Creating innovative antibodies for cancer & severe autoimmune diseases

J.P. Morgan 33rd Annual Healthcare Conference, 11-14 Jan 2016

DISCLAIMER

Introduction

Creating value from highly differentiated antibodies

Rich pipeline with multiple proprietary programs
- Oncology & severe autoimmune diseases
- 4 products in clinical phase

Strategic alliances with premier pharma partners
- Industrial partners
- Innovative Access Program

Competitive technology suite
- Antibodies with differentiated modes of action
- Based on llama immune system and unique Fc engineering

Financial strength
- Strong cash position (€ 46.6M/$ 49.3M Sept 2015)
- € 1.4B potential future income from partnerships

Business model maximizing shareholder value

Generating differentiated antibody product candidates...

Novel + **arGEN-X technology suite** = **Maximally differentiated mAbs**

... towards Phase II value inflection point

Value

Aug 2015 Product portfolio

ARGX-110: Ph I ☑
ARGX-111: Ph I ☑
ARGX-113: CTA submission ☑
ARGX-115: Preclinical PoC ☑

End 2017 Product portfolio

ARGX-110: Ph II ☐
ARGX-111: Ph II, partnered ☐
ARGX-113: Ph II autoimmune ☐
ARGX 115: Ph I oncology ☐
Strategic pharma alliances ☐

Platform deals

Shire ☑
BAYER ☑
IAP*: ☑
UCL, de Duve

Preclinical product deals

锐意 RuiYi ☑
LEO ☑

Preclinical PoC

Clinical PoC

Discovery → **Preclinical development** → **Early clinical development** → **Late clinical development**

* IAP: Innovative Access Program

Rich pipeline approaching major value inflection points

- **Cancer immunotherapy**

- **Cancer metastasis**

- **Autoimmune diseases**

- **Non-dilutive income**

Drug Candidate	Indication	Preclinical	Phase 1	Phase 1b	Owner-ship
ARGX-110 (CD70)	Blood cancers *TCL*				
ARGX-110 (CD70)	Solid tumors				
ARGX-115 (GARP)	Cancer immunotherapy				Wholly owned
ARGX-111 (c-MET)	Solid tumors Blood cancers				
ARGX-113 (FcRn)	Autoimmunity *Myasthenia gravis*				
ARGX-110 (CD70)	Autoimmunity				
Discovery	Autoimmunity Cancer	*multiple*			
锐意 RuiYi	Autoimmunity Cancer				
Shire	Undisclosed				Partnered
LEO	Chronic inflammation				
BAYER	Undisclosed				

Creating innovative antibodies

Unique technology platform: multiple modes of action

Broad range of leads of therapeutic quality

Extend half-life

Boost cell killing

Clear autoantibody/disease target, Sweeping concept
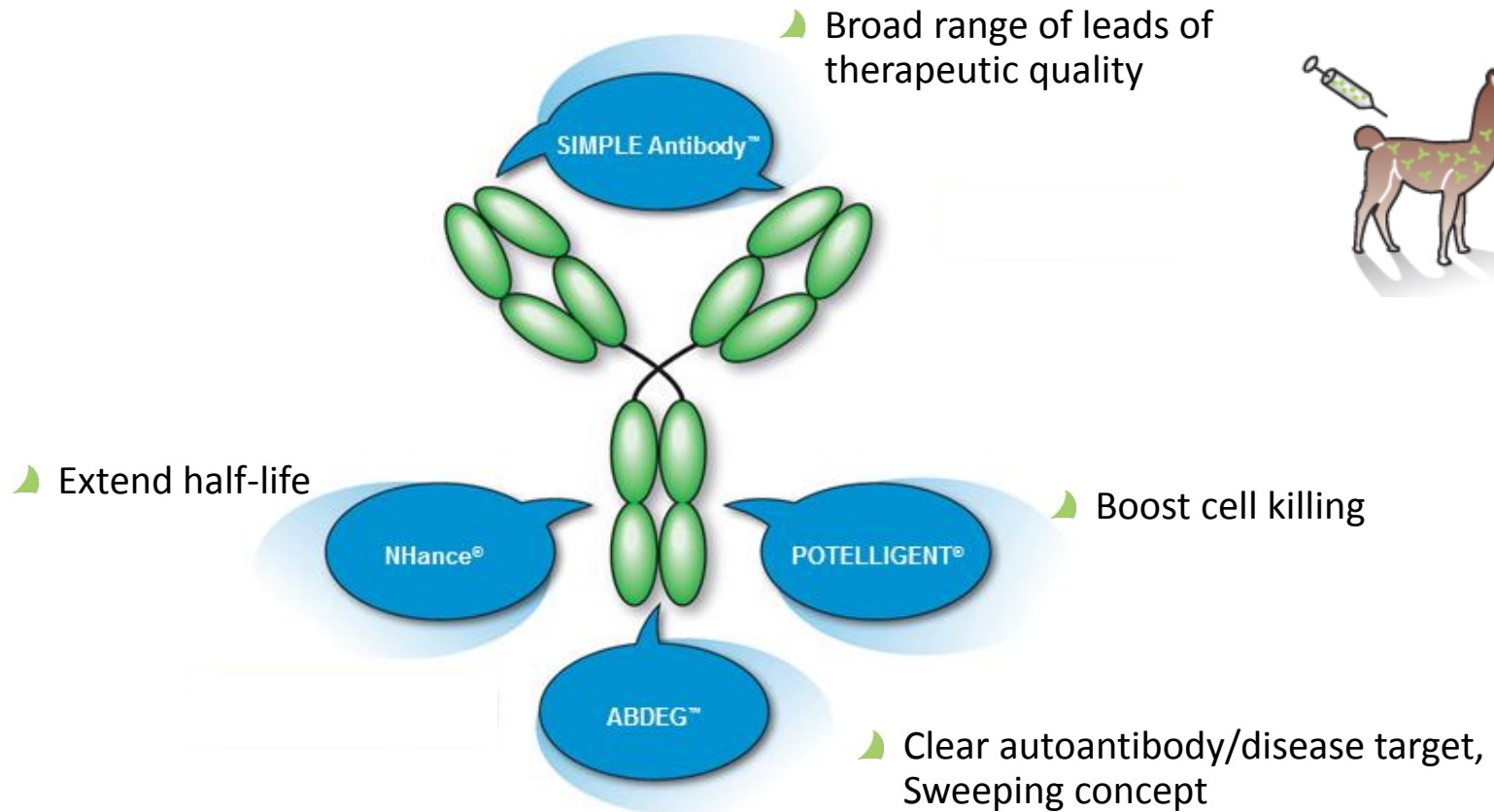
- SIMPLE Antibody™: Unlock novel and complex targets
- NHance™, ABDEG™, POTELLIGENT®: Enhance SIMPLE Antibody™ leads
- Multiple layers of IP protection in place until 2028-2033 (excluding any PTE)

Continuous technology innovation – antibody mediated target clearance

NHance™/ABDEG™
FcRn modulation

SIMPLE ANTIBODY™
pH-dependent target binding
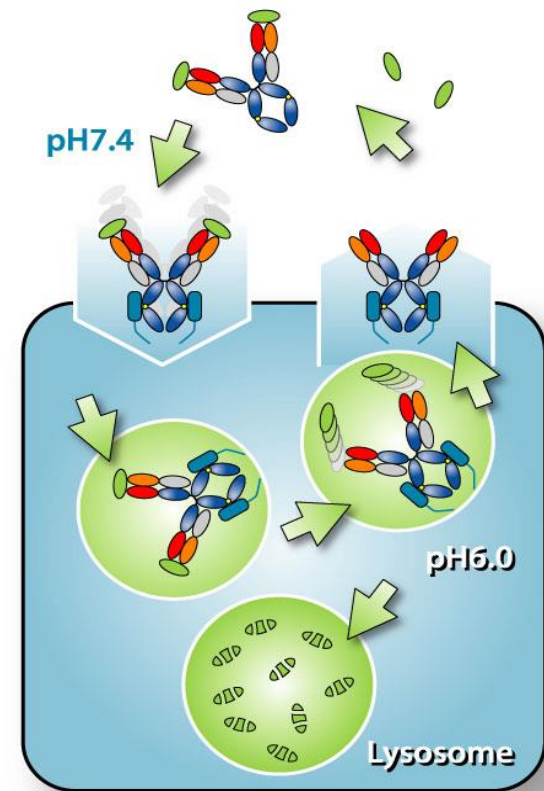
- Clinical potential for indications:
    - with high circulating target concentrations
    - which require fast target clearance
    - e.g. inflammatory cytokines (receptors)

ARGX-113

What is autoimmune disease?

