Recent developments and global trends in the biosimilar market: What would oncology look like?

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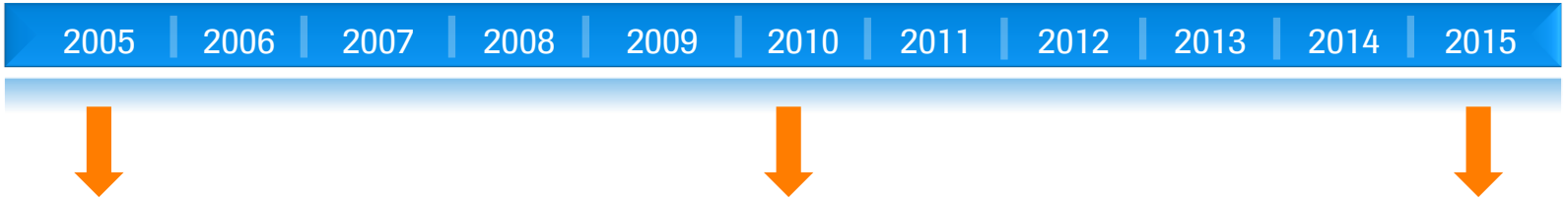
Biosimilar: Ten years on the making

Roche's Strategy: Innovate, Protect, Expand

Portfolio outlook

- HER2 franchise
- CD20 franchise
- Avastin franchise

Biosimilars: Ten years in the making



EU pioneered the biosimilar concept

- Six products approved, including the first mAb biosimilar (infliximab)
- Uptake did not achieve saving expectations

WHO leading global efforts; many emerging countries implemented WHO biosimilar guidelines as a reference

US published final biosimilars guideline

- FDA pathway operating, 7 applications pending, one approval

Differential adoption of WHO biosimilar guidelines led to registration of Non-Comparable Biotherapeutic products (NCBs)*, driven by:

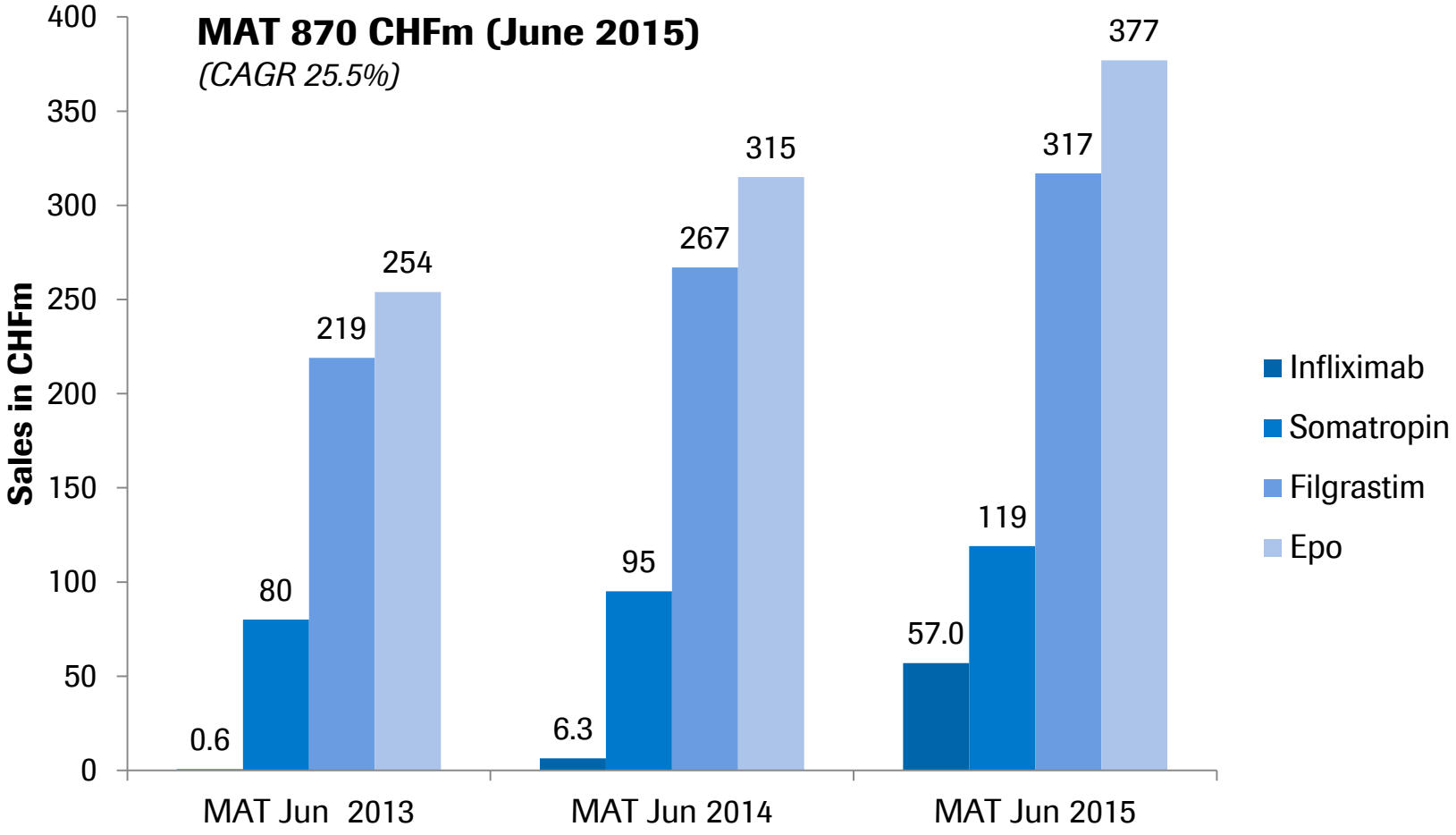
- Capacity issues at National Regulatory Agencies
- Local economic development policies

Biosimilar entry timelines delayed (incl. Herceptin & MabThera)

*For definition and industry position on NCBs please refer to IFPMA Policy Statement:
http://www.ifpma.org/uploads/media/Non-comparable_Biotherapeutic_Products__English__01.pdfr

Current biosimilar trends

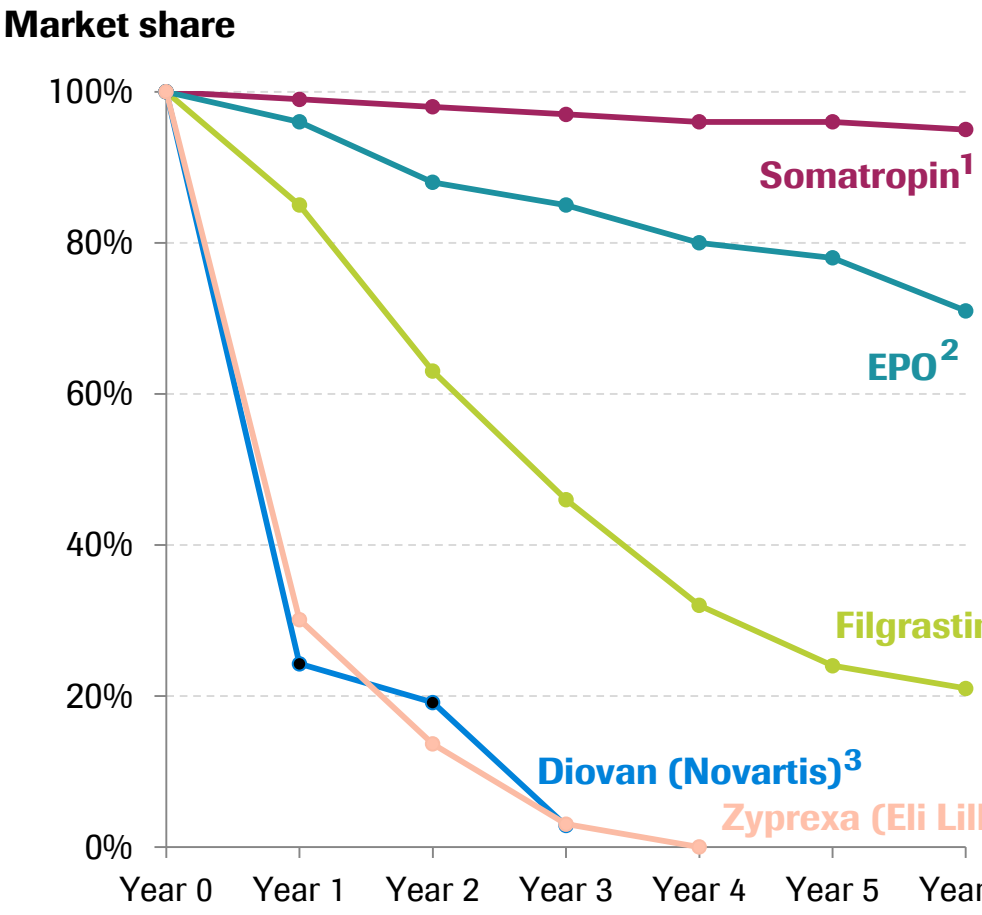
So far, sales have not achieved initial expectations



*Excludes US as no biosimilars have been approved in the US so far (Omnitrope was approved under the 505(b) pathway)
IMS Health; MAT=moving annual total

Generics versus biosimilars

Clear divide in uptake; complex market drivers



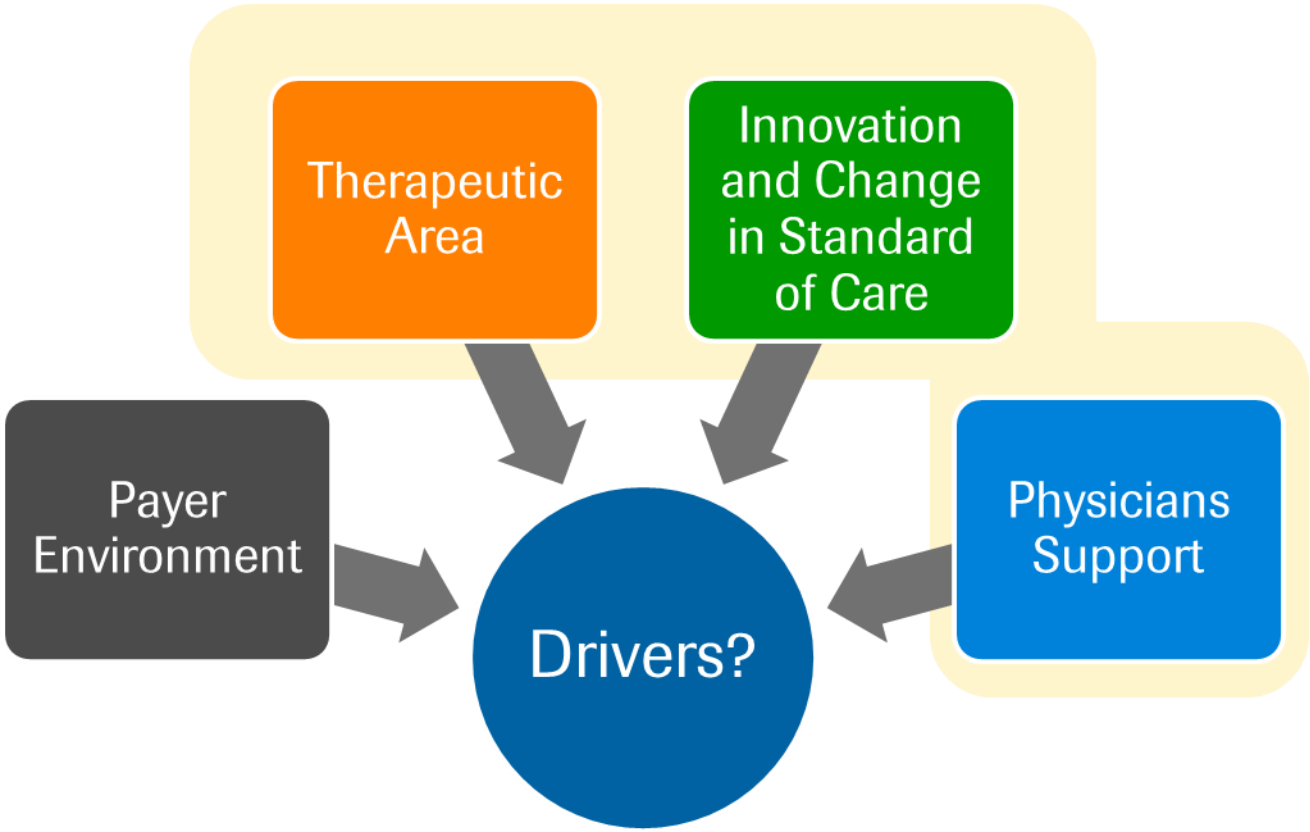
Driven by price <u>and</u> patient offering
9 innovators, one biosimilar
Efficacy visible only longer term
No switching

