Daratumumab for multiple myeloma: A journey from phase 1 towards approval for marketing

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Summary

- Multiple myeloma is a rare hematological malignancy with a high unmet need for new therapies
- Daratumumab is directed against CD38, which is a promising target in myeloma and clinical results so far support this
- Development of Daratumumab demonstrates successful collaboration between academia, industry and regulatory authorities

Multiple myeloma

- **It is rare: approximately 1% of all cancers**
  - **Second most prevalent hematological cancer**
  - **Prevalence worldwide (1 year)**
    - **32,947 (♂); 27,925 (♀)**
  - **Incidence worldwide (age-standardized rates)**
    - **1.7/100,000 (♂); 1.2/100,000 (♀)**
- **It is a disease of the elderly**
  - **Median age at diagnosis: 65 – 70 years**

Kröger N. EBMT slide bank; http://www.ebmt.org

What is multiple myeloma?

- A cancer of the bone marrow caused by uncontrolled growth of plasma cells
- Plasma cells
  - Critical part of the immune system
    - Produce antibodies (=immunoglobulins) (released in response to foreign body invasion)
  - Normally make up < 5% of the cells in the bone marrow
  - In patients with MM, bone marrow contains > 10% and sometimes > 90% plasma cells

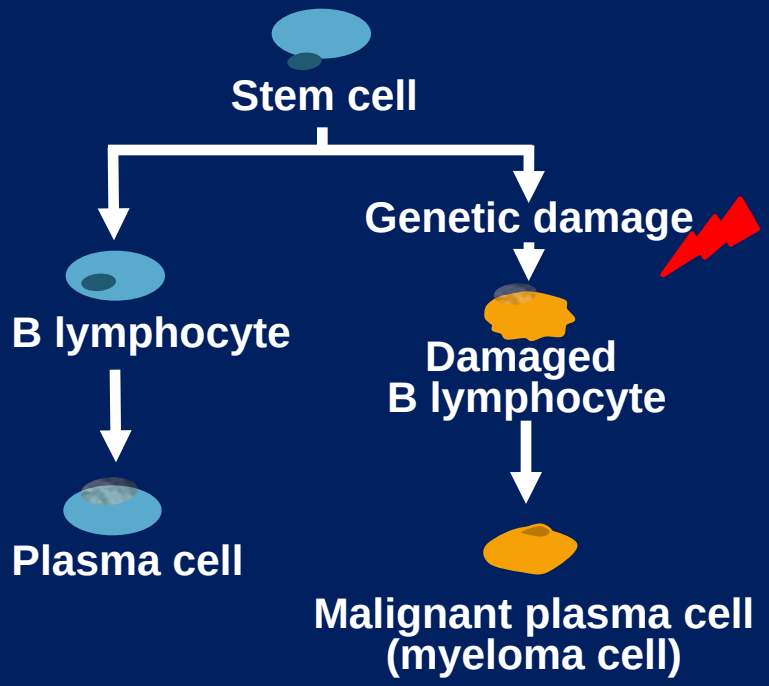
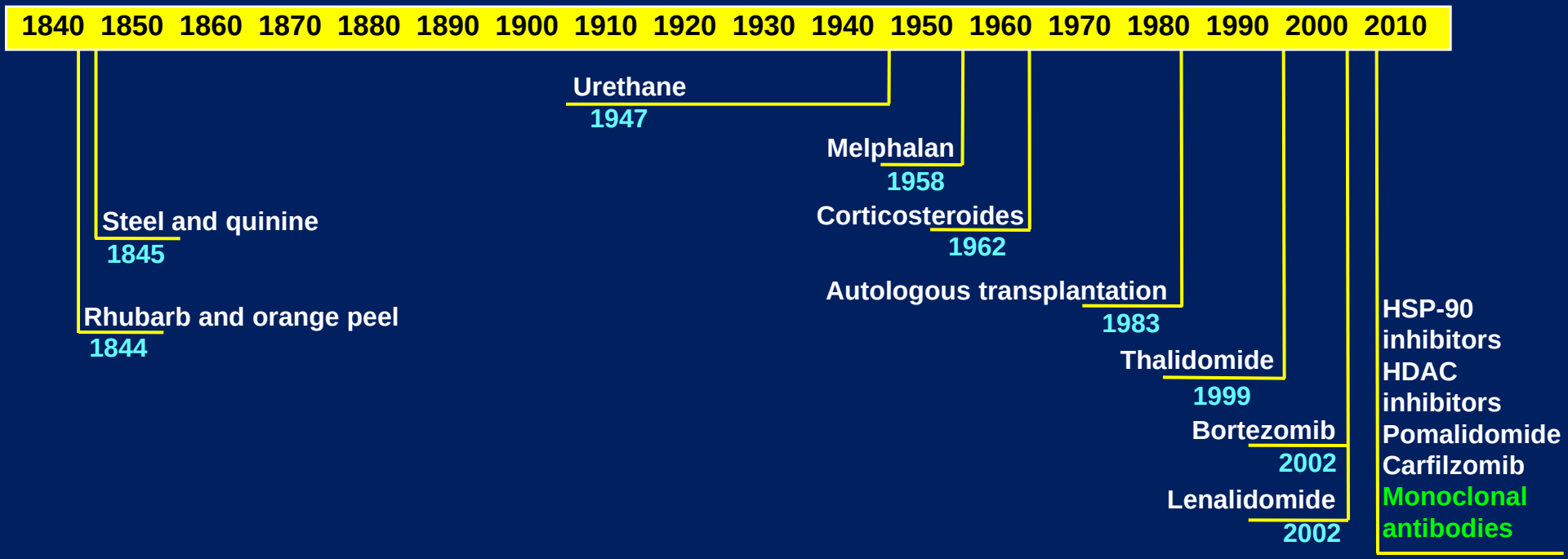


Image courtesy of www.multiplemyeloma.org.

How does myeloma cause problems?

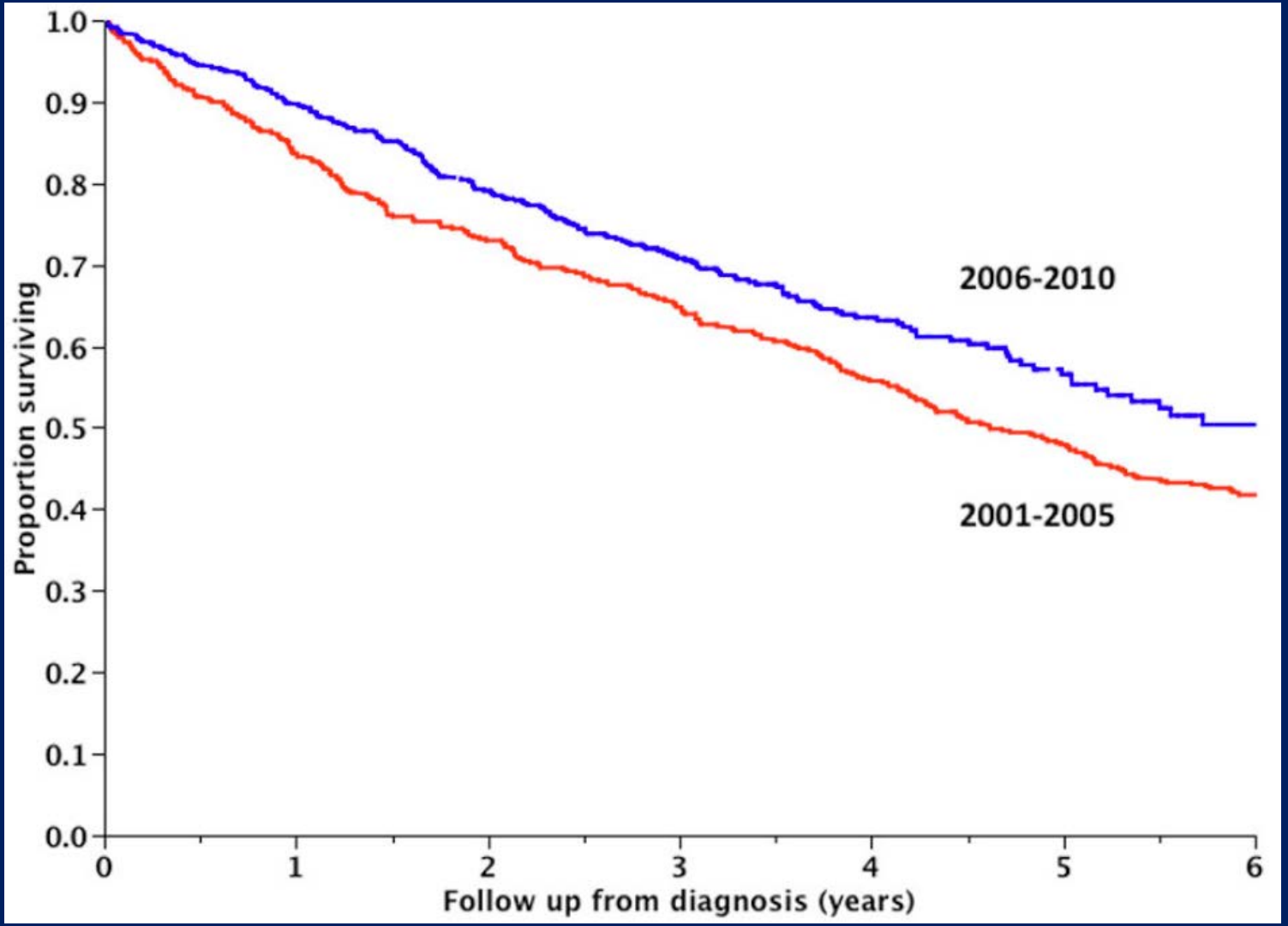
- **Bone marrow replacement by malignant plasma cells** → anemia and other cytopenias
- **Bone destruction** through dysregulation of normal bone remodelling processes → lesions, fractures
- **Hypercalcemia** (increased levels of calcium in the blood) due to bone destruction
- **Renal failure** due to deposition of abnormal protein produced by myeloma cells in kidney tubules
- **Impaired immunity** due to ↓ normal immunoglobulins