- Immune system attacks own organs

- Tissue destruction by autoantibodies

- Common diseases include: multiple sclerosis, lupus, rheumatoid arthritis, psoriasis, myasthenia gravis

Why target autoimmune diseases?

- 10% of population suffers from autoimmune diseases

- Antibody therapy used for rheumatoid arthritis, multiple sclerosis & psoriasis

- ARGX-113 targets severe autoimmune diseases

Current treatment

- High dose corticosteroids and broad immunosuppressive agents: severe side effects

- IVIg or Plasmapheresis: incomplete effect, slow onset of action

ARGX-113: Potential breakthrough in autoimmune disease

Treatment	Plasmapheresis in human *	ARGX-113 in primate **
Decrease in antibody levels (%)	62.8	75
Decrease in disease score (%)	60.8	N/A
Speed of onset	slow	fast

ARGX-113: How it works - Antibody clearance capability

Proprietary Fc mutations	Block IgG recycling	Resulting in rapid autoantibody clearance

ABDEG™

MST

HN

pH7.4

pH6.0

Lysosome

Repeat dose ARGX-113

20 mg/kg

cyno IgG % T_0

days after infusion
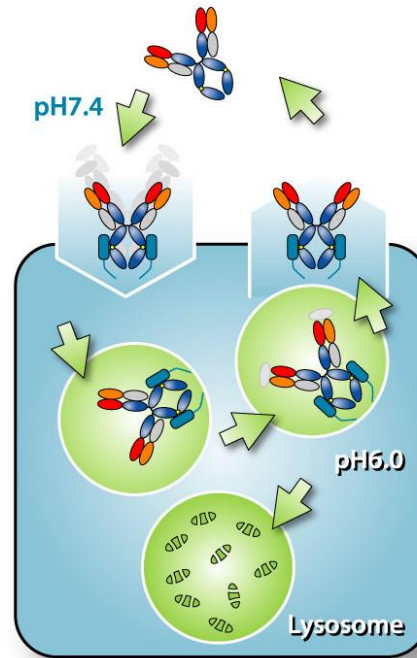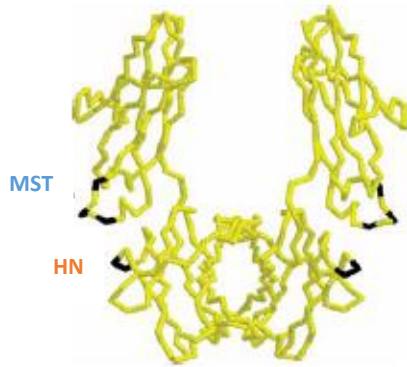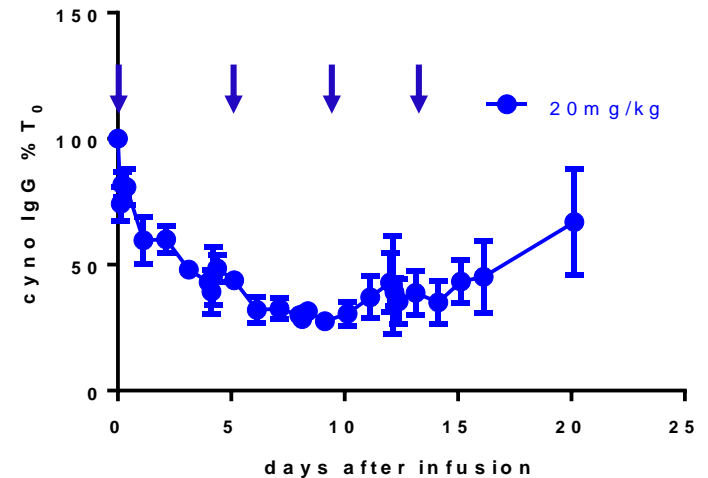
- Saturation of PD effect at doses ≤ 20 mg/kg
- Repeat dosing > single dose

Vaccaro and Ward, 2005, Nature Biotechnology

Clinical rationale for targeting autoantibody clearance

Myasthenia gravis autoantibody levels and disease score following therapy			
Treatment*	**Plasmapheresis**	**Immunoadsorption**	**IVIg**
Decrease in antibody levels (%) after treatment	62.2 ± 6.3	55.1 ± 3.2	28.9 ± 3.8
Decrease in disease score (%) after treatment	60.8 ± 3.5	42.4 ± 4.2	23.8 ± 3.7
Clinical efficacy rate after 14 days**	12/15	7/10	6/15
Duration of hospital stay (days)	12.80 ± 0.28	13.50 ± 0.50	16.00 ± 0.50

* Comparison between 3 cycles of Plasmapheresis/Immunoadsorption every 24h-48h and 5 cycles of IVIG every 24h   (Liu et al, 2009)

** Clinical ly effective if disease score has improved by >50% 14 days after treatment

- Degree of autoantibody reduction: correlates with clinical improvement & reduced hospital stay
- Similar observations reported for other autoimmune disorders

ARGX-113: *In vivo* PoC
MuSK-MG transfer model – therapeutic setting
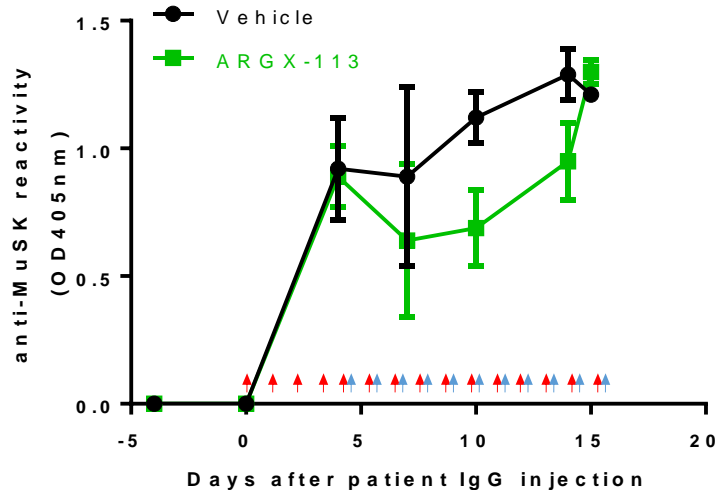
Anti-MuSK Ab-levels	Inverted Mesh
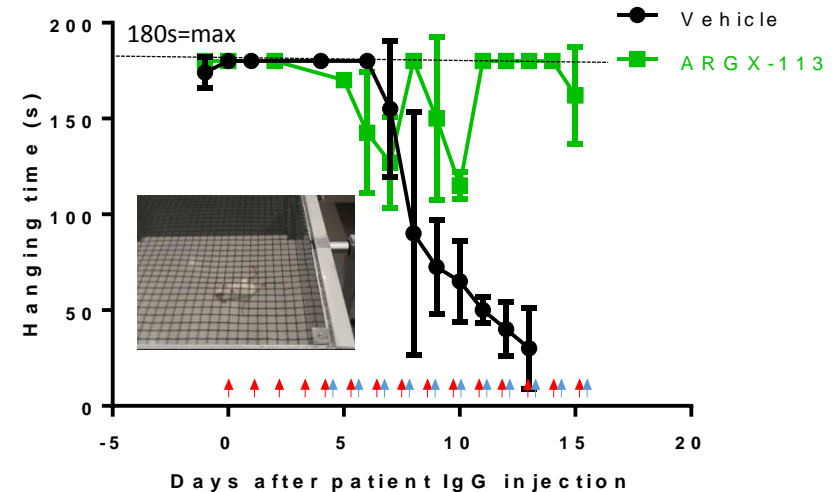
↑ **Patient IgG injection (37 mg)**
↑ **ARGX-113 treatment (1 mg)**

- Daily injection of MuSK-MG patient IgG causes Myasthenia gravis in NOD/SCID mice
- ARGX-113 (1mg) administration:
  - reduces autoantibody levels (anti-MuSK Ab-levels)
  - stabilizes disease: measured by inverted mesh (see graph) and grip strength (not shown)