Payer driven: 7 biosimilars
Efficacy visible immediately
High turnover of patients

Small molecule
Virtually disappear

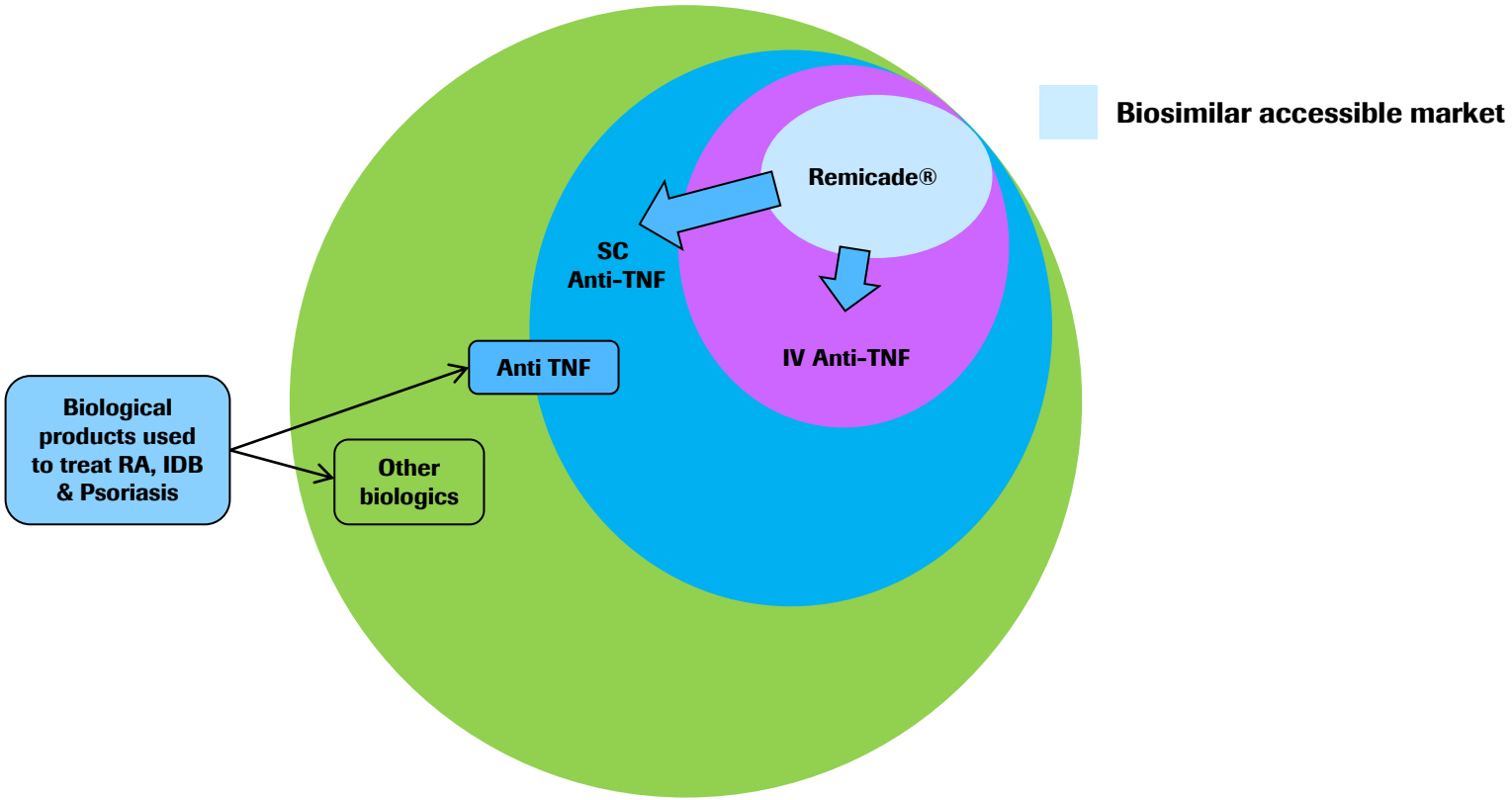
Sources: IMS Biosimilar Dashboard, IMS & Roche analysis
[1] Volume market share based on EU5 average; [2] Volume market share based on average of France & Germany EPO;
[3] Data based on % remaining sales in EU

Payer environment is one of multiple drivers for Biosimilar uptake



Anti-TNF antibody market is not a good analogue for oncology

Infliximab biosimilar could expand beyond it's accessible market and obtain market share from Enbrel® and Humira®



Emerging trends

Consolidation of biosimilar companies and shift to 'Big Pharma'

- New players are 'Big Pharma' companies with fully developed vertical capabilities
- *Brand sales* model as the most likely go-to-market scenario
- Integration (Pfizer & Hospira) or partnerships with generic companies or CMOs provide portfolio synergies and comprehensive commercial capabilities

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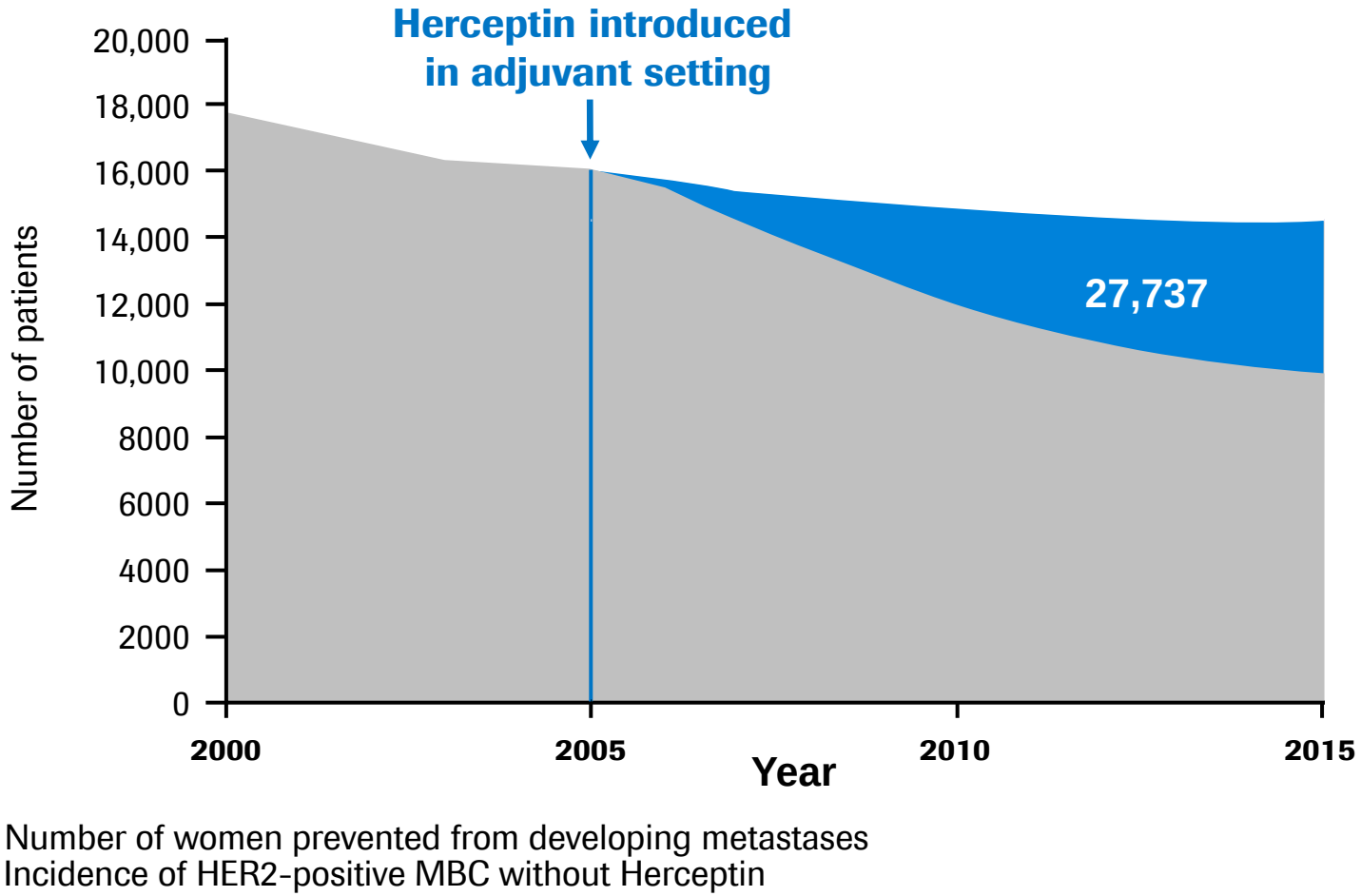
Roche strategy is aligned with our business model

Innovate	**Re-define the standard of care** Mode of administration, combination therapies and new drugs
Protect	**Protect high standards** Enforce efficacy and safety standards, defend intellectual property
Expand	**Act to expand patient access in emerging markets** Change from global pricing to tiered pricing, including 2nd brand

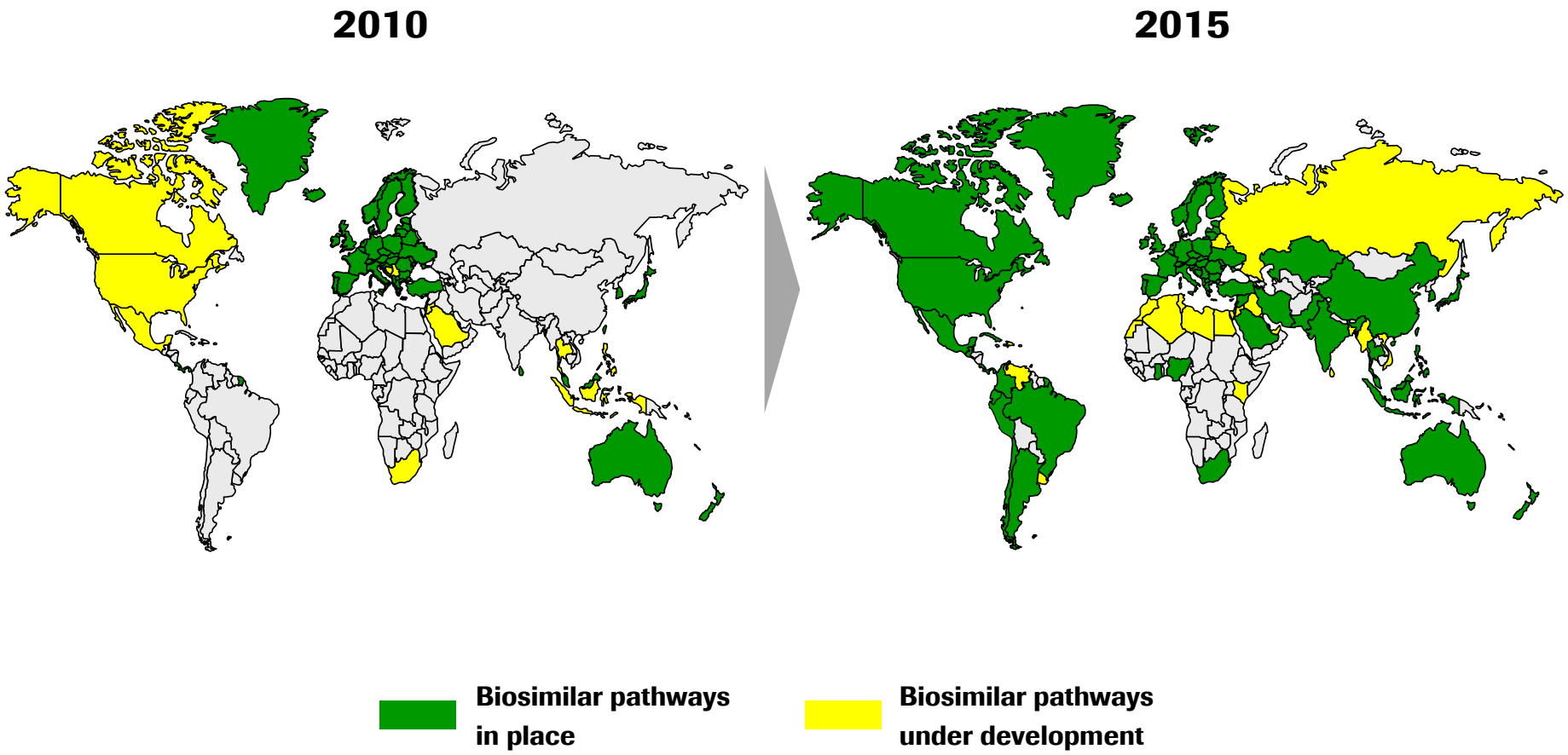
Herceptin

More than 27,000 women in Western Europe did not develop metastatic disease



Weisgerber-Kriegl, U. et al. Estimation of the epidemiological effect of trastuzumab over 10 years in 5 European Countries. *J. Clin. Onco.,* 2008. ASCO Annual Meeting Proceedings: 26:15S

