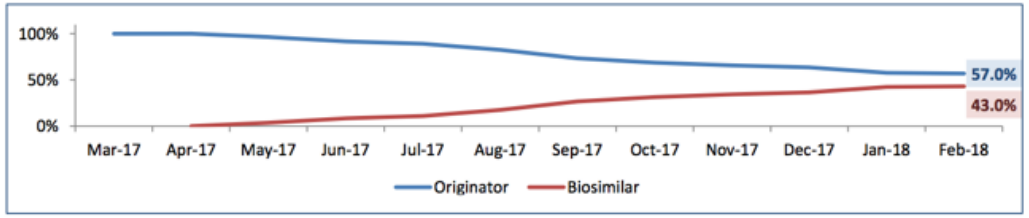
UK, Germany and The Netherlands

10–20% increase in overall use of filgrastim following biosimilar introduction

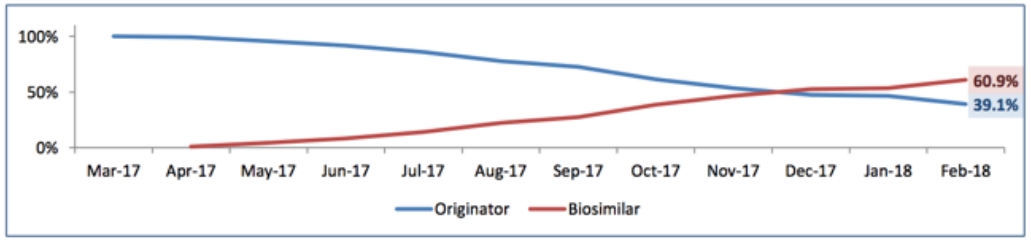
1. Bauchner H, et al. *JAMA* 2017;317:33–4;
2. 2. QuintilesIMS Institute. 2017;
3. 3. Cornes P. *Target Oncol* 2012;7 Suppl 1:S57–67;
4. 4. IMS Institute for Healthcare Informatics. 2016.

Truxima & Rixathon achieved a very fast biosimilar penetration throughout Europe

Volume market share

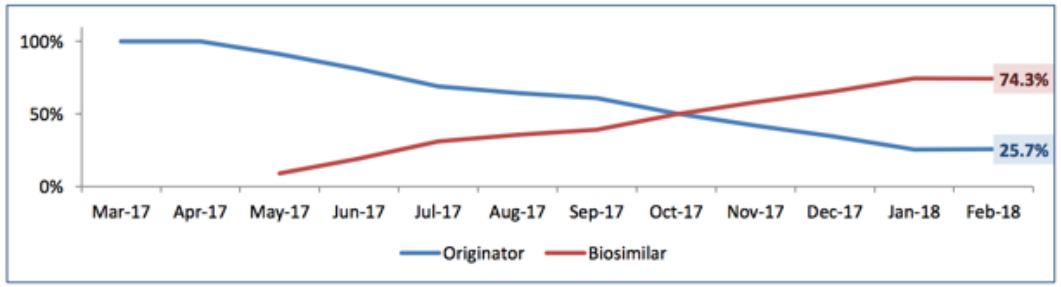


Germany

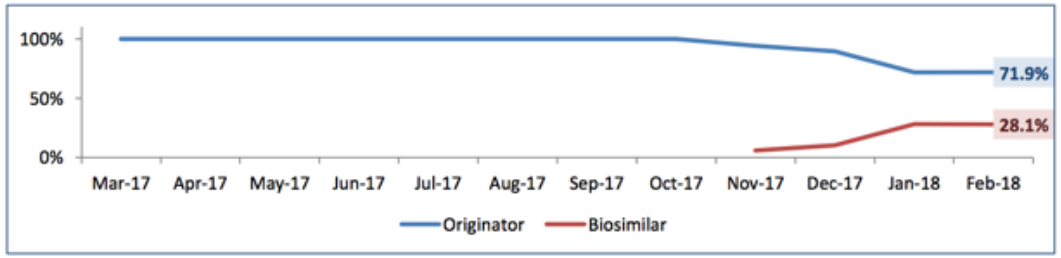


UK

Volume market share



Netherlands



Austria*

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MoAb in NHL: Everything Started With Rituximab

Development and registration of original particle (Roche)

Subcutaneous Rituximab (Roche)

Rituximab biosimilars:

- **CT-P10 (Celltrion)**
- **GP2013 (Sandoz Novartis)**

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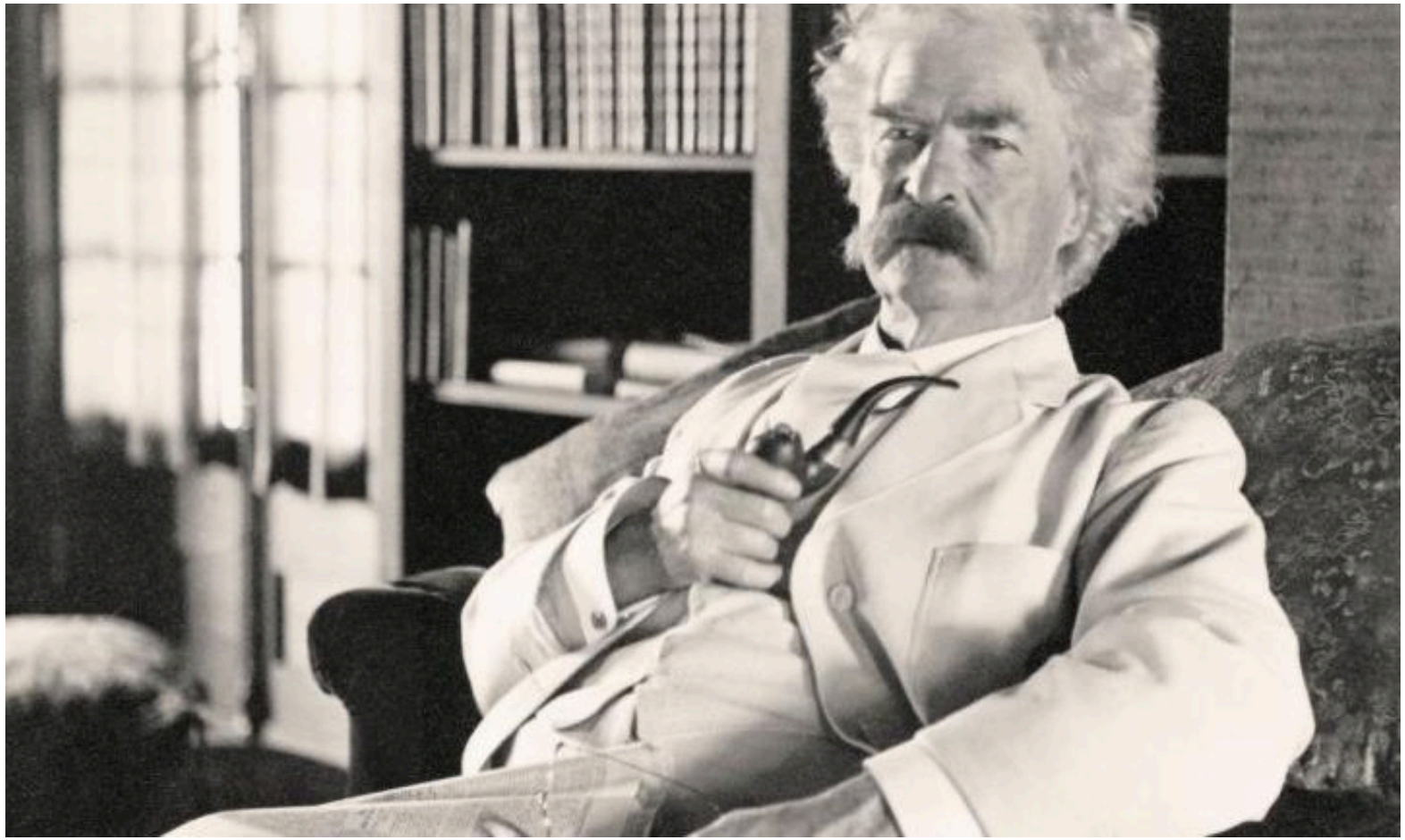
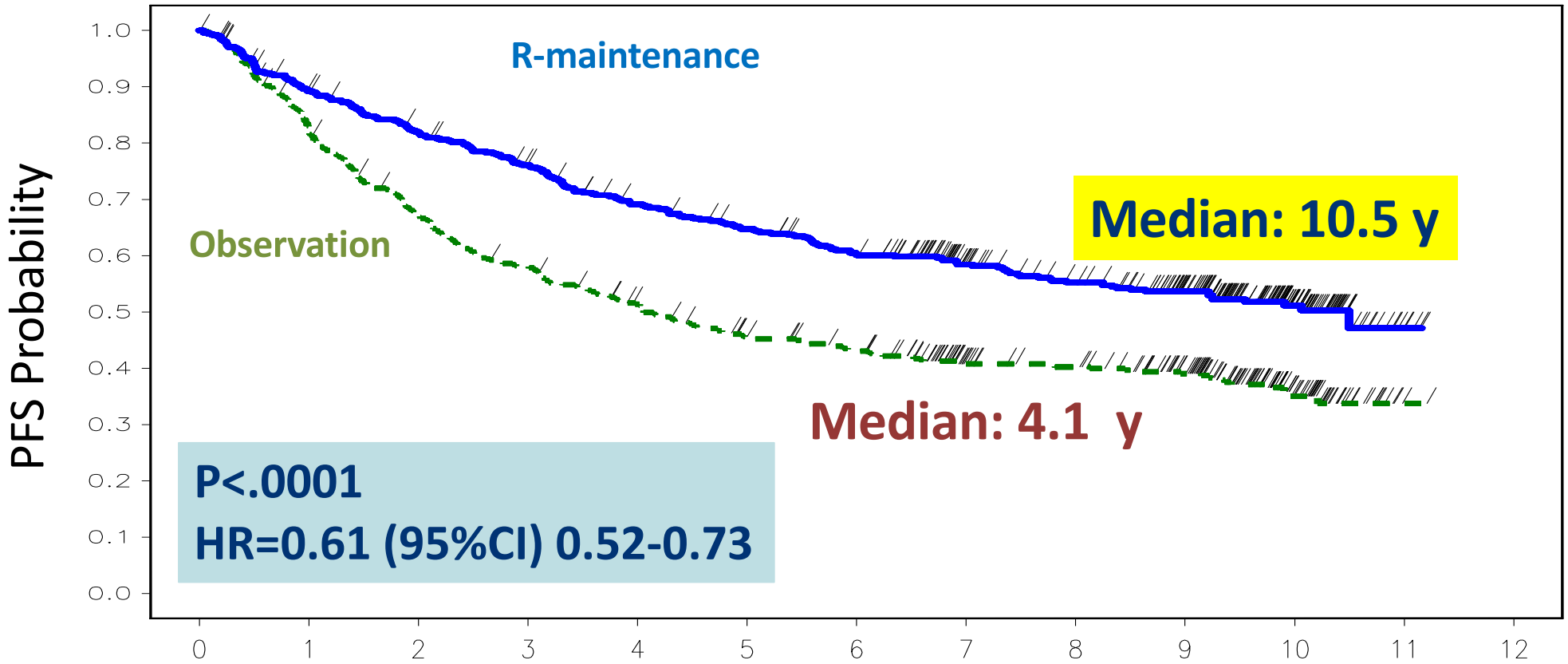
“The reports of my death are greatly exaggerated”