ARGX-113: Phase 1 study design & interim safety read out
Double-blinded, placebo-controlled study in healthy volunteers

| Single ascending dose (SAD) | Multiple ascending dose (MAD) | Data analysis |

(mg/kg)

50

End SAD in-life phase

25

End MAD in-life phase

25

10

10

2

- **Complete safety profile**
- **Complete PK/PD profile**
- **Ph2 dose selected**

0.2

4:2 → active:placebo

6:2 → active:placebo
Up to 6 doses

4 months | **4 months** | **2 months**
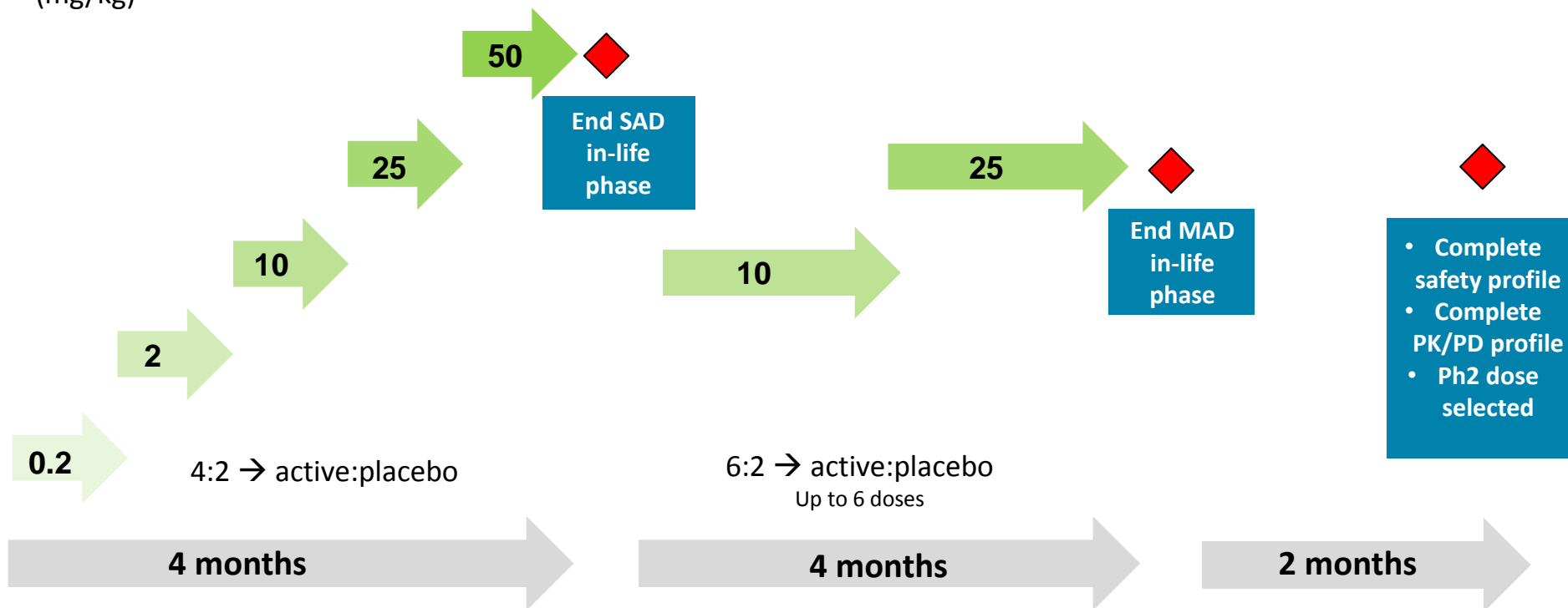
- SAD completed according to plan (38 healthy volunteers in total)
- Favourable safety and tolerability profile observed (no serious adverse events reported)

16

ARGX-113: PD marker readout for SAD
Double-blinded, placebo-controlled study in healthy volunteers

Rapid, deep and specific IgG reduction
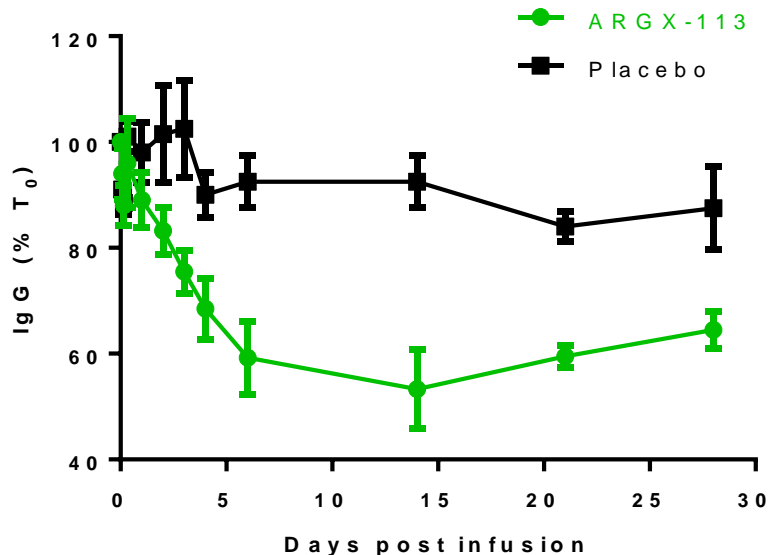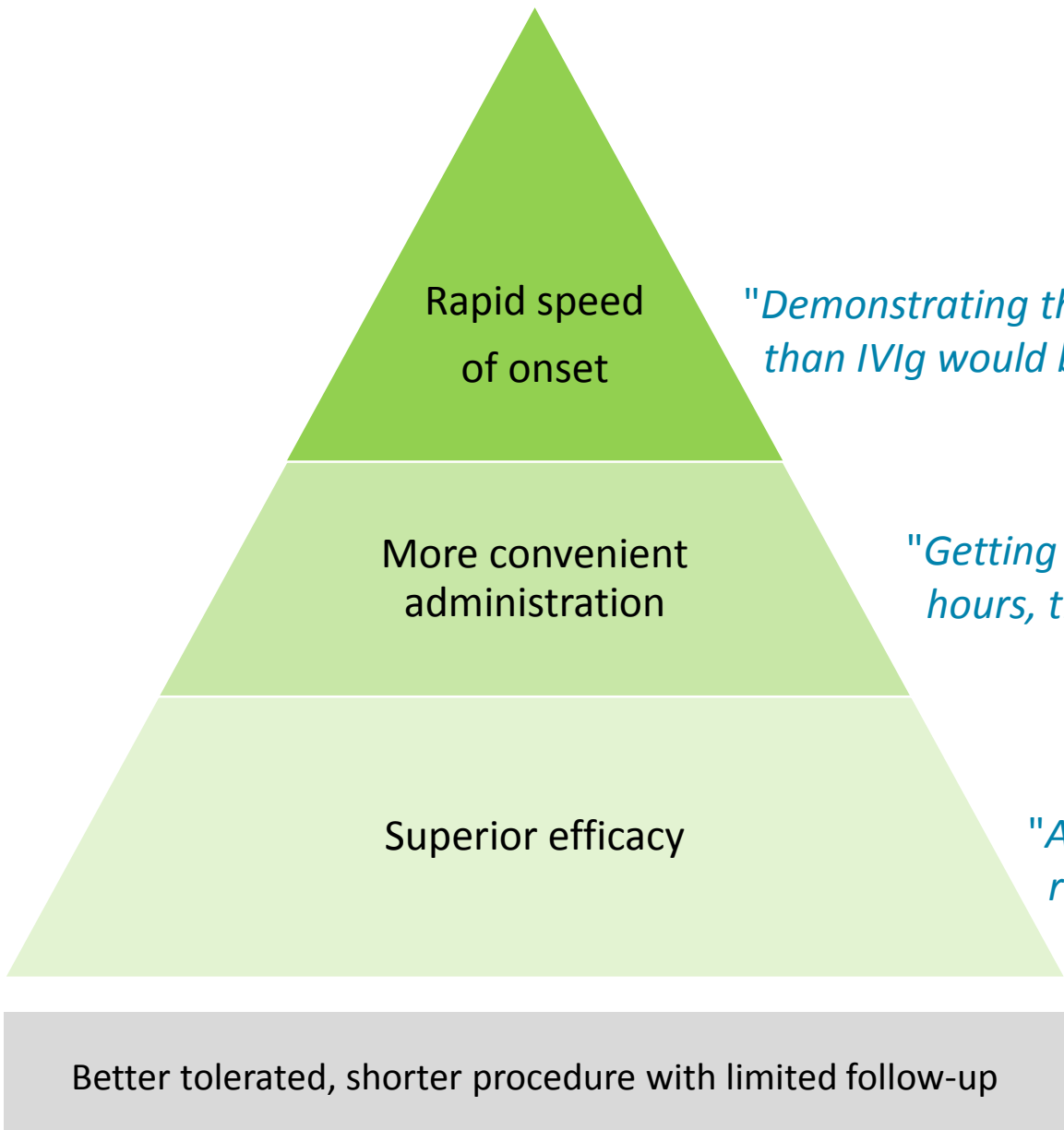
	ARGX-113 vs. IVIg[*]
Speed of IgG reduction	>>>
Level of IgG reduction	>>
Duration of PD effect	>