Advances in the treatment of multiple myeloma from 1844 to the present



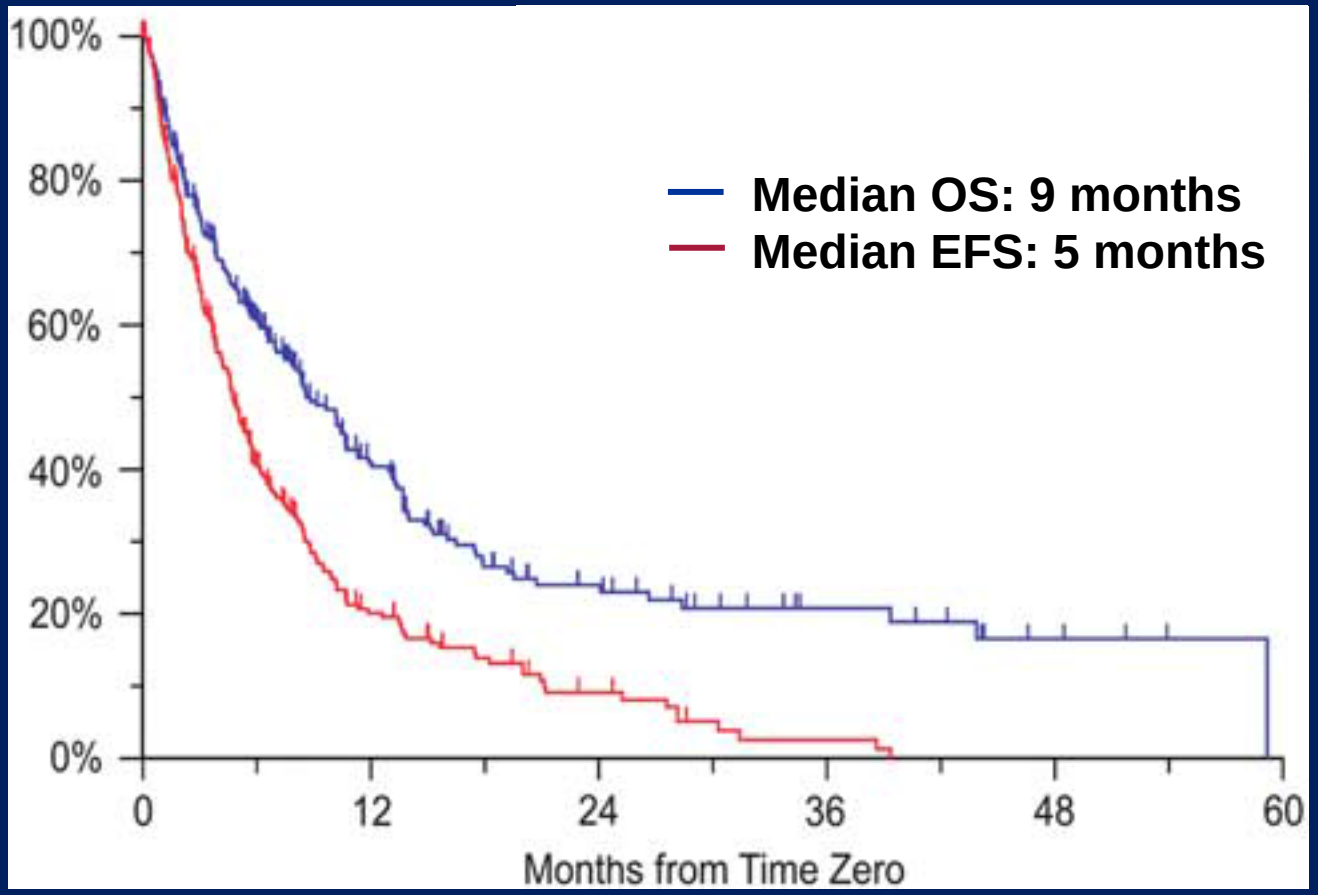
Adapted from: Kyle and Rajkumar. Blood 2008;111:2962-2972

Continued Improvement in Survival Since the Introduction of Novel Agents



Kumar et al. Leukemia. 2014;28(5):1122-1128.

Poor Survival Outcomes for Patients with disease that is refractory to the novel agents



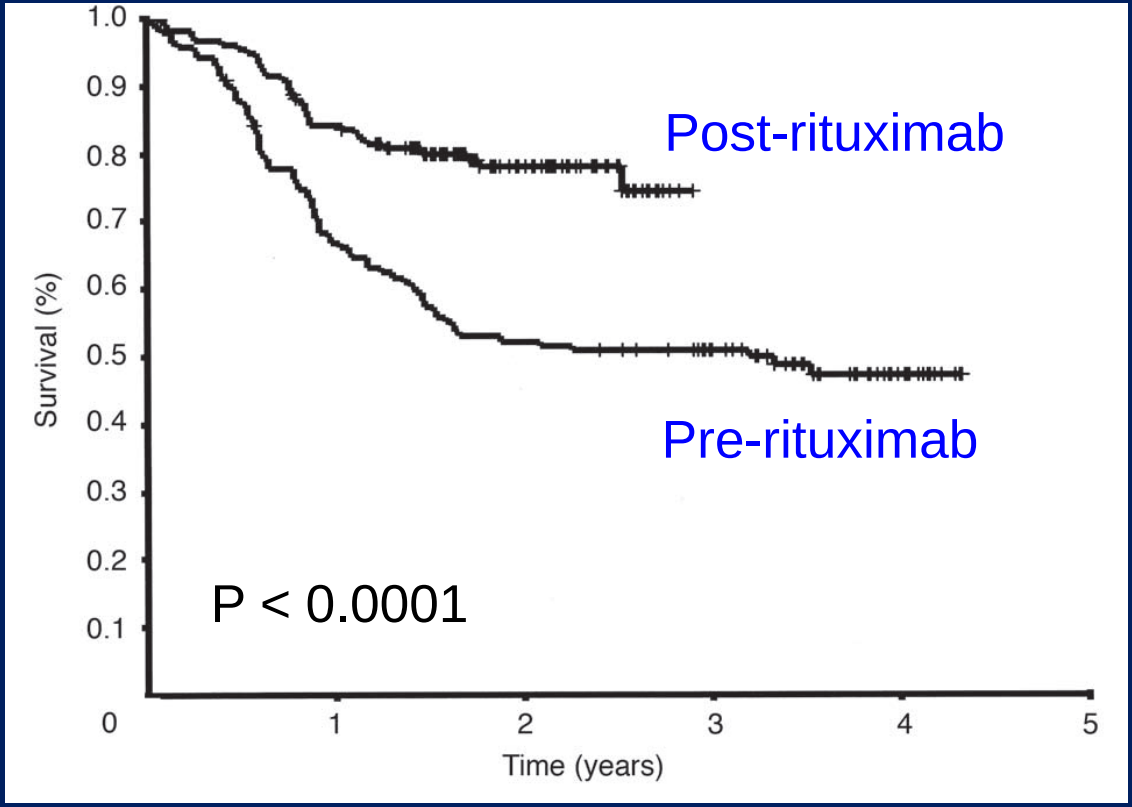
New treatments needed

Kumar et al. Leukemia. 2012;26(1):149-157.

Monoclonal antibodies

The impact of rituximab in diffuse large B-cell lymphoma

Overall survival by treatment era

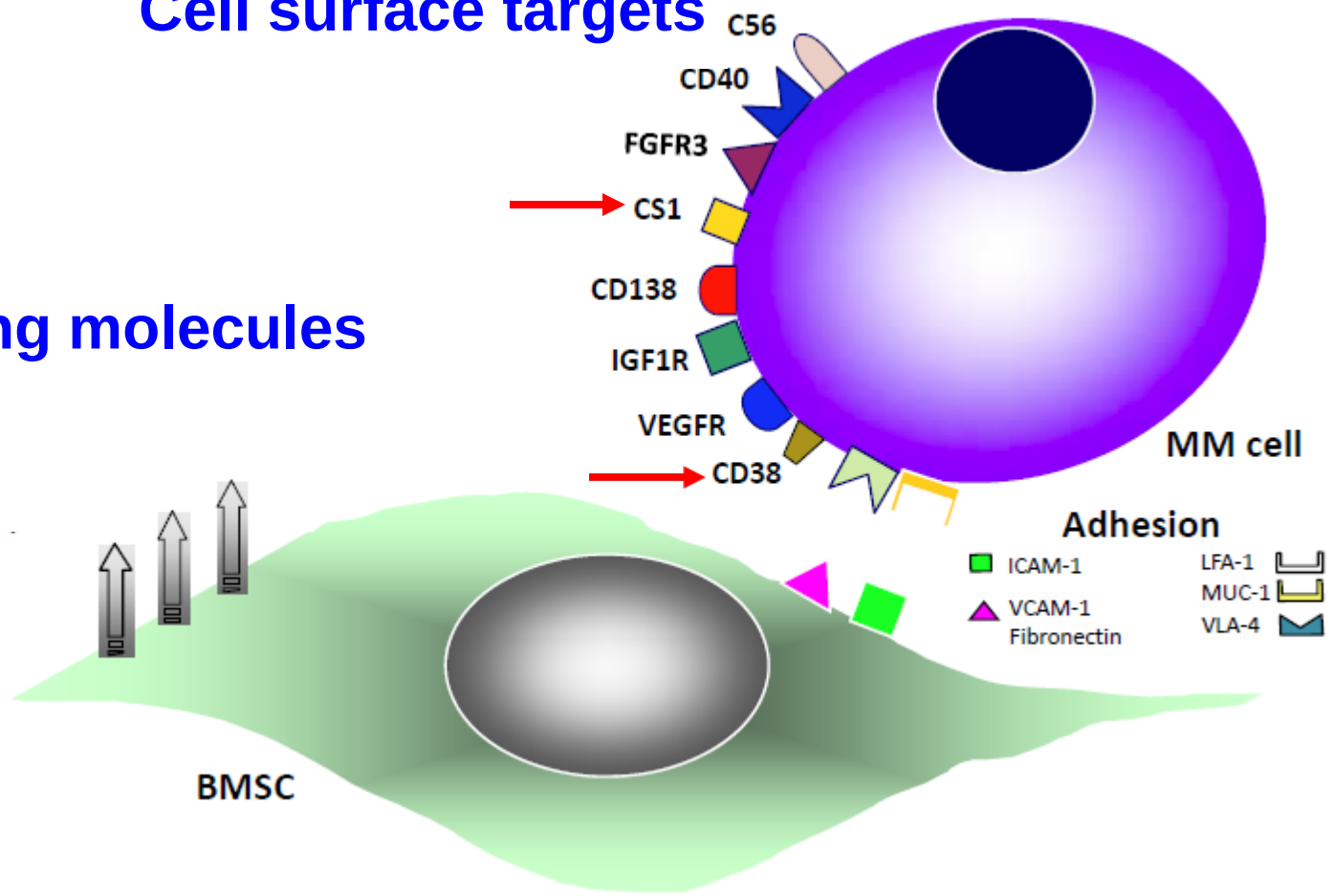


Can we find a monoclonal antibody that will change the course of myeloma in a similar way?