Establishment of biosimilar guidelines has increased driven by WHO efforts



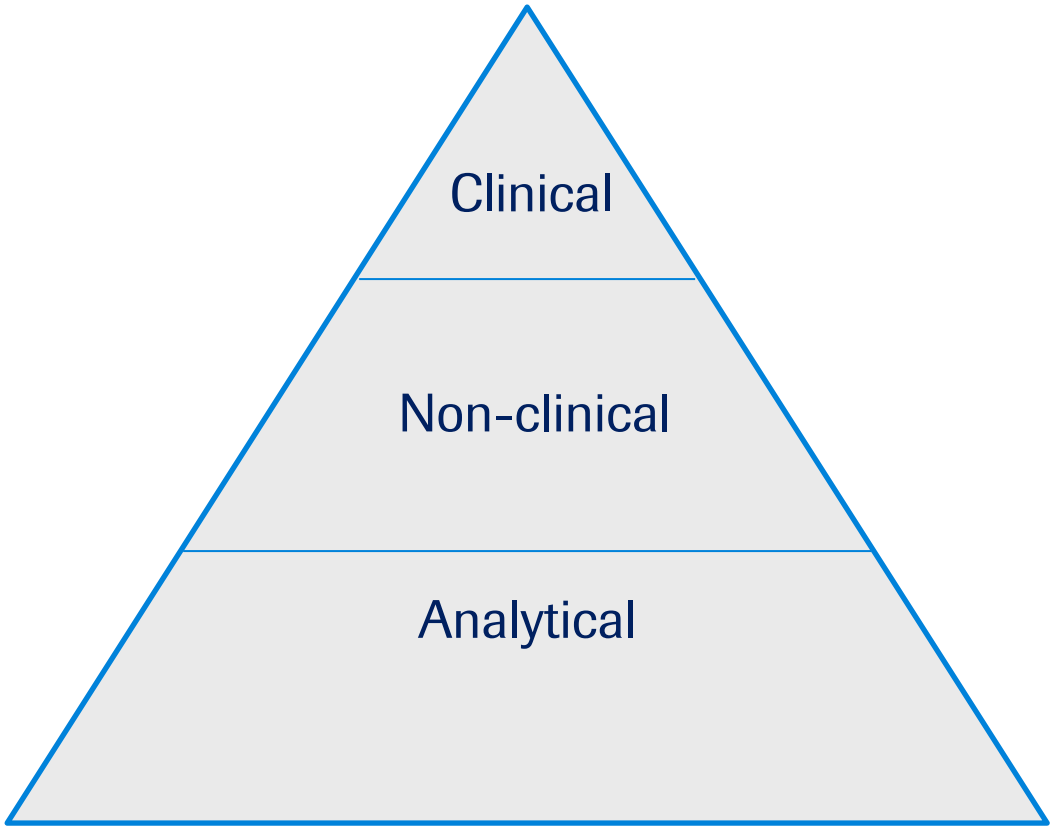
Requirements and study designs are different for the biosimilar versus innovator

Aspects of development	Biosimilar	Innovator
Patient population	Sensitive and homogeneous (patients are *models*)	Any
Clinical design	Comparative versus innovator, normally equivalence	Superiority vs standard of care (SoC*)
Study endpoints	Sensitive, clinically validated PD markers	Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)
Safety	Similar safety profile to innovator; no new findings	Acceptable benefit/risk profile versus SoC*
Immunogenicity	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile versus SoC*
Extrapolation	Possible if justified	Not allowed

* In some cases SoC may not exist; PD=pharmaco dynamics; OS=overall survival; PFS=progression free survival

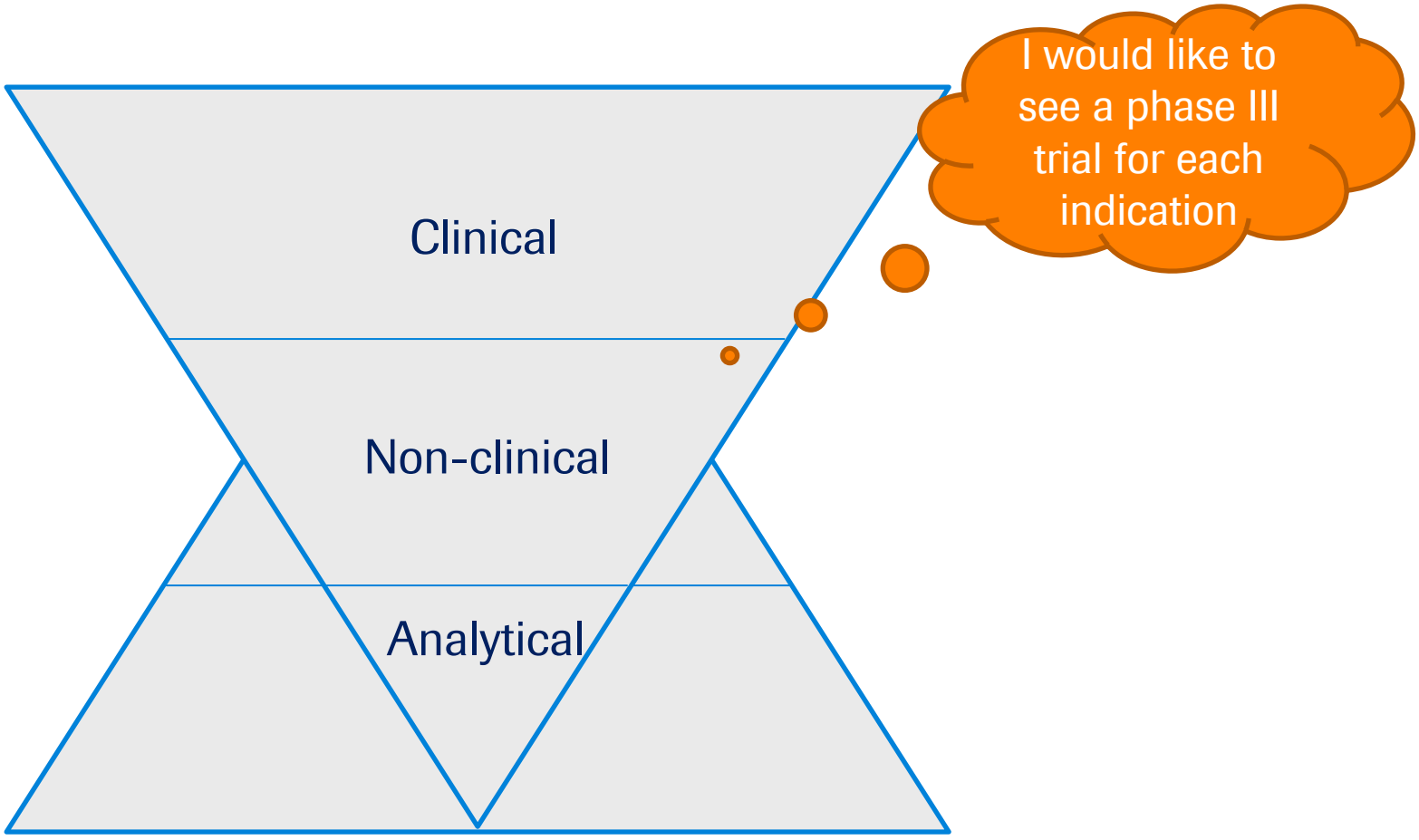
How should extrapolation risk be managed?

The regulator's perspective

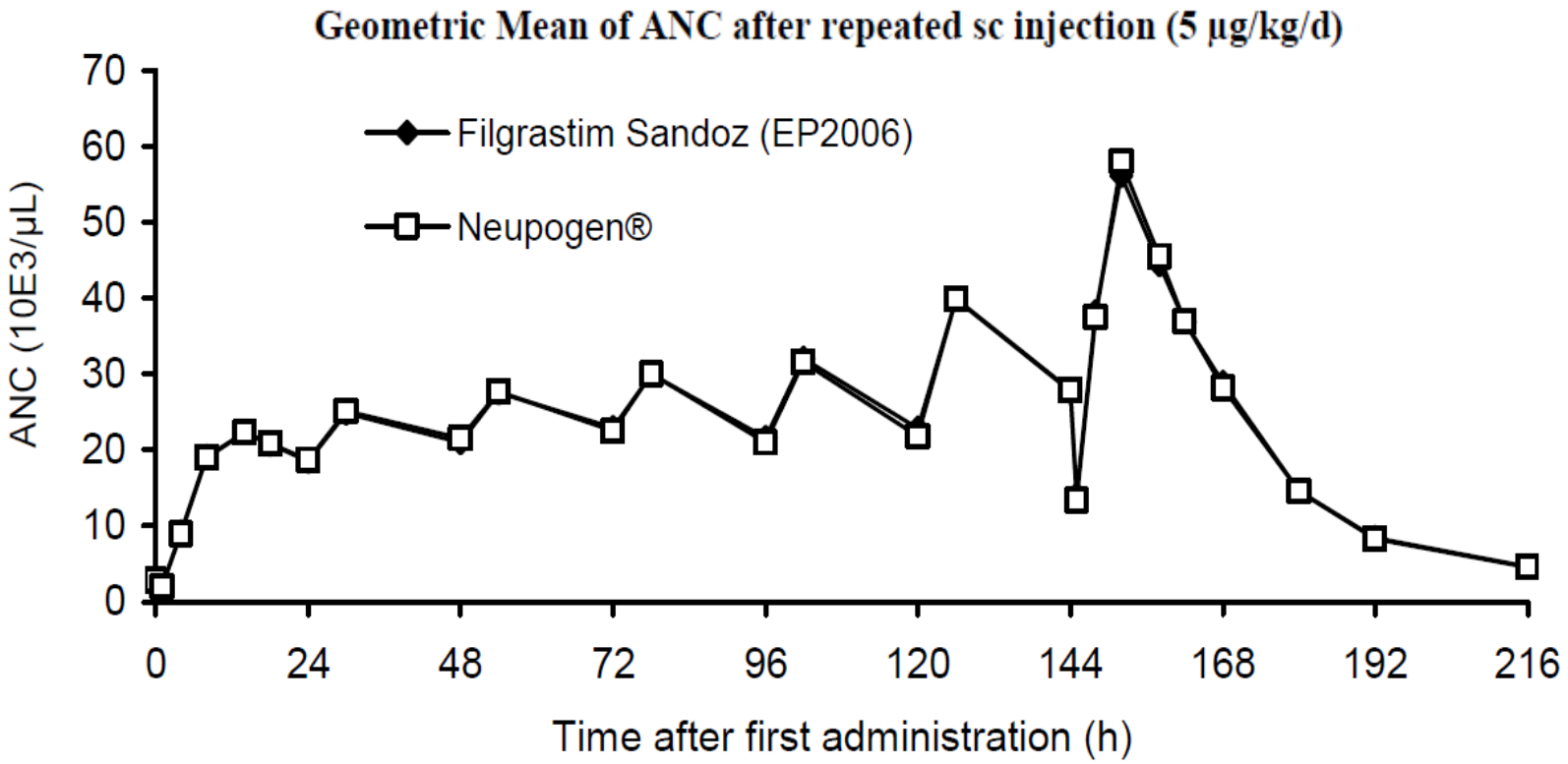


How should extrapolation risk be managed?