* Extrapolated based on literature data

- Single 2h infusion: rapid reduction of IgG, not affecting IgM/IgA levels
- Maximal PD effect (~50% IgG reduction) as of 6 days after infusion
- Low IgG levels maintained for >1 week

ARGX-113 vs. IVIG/PLEX: Key differentiators for MG

Rapid speed of onset

"Demonstrating that its onset of action is faster than IVIg would be fantastic," MG KOL

More convenient administration
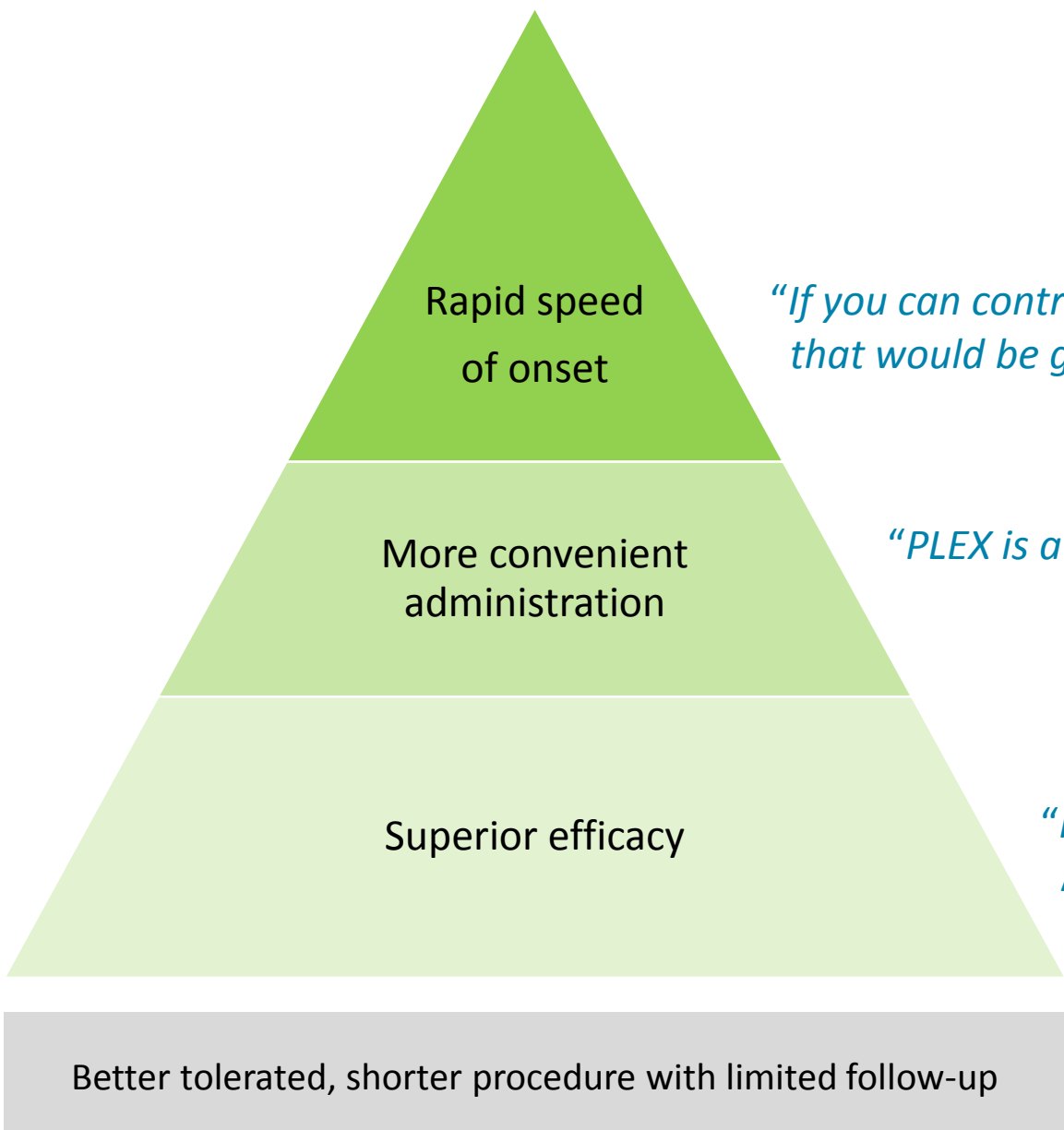
"Getting an infusion done within 2 hours, that is an attractive piece" MG KOL

Superior efficacy

"Acute MG crisis, I don't think it responds all that well to IVIg," MG KOL

Better tolerated, shorter procedure with limited follow-up

ARGX-113 vs. IVIG/PLEX: Key differentiators for ABD

Rapid speed of onset

"If you can control the disease within a week or two, that would be great," ABD KOL

More convenient administration

"PLEX is a nightmare to apply," ABD KOL

Superior efficacy

"IVIg just doesn't work that great," ABD KOL

Better tolerated, shorter procedure with limited follow-up

ARGX-113:   What next?

Next steps

Clinical Status

- First healthy volunteer study ongoing (SAD)
- Multiple Ascending Dose study (MAD)

Market potential

Benchmark therapeutic treatments

- IVIg: annually > $ 4B (autoimmune diseases approx. 50%)
- IVIg: $ 79K/cycle
- Benlysta®: $ 35K/year
- Plasmapheresis: $ 101K/cycle
- Xolair® annual sales exceed $ 800M

ARGX-110

ARGX-110:   3 distinct modes of action

1. Block tumor growth signal

2. Kill tumor

3. Restore immune surveillance

Tumor cell

CD27
CD70
CD70
CD27
CD70
CD70
CD27
CD70
Tregs

1
2
3
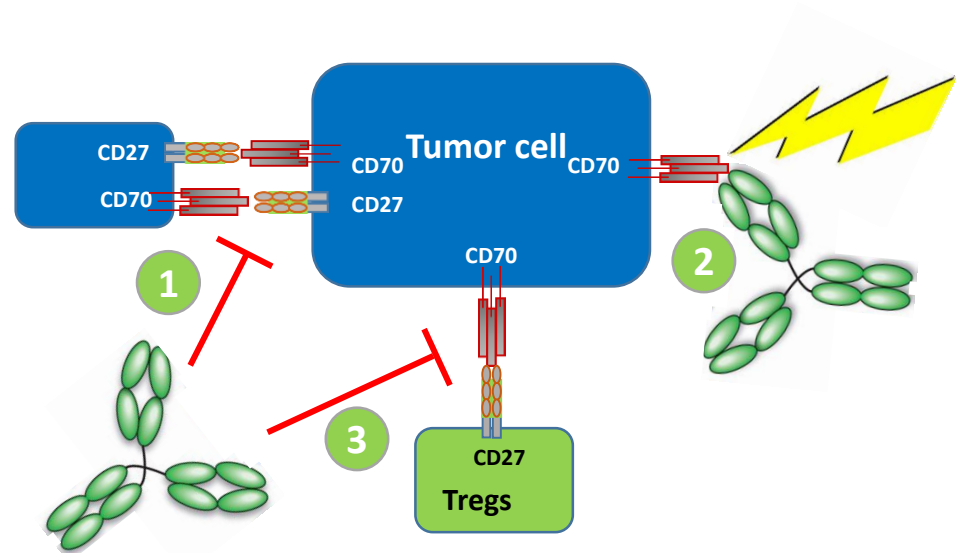
Silence 2014

ARGX-110: CD70/CD27 pathway highly relevant in TCL

CD70/CD27 on tumor cells
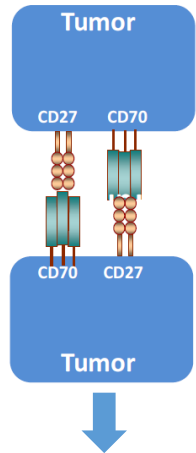
Proliferation & survival