Rituximab



PRIMA : Progression Free Survival at 10 years



No. left													
Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4	0

Salles et al, ASH 2017

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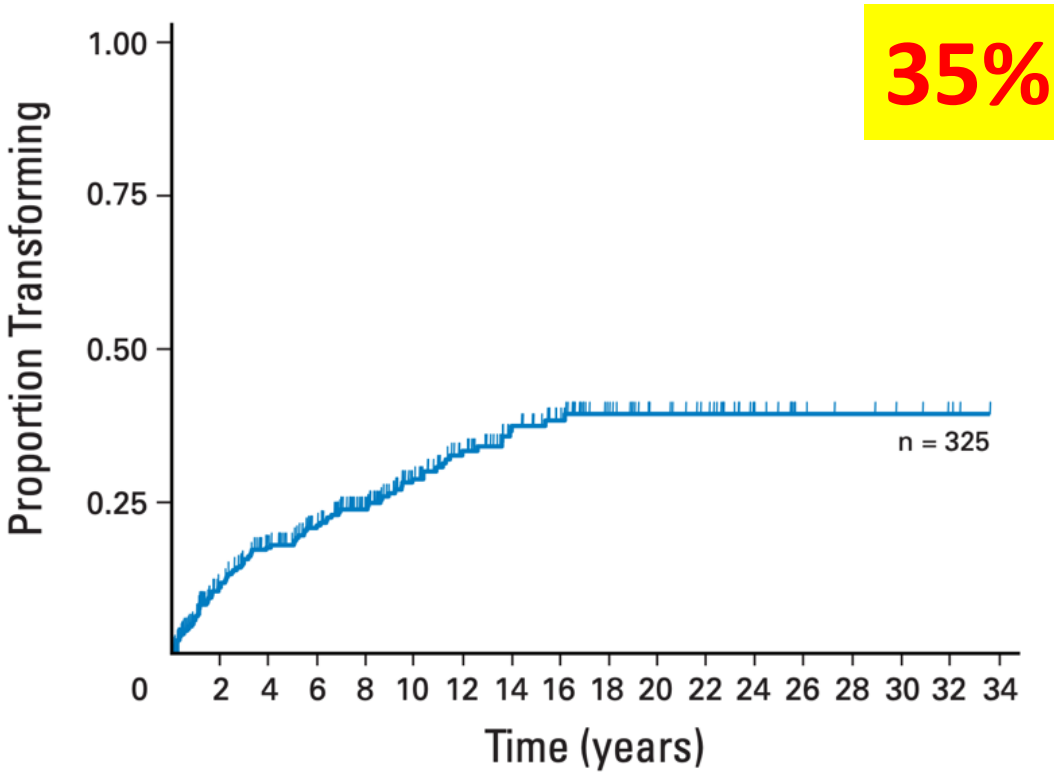
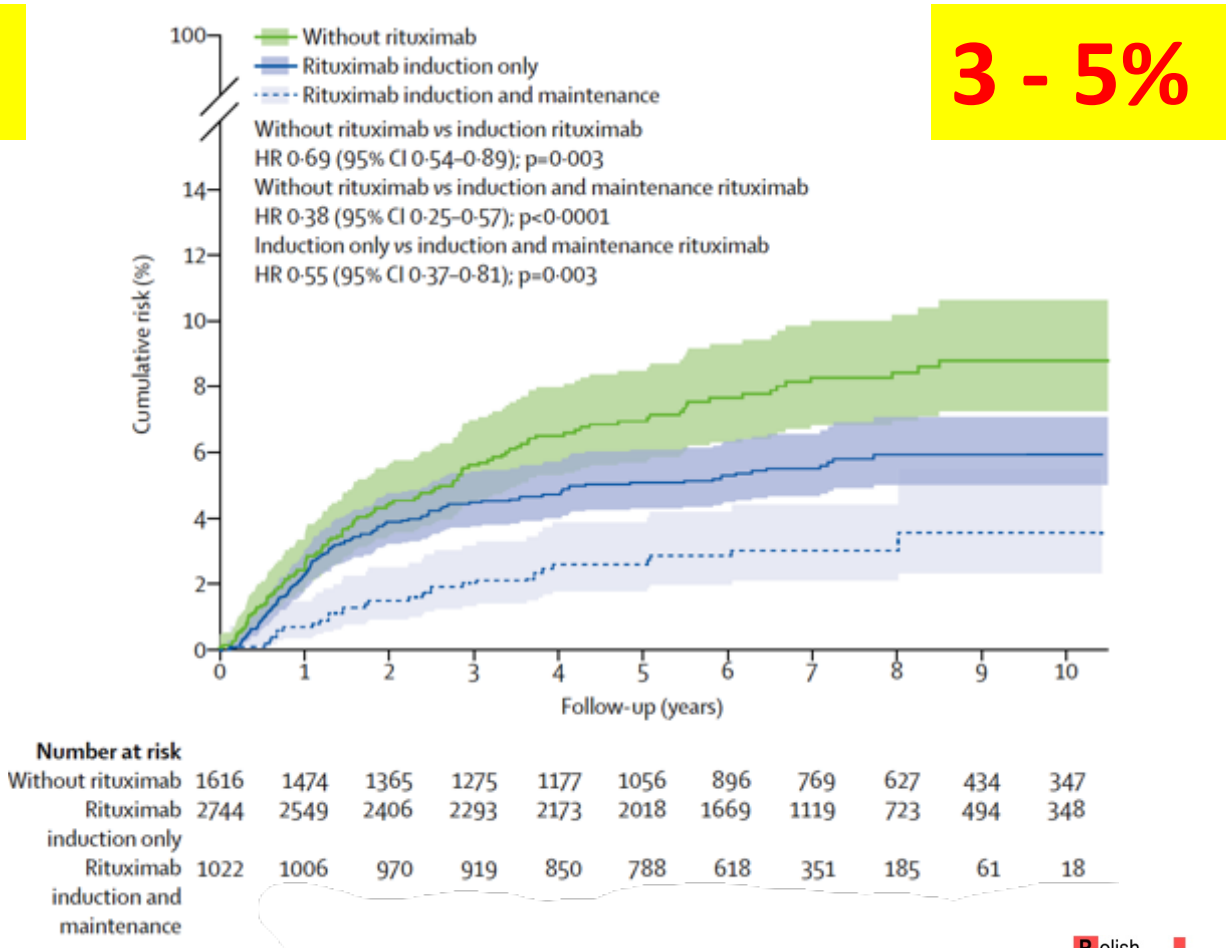
Rituximab and risk of FL transformation

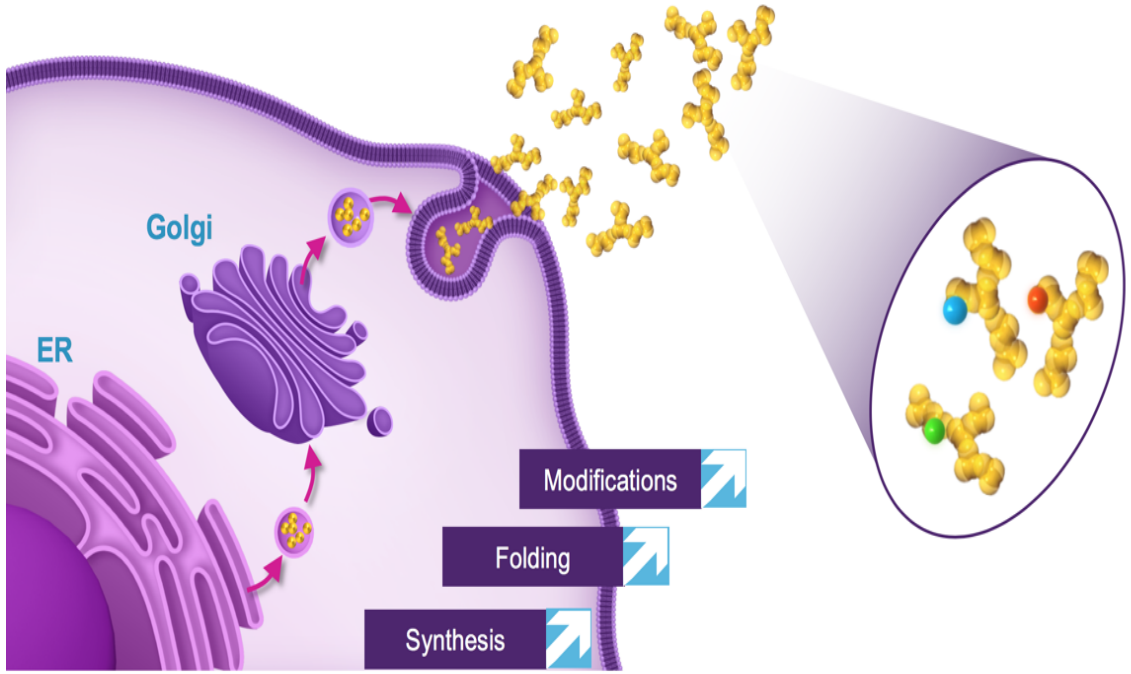


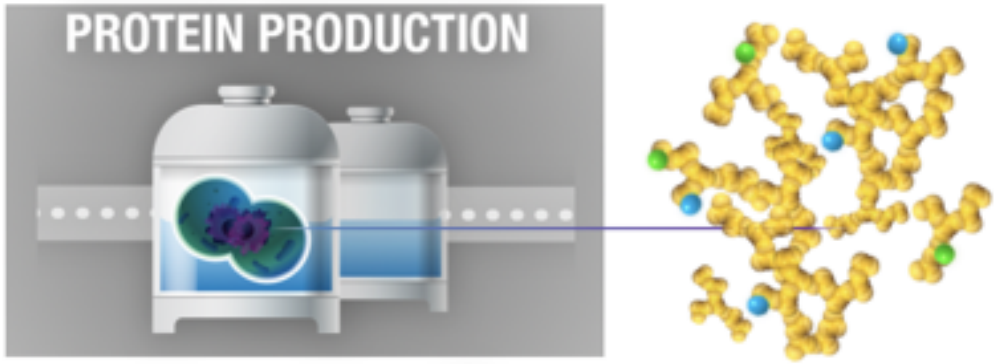


Montoto et al, JCO 2007
Fedeerico et al, Lancet Haemtol 2018

Rituximab Biosimilar / Company		Published supporting data						Approved/status
		Physico-chemical	Functional	Pre-clinical data	Clinical data			
					Indolent NHL/FL	DLBCL	RA	
Biosimilars (approved by EMA or FDA)								
GP2013	Sandoz (Germany)	✓	✓	✓	✓	×	✓	Europe (2017)
CT-P10	Celltrion (S. Korea)	✓	✓	×	✓	×	✓	Europe (2017); US (2019)
Biosimilars but under clinical development (not yet approved by the EMA or FDA)								
PF-05280586	Pfizer (US)	✓	✓	✓	✓	×	✓	Phase III
RTXM83	mAbxience (Spain)	✓	✓	✓	×	✓	×	Phase III (approved in Brazil)
ABP 798	Amgen (US)	✓	✓	×	×	×	×	Phase III
Mabion CD20	Mabion (Poland)	×	×	×	×	×	×	Submitted to EMA (2018)
SAIT101	Archigen (UK)	×	×	×	×	×	×	Phase III
Biomimics (distributed in some countries, but not approved to the regulatory standards of EMA or FDA)								
BCD-020	Biocad (Russia)	×	×	×	✓	×	✓	Russia (2014)†
Reditux	Dr. Reddy's (India)	×	×	×	×	✓	×	India (2007)‡