The physician's perspective



Phase III clinical trials will be required for biosimilar antibodies



PD markers only suitable for some products

PD=pharmaco dynamics; Source: CHMP Assessment report for Zarzio, page 20; EMA/CHMP/651339/2008

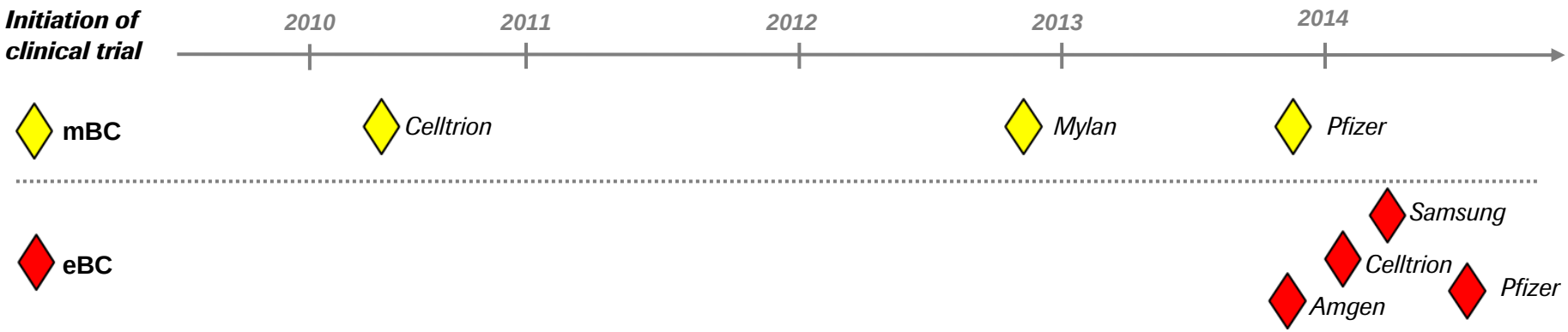
What is the right patient population to establish clinical similarity to Herceptin?

Topic	mBC Advanced metastatic population	eBC Neoadjuvant/adjuvant population
PK	✘ Affected by patients status & tumor burden	✓ Homogeneous population can be selected
PD	✘ Clinically validated PD marker not available	
Clinical efficacy/safety	✘ • Difficult to select homogeneous group. • Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status…). • Population with heterogeneous characteristics affecting final clinical outcome.	✓ Populations less likely to be confounded by baseline characteristics and external factors
Immunogenicity	✘ Immune system affected by performance status and concomitant chemotherapies received	✓ Immune system impaired during chemotherapy cycles, but likely to recover to *normal* status thereafter

mBC=metastatic breast cancer; eBC=early breast cancer; PK=pharmaco kinetics; PD=pharmaco dynamics

The regulatory thinking is evolving

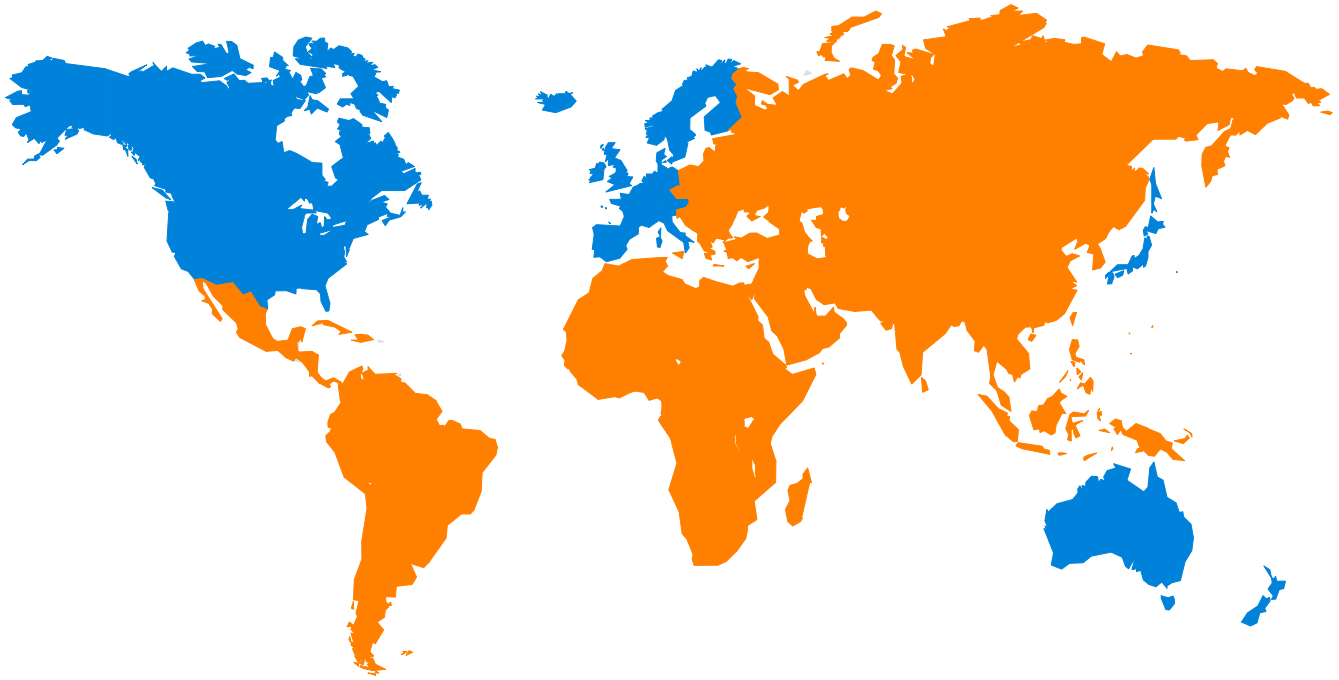
The Herceptin case



	mBC Phase III Start	Regulatory Filing	eBC Phase III Start
Celltrion	Q2 2010	✖	Q1 2014
Mylan	Q4 2012	✖	
Pfizer	Q4 2013		Q2 2014
Samsung			Q2 2014
Amgen			Q4 2013

mBC=metastatic breast cancer; eBC=early breast cancer

Innovative approaches to improve market access



Established markets

Environment increasingly complex
Payers more active/influential

Emerging markets

Build-up of healthcare systems,
but applying stricter cost regulations already

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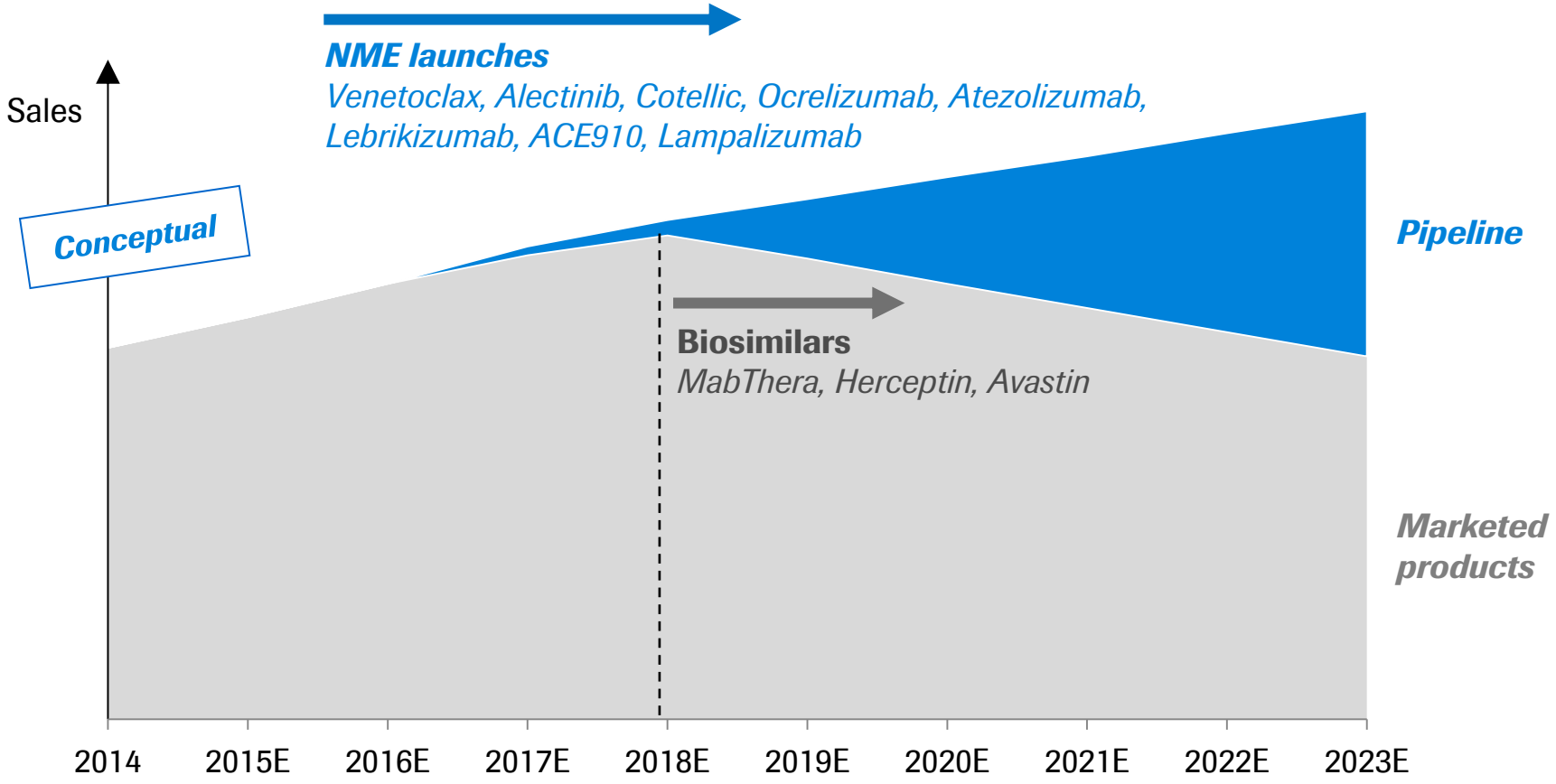
Positive outlook provided at Investor Day 2015

Strong pipeline mitigates biosimilar impact



NME=new molecular entities

Multiple major pivotal trials reading out near term

Significant filing and launch activities ahead

Year	Molecule	Indication	Market opportunity	Incremental infrastructure
2015	Alectinib	ALK+ NSCLC	●◐○	Low to medium
	Cotellic/Zelboraf	Melanoma	●○○	Low
	Venetoclax	Hematology (CLL 17p del)	●●●	Low
2016	Ocrelizumab	Multiple Scelerosis	●●●	Medium
	Atezolizumab	NSCLC, bladder (2/3L)	●●●	Medium
	Lebrikizumab	Asthma, AD, IPF, COPD	●●●	Large
	APHINITY	Adj HER2+ breast cancer	●●●	Low
	GOYA	NHL (aggressive)	●●●	Low
2017	ACE 910	Hemophilia A	●●●	Low to medium
	Lampalizumab	Geographic atrophy	●●●	Low to medium
	GALLIUM	NHL (indolent)	●●●	Low
	Atezolizumab+chemo	NSCLC (1L)	●●●	Low
Post 2017	Taselisib (PI3Ki)	HER2-/HR+ breast cancer	●●●	Low to medium
	Idasanutlin (MDM2)	Acute myeloid leukemia	●●●	Low to medium