IHC of CD70 expression in TCL biopsies

ALCL-T (n=14) — 40%/1+

CTCL (n=14) — 100%/3+

PTCL (n=3) — >80%/3+

TCLnos (n=2) — >80%/3+
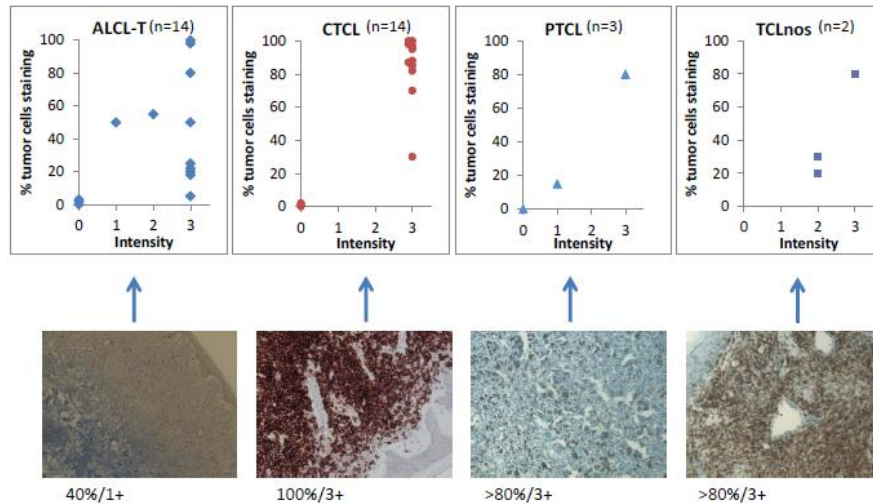
sCD27 levels in TCL patient sera

TCL patients: Serum sCD27 levels
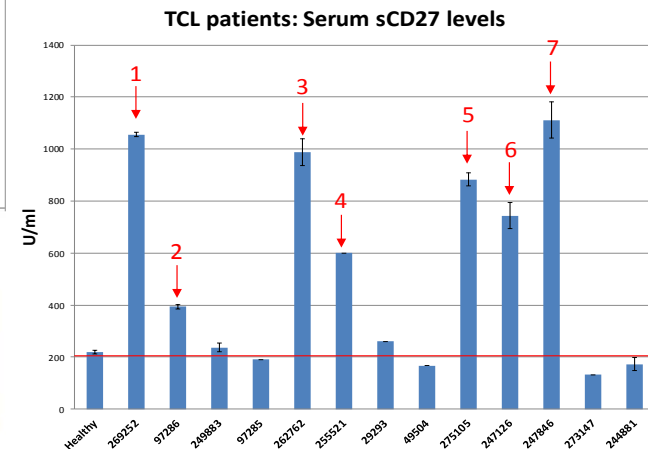
- CD70 strongly overexpressed across different TCL types
- Elevated sCD27 levels suggest strong pathway activity in TCL

ARGX-110: Proof of biological activity in 2 patients with Cutaneous T-Cell Lymphoma (Sézary-Syndrome)

Blood compartment cleared from malignant cells (■)
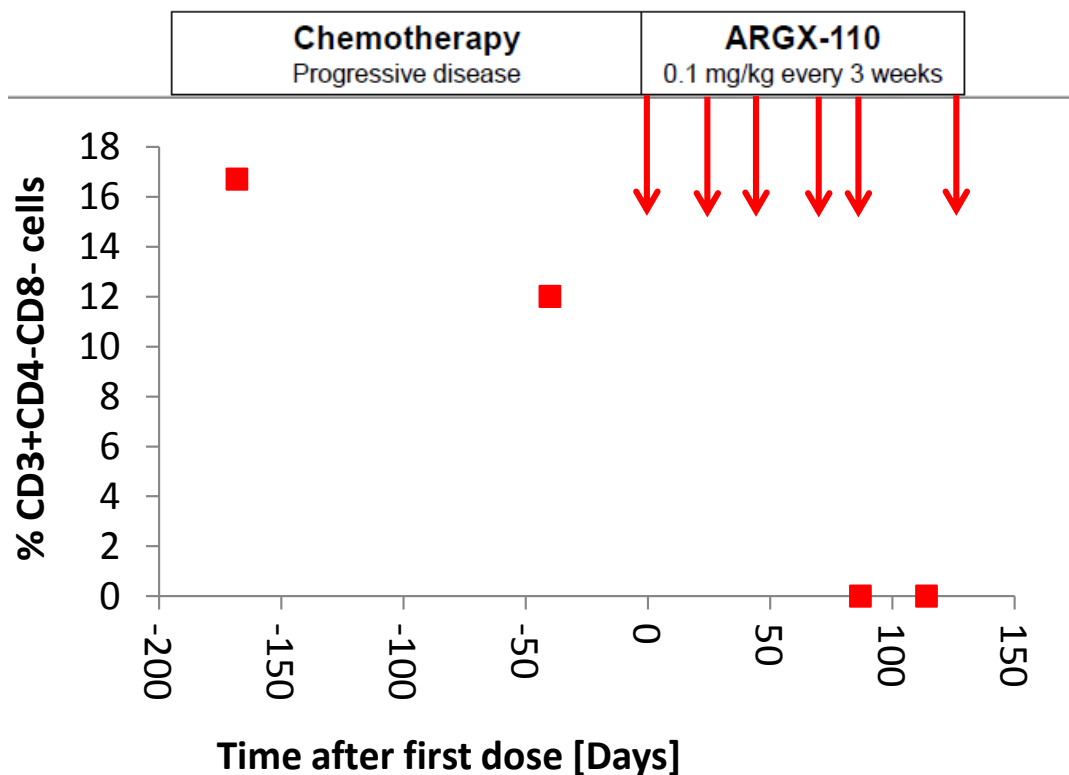
Stabilized skin lesions

Chemotherapy	ARGX-110
Progressive disease	0.1 mg/kg every 3 weeks

% CD3+CD4-CD8- cells vs **Time after first dose [Days]**

a. Pre treatment

b. Post cycle 2

c. Post cycle 3
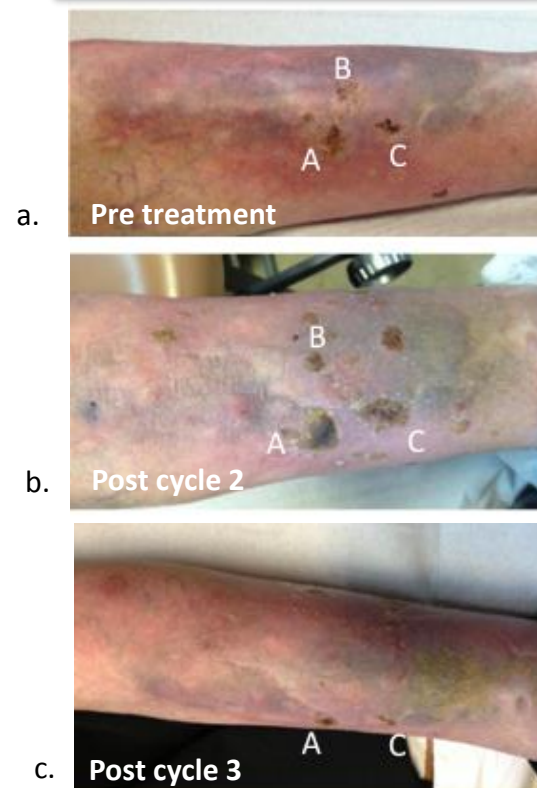
- 78 year old woman with CTCL-SS; refractory to multiple lines of chemotherapy
- ARGX-110 treatment (0.1 mg/kg every 3 weeks)
    - Complete response in blood compartment
    - Stabilized disease in skin lesions (see image a. & c.) & lymph nodes
- Elimination of CD70 positive Sézary cells from blood in 2nd CTCL-SS patient