Sehn et al. J Clin Oncol 2005;23:5027-5033

Targets for monoclonal antibody therapy in myeloma

Cell surface targets



Signaling molecules

- IL-6
- RANKL
- DKK1
- VEGF
- IGF-1
- SDF-1α
- BAFF, APRIL

Adapted from: Anderson KC. J Clin Oncol 2012;30:445-452

Rationale for targeting CD38

- CD38 combines important functions
  - Adhesion
  - Signalling
  - Enzymatic activities

- High level of expression on MM cells,but low level of expression on normal lymphoid and myeloid cells

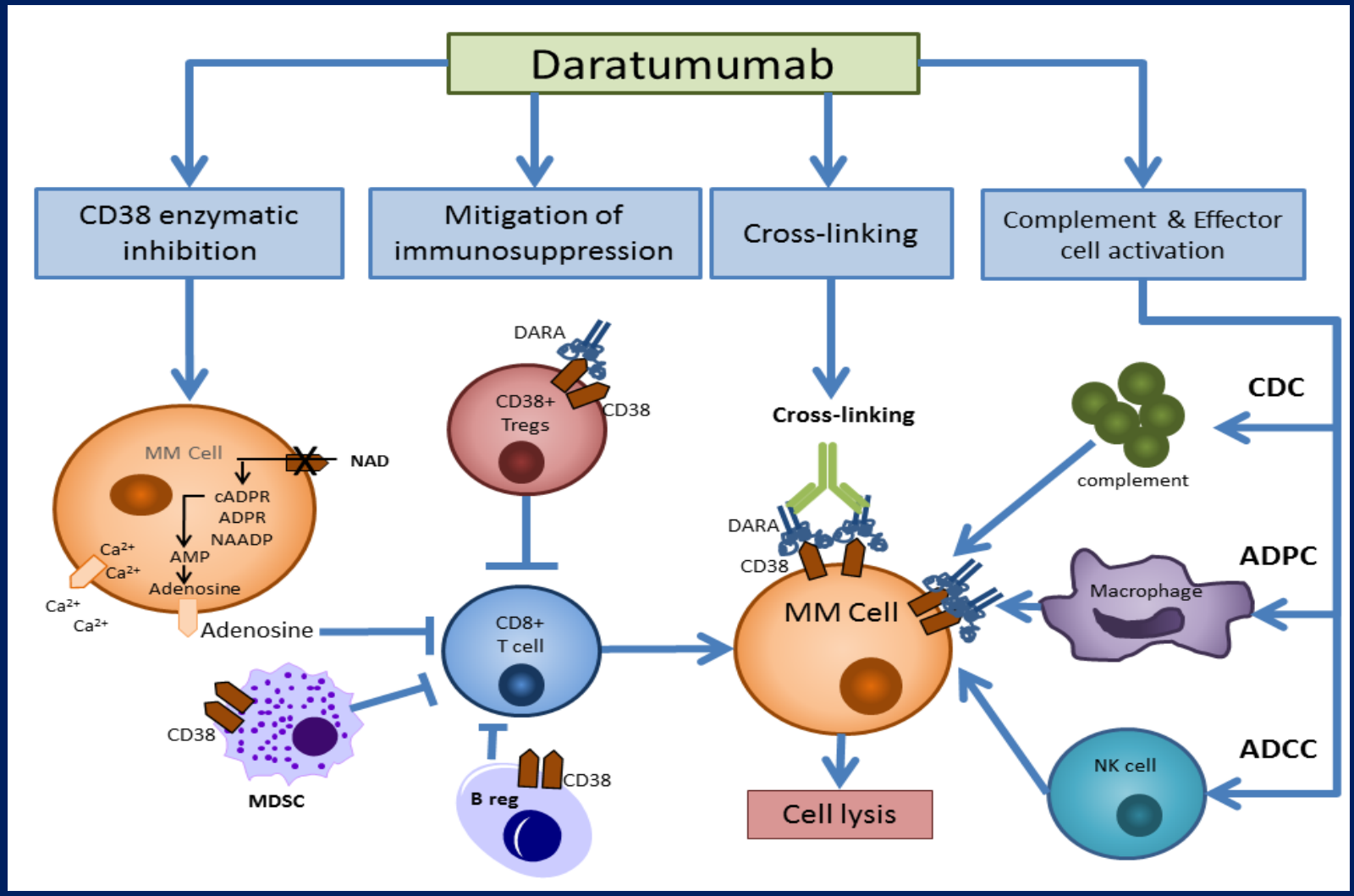
Chillemi et al Mol Med 2013;19:99-108.
Quarona et alAnn N Y Acad Sci 2015;1335:10-22.

Daratumumab

- Human $IgG1_K$ monoclonal antibody
- Generated by immunization of transgenic mice possessing the human immunoglobulin gene with recombinant CD38 protein and NIH 3T3 (expressing human CD38) cells until CD38-specific serum titer development
- The antibodies generated showed good binding to Daudi (B-lymphoblast cell line) and fresh MM cells

De Weers et al. J Immunol 2011;186:1840–8

Modes of action of Daratumumab



Summary of preclinical results with Daratumumab

- Potent *in vitro* activity against myeloma cells isolated from patients and myeloma cells lines[1,2]
- Synergy in inducing ADCC between lenalidomide or bortezomib and daratumumab[3,4]
- Synergistic activity of daratumumab and lenalidomide in lenalidomide/bortezomib-resistant multiple myeloma cell lines and in primary multiple myeloma cells derived from lenalidomide- and/or bortezomib-refractory patients[5]

1. de Weers et al. J Immunol. 2011;186(3):1840-1848
2. Overdijk et al. MAbs 2015;7(2):311-21
3. van der Veer et al. Haematologica 2011;96(2):284-90
4. van der Veer et al. Blood Cancer J 2011;1(10):e41
5. Nijhof et al. Clin Cancer Res 2015;21(12):2802-10

Preclinical studies in animal models not feasible

- Daratumumab does not bind to CD38 in animals mostly used for preclinical testing

- Observation of some cross-reaction with CD38 in chimpanzees

→ No possibility of preclinical safety testing in animals

March 2006: Report of cytokine storm and multiorgan failure in six healthy volunteers in phase 1 trial of CD28 mAb

- First phase 1 clinical trial of TGN1412, a superagonist anti-CD28 monoclonal antibody that directly stimulates T cells
- Six healthy young male volunteers were enrolled at a contract research organization
- Within 90 minutes of single iv dose, all volunteers had a systemic inflammatory response
- Within 12-16 hours, they became critically ill: pulmonary infiltrates and lung injury, renal failure, disseminated intravascular coagulation
- Within 24 hours: severe and unexpected depletion of lymphocytes and monocytes

Suntharalingam et al. N Engl J Med 2006;355(10):1018-28

March 2006: Report of cytokine storm and multiorgan failure in six healthy volunteers in phase 1 trial of CD28 mAb

- Transfer to intensive care unit:
  - intensive cardiopulmonary support (including dialysis)
  - high-dose methylprednisolone
  - anti–interleukin-2 receptor antagonist antibody
- All survived

Animal modlels, even if available, may not alert to all possible issues
Need for special focus on possible risk of an agent with a novel mode of action

Suntharalingam et al. N Engl J Med 2006;355(10):1018-28
St. Clair EW. J Clin Invest 2008;118(4):1344-1347

Consequences for the design of the daratumumab trials

- Special focus on safety
- Authorities required particular design of the trials
  - One patient at a time
  - Wait for a certain period before treating the next patient
  - Start with very low dose levels
  - Short period of treatment in the first part of the study to look for long term toxicity

Clinical development of Daratumumab

Single-agent studies

Phase 1/2 trial: Daratumumab in relapsed/refractory MM (GEN501)

Part 1: Dose escalation
Part 2: Expansion cohort

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Study design

Dose-escalation cohorts

Part 1: 32 pts

Open label, weekly iv infusion, 8 weeks

Dose-escalation: 3+3 scheme*

0.005→0.05→0.1→0.5→1.0 →2.0→4.0→8.0→16.0 →24.0 mg/kg

* - start with pre-dose at 10% of full dose, max 10 mg
- 3 weeks' delay after first full dose
- governed by independent data monitoring committee