Oncology **Neuroscience** **Ophthalmology** **Immunology**

●○○ Small: up to CHF 0.5 bn ●◐○ medium= CHF 0.5 to CHF 1bn ●●● large > CHF1bn

NSCLC=non-small cell lung cancer; CLL=chronic lymphocytic leukemia; AD=atopic dermatitis; IPF=idiopathic pulmonary fibrosis; COPD=chronic obstructive pulmonary disease; NHL=non-Hodgkin's lymphoma; Venetoclax in collaboration with AbbVie

Multiple major pivotal trials reading out near term

Several read-outs to protect established franchises

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Franchise strategies for long term growth

New indications, longer duration and SC conversion

Growth opportunity	Indication	Global peak sales potential
HER2 franchise	Perjeta adjuvant (APHINITY)	
	Herceptin SC*	
CD20 franchise	Gazyva aNHL (GOYA)	
	Gazyva iNHL (GALLIUM)	
	Venetoclax	
	MabThera SC*	

Small: up to CHF 0.5 bn medium= CHF 0.5 to CHF 1bn large > CHF1bn

*Sales replacing current intravenous products; SC=subcutaneous; iNHL=indolent non-hodgkin's lymphoma; aNHL=aggressive NHL

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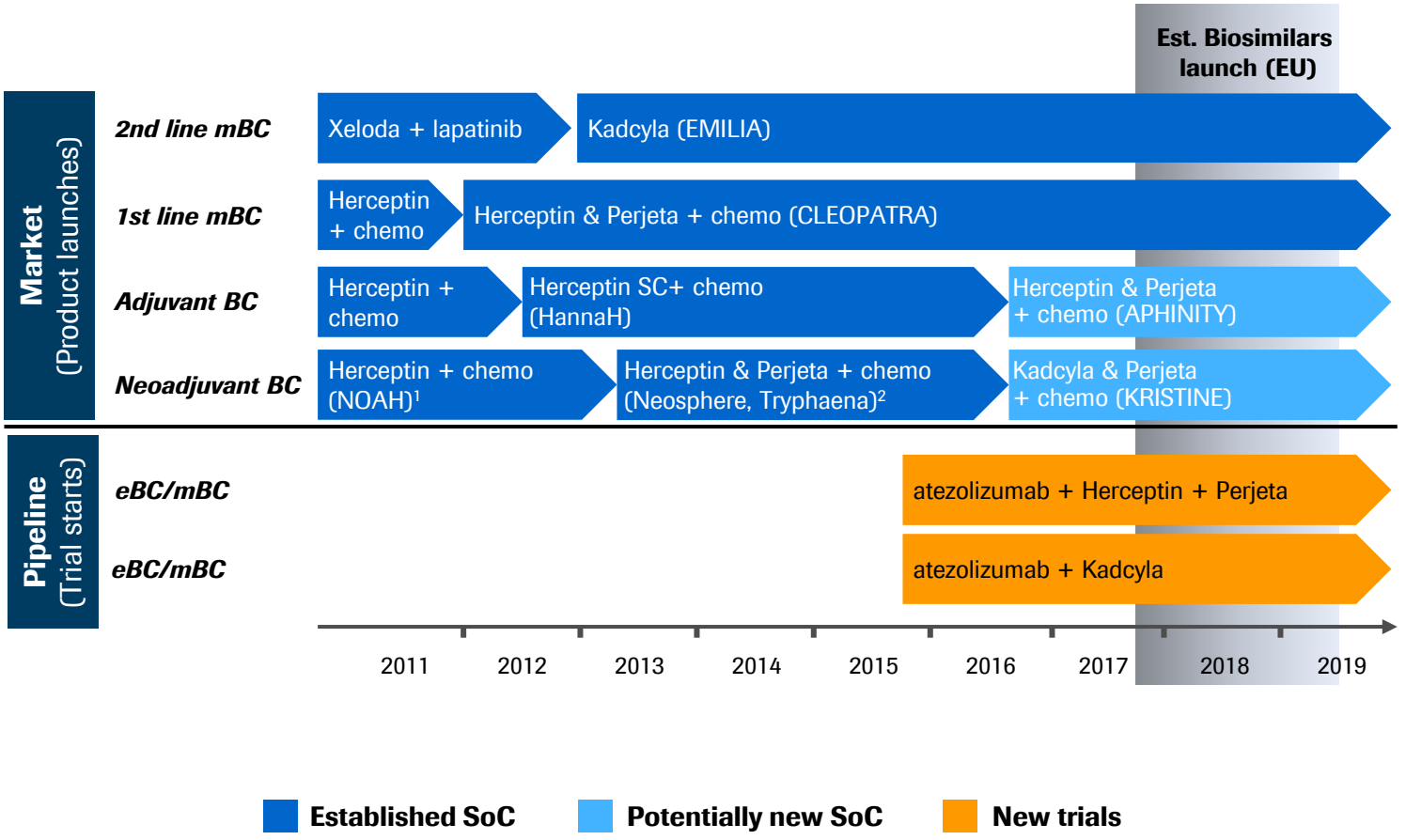
CD20 franchise

Avastin franchise

HER2 franchise

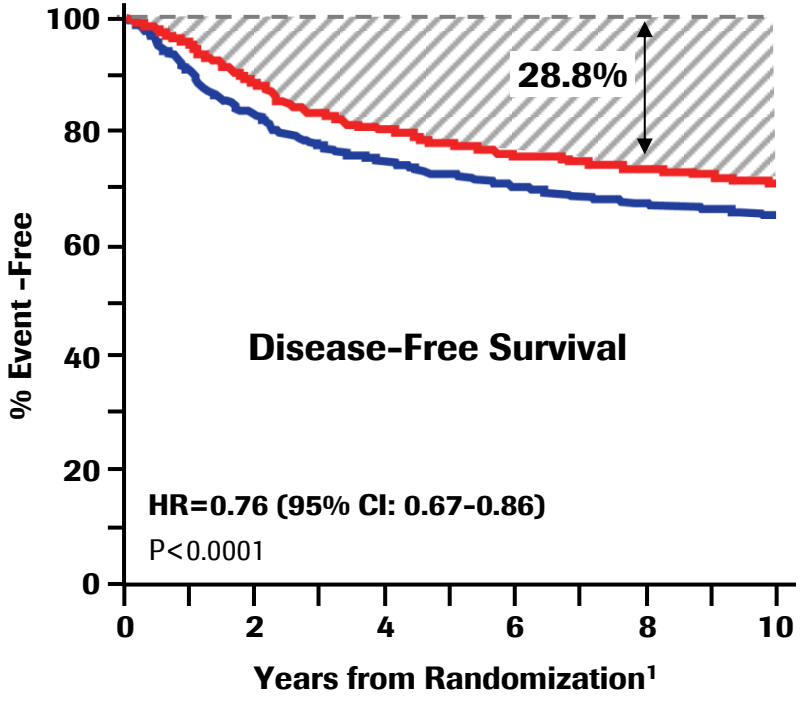
Strengthening standard of care



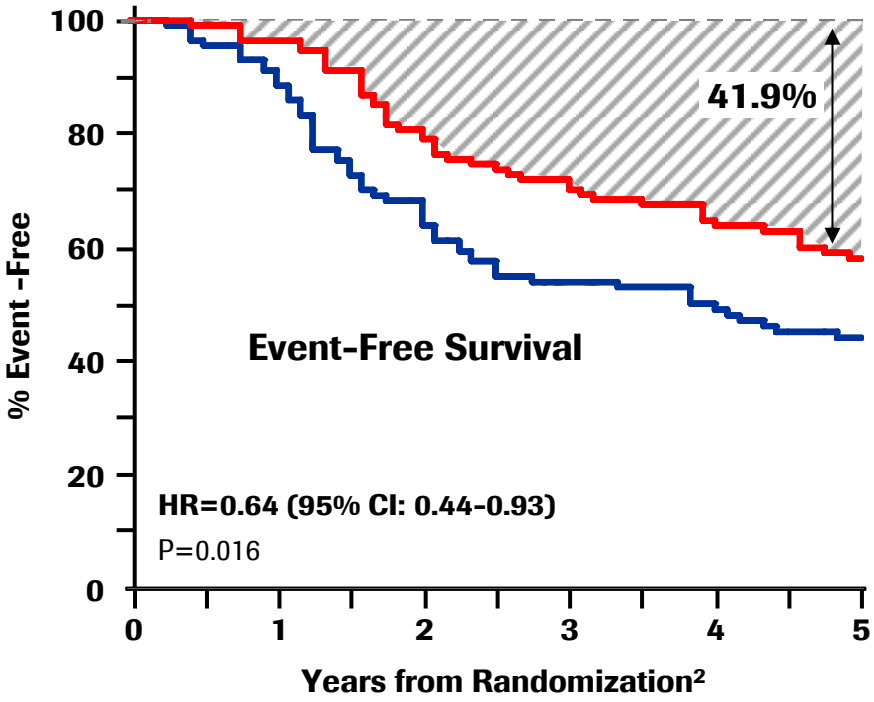
atezolizumab (aPD-L1 MAb); mBC=metastatic breast cancer; eBC=early breast cancer; SC=subcutaneous; SoC=standard of care

HER2 positive eBC: Still high medical need despite major advances

Adjuvant – HERA trial



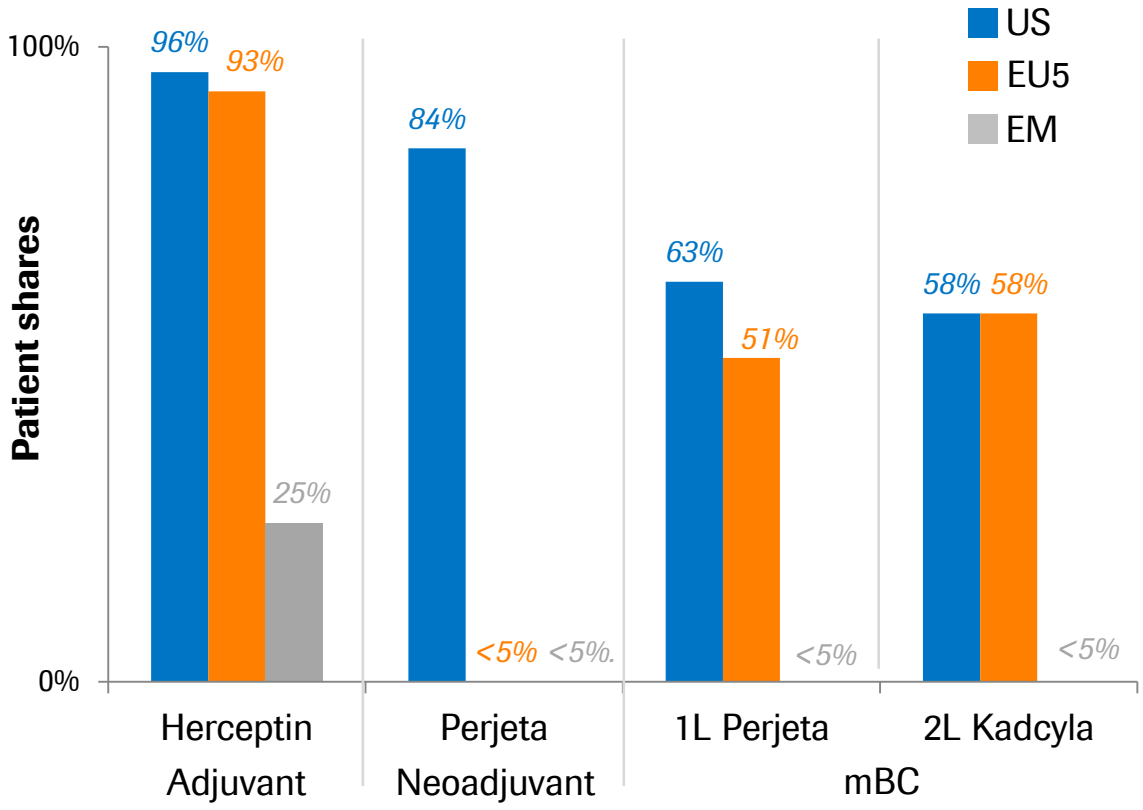
Neoadjuvant – NOAH trial



Without Herceptin With Herceptin

[1] Roche data on file; [2] L. Gianni et al, ASCO Annual Meeting 2013
eBC=early breast cancer