ARGX-110: Proof of biological activity in patient with Cutaneous Follicular Helper T Cell Lymphoma

Stable disease in skin lesions

Illustration CTCL patient

- 55 year old male with cutaneous T_{FH} lymphoma
- Disease in skin
- Treated with Interferon and PUVA

- ARGX-110 treatment (5 mg/kg)
  - Stabilized disease up to cycle 3
  - After 3 cycles: skin lesions decreased in number and size
  - Patient already 10 cycles on study (6 months)

ARGX-110: Proof of biological activity in patient with Angioimmunoblastic T-Cell lymphoma (AITL)

Tumor shrinkage in lymph nodes
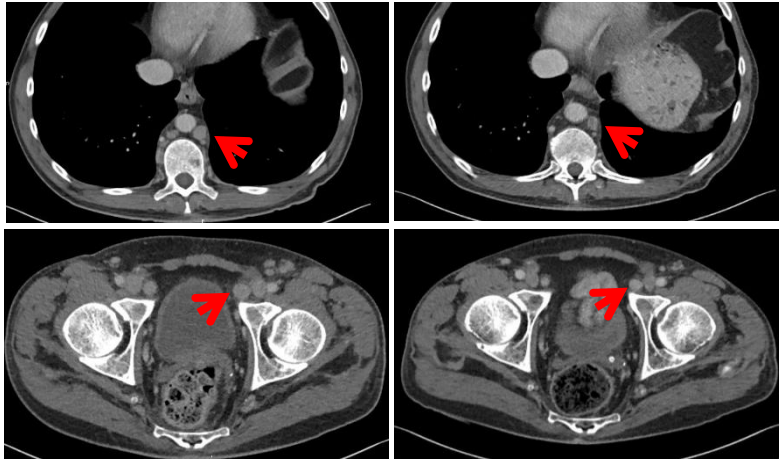
Ref. Lesions	Shrinkage
L1	24%
L2	4%
L3	4%
L4	39%
Non-Ref. Lesions	
L5	65%
L6	50%
L7	59%
L8	43%

Transfusion independent

LDH

ARGX-110   ARGX-110   ARGX-110

IU/ml

Days after first dose ARGX-110
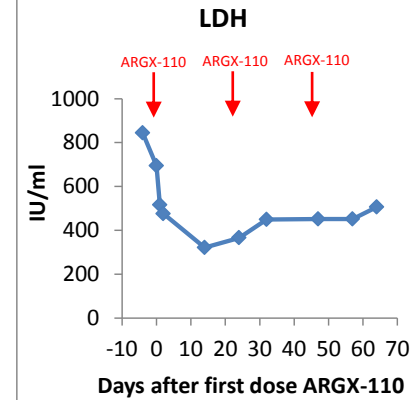
- 61 year-old male AITL patient with severe Hemolytic Anemia
- Refractory to chemotherapy: CHOP + Etoposide/Cyclosporine /Bendamustine - Transplant

- After 2 doses of ARGX-110 (5 mg/kg)
  - Clinical response in lymph nodes
    - Reference lesions shrink between 4-40 %
    - Clear tendency for all other lesions to shrink
  - Clinical response in blood
    - Transfusion independent
    - Coomb positive → Coomb negative after 1 cycle

- Patient anecdote -

Hb

ARGX-110   ARGX-110   ARGX-110

g/dl

Days after first dose ARGX-110

26
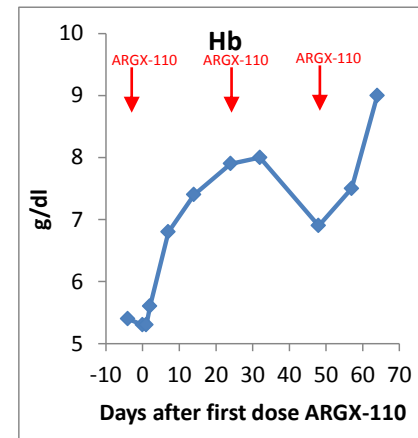
ARGX-110/BCR-ABL1 inhibitor eliminates leukemic stem cells in CML model

Curative potential of combo treatment ARGX-110/BCR-ABL1 inhibitor
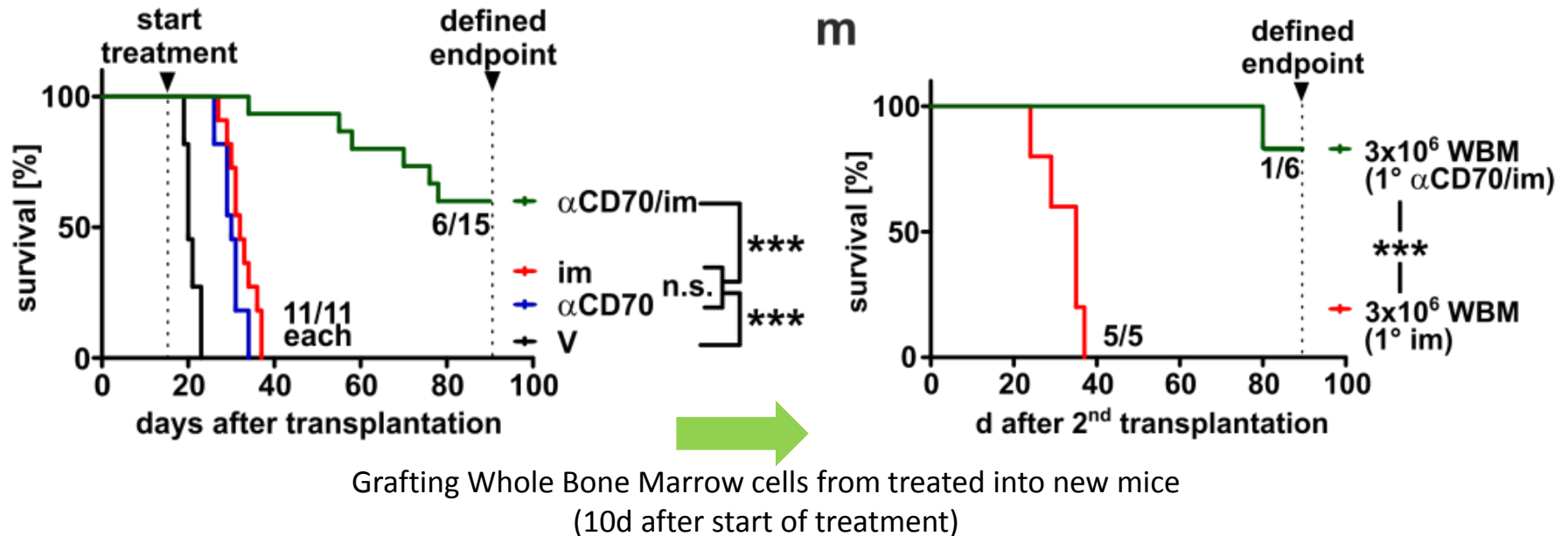
Grafting Whole Bone Marrow cells from treated into new mice
(10d after start of treatment)

- Leukemic stem cells (LSCs) resistant to BCR-ABL1 inhibitors via CD70 overexpression
- Combo treatment with CD70 blocking mAb eliminates LSCs by synergistic blockade of Wnt signalling pathway

Im: imatinib; V: vehicle; WBM: whole bone marrow

Riether and Schürch et al., 2015, Science Translational Medicine

ARGX-110: What next?