Variability is a natural and expected property of all biologics[1,2]





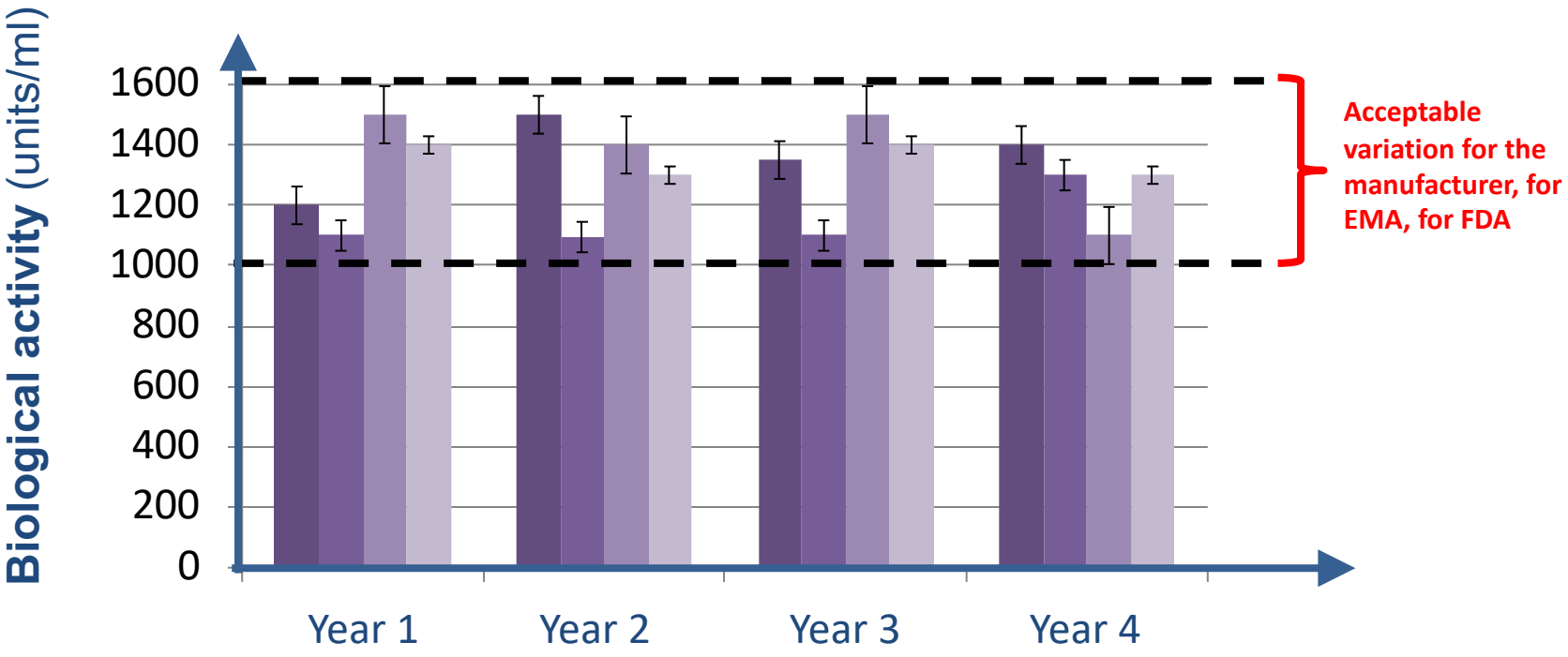
- Glycosylation
- Tertiary structure
- Aggregation
- False amino acids
- Degradation/fragmentation

ER, Endoplasmic Reticulum.

1. Weise et al. *Blood.* 2012;120:5111. 2. Schiestl et al. *Nat Biotechnol.* 2011;29:310.

Biologicals Are Similar But Not Identical

"Nonidenticality" is a normal principle in biotechnology.
No batch of any biologic is "identical" to the others.



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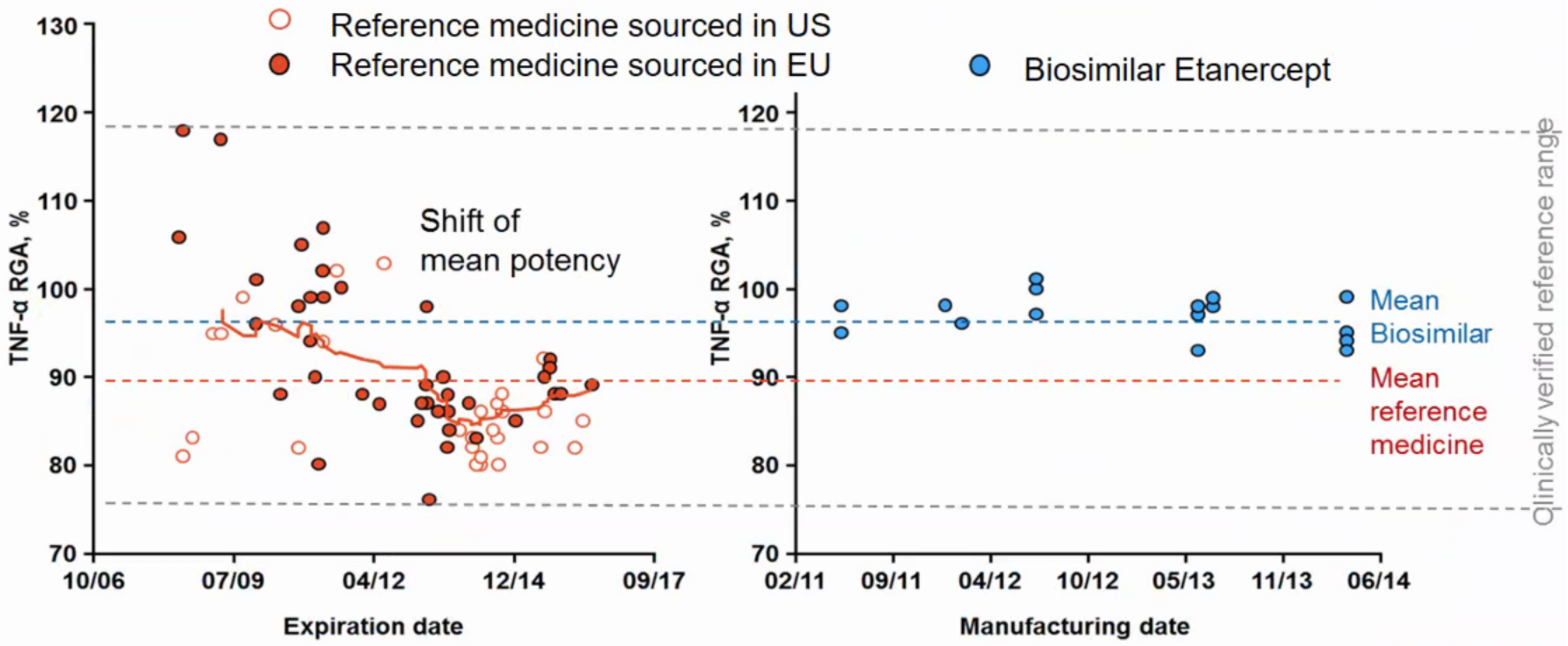
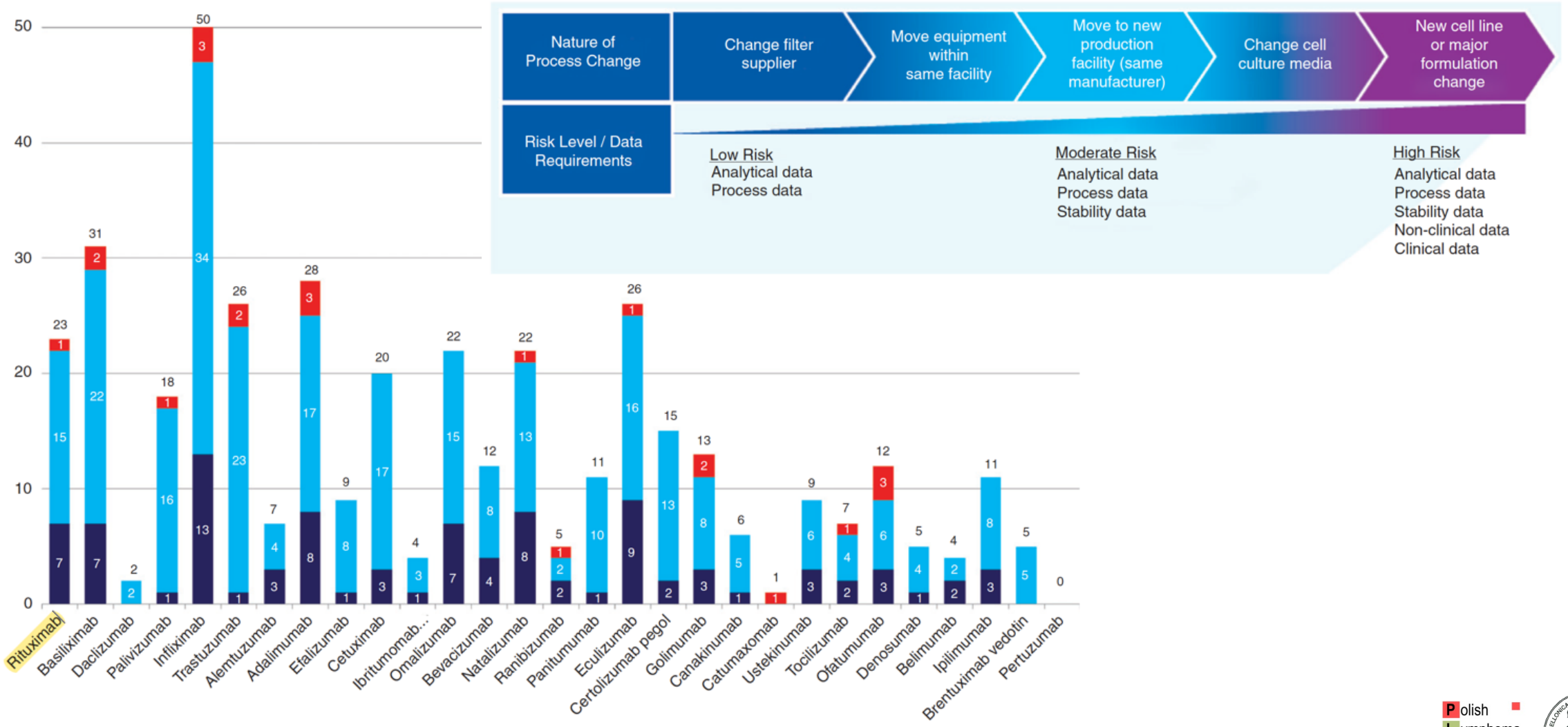
Developing biosimilar is a moving target