Expansion cohort: Extended treatment for close to 2 years

Part 2: 72 pts

Open label, single arm, 8 and 16 mg/kg

8 weekly infusions followed by

8 biweekly infusions followed by up to

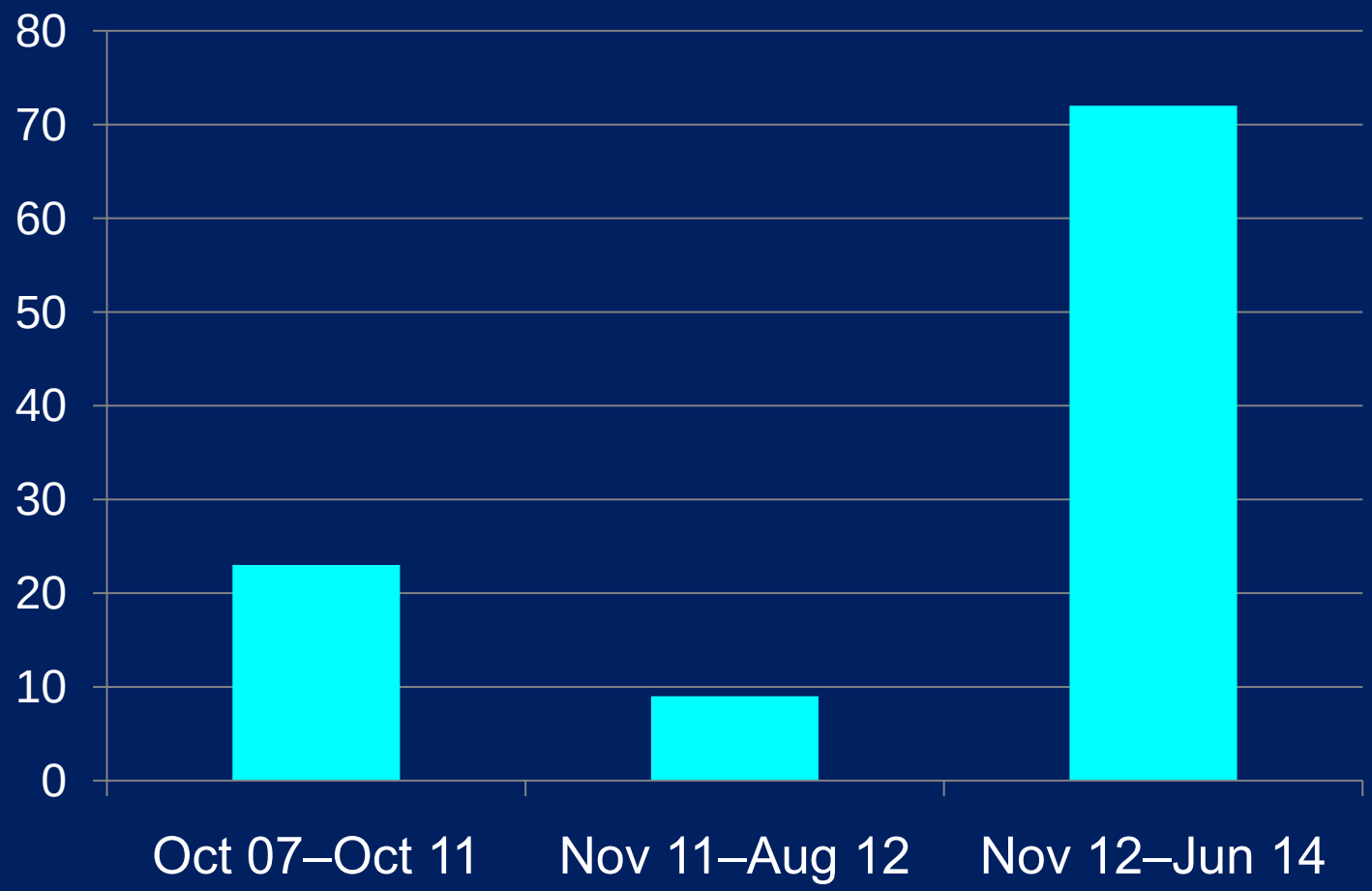
72 monthly infusions

Different combinations of premedications, predose infusions, infusion volumes, and infusion rates (3 – 4 hours)

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Sequential numbers

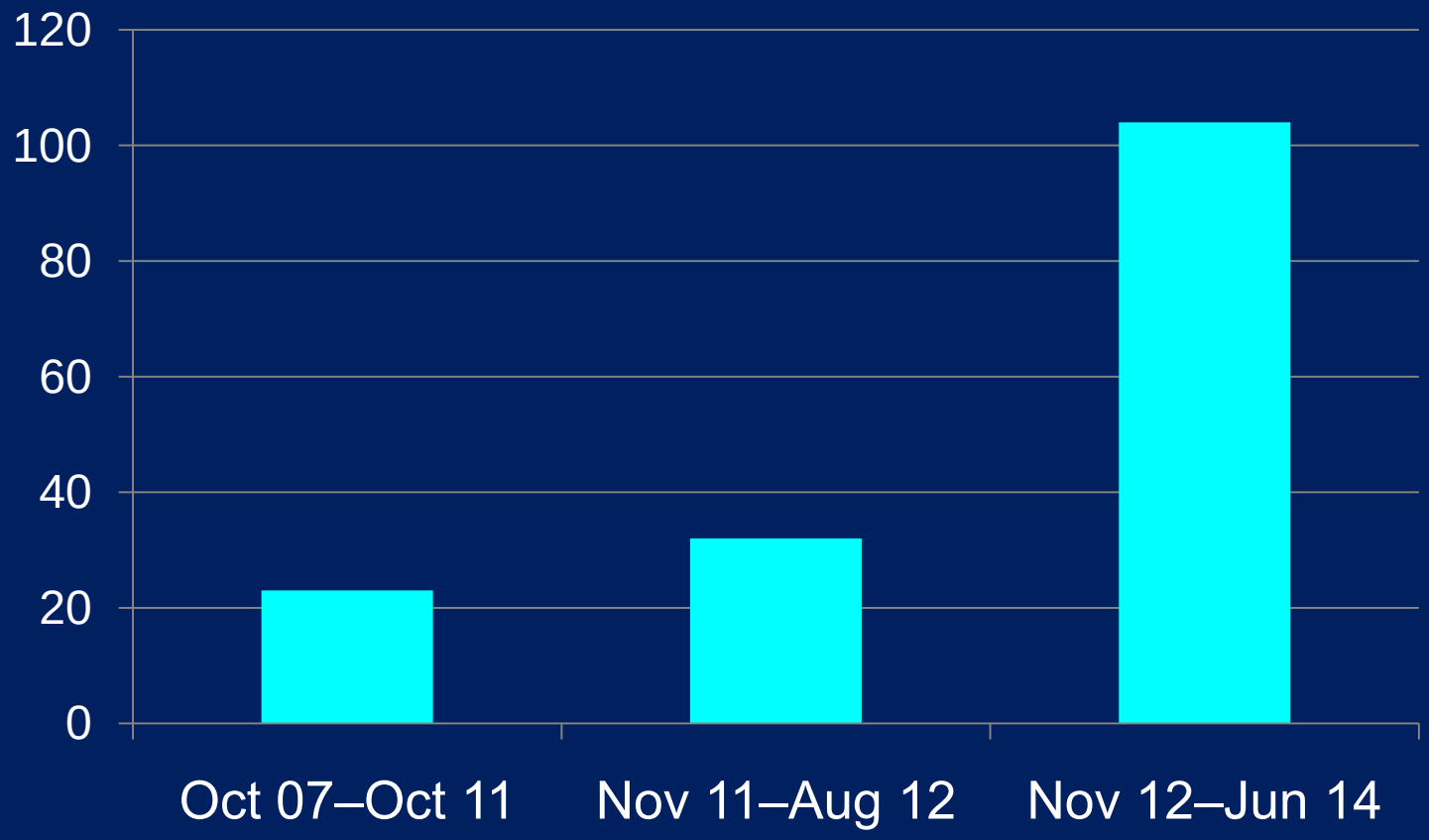
Slow recruitment at the start of the trial



Genmab. Data on file

Cumulative numbers

Slow recruitment at the start of the trial



Genmab. Data on file

Part 1: Safety findings

- Infusion-related reactions observed during the initial infusions:
  - 9% during pre-dose infusion
  - 26% during first full infusion with a gradual decrease in frequency during subsequent infusions
  - No dose relationship
  - Two grade 3 events, the remaining grade 1-2
  - Onset of events within 3 to 4 hours of infusion
  - Five late reactions:
    - 2 bronchospasm, 1 headache, 1 dyspnoea, 1 fever
    - Patients with bronchospasm had a history of chronic bronchitis and asthma
  - No major changes in platelet count or hemoglobin
- Dose-dependent decrease in NK cells, with full recovery after treatment

Plesner et al. ASH 2012 (Abstract 73), oral presentation

Part 1: Safety findings

Event	PART 1 N=32
Bronchospasm	1 patient: grade 2 (2 mg/kg) (2 days later grade 3) 1 patient: grade 2 (24 mg/kg)
Anemia	1 patient: grade 3 (0.1 mg/kg) (DLT)
Thrombocytopenia	1 patient: grade 4 (0.1 mg/kg)
ASAT > 5.2 times upper limit of normal	1 patient: grade 2 + grade 3 (1.0 mg/kg) (DLT)
Cytokine release syndrome	1 patient: grade 2 (0.1 mg/kg)

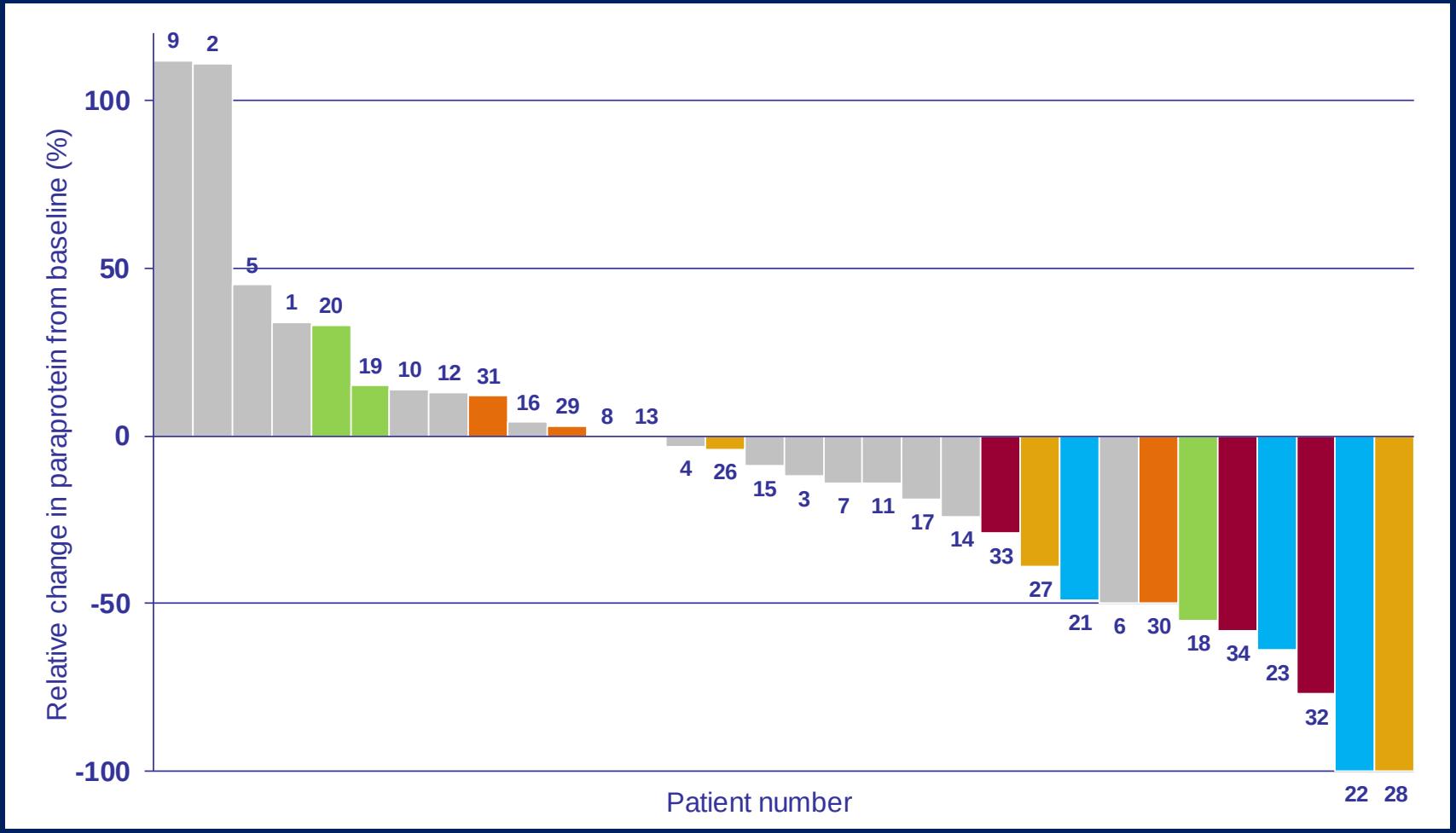
Plesner et al. ASH 2012 (Abstract 73), oral presentation
Lokhorst et al. ASCO 2013 (Abstract 8512), oral presentation