Ongoing clinical studies
- **Hematological tumors**
  - T-Cell Lymphoma (TCL): Phase 1b → 6 sites (BE, FR, IT)
  - Recruiting 10 CTCL (min 5 Sz) - 10 PTCL (min 5 AITL) patients
  - 10 patients identified, 1 patient treated

Site	Investigator	Status	Patients (pre)screening	Treated
UZ Ghent (BE)	Dr. Offner	Open		1X CTCL
Jules Bordet Institute (BE)	Dr. Maerevoet	Open	1x CTCL	
Gustav Roussy (FR)	Dr. Ribrag	Open	5X CTCL & PTCL	
St. Louis (FR)	Dr. Bagot	Open	3 X CTCL	
Lille (FR)	Dr. Morschhauser	Open in Jan		
Bologna (IT)	Dr. Zinzani	Open in Jan		

- **Solid tumors**
  - Nasopharyngeal carcinoma (NPC): Phase 1b (UZ Gent)

ARGX-111

ARGX-111:   Addressing the end game of cancer

Targeting MET, receptor responsible for tumor growth and metastasis

1. HGF independent blocking
2. HGF dependent blocking
3. Kill cMet+ cells via increased ADCC-Potelligent®
4. Increased tissue penetration-NHance®

CTC - Circulating Tumor Cells
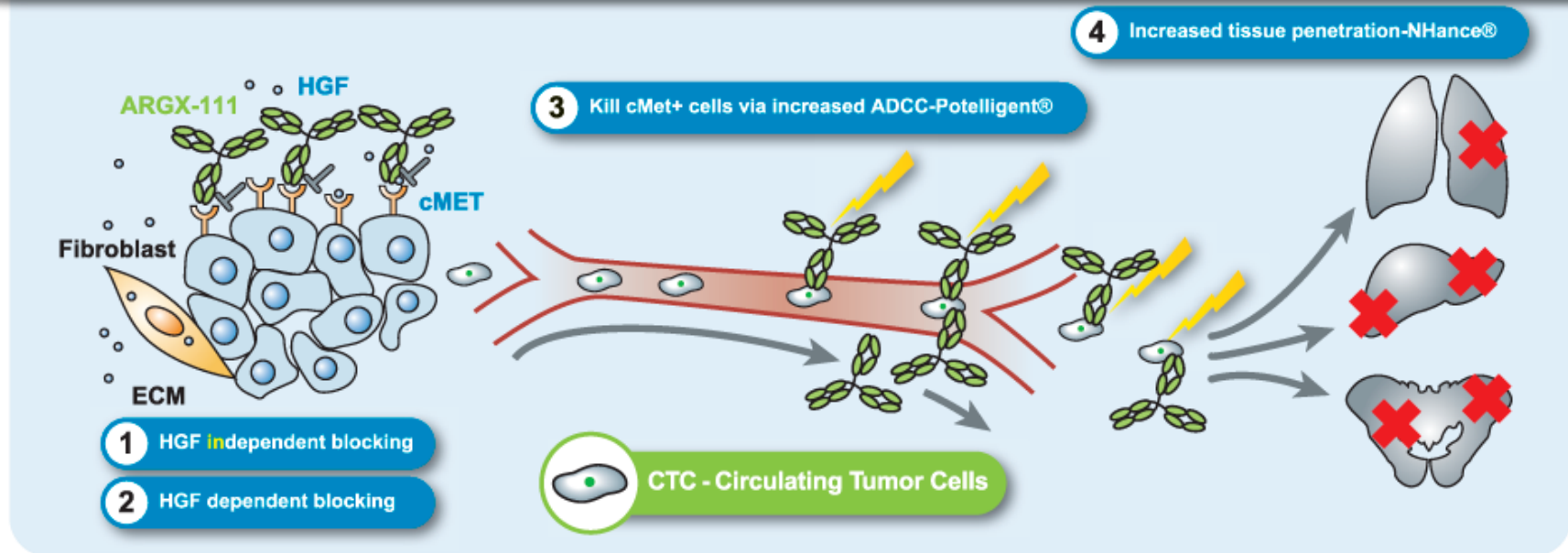
Hultberg 2014; Pachmann 2008

- ARGX-111 has several distinct modes of action
  - HGF-dependent blocking
  - HGF-independent blocking
  - Killing MET-expressing cells

ARGX-111:   Phase 1 trial design

1Q 2014

Dose escalation

Phase 1

(mg/kg)

10

3

1

0.3

1H 2015

Adaptive safety expansion

Phase 1b

MET-amplified cancers

2H 2016

Details

- **Advanced cancer population (34 patients)**
  - Progressive, end stage disease
  - MET+ by IHC and CTCs by Veridex
  - Monitor tumor metabolism (PET scan)
- **ARGX-111 monotherapy**
- **'Off study' criteria**
  - Progressive disease (ir-RECIST)
  - Safety
- **Translational biomarkers**
- **Efficacy: response and duration of therapy**

- ~50% of patients screened have CTCs
- Safety observations: Infusion related reactions (class effect)
- Biological activity observed in individual patient with gastric cancer with bone metastases

ClinicalTrials.gov Identifier: NCT02055066

ARGX-111: Proof of biological activity in MET-amplified cancer patients

Gastric cancer patient

- 50 year old gastric cancer patient with bone metastases; MET-amplified

- Multiple lines of previous treatment

- PET/CT scan: biological activity

- CTCs reduced by 75%

- Good clinical performance

Biological activity
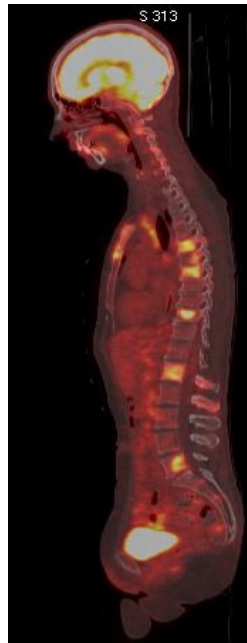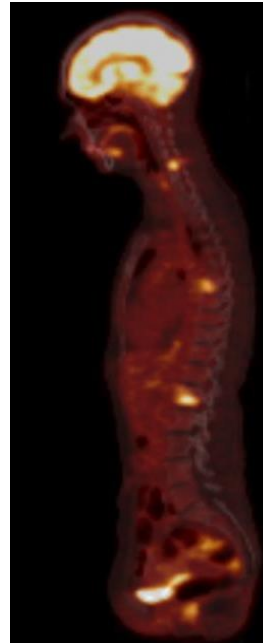
Baseline PET scan | Improvement after 4 doses | Baseline PET scan | Improvement after 4 doses
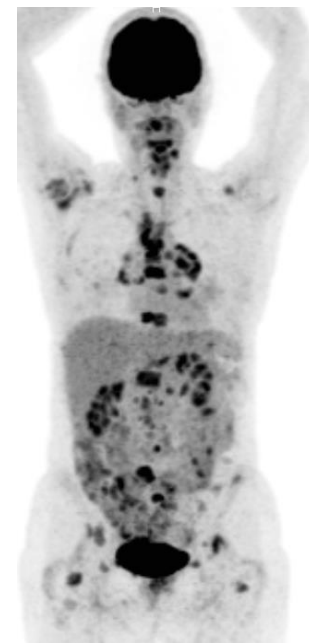
Renal cancer patient

- 57 year old renal cancer patient with metastases; MET-amplified
- Progressive disease stabilized after 2 cycles ARGX-111
- PET/CT scan: biological activity
- 30% reduction of lesion in lymph node

- Patient anecdotes -   32

ARGX-111:   What next?