Example: batch-to-batch variability in potency of etanercept reference product



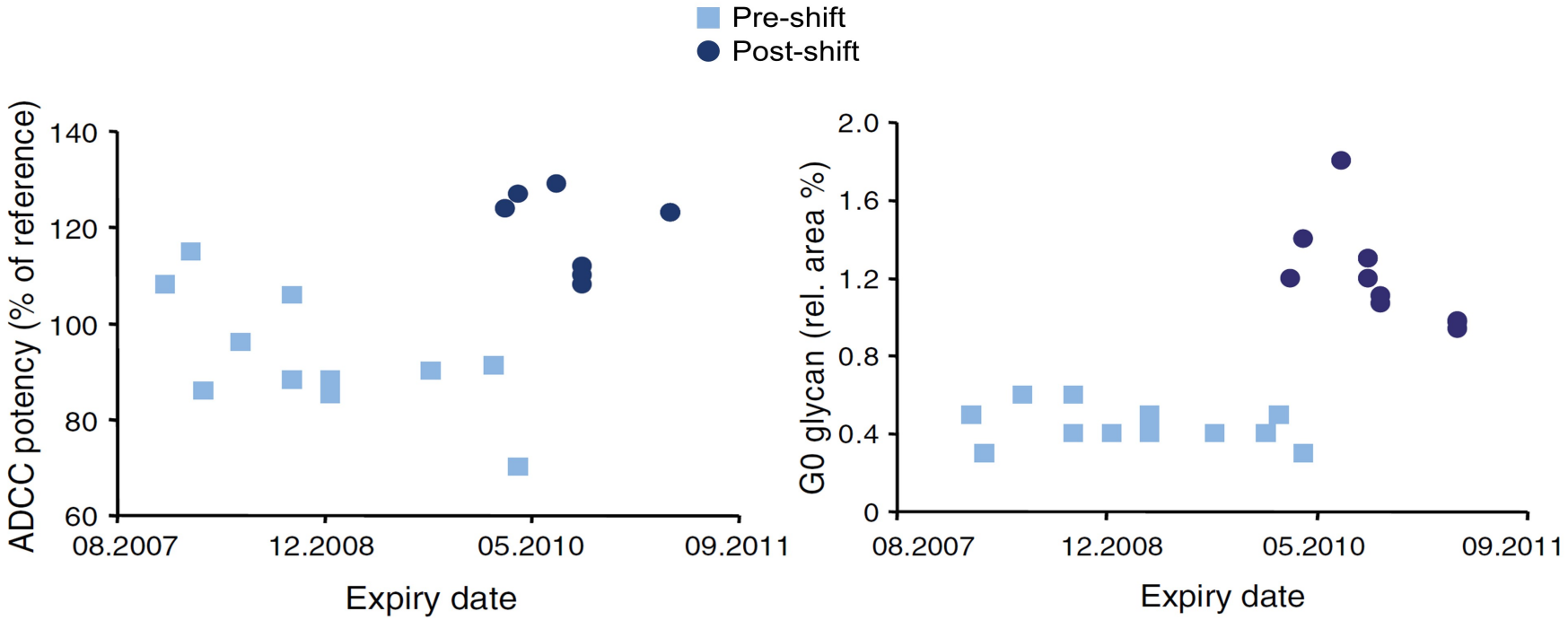
- Variability of reference medicine was mainly triggered by amount of folding variants
- Folding variants refold to the correct structure under physiological conditions → variability is clinically meaningless

Manufactural changes for biotechnology products



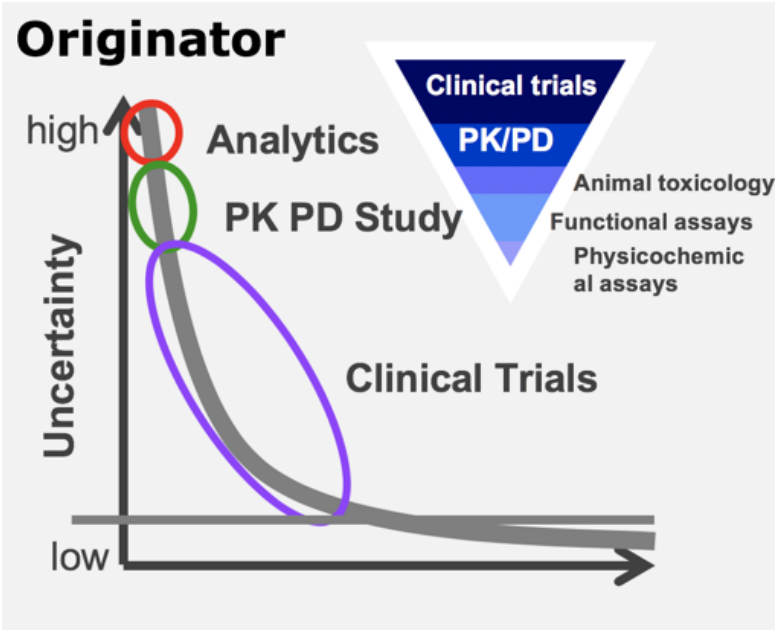
Lee et al, CMRO 2012,
Vezer et al, Current Med Res 2016

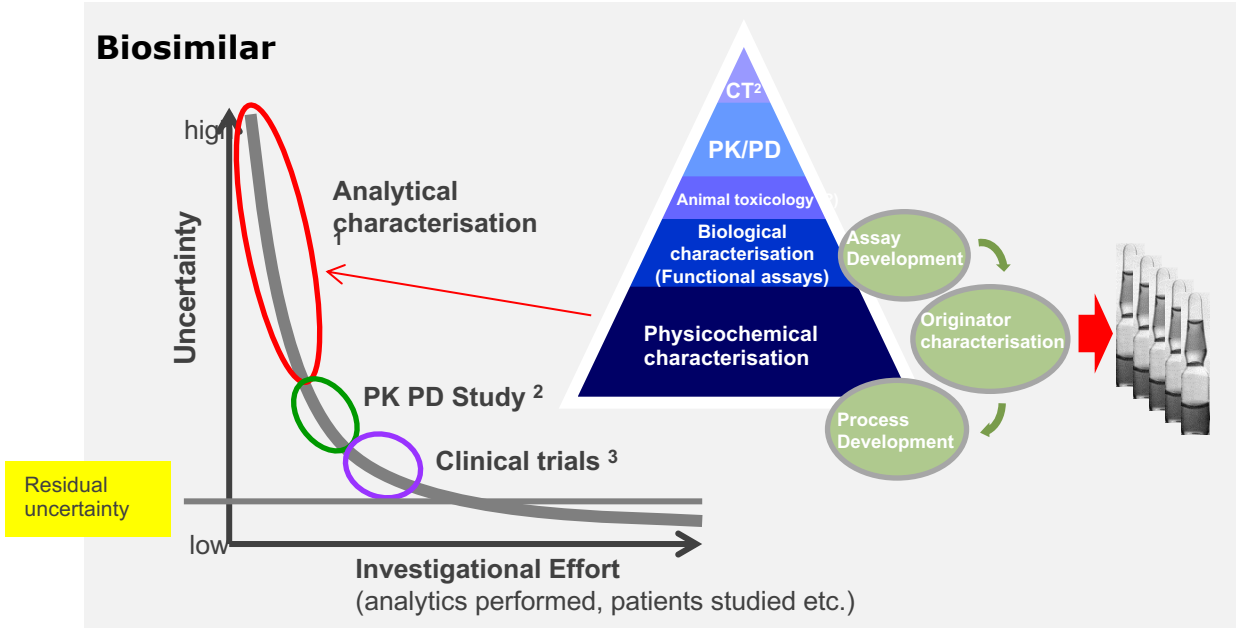
Shifts in quality attributes of Rituxan®/Mabthera® between different batches



Shields et al J Biol Chem. 2012

Different focus between originator & biosimilar development





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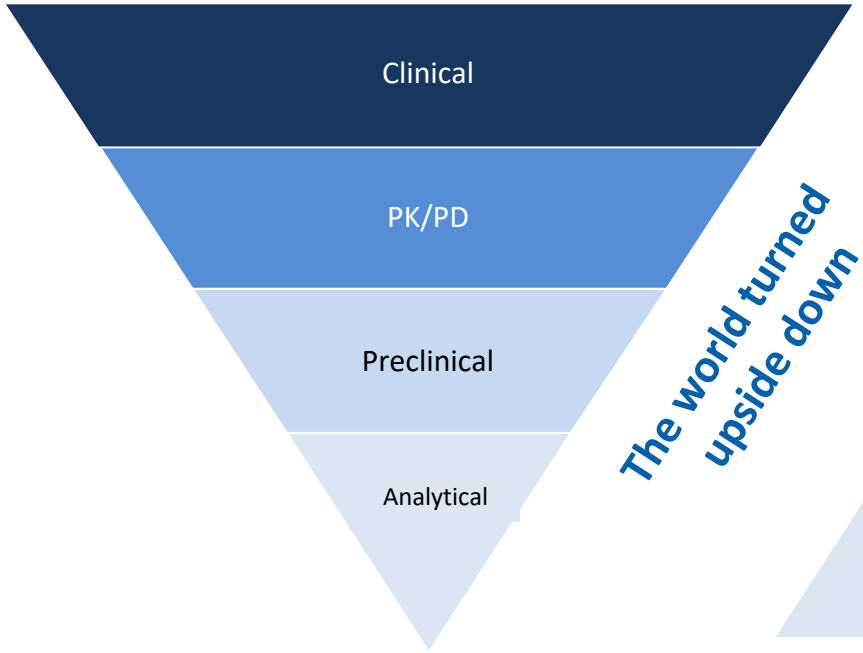
Different focus between originator & biosimilar development