Part 1: Pharmacokinetics

- Plasma peak levels after first full dose: as expected for IgG
- Rapid clearance at low dose: indicates target-mediated clearance
- High inter-patient variability suggests effect of tumor load on PK
- 2 mg/kg: pre-dose trough levels far below prediction
- Doses of 4 mg/kg or greater resulted in adequate and sustained trough levels and abrogated the effect of target-mediated clearance
- Elimination half-life predicted using a two-compartment pharmacokinetic model: 21 days

Plesner et al. ASH 2012 (Abstract 73), oral presentation

Part 1: Response



Twelve patients dosed 4–24 mg/kg: 4/12 (33%) achieved a PR as best response

Plesner et al. ASH 2012 (Abstract 73), oral presentation
Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Daratumumab monotherapy
Part 2: Patients characteristics (72 Pts)

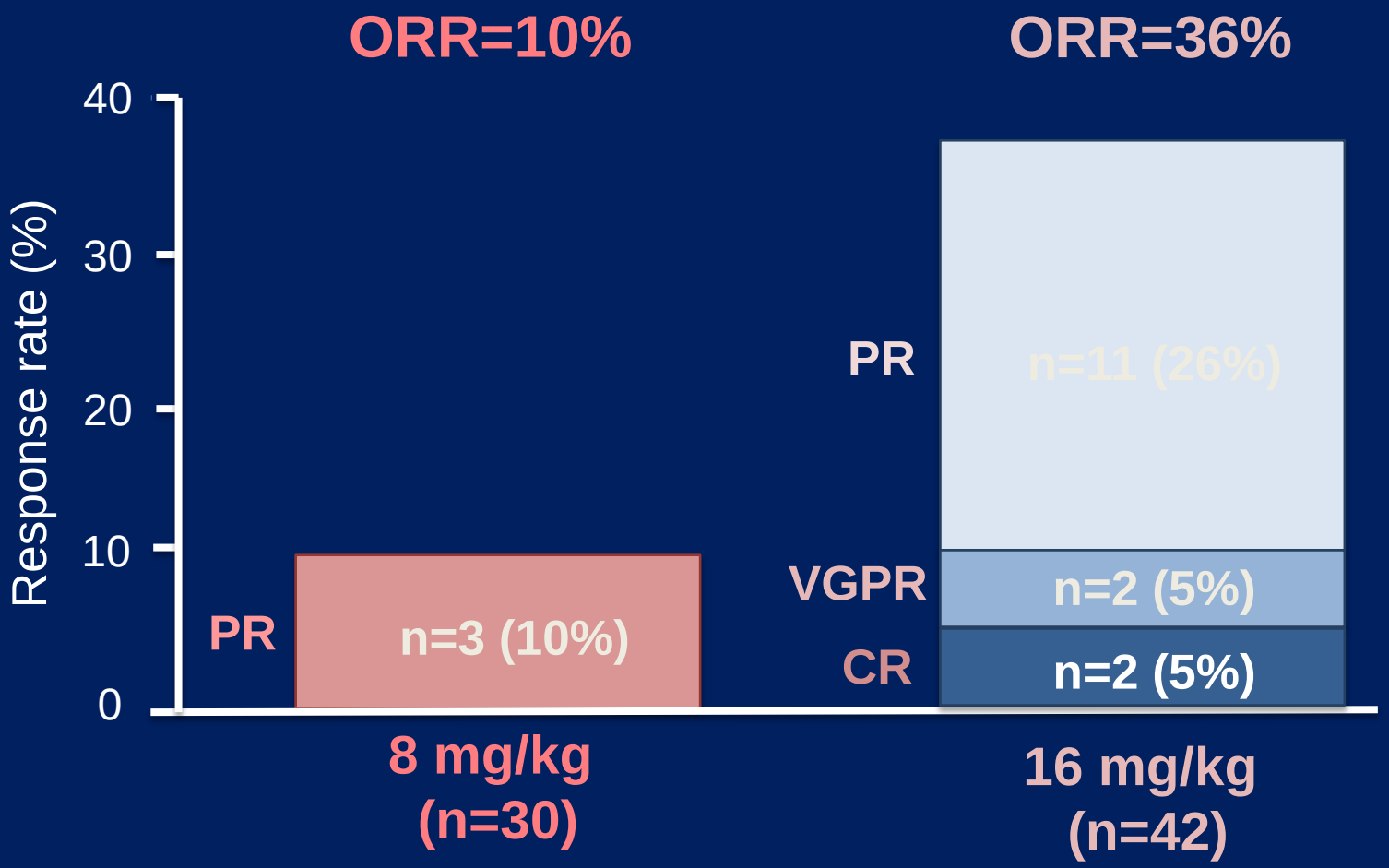
	8 mg/kg (n=30)	16 mg/kg (n=42)
Median prior lines	4	4
Refractory to		
Bortezomib	70%	71%
Lenalidomide	87%	74%
Bortezomib & lenalidomide	63%	64%

Overall, 79% were refractory to last line and 76% had received ASCT

- Phase 2, open label, single arm (72 Pts)
  - Extended treatment period up to 2 years: Weekly, twice monthly, monthly
  - Two dosing cohorts: 8 and 16 mg/kg

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Part 2: Response



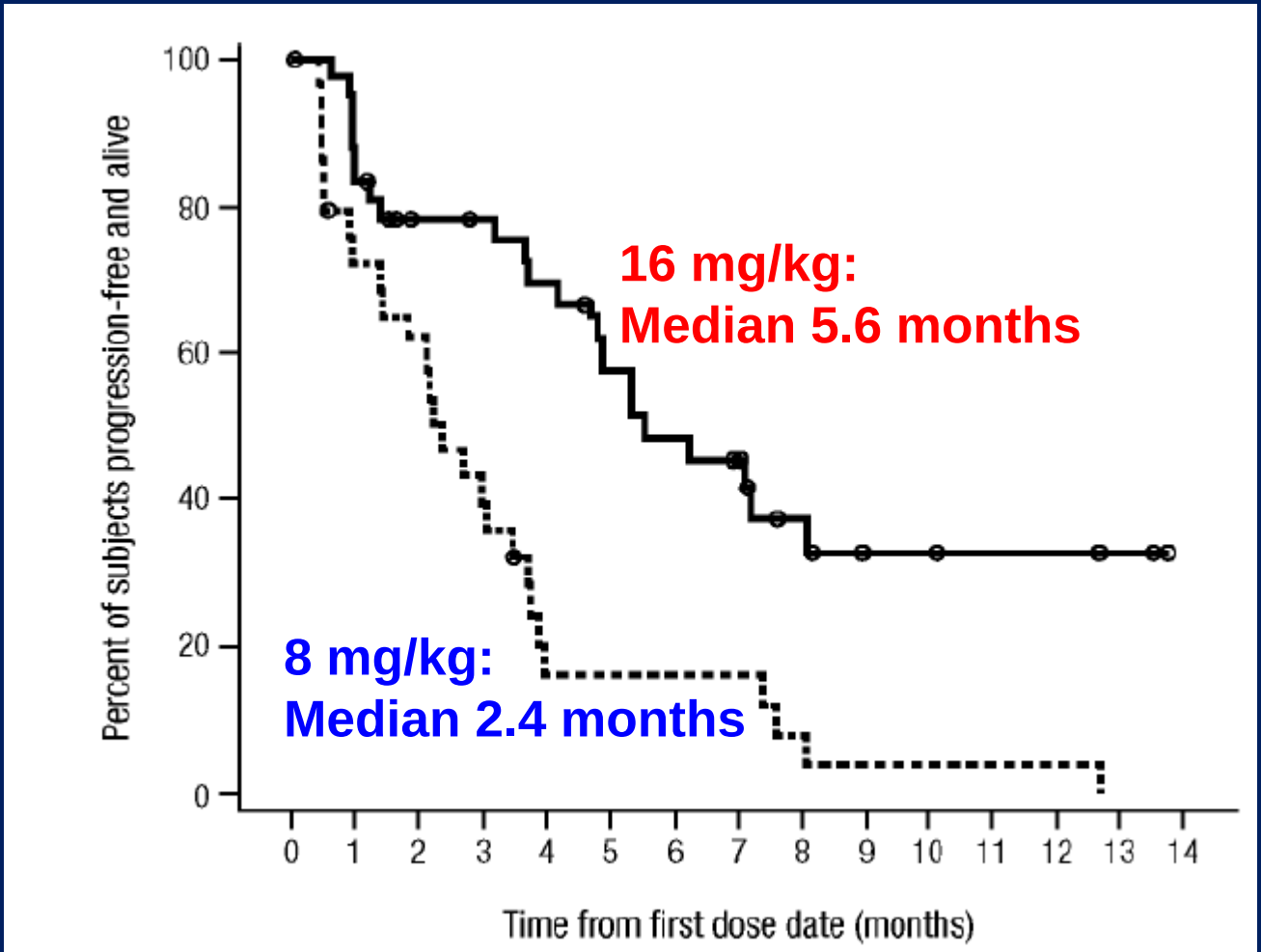
Response increased to 56% in patients with <3 lines

Median time to first & best response: 0.9 & 1.8m

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Part 2: Progression-free survival

Median follow-up: 16.9 months (8 mg/kg), 10.2 months (16 mg/kg)



- DOR: 6.9m & NR
- 65% of the patients who had responded to 16 mg did not have progression @ 12 months

OS @ 12 months: 77% in both groups

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

Part 2: Tolerability

- **Most AEs grade 1 or 2**
  - **Most common (≥ 25% of pts): fatigue, allergic rhinitis, pyrexia**
  - **Nasopharyngitis 24%, cough 21%**
- **Grade 3 or 4 AEs:**
  - **53% in 8mg/kg group and 26% in 16 mg/kg group**
  - **In ≥ 2 patients: pneumonia (5 pts), thrombocytopenia (4 pts), neutropenia, leukopenia, anemia, hyperglycemia (2 each)**
- **Infusion-related reactions:**
  - **71% (all grade 1/2, except 1 grade 3)**
  - **Mostly during first infusion (only 8% in subsequent infusions)**
  - **No discontinuation**