Next steps

Clinical Status

- Phase 1b in MET-amplified patients ongoing
- 4 clinics open (BE, FR)
- Opening 3 clinics in Asia
- Recruiting up to 15 MET-amplified patients

Market potential

Benchmark cancer treatments

- Herceptin®: $ 54K/y
- Avastin®: $ 42.8K– 55K/y
- Erbitux®: $ 80K/y
- Crizotinib: $ 1B sales based on 3% of ALK-positive NSCLC patients

ARGX-115

ARGX-115: Towards a next generation Yervoy®

GARP: a novel immune checkpoint
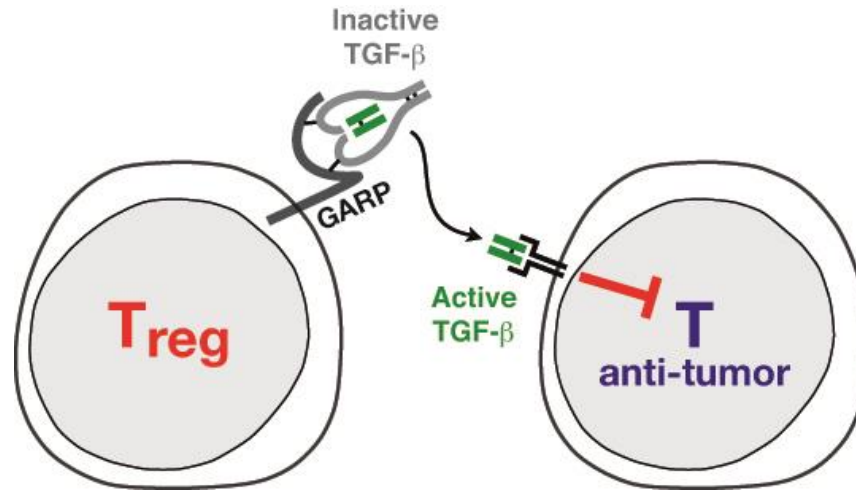
- GARP upregulated specifically on surface of Tregs only

- GARP presents and activates latent TGF-ß1, activating Tregs and suppressing Teff cells

- SIMPLE Antibody™ hitting unique, patented epitope on GARP

- GARP blockade sufficient for MoA – no Treg depletion

- Graft-versus-host-disease model delivered convincing PoC

Cuende et al., 2015, Science Translational Medicine

ARGX-115: Towards a next generation Yervoy®

NSG mice injected with:

hPBMC → hPBMC (i.e. CTLs) attack host cells (GVHD)

+/- hTregs → hTregs delay GVHD

+/- anti GARP → LHG-10.6 blocks Treg-mediated protective activity
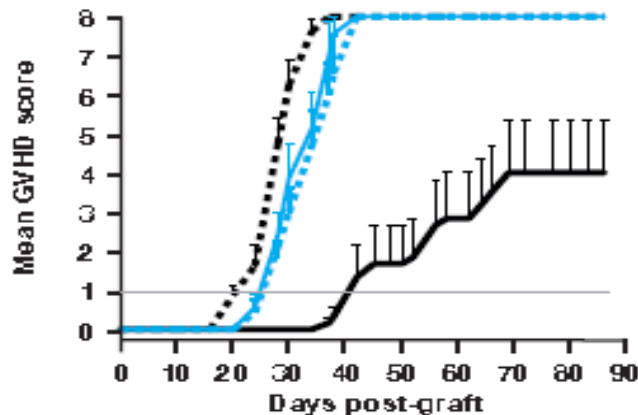
Legend:
- ▪▪▪ PBMCs
- — PBMCs + Tregs
- — PBMCs + Tregs + LHG-10.6
- ▪▪▪ PBMCs + Tregs + LHG-10.6$_{N297Q}$

Cuende et al., 2015, Science Translational Medicine

Partnerships

Building partnerships for the long term

Strategic Alliances

- Non-exclusive product discovery and development, leveraging entire technology suite
- Upfront funding, R&D support, development milestones, royalties, product reversion rights

Collaboration Agreements

- Non-exclusive discovery collaborations, applying SIMPLE Antibody™ to complex targets
- Technology access fees, R&D support, milestones, royalties

Innovative Access Program

- Non-exclusive access to antibody technologies for academic and biotech centers of excellence
- Creative deal structures including option to acquire asset, golden share,...

- € 22.7M in cumulative revenue (30 June 2015)
- >€ 1.4B* potential cumulative revenues from existing partnerships

Assuming specific development and sales milestones are met for all potential discovery targets

Financials

Well capitalized to execute strategic plan

Operating income and expenses (MEUR) 3Q15

48 HC

- Operating income 7.3
- R&D 14.2
- G&A 3.3
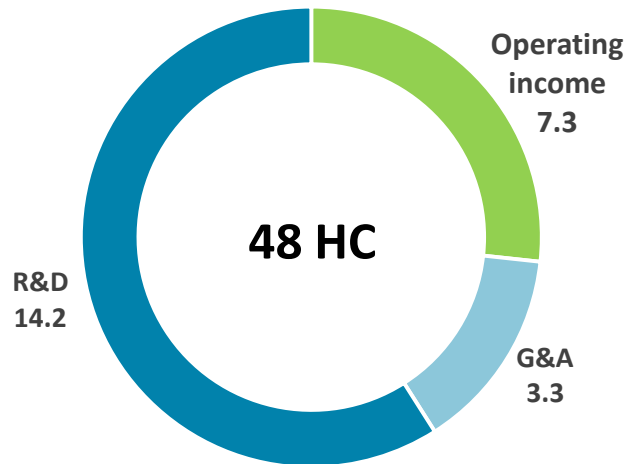
Operating income, expenses and capital raised since inception (MEUR) 3Q15 (*)

(*) not including deferred revenue and accruals

Operating income	24.6
R&D expenses	55.9
G&A expenses	14.5
Capital raised	87.8
Cash and cash-equivalants	46.6

Internal R&D funded

0   20   40   60   80   100
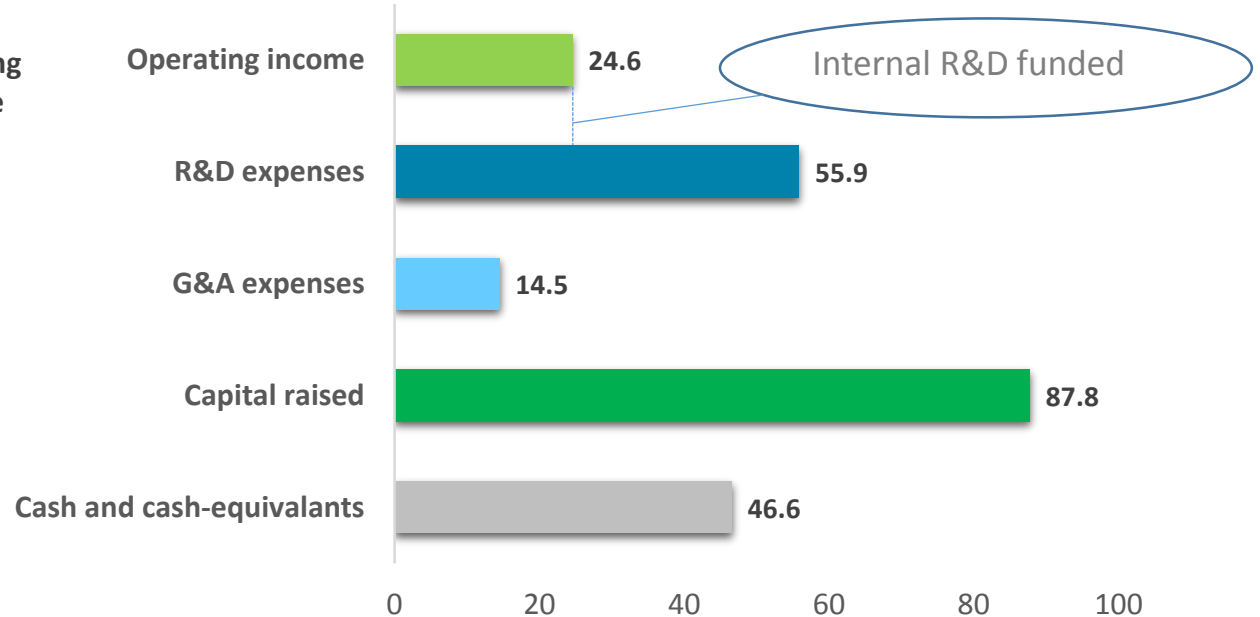
Shareholder structure (30 Sept 2015)
Fully diluted

8.7 %
25.8 %
65.5 %

- Historical shareholders (co-founders and VCs)
- Free float
- Stock options

40

Upcoming news flow 2016

December	January	February	March	April	May

110 ASH/event: clinical update TCL & preclinical results AML

110 SAKK Grant combo trial

111 opening clinical centers in Asia

113 JP Morgan: preliminary SAD HV data

115 IBC: 115 preclinical update

⬤ Collaboration milestone payment

June	July	August	September	October	November

110 ASCO: TCL mono update

110 Anticipated start combo trial

110 TCL & NPC mono results

111 ASCO: Ph1 safety expansion update

113 SAD & MAD HV top line data

113 Start Ph2 Dec 2016

115 Preclinical update

Creating innovative antibodies for cancer & severe autoimmune diseases

J.P. Morgan 33rd Annual Healthcare Conference, 11-14 Jan 2016