HER2 franchise: Significant growth opportunities in approved indications remain



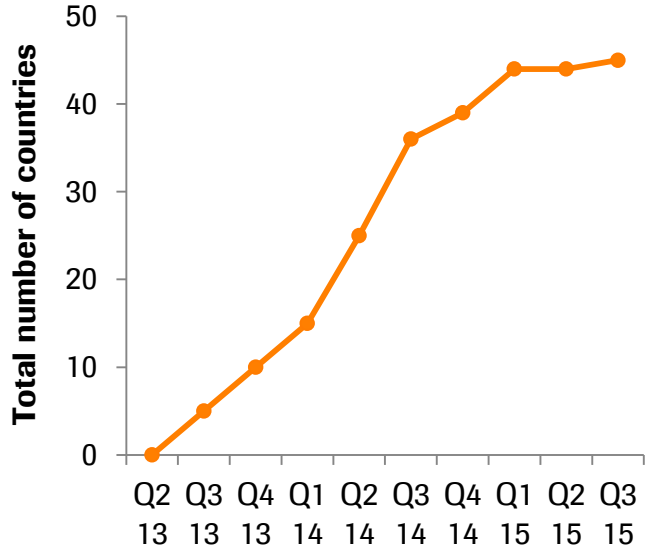
- Increased patient share
- Longer treatment duration
- Emerging markets

Sources: Market research tracking studies - Latest quarter Q315 in EU5 and US; mBC=metastatic breast cancer

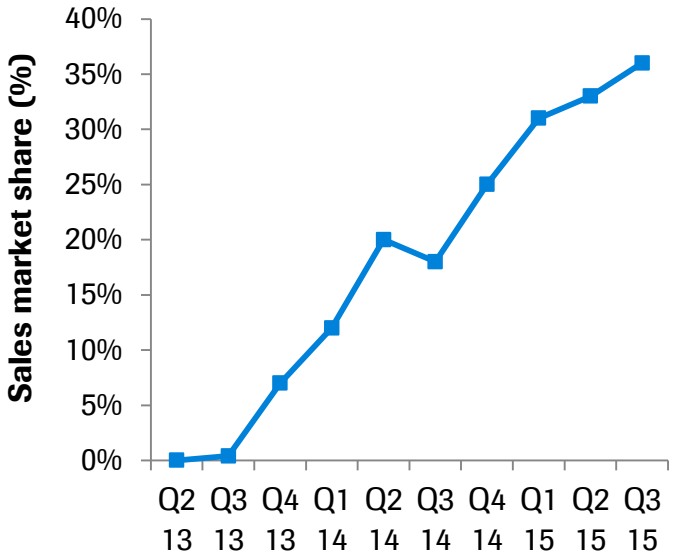
Herceptin SC

Conversion rate exceeds 35% after two years

Number of countries where Herceptin SC has been launched



SC share of Herceptin sales in launched countries



SC=subcutaneous

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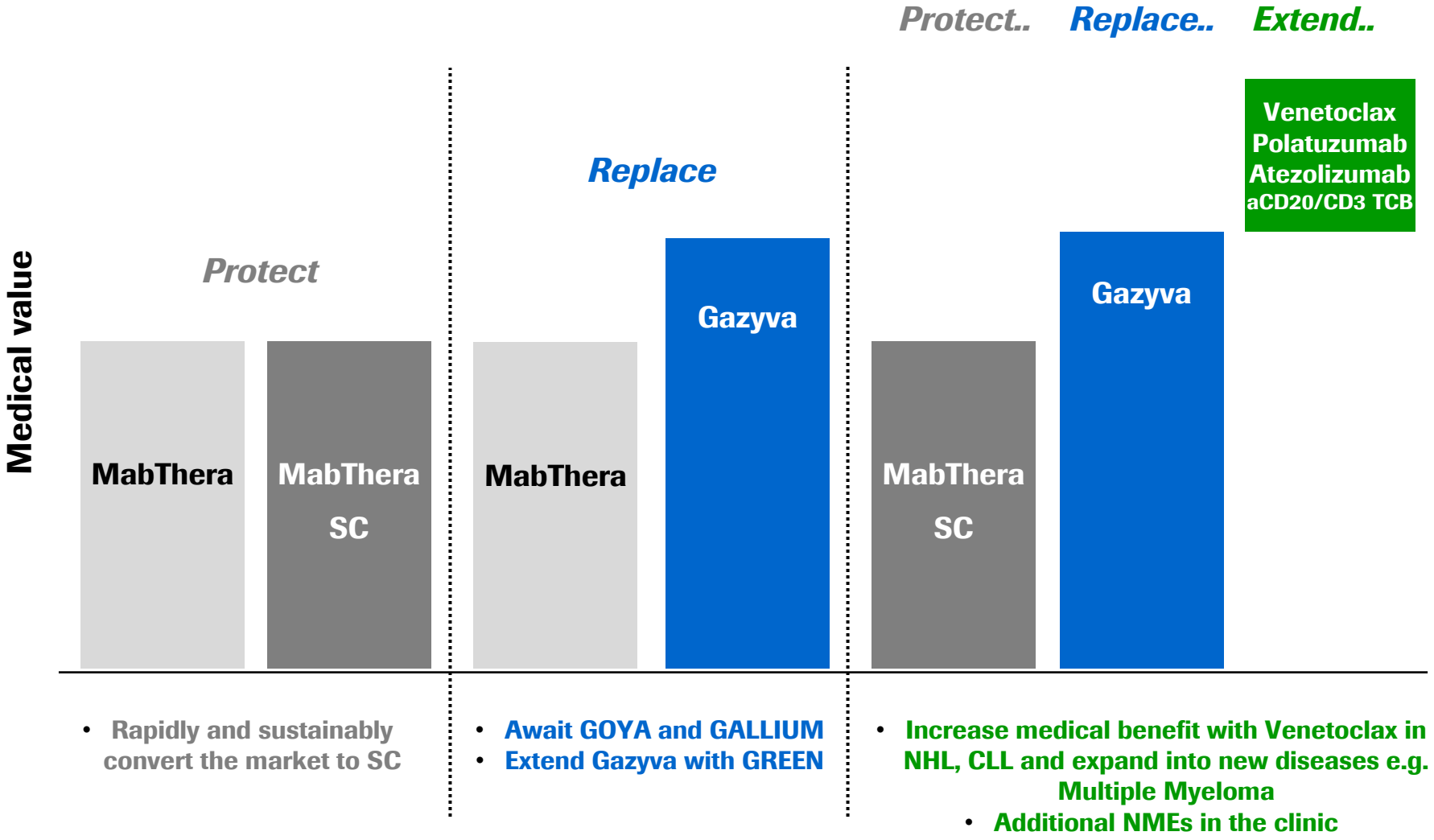
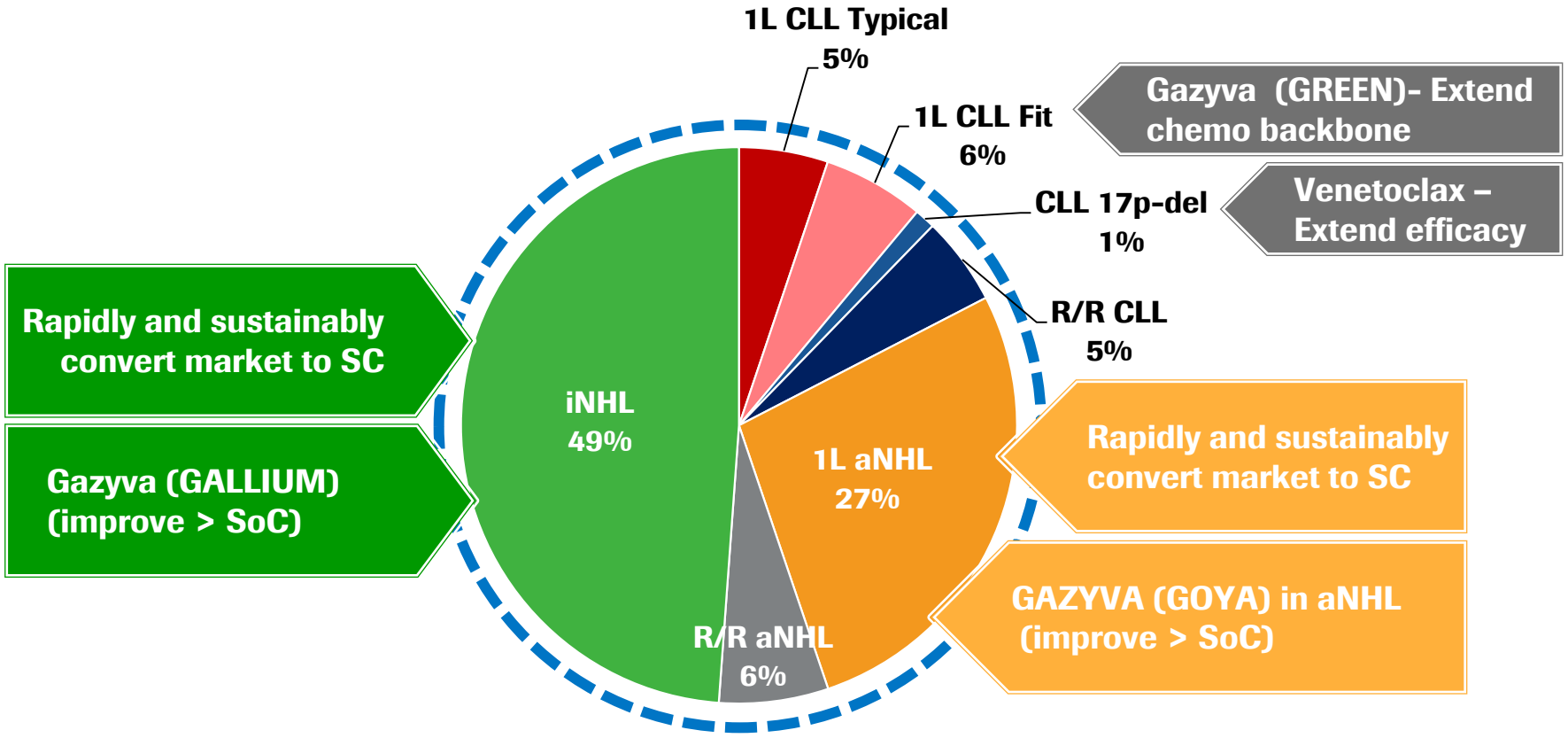
CD20 franchise

Strategy for long term growth



SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin's lymphoma; TCB=T cell bispecific; NMEs=new molecular entities; Venetoclax in collaboration with AbbVie