Lokhorst et al. N Engl J Med 2015; 373:1207-1219

SIRIUS (Phase 2 international trial): Daratumumab monotherapy in refractory MM

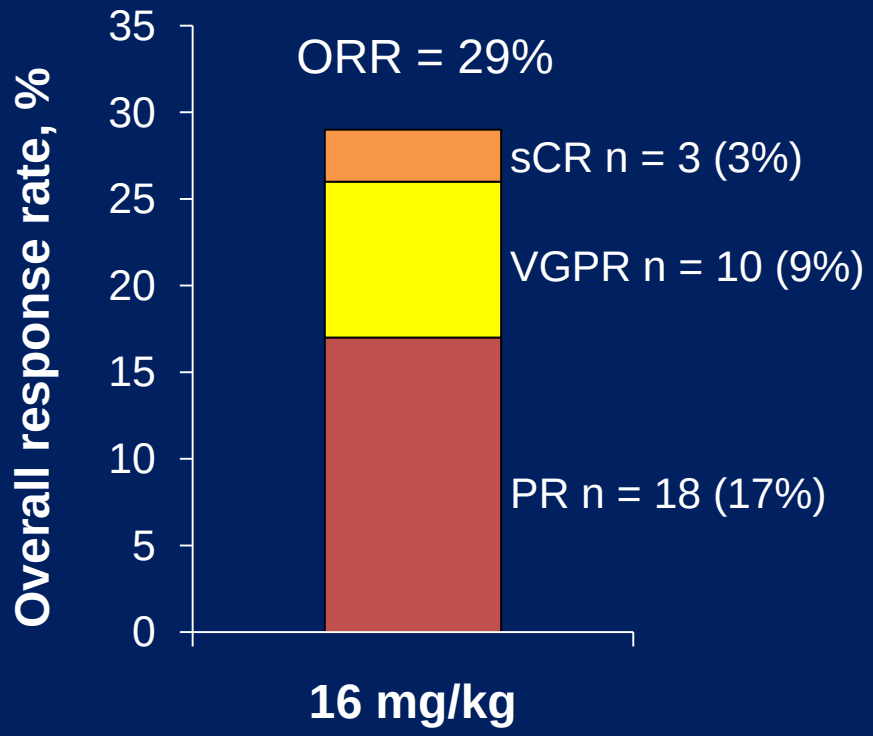
Baseline characteristics

- Patients (n=106)
  - ≥3 prior lines
  - 97% refractory to last line
  - 95% refractory to proteasome inhibitor and IMiD
  - 77% refractory to alkylating agents
  - 66% refractory to 3 of 4 therapies (Bort, Len, Carf, and Pom)
  - 63% refractory to pomalidomide
  - 48% refractory to carfilzomib
- Treatment:
  - Daratumumab monotherapy (16 mg/kg)

Lonial et al. ASCO 2015 (Abstract LBA8512); oral presentation

SIRIUS (Phase 2 international trial): Daratumumab monotherapy in refractory MM

Efficacy



- ≥ VGPR 12%
- ≥ MR 34%
- Median time to response: 1 month
- Median duration of response: 7.4 months
- Median PFS = 3.7 months
- 29 of 31 responders are still alive
- 1-year OS 65% (95% CI, 51.2–75.5)

Lonial et al. ASCO 2015 (Abstract LBA8512); oral presentation

SIRIUS (Phase 2 international trial): Daratumumab monotherapy in refractory MM

Safety

- Serious AEs 30%, Grade 3/4 23%
- No discontinuations due to DARA-related AEs
- No febrile neutropenia reported
- Infusion-related reactions
  - 42.5% (mainly grade 1/2 and >90% during first infusion)
  - 4.7% grade 3
  - No grade 4

Lonial et al. ASCO 2015 (Abstract LBA8512); oral presentation

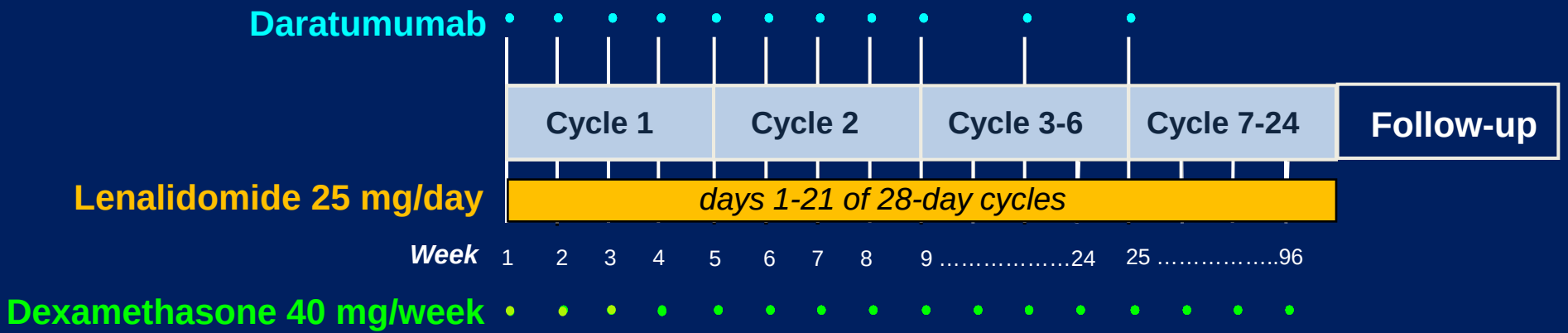
Clinical development of Daratumumab

Combination studies

Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed, or Relapsed and Refractory Multiple Myeloma

Plesner et al. ASH 2014 (Abstract 84); oral presentation

Study design: dose-escalation and expansion parts



Daratumumab dosing

- **Part 1 (n=13):**
  Dose escalation study: 2-16 mg/kg
- **Part 2 (n=32):**
  Expansion cohort: 16 mg/kg

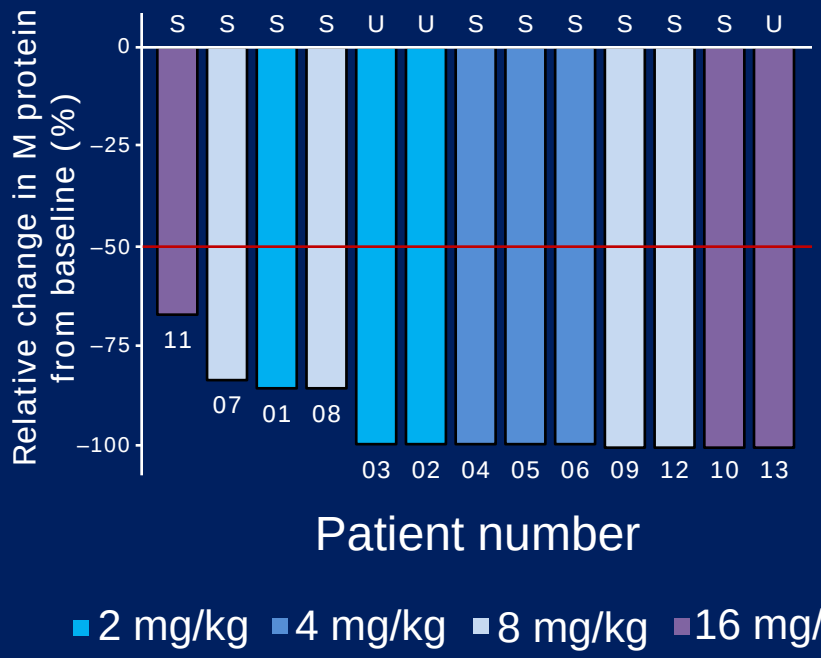
Key inclusion criteria:

- Part 1: relapsed and refractory MM following 2-4 prior lines
- Part 2: relapsed and refractory MM following ≥ 1 prior lines (no upper limit)
- Patients refractory or intolerant to LEN excluded

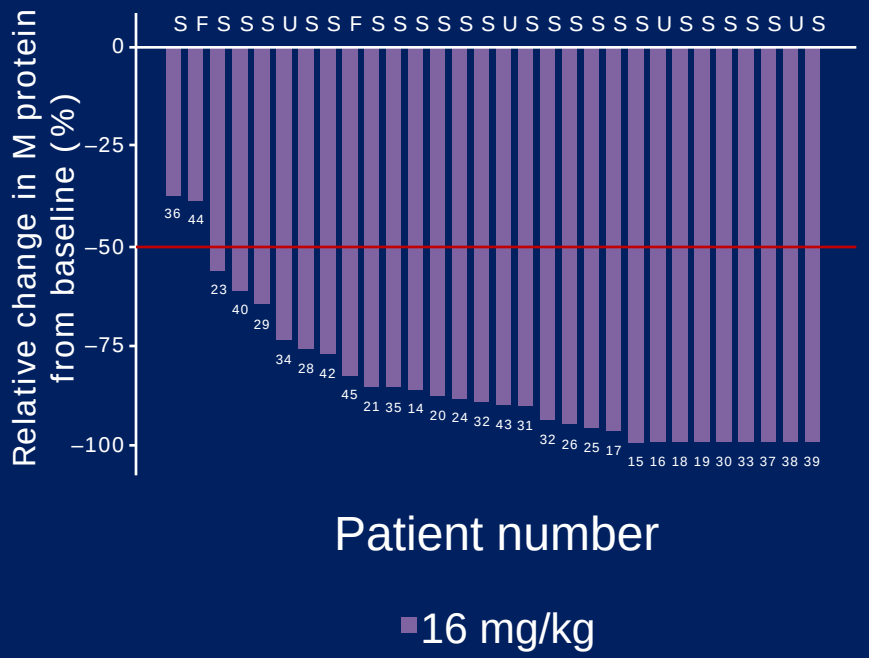
Plesner et al. ASH 2014 (Abstract 84); oral presentation

Maximum percentage change in M-protein from baseline

Part 1
Dose Escalation Study
2-, 4-, 8- , 16 mg/kg dose
n = 13



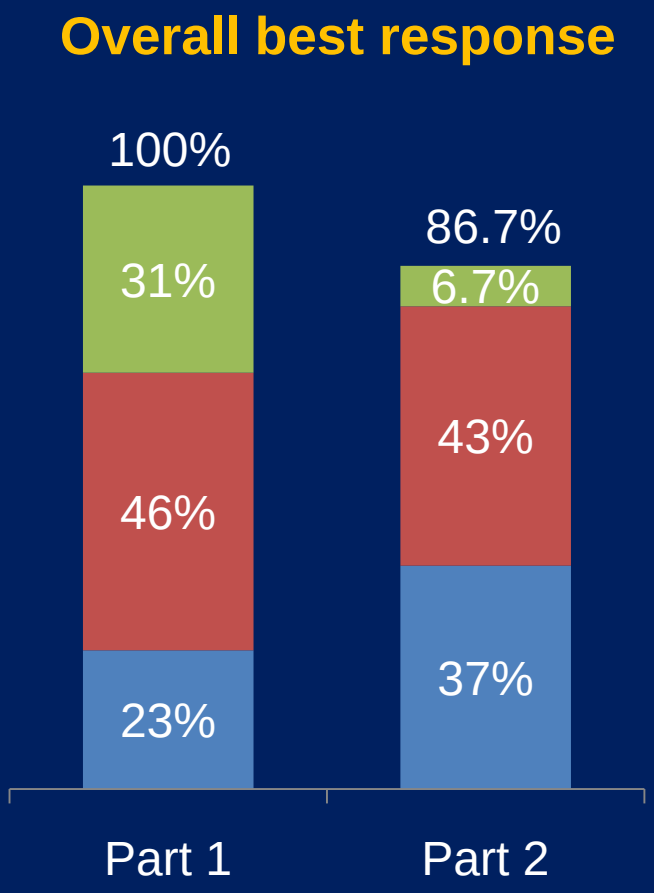
Part 2
Expansion Cohort Study
16 mg/kg dose
n = 30