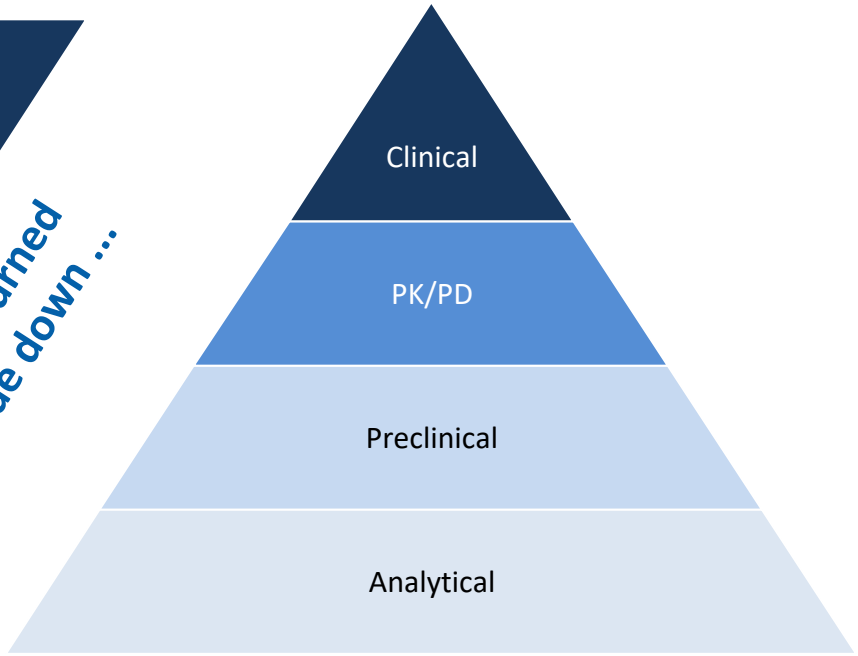
Reference medicine



Major goal is to
determine the clinical effect

The world turned upside down …

Biosimilar

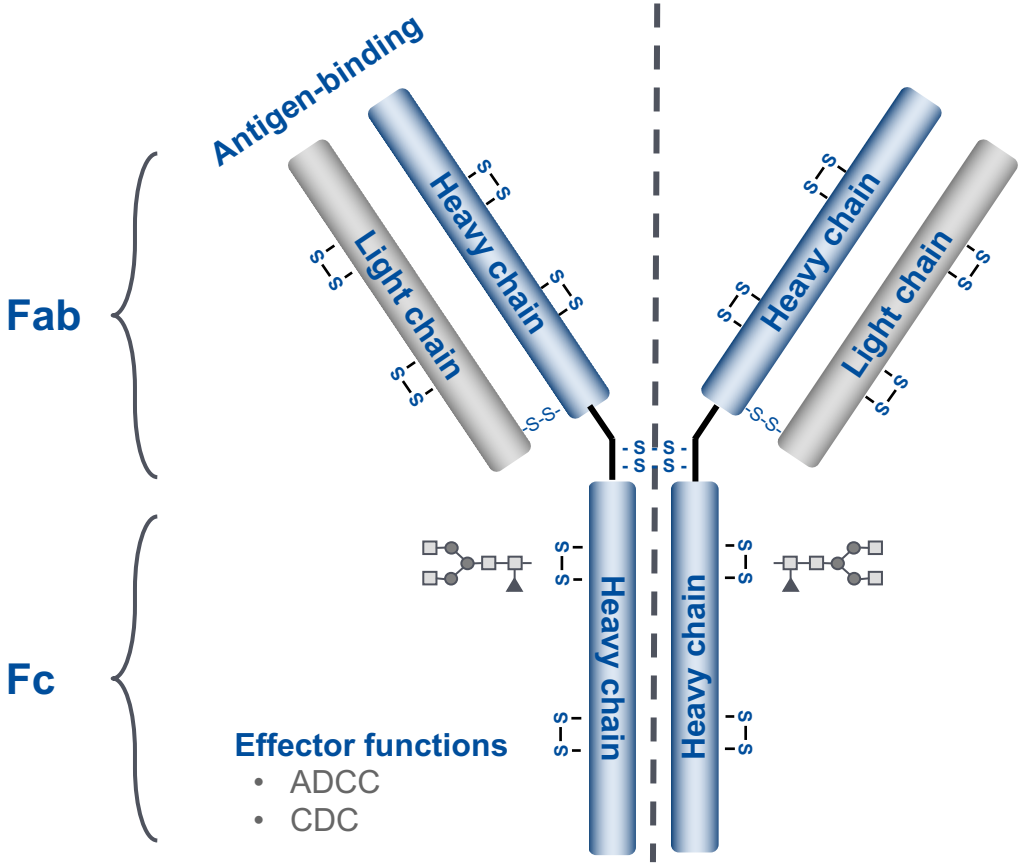


Major goal is **to determine similarity**;
establishment of the scientific bridge
to the clinical experience of the originator

In the end, both approaches provide the same level of confidence with regard to safety and efficacy of the medicine

A monoclonal antibody can be fully characterized…

Biological attributes



Physico-chemical attributes

N-terminal heterogeneity
Pyroglutamate formation, Other modifications

Amino acid modifications
Deamidation, oxidation, glycation, isomerization

Fragmentation
Cleavage in the hinge region, Asp-Pro

Aggregation

Glycosylation, Fucosylation, Sialylation

Disulfide bonds
Free thiols, disulfide shuffling, thioether

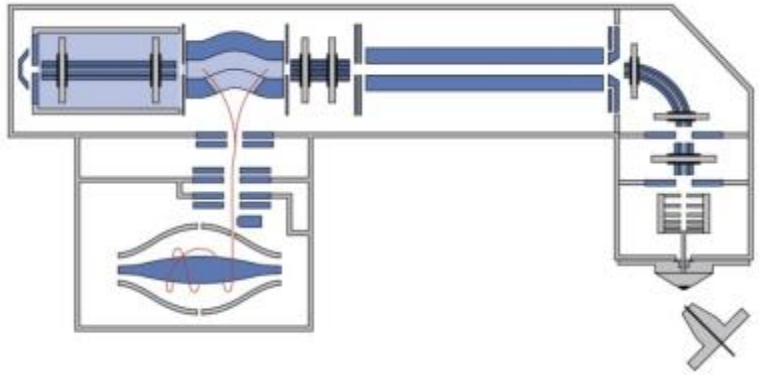
C-terminal heterogeneity
Lysine processing, proline amidation

CDC: complement-dependent cytotoxicity.
Hmiel LK et al., 2015. Anal Bioanal Chem;407(1):79–94.
Schaubild entwickelt von Sandoz (18. November 2014)

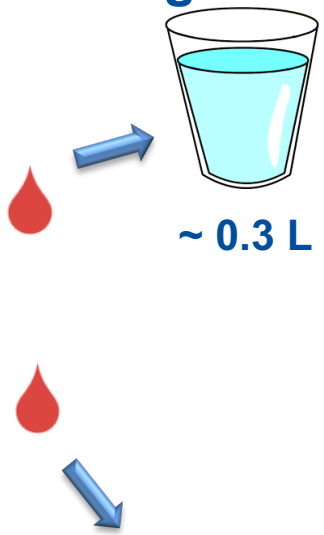
Powerful tools have evolved to allow comprehensive characterization: e.g. mass spectrometry

Year	MS-detection limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001

Mass spectrometry



Analogue:

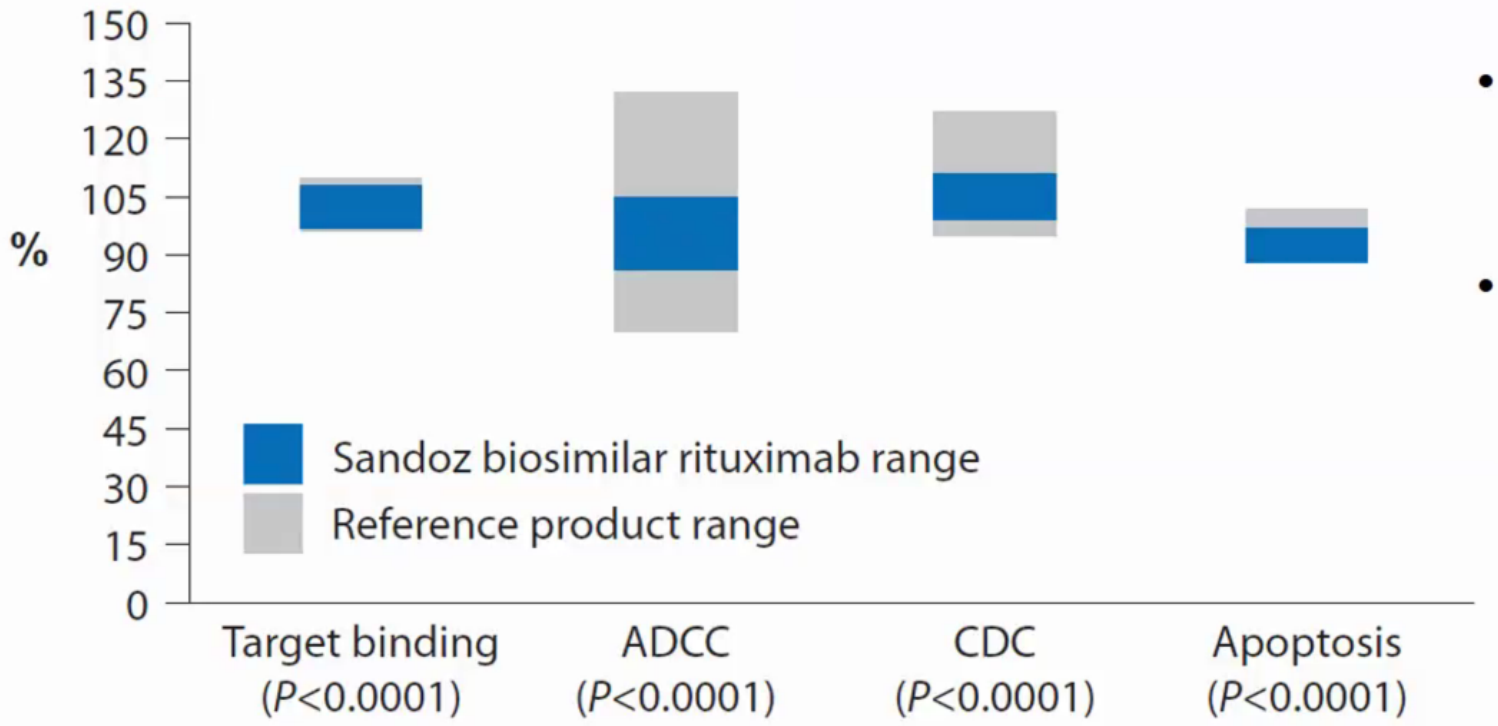


~ 3,000,000 L

10-million-fold increase

van Duijn E 2010. J Am Soc Mass Spectrom;21(6):971–8.
Adapted from Mire-Sluis T 2012, CASSS (Mass Spec) [online].
Available: http://c.ymcdn.com/sites/www.casss.org/resource/resmgr/Mass_Spec_Speaker_Slides/2012_MS_Mire-SluisTony.pdf
[accessed at March 23rd, 2016].