Multiple approaches to protect MabThera sales

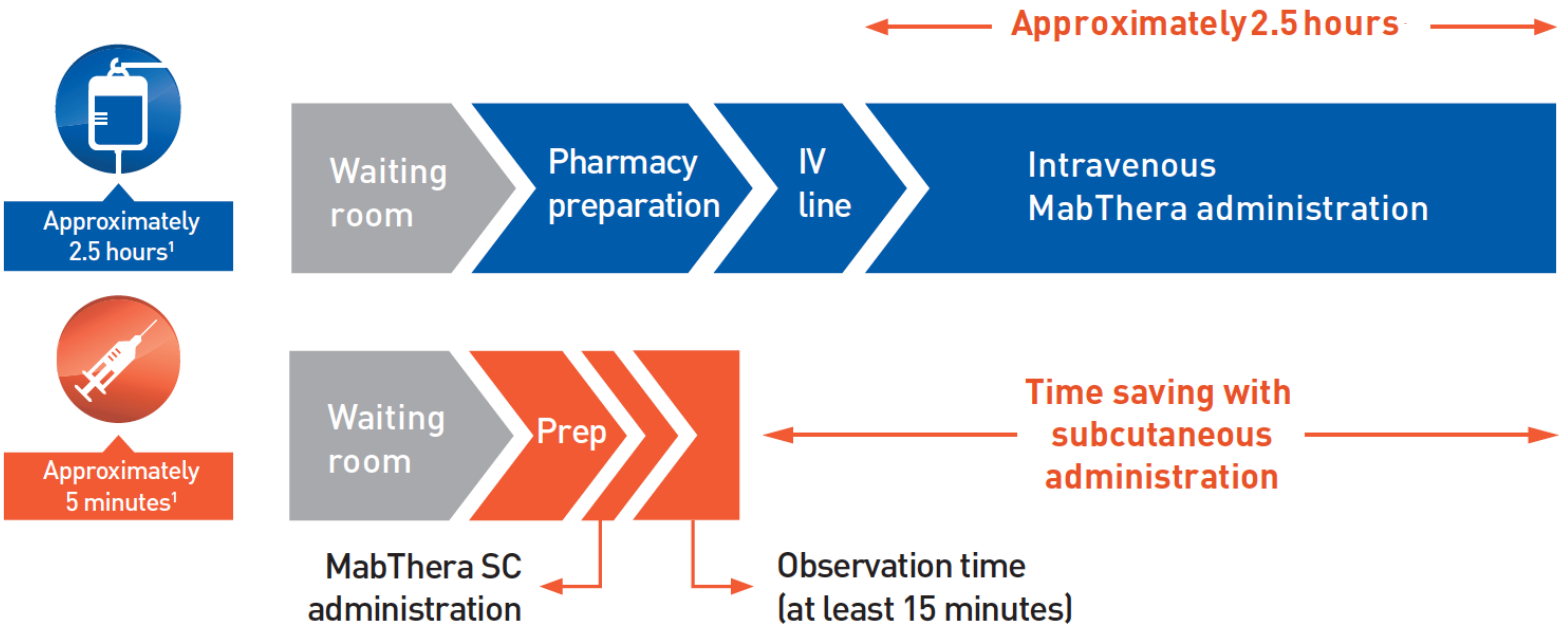


Broad development program for venetoclax as add on and in new tumour types

SoC=standard of care; SC=subcutaneous; CLL=chronic lymphocytic leukemia; iNHL=indolent non-hodgkin's lymphoma; aNHL=aggressive NHL; R/R=relapsed/refractory

MabThera SC

NHL launch ongoing, strong uptake in most markets



- First EU launches in 2014, ongoing or imminent in further countries
- Encouraging initial uptake in majority of markets, comparable to Herceptin SC
- Slower conversion in countries with strong incentives to use IV (Germany) or limited reimbursement (UK)

SC=subcutaneous; IV=intravenous

Development plan hematology franchise I

8 NMEs in the clinic

Roche

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Orlando, 5-8 Dec

	Compound	Combination	Study name	Indication	Ph1 Ph2 Ph3	
NHL	***Gazyva***	*+bendamustine*	*GADOLIN*	iNHL (Rituxan refractory)		✓
	Gazyva	*+CHOP*	*GOYA*	aNHL		
	Gazyva	*+chemo*	*GALLIUM*	1L iNHL		
CLL	***Gazyva***	*+FC/bendamustin/Clb*	*GREEN*	CLL and R/R CLL		
NHL	***venetoclax****	***+Rituxan/+Rituxan****+bendamustine*	*CONTRALTO*	R/R FL (iNHL)		
	venetoclax	***+Rituxan****+CHOP****/Gazyva****+CHOP*	*CAVALLI*	1L aNHL		
	venetoclax	***+Rituxan****+bendamustine*		R/R NHL		
	venetoclax			R/R CLL and R/R NHL		
CLL	***venetoclax***	***+Rituxan***		R/R CLL and SLL		
	venetoclax	***+Gazyva***	*CLL14*	CLL		
	venetoclax	***+Rituxan***	*MURANO*	R/R CLL		
	venetoclax			R/R CLL 17p		✓
	venetoclax			R/R CLL after ibru/idel		
	venetoclax	***+Rituxan****+bendamustine*		R/R CLL and CLL		
	venetoclax	***+Gazyva***		R/R CLL and CLL		
MM	***venetoclax***			R/R MM		
	venetoclax	*+bortezomib+dexamethasone*		R/R MM		
AML	***venetoclax***			AML		
	venetoclax	*+decitabine/+azacitidine/+LdAraC*		AML		

✓ = filed

venetoclax (Bcl2 inhibitor); NME=new molecular entity; iNHL=indolent non-hodgkin`s lymphoma; aNHL=agressive NHL; CLL=chronic lymphoid leukemia; R/R CLL=relapsed/refractory CLL; MM=multiple myeloma; AML=acute myeloid leukemia; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; FC=fludarabine, cyclophosphamide; LdAraC=low dose cytarabine; * venetoclax in collaboration with AbbVie

Development plan hematology franchise II

8 NMEs in the clinic

	Compound	Combination	Study name	Indication	Ph1	Ph2	Ph3
NHL	***polatuzumab****	***+Rituxan/Gazyva***	*ROMULUS*	R/R FL and aNHL			
	polatuzumab	***+Gazyva+benda/Rituxan+benda***		R/R FL (iNHL) and aNHL			
	polatuzumab	***+Gazyva+CHP/Rituxan+CHP***		1L aNHL			
	polatuzumab	***+Gazyva****+lenalidomide*		R/R FL and aNHL			Q4
	polatuzumab	***+Gazyva+venetoclax***		R/R FL and aNHL			Q4
NHL	***undisclosed ADC***			R/R NHL			
NHL	***atezolizumab***	***+Gazyva***		R/R FL (iNHL) and aNHL			
	atezolizumab	***+Gazyva****+lenalidomide*		R/R FL and aNHL			Q4
	atezolizumab	*+CHOP*		aNHL			Q4
	atozolizumab	*+bendamustine*		R/R FL and aNHL			Q4
	atezolizumab	***+Gazyva+polatuzumab***		R/R FL and aNHL			Q1
MM	***atezolizumab***	*+lenalidomide*		MM			
MDS	***atezoliozumab***	*+azacitidine*		MDS			
	aCD20/CD3 TCB			Heme tumors			
AML	***LSD1 inhibitor****			AML			
	idasanutlin			Heme tumors			

= additional trials starting in Q4 15 and Q1 16

polatuzumab vedotin (aCD79b ADC); atezolizumab (aPD-L1 MAb); aCD20/CD3 TCB (RG7828); LSD1 inhibitor (RG6016); idasanutlin (MDM2 antagonist); iNHL=indolent non-hodgkin`s lymphoma; R/R FL=relapsed/refractory follicular lymphoma; aNHL=agressive NHL (DLBCL); MM=multiple myeloma; MDS=myelodysplastic syndrom; AML=acute myeloid leukemia; *in collaboration with Seattle Genetics; ** in collaboration with Oryzon Genomics

Gazyva and venetoclax read-outs in CLL

Roche

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	Venetoclax[1]	R-Venetoclax[8]	Gazyva-bendamustine[7]	Gazyva-chlorambucil[2]	R-chlorambucil[2]	R-FC[3]	Ibrutinib[4]		Idelalisib[5]	R-Benda-Ibrutinib[6]
Line	R/R	R/R	1L	1L	1L	1L	1L	R/R	R/R	R/R
N	78	49	158	238	233	408	31	61	54	30
ORR	77%	86%	78.5%	75.5%	65.9%	90%	71%	67%	56%	90%
CR/CRi	23% CR/CRi	41% CR/CRi	32.3%	22.2% CR/CRi	8.3% CR/CRi	44%	10 %	3%	4%	10%
MRD-negative	**BM: 55% (6/11)***	**BM: 75% (15/20) 53% (ITT)**	**PB: 58.9% BM: 27.8% (ITT)**	**PB: 31% (41/132) BM: 17% (15/88)**	**PB: 2% (3/150) BM: 3% (2/72)**	**PB: 63% (90/143)**	**Not reported**		**Not reported**	**Not reported**

References:
1. John Seymour, EHA 2014
2. Goede *et al. J Clin Oncol* 2013; 31:suppl; abstr 7004 (presentation update)
3. Böttcher *et al. J Clin Oncol* 2012 ;30:980-988
4. Byrd *et al. Blood* (ASH Annual Meeting Abstracts) 2012 120: Abstract 189
5. Flinn *et al. Hematol Oncol* 2013; 31 (Suppl. 1): Abstract 297
6. Brown *et al. Haematologica* 2012; 97(s1) : Abstract 0543
7. Stilgenbauer et al., ASH 2015 (GREEN subgroup analysis)
8. Ma Shuo et al., ASH 2015 (abstract 80273)

CLL=chronic lymphoid leukemia; R=Rituxan; FC=fludarabine; R/R=relapsed/refractory; 1L=first-line; ORR=overall response rate; CR=complete response; CRi=complete response with incomplete bone marrow recovery; MRD=minimal residual disease; BM=bone marrow; PB=peripheral blood
*MRD tests performed in local unvalidated laboratories in a small number of patients; in patients with a CR who have been tested