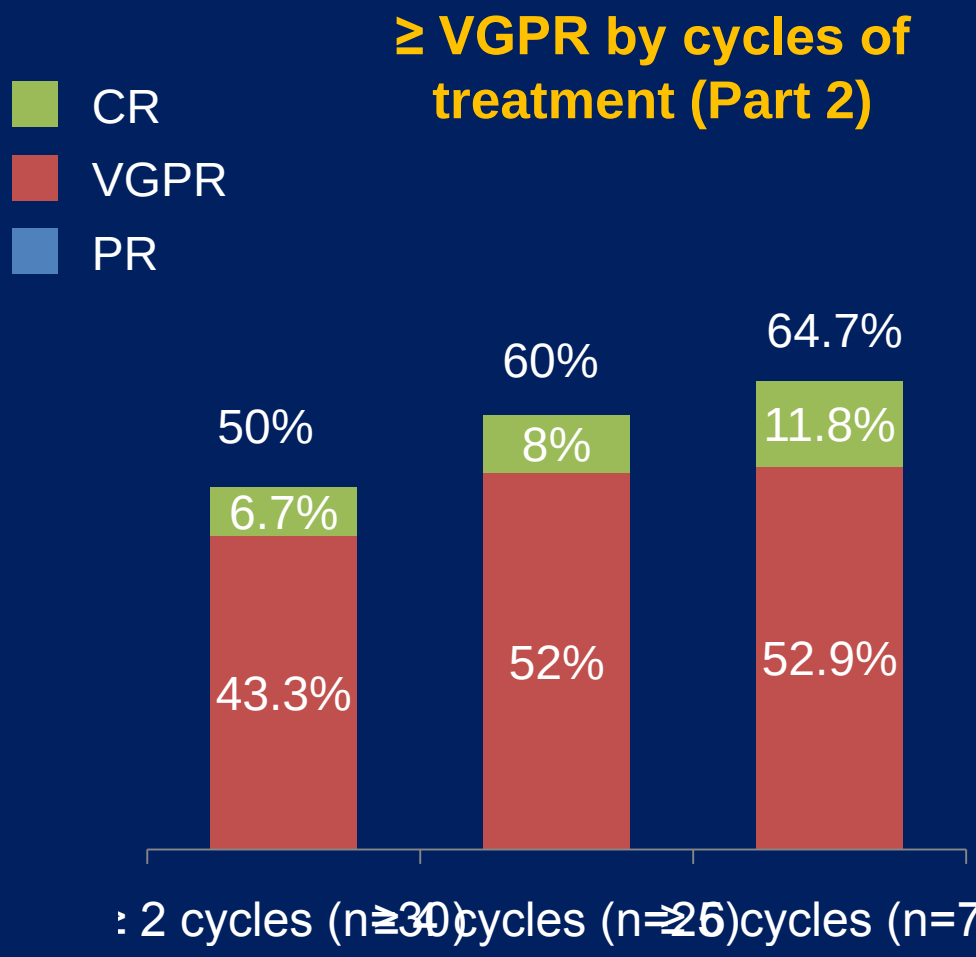


Plesner et al. ASH 2014 (Abstract 84); oral presentation

Improvement in response with longer therapy

Mean duration of follow-up: 12.9 months (Part 1), 5.6 months (Part 2)





Plesner et al. ASH 2014 (Abstract 84); oral presentation

Serious Adverse Events and Infusion-related reactions (IRRs)

Part 1	Part 2
7 SAEs all unrelated to DARA	8 SAEs 4 SAEs DARA-related: • Pneumonia, neutropenia, diarrhea (1 patient each receiving 16 mg/kg, early infusion program) • Laryngeal edema (1 patient receiving 16 mg/kg, accelerated infusion program)

- 19/45 patients reported IRRs
- Majority grade 1 and 2
- Most (86%) during first infusion
- 18/19 patients with IRRs recovered and continued subsequent infusion

Plesner et al. ASH 2014 (Abstract 84); oral presentation

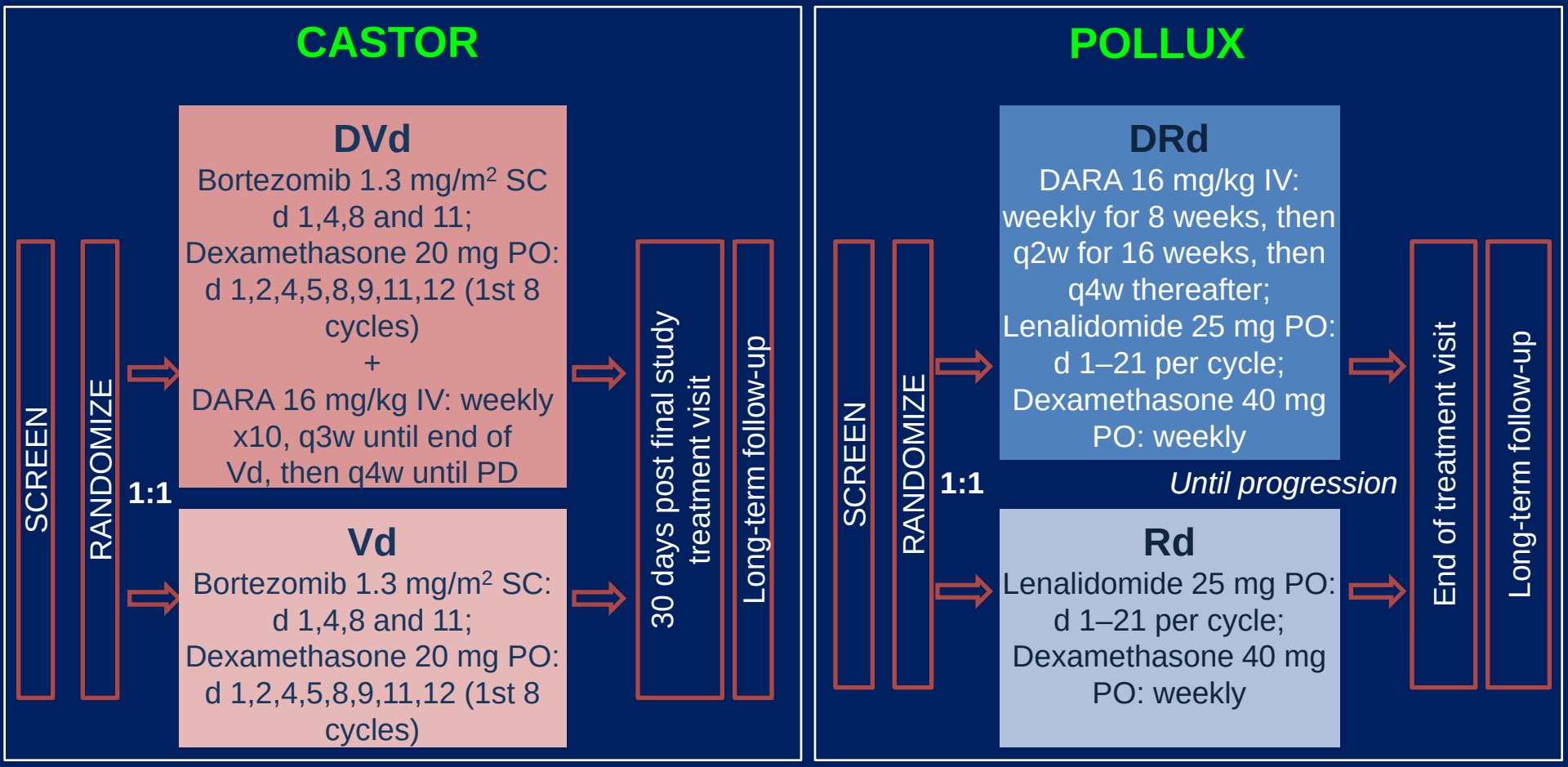
Summary of main results from daratumumab trials in rel/ref MM

- Recommended dose: 16 mg/kg
- Impressive single-agent activity in very heavily pretreated patients
- High response rates in combination with Len/Dex and current backbone agents
- Favorable safety profiles with manageable toxicities
  - Addition of DARA to backbone therapies did not result in additional toxicity apart from infusion-related reactions

Lokhorst et al. N Engl J Med 2015; 373:1207-1219
Lonial et al. ASCO 2015 (Abstract LBA8512); oral presentation