Biological characterisation of Sandoz Rituximab

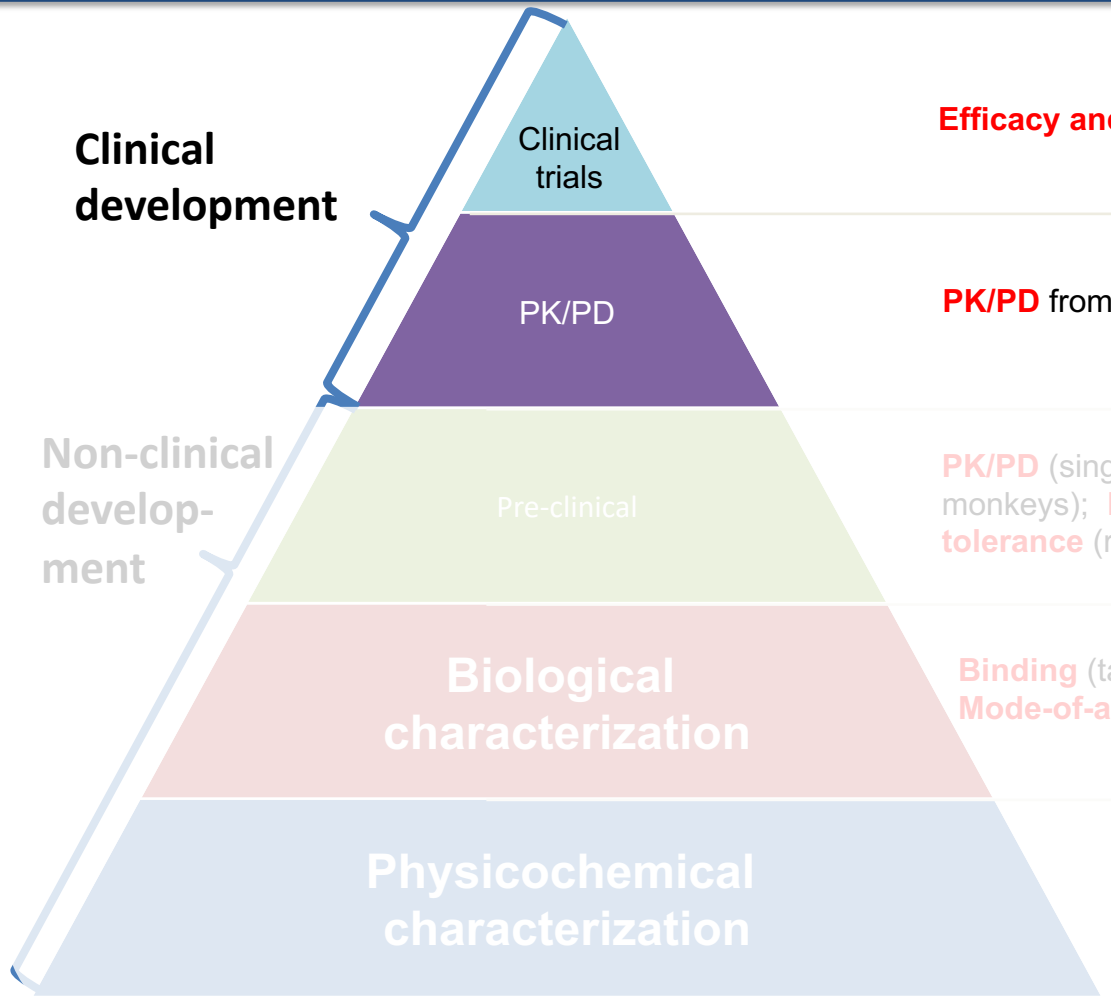


- Potency bioassays designed to give quantitative results
- The Sandoz biosimilar rituximab is functionally indistinguishable from its reference product

The reference product range reflects the minimum and maximum value of 59 batches for the ADCC, 62 batches for the CDC bioassay, 48 batches for target binding and 7 batches for the apoptosis bioassay, which was developed later. The Sandoz biosimilar rituximab range reflects the minimum and maximum value of 11 clinic batches for binding, ADCC and CDC and 5 batches for the apoptosis assay
*Assessed using the two-sided test procedure (TOST) with bioequivalence limits of 0.8–1.25

Visser et al. BioDrugs 2013;27:495–507. ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity;

GP2013 and CT-P10 development program



Efficacy and safety from two indications: RA & FL

PK/PD from two indications: RA & FL

PK/PD (single dose in monkeys); **toxicity** (repeat dose in monkeys); **Efficacy** (xenograft tumor models in SCID mice); Local **tolerance** (rabbits); **Tissue cross reactivity**, **ADCC** (in vitro)

Binding (target binding, receptor binding)
Mode-of-action (programmed cell death, CDC, ADCC)

Primary structure, higher order structure, size, **heterogeneity** (C-and N-terminal),**post-translational modifications** (variants glycosylation, glycation, oxidation, deamidation). **Purity**, **Aggregates**

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; FL, follicular lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency

Key considerations for Phase III trial designs

	Originator	Biosimilar
Patient population	Any	Sensitive and homogeneous
Clinical design	**Superiority versus standard of care**	**Comparative versus innovator** (therapeutic equivalence studies)
Study endpoints	Clinical outcomes data (**OS & PFS**) or accepted/established surrogates	**Pharmacokinetic and Pharmacodynamic** markers; objective **response rate (RR)**
Safety	**Acceptable risk/benefit profile** versus standard of care	**Similar safety profile** to innovator
Immunogenicity	**Acceptable risk/benefit profile** versus standard of care	**Similar immunogenicity profile** to innovator
Extrapolation	**Not allowed**	**Possible** if justified

Clinical development program for Sandoz rituximab and Celltrion rituximab

Study	Design	Indica-tion	Primary endpoint	N	Status
GP2013					
JP-trial	Phase I Open-label Single-arm	Indolent LTB NHL	Safety and PK of SDZ-RTX	6	**Completed** NCT01933516
ASSIST-RA	Phase II RCT (1:1:1) Double-blind	RA	PK equivalence between SDZ-RTX and Ref-RTX	312	**Completed** Published[1]
ASSIST-FL	Phase III RCT (1:1) Double-blind	Advanced FL	Therapeutic equivalence between SDZ-RTX and Ref-RTX-EU	629	**Study ongoing** Published[2]
ASSIST-RT	Phase III RCT (1:1) Double-Blind	RA	Safety and immunogenicity	107	**Completed** Published[3]

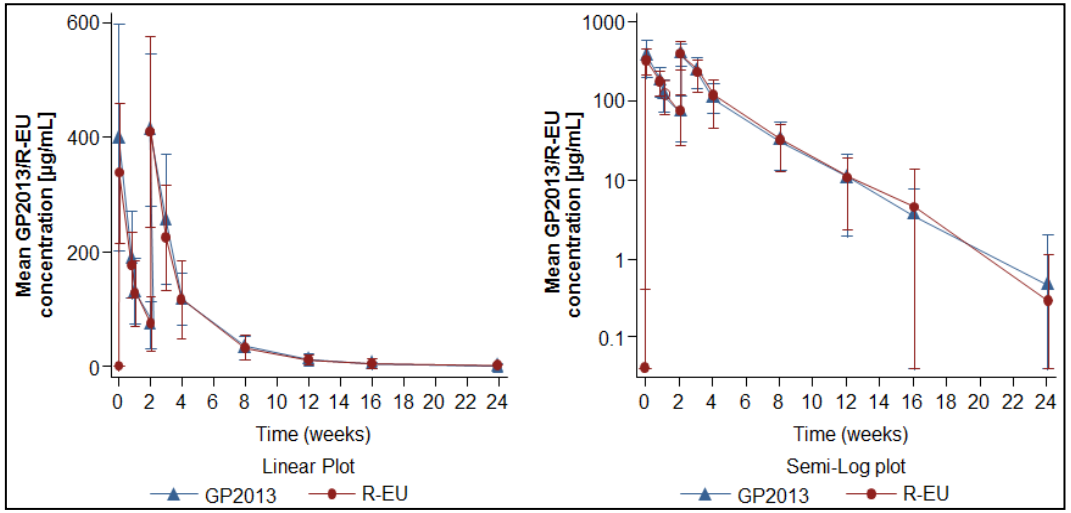
1054 patients

Study	Design	Indica-tion	Primary endpoint	N	Status
CT-P10					
1.1	Phase I RCT (2:1) Double-blind	RA	PK equivalence between CT-P10 and Ref-RTX	154	**Completed** Published[4,5]
1.3 (1.1 follow-on study)	Phase I Open-label Single-arm	RA	Long-term efficacy and safety of CT-P10	58	**Completed** Published[6]
1.2	Phase I Open-label Single-arm	DLBCL	Initial evidence of CT-P10 safety	N/A	**Terminated** recruitment difficulties[7,8]
3.2	Phase III RCT (1:1:1) Double-blind	RA	PK and therapeutic equivalence between CT-P10 and Ref-RTX	372	**Study ongoing** Published[9]
3.3	Phase I/III RCT (1:1) Double-blind	Advanced FL	PK equivalence and therapeutic non-inferiority between CT-P10 and Ref-RTX-US	140	**Study ongoing** Published[10]
3.4	Phase III RCT (1:1) Double-Blind	LTB FL	Therapeutic equivalence between CT-P10 and Ref-RTX	258	**Study ongoing** Published[10]

982 patients

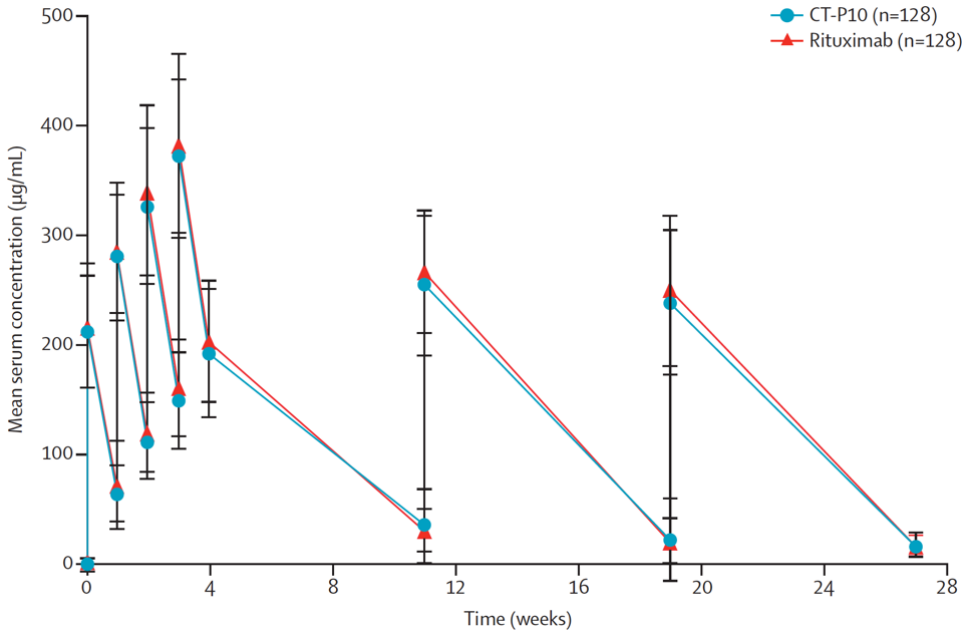
Pharmacokinetics - ($AUC_{(0\text{-}inf)}$)- (PAS)