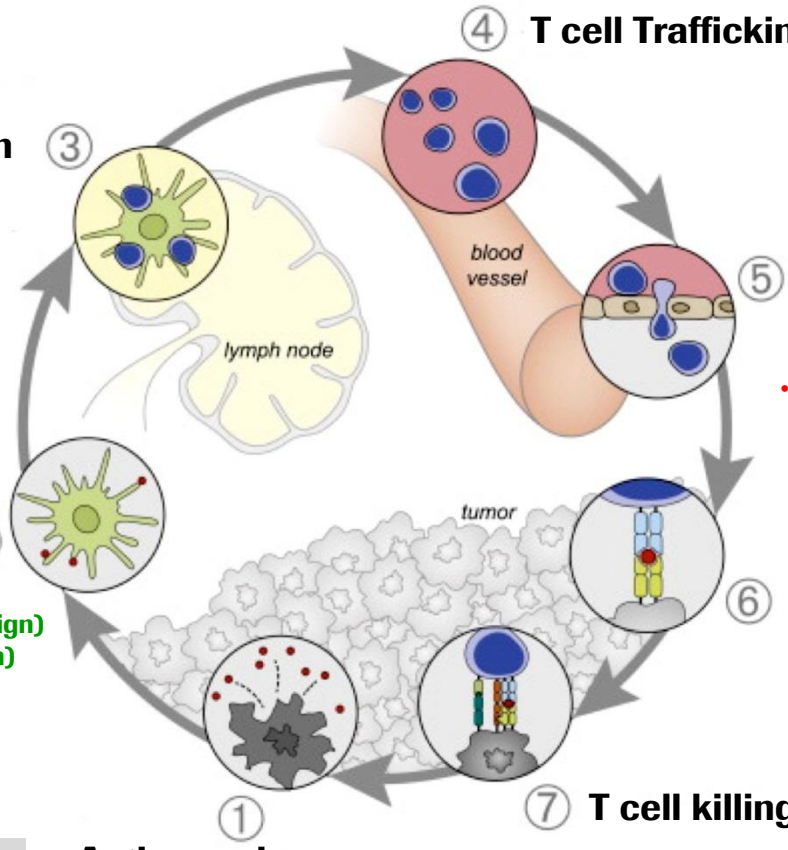
Biosimilar: Ten years on the making

Roche's Strategy: Innovate, Protect, Expand

Portfolio outlook

- HER2 franchise
- CD20 franchise
- **Avastin franchise**

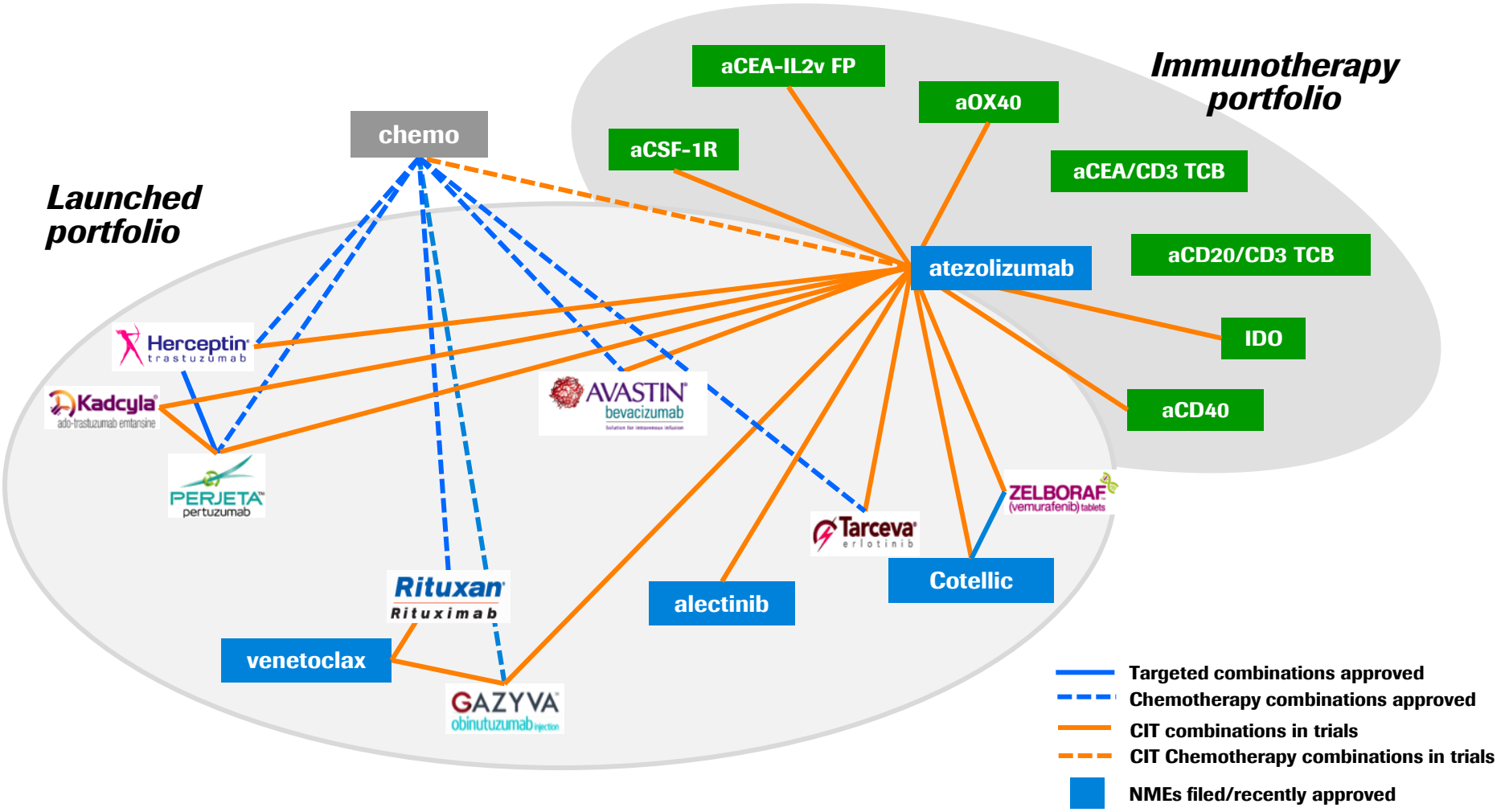
Cancer immunotherapy (CIT): 8 NMEs in the clinic



- Clinical development CIT
- Preclinical development CIT
- Established therapies outside CIT
- * Partnered projects (external)

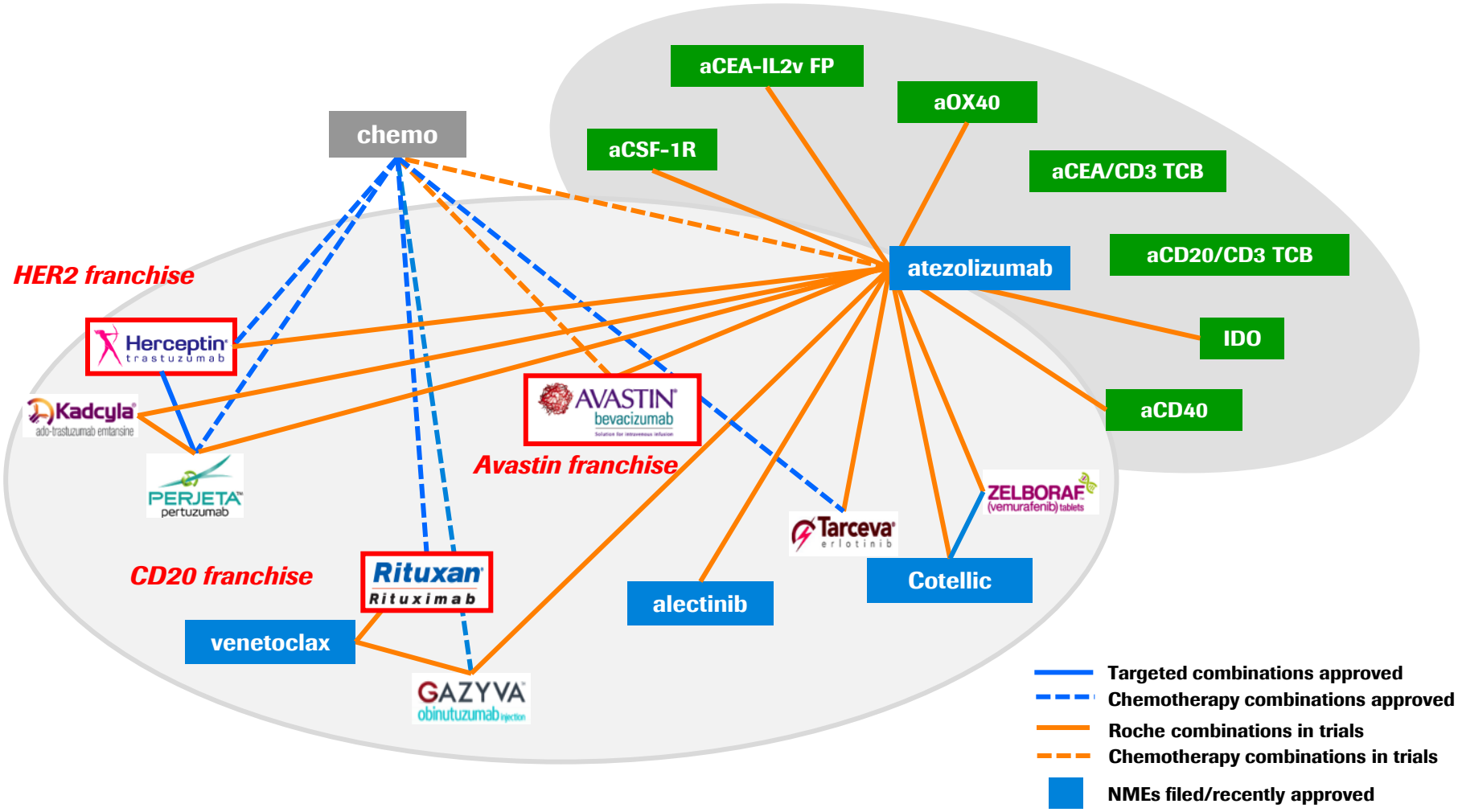
Chen and Mellman. Immunity 2013

Setting new standards, developing combinations



Setting new standards, developing combinations

Building on established backbones



Avastin+atezolizumab combos entered Ph3

Phase I

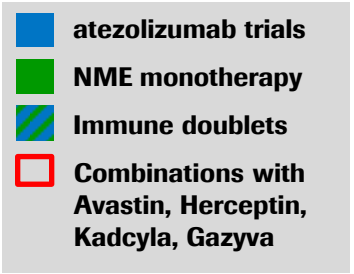
- **atezo** Solid tumors
- **atezo+chemo** Solid tumors
- **atezo+Tarceva** NSCLC
- **atezo+Zelboraf** Melanoma
- **atezo+Cotellic** Solid tumors
- **atezo+Avastin** Solid tumors
- **atezo+Gazyva** R/R FL / aNHL
- **atezo+Avastin+chemo** Solid tumors
- **atezo+lenalidomide** MM
- **atezo+Zelboraf+Cotellic** Melanoma
- **atezo+alectinib** ALK+ NSCLC
- **atezo+/-azacitidine** MDS
- **atezo+Gazyva+chemo** R/R FL/aNHL
- **atezo+Gazyva+lenalidomide** R/R FL/aNHL
- **atezo+Herceptin+Perjeta** HER2+ eBC/mBC
- **atezo+Kadcyla** HER2+ eBC/mBC
- **aCEA-IL2v FP** Solid tumors
- **aOX40** Solid tumors
- **aCEA/CD3 TCB** Solid tumors
- **IDO** Solid tumors
- **aCSF-1R** Solid tumors
- **aCD20/CD3 TCB** heme tumors
- **atezo+ipilimumab** Solid tumors
- **atezo+IFN-alfa** Solid tumors
- **atezo+aCD40** Solid tumors
- **atezo+aOX40** Solid tumors
- **atezo+aCSF-1R** Solid tumors
- **atezo+aCEA-IL2v FP** Solid tumors
- **atezo+IDO** Solid tumors

Phase II

- **atezo** NSCLC (Dx+)
- **atezo** 2/3L NSCLC
- **atezo+Avastin** 1L Renal
- **atezo** 1/2L Bladder

Phase III

- **atezo** 2/3L NSCLC
- **atezo** 2/3L Bladder
- **atezo+Avastin+chemo** 1L non sq NSCLC
- **atezo+chemo** 1L non sq NSCLC
- **atezo+chemo** 1L sq NSCLC
- **atezo** 1L non sq NSCLC (Dx+)
- **atezo** 1L sq NSCLC (Dx+)
- **atezo+chemo** 1L TNBC
- **atezo+Avastin** 1L RCC
- **atezo** Adjuvant MIBC (Dx+)
- **atezo** Adjuvant NSCLC (Dx+)

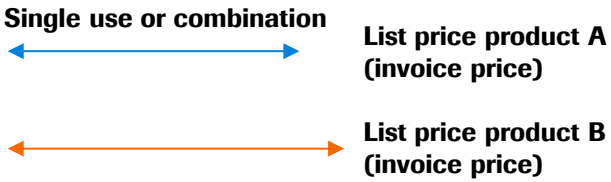


Status as of Nov 5, 2015

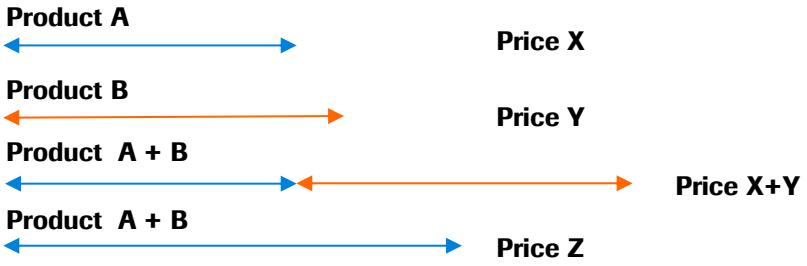
Combination pricing in oncology

"Ensures benefits of combination therapies are reflected while considering the limits of healthcare budgets"

***Now** – unit of drug has same price, whether used as single agent or in combination*



***Future** – price varies by single or combination use based on benefit*



(+)

- Addresses the reality of combination treatments, particularly oncology
- Takes healthcare budget into consideration

(-)

- Not all drug combos are from the same company
- High complexity with many possible combinations

Doing now what patients need next