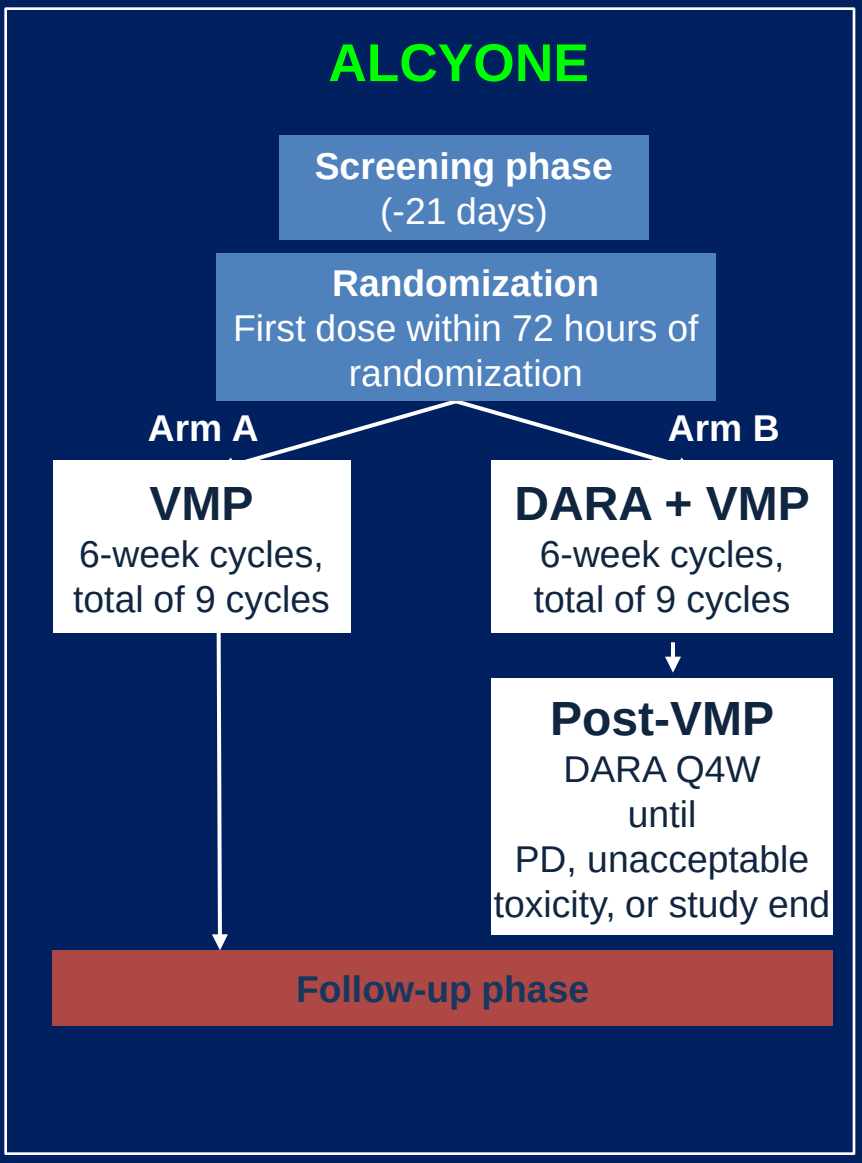
Plesner et al. ASH 2014 (Abstract 84); oral presentation
Mateos et al. EHA 2015 (Abstract P275); poster presentation

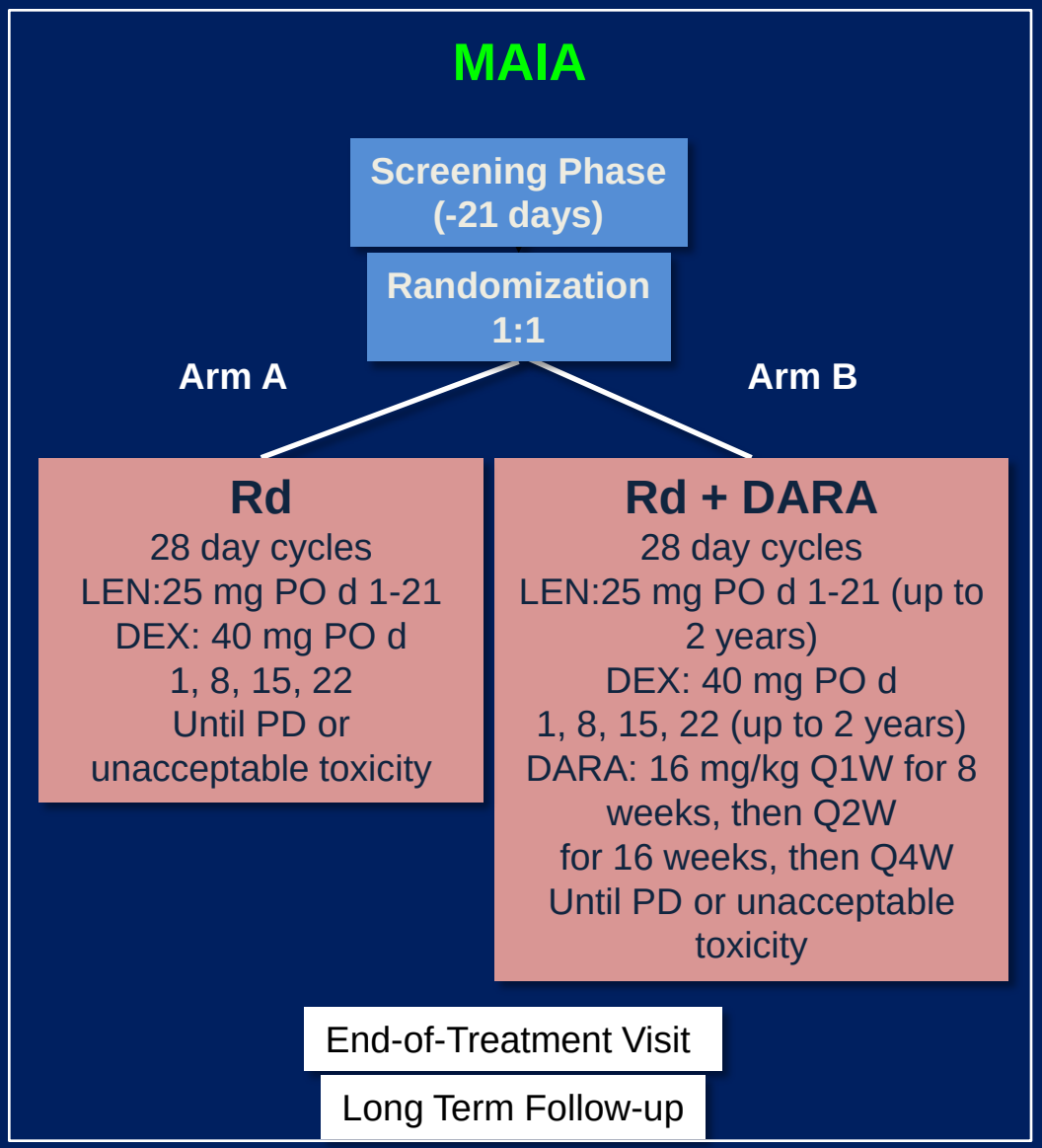
Ongoing studies in rel/ref MM



www.clinicaltrials.gov

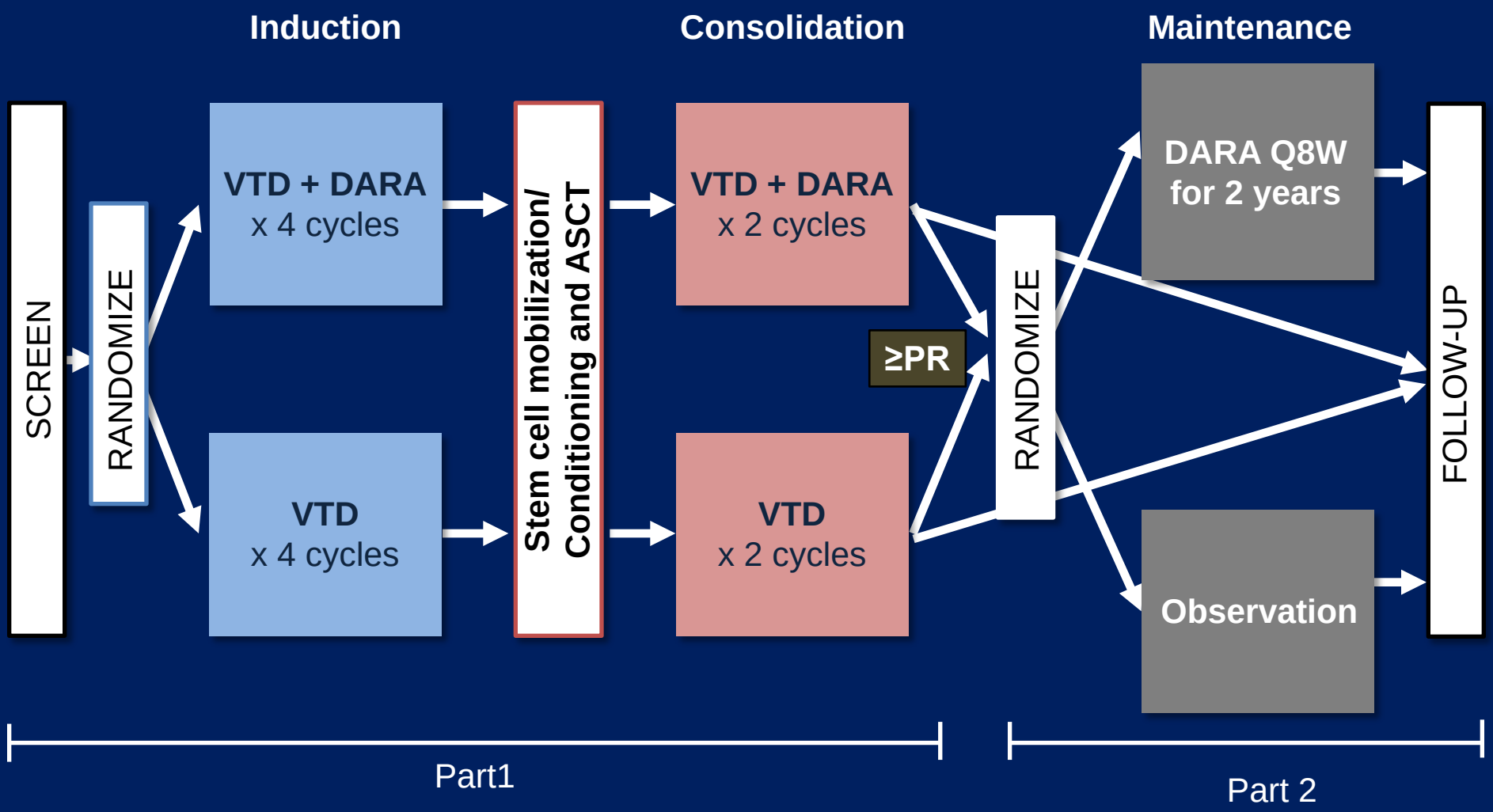
Ongoing studies in newly diagnosed MM





www.clinicaltrials.gov

CASSIOPEIA (IFM & HOVON)



www.clinicaltrials.gov

Daratumumab is currently undergoing regulatory review

- U.S. FDA Grants Priority Review to Janssen for Daratumumab as a Treatment for Multiple Myeloma

  4 September 2015

- Daratumumab accepted for accelerated CHMP assessment for treatment of European patients with heavily pre-treated multiple myeloma

  25 September 2015

http://www.prnewswire.com/news-releases/us-fda-grants-priority-review-to-janssen-for-daratumumab-as-a-treatment-for-multiple-myeloma-300138342.html
http://www.jnj.com/news/all/Janssens-daratumumab-accepted-for-accelerated-CHMP-assessment-for-treatment-of-European-patients-with-heavily-pre-treated-multiple-myeloma

FDA News Release

FDA approves Darzalex for