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment



Smolen J et al., Ann Rh Dis. 2017

CT-P10 3.4 FL

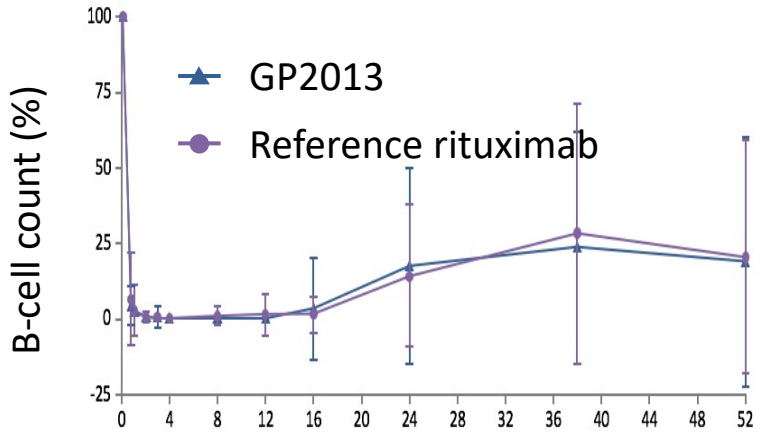


Ogura et al Lancet Haematol 2018

Pharmacodynamics - peripheral B cell depletion

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

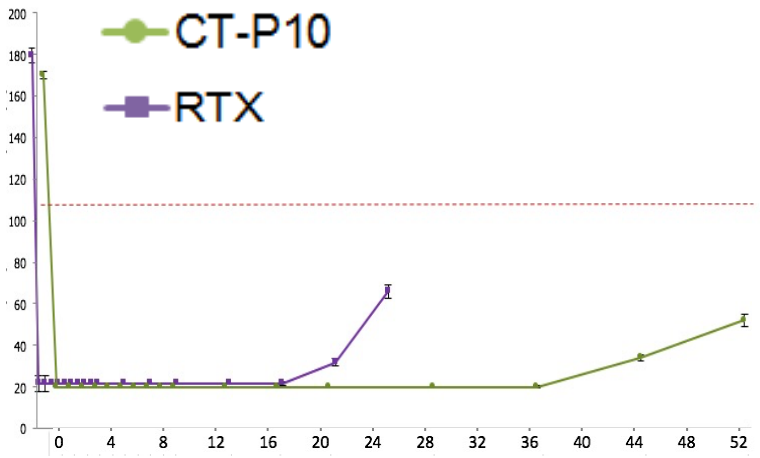
Geometric mean ratio in $AUEC_{0\text{-}14d}$
1.019 (95% CI: 0.997, 1.042)



Time (weeks) GP2013

CT-P10 3.2 RA

Median (±SE) B-cell Kinetics (cells/µL)



Time (weeks) CT-P10

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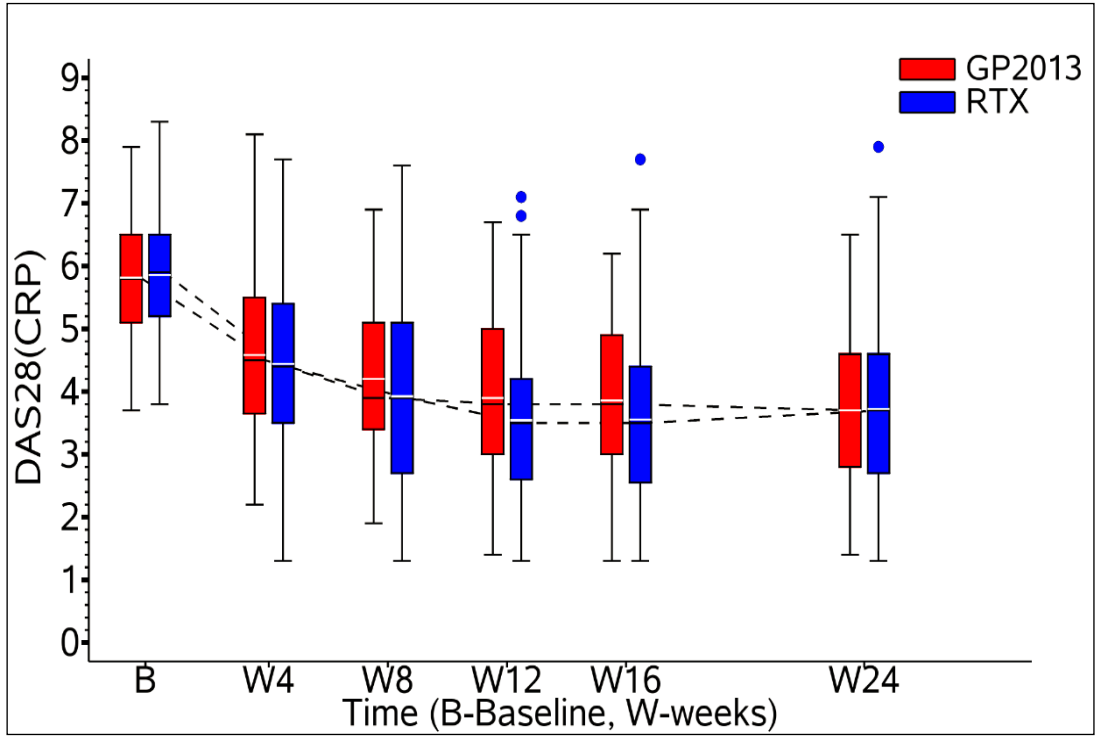
Efficacy DAS (Disese Activity Score)

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

CT-P10 3.2 RA



Parameters TreMedian (±SE) B-cell Kinetics (cells/µL)	n	Adjusted Mean (SE)	Estimate of Treatment Difference (95% CI)
DAS28 (CRP) – Efficacy Primary endpoint			
CT-P10	139	-2.14 (0.177)	-0.29 -0.05 0.20
US/EU-RTX	196	-2.09 (0.176)	
DAS28 (ESR)			
CT-P10	140	-2.41 (0.182)	-0.31 -0.06 0.19
US/EU-RTX	196	-2.35 (0.182)	

-0.6 -0.3 0 0.3 0.6

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GP13-302
ASSIST-RT

GP13-302 clinical trial assessing AE in RA patients treated previously with originator Rituximab

	GP 2013 (N)	MabThera (N)	Total (N)
No of treated patients	53	54	107
Anaphylactic Reactions	0	1	1
Hypersensitivity Reactions	5	6	11
Immunogenicity	0	1	1
Infusion-Related Reactions	6	10	16
SAE	0	4	4
AE	19	21	40

www.clinicaltrials.gov/ct2/show/results/NCT02514772

Study rationale in FL

- Studies were **designed to confirm non-inferior clinical effectiveness** of biosimilar as compared to originator rituximab in a sensitive population
- **Follicular lymphoma** was chosen as the most appropriate indication as the disease **has a more homogeneous nature** amongst the approved oncology indications of rituximab
- Further, the combination **R-CVP was considered the most sensitive treatment option**, as rituximab had shown the largest additive treatment effect to a chemotherapy backbone treatment in the combination with CVP
- Immunochemotherapy with Rituximab **remains the current standard of care** for previously untreated patients , the combination regimen increases the **RR** and prolongs both PFS and **OS**

Jurczak W, et al. Lancet Haematol 2017
Coiffier B ,et al. Lancet Haematol 2017

Comparison of study design – phase III studies in advanced FL

	ASSIST-FL[1] Phase III	CT-P10 3.3[2] Phase III
Number of patients randomized	N=627	N=140 (N=121 in part 1)
Patient characteristics	• Advanced FL (Ann Arbor stage III–IV) • WHO grade 1-3a (confirmed by central pathological testing)	• Advanced FL (Ann Arbor stage III–IV) • WHO grade 1-3a (based on local laboratory review)
Induction therapy	R-CVP (8 x 3-week cycles)	R-CVP (8 x 3-week cycles)
	IV cyclophosphamide (750 g/m^2) on Day 1	IV cyclophosphamide (750 g/m^2) on Day 1
	IV vincristine (1.4 mg/m^2) on Day 1	IV vincristine (1.4 mg/m^2) on Day 1
	Oral prednisone (100 mg) on Days 1–5	Oral prednisone/prednisolone (40 mg/m^2) on Days 1–5
	IV SDZ-RTX or Ref-RTX-EU (375 mg/m^2) on Day 1	IV CT-P10 or Ref-RTX-US (375 mg/m^2) on Day 1
Maintenance therapy	IV SDZ-RTX or Ref-RTX-EU (375 mg/m^2) Every 3 months for 2 years (every 2 months in Italy)	IV CT-P10 or Ref-RTX-US (375 mg/m^2) Every 2 months for 2 years
Primary objective(s)	• To demonstrate equivalent efficacy between SDZ-RTX and Ref-RTX-EU in terms of centrally assessed overall response (CR+PR) at 24 weeks	• Part 1 - To demonstrate PK equivalence between CT-P10 and Ref-RTX-US in terms of AUC_{tau} and C_{maxSS} over induction Cycle 4 (Weeks 9–12) • Part 2 - To demonstrate non-inferior efficacy of CT-P10 compared with Ref-RTX-US in terms of centrally assessed overall response (CR+CRu+PR) at 24 weeks
Secondary objectives	PK: C_{max}, C_{trough}, AUC_{0-21d}, AUC_{all} PD: Median B-cell count, AUEC Efficacy: PFS, OS Safety and immunogenicity	PK: C_{max}, C_{trough}, C_{av}, T_{max}, V_{SS}, $T_{1/2}$, MRT, PTF PD: Median B-cell count Efficacy: PFS, TTP, TTF, DFS, OS Safety and immunogenicity

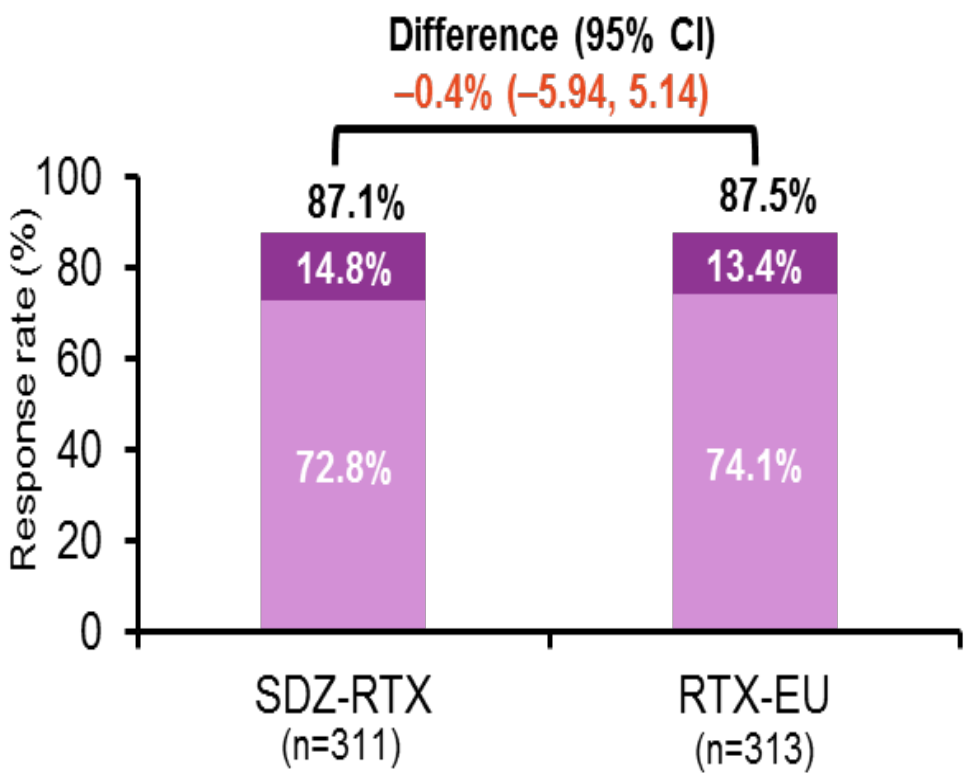
Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

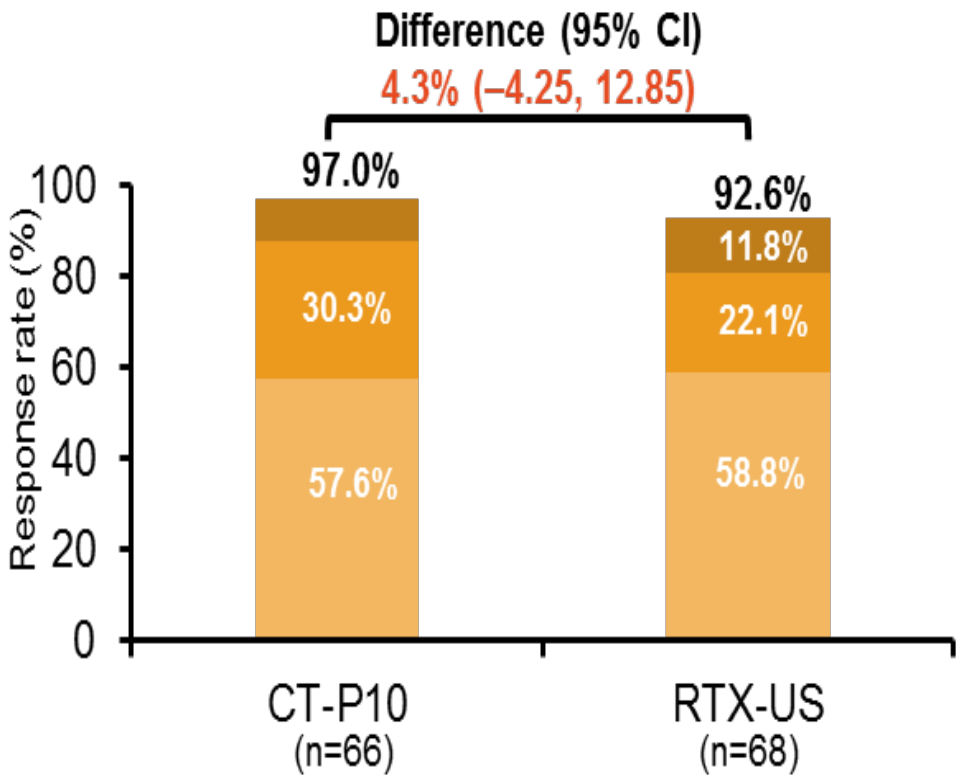
Patient demographics and baseline characteristics - phase III studies in advanced FL

		ASSIST-FL[1] (N=627)		CT-P10 3.3[2] (N=140)	
		SDZ-RTX (N=312)	Ref-RTX-EU (N=315)	CT-P10 (n=70)	Ref-RTX-US (N=70)
Age, years		57.5 (SD: 11.86)	56.4 (SD: 11.72)	57.0 (IQR: 45–66)	58.5 (IQR: 47–66)
Gender – female, n (%)		181 (58)	169 (54)	40 (57)	37 (53)
FLIPI score, n (%)	0-1	30 (10)	35 (11)	8 (11)	6 (9)
	2	106 (34)	103 (33)	25 (36)	21 (30)
	>3	176 (56)	177 (56)	37 (53)	43 (61)
ECOG performance score, n (%)	0	179 (57)	175 (56)	44 (63)	47 (67)
	1	125 (40)	123 (39)	25 (36)	22 (31)
	2	5 (2)	13 (4)	1 (1)	1 (1)
	Missing	3 (1)	4 (1)	0	0
Bulky disease (tumour > 7cm), n (%)		44 (14)	56 (18)	11 (16)	14 (20)

Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

Primary efficacy results – phase III studies in advanced FL





Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

Safety and immunogenicity results - phase III studies in advanced FL

	ASSIST-FL[1] (N=627)		CT-P10 3.3[2] (N=140)	
	SDZ-RTX (N=312)	Ref-RTX-EU (N=315)	CT-P10 (N=70)	Ref-RTX-US (N=70)
Any adverse event (AE)	289 (92.6)	288 (91.4)	58 (82.9)	56 (80.0)
Grade 3 neutropenia	48 (15.4)	51 (16.2)	15 (21)	7 (10)
Serious AE	71 (22.8)	63 (20.0)	16 (22.9)	9 (12.9)
Infusion-related reaction	41 (13.1)	37 (11.7)	16 (22.9)	17 (24.3)
Deaths	4 (1.3)	7 (2.2)	1 (1.4)	0
Anti-drug antibodies	5/268 (2)	3/283 (1)	3 (4)	2 (3)

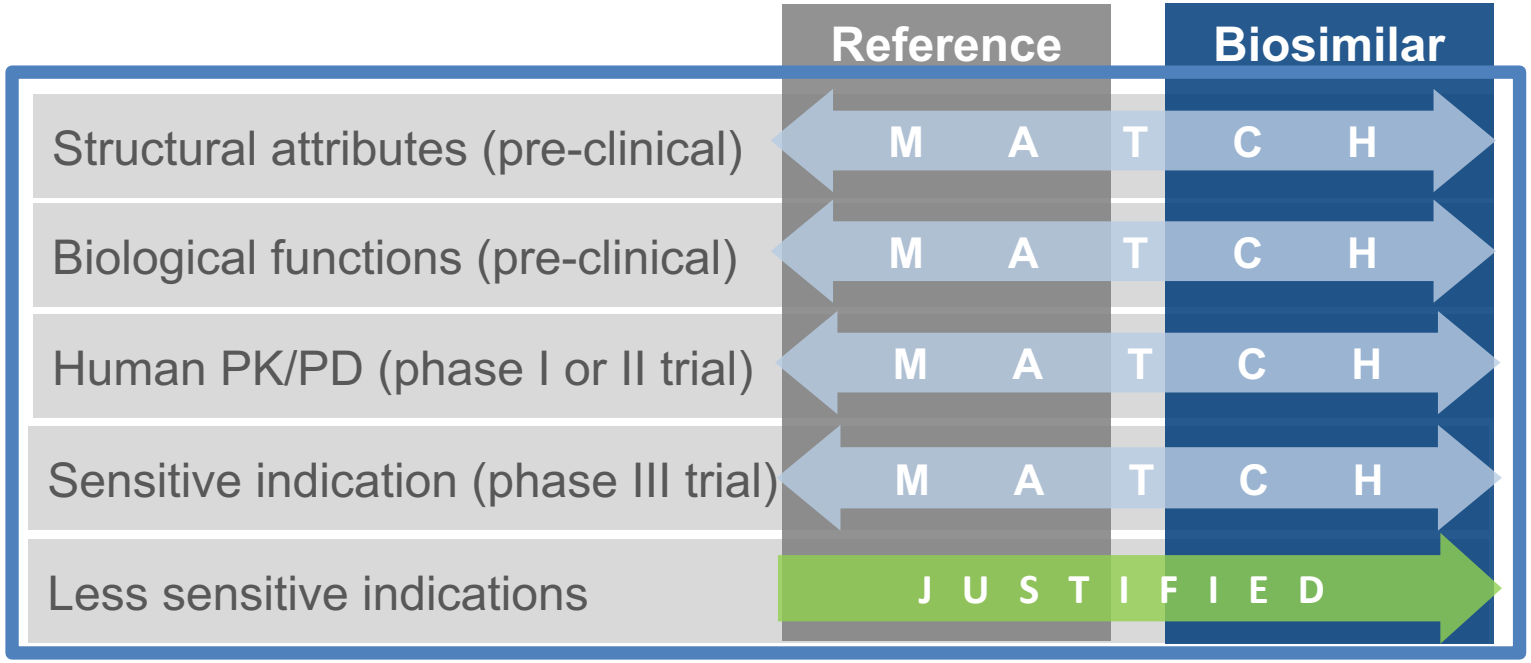
Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

The largest prospective study with Rituximab monotherapy in LTB FL

	CT-P10	Rituximab	Treatment difference estimate*	90% CI*	95% CI*
Intention-to-treat population					
Overall response	108/130 (83%)	104/128 (81%)	1·8%	−6·43 to 10·20	−8·22 to 11·53
Complete response	36/130 (28%)	43/128 (34%)	..	..	..
Unconfirmed complete response	6/130 (5%)	2/128 (2%)	..	..	..
Partial response	66/130 (51%)	59/128 (46%)	..	..	..
Stable disease	17/130 (13%)	18/128 (14%)	..	..	..
Relapsed or progressive disease	0/130	4/128 (3%)	..	..	..
Unable to assess	0/130	1/128 (1%)†	..	..	..
Data missing‡	5/130 (4%)	1/128 (1%)	..	..	..
Per-protocol population					
Overall response	99/114 (87%)	100/120 (83%)	3·5%	−4·56 to 11·56	−6·28 to 13·01
Complete response	35/114 (31%)	41/120 (34%)	..	..	..
Unconfirmed complete response	6/114 (5%)	2/120 (2%)	..	..	..
Partial response	58/114 (51%)	57/120 (48%)	..	..	..
Stable disease	15/114 (13%)	15/120 (13%)	..	..	..
Relapsed or progressive disease	0	4/120 (3%)	..	..	..
Unable to assess	0	1/120 (1%)†	..	..	..
Data missing‡	0	0	..	..	..

Ogura et al Lancet Haematol 2018

Extrapolation is based on the entire similarity exercise



PD, pharmacodynamics; PK, pharmacokinetics
Kurki P, et al. J Crohns Colitis 2014;8:258; Weise M, et al. Blood 2014;124:3191–6; Weise M, et al. Blood 2012;120:5111–17; Sandoz-generated/owned figure (November 18 2014).

Rituximab biosimilar GP2013 and extrapolated indications

GP2013 registration was based on clinical trials in :

- FL
- RA

- FL
- I line DLBCL
- CLL
- RA
- GPA (Wegener's granulomatosis) and MPA (microscopic polyangiitis)

Rituximab registration and clinical practice

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MabThera is a medicine used to treat the following blood cancers and inflammatory conditions:

- FL
- I line DLBCL
- CLL
- RA
- GPA (Wegener's granulomatosis) and MPA (microscopic polyangiitis)

AUTHORISED
This medicine is approved for use in the European Union

Clinical Practice Guidelines

- FL, MZL, LPL
- I line DLBCL, R/R DLBCL
- CLL
- MCL
- RA
- GPA (Wegener's granulomatosis) and MPA (microscopic polyangiitis)

Conclusions:

- **Rituximab biosimilars are good quality MoAb** with a safety and efficacy profile identical to their originator

- Their similarity to Rituximab was determined by extensive pre-clinical analyses, and finally confirmed by clinical trials, with **nearly 2000 participating patients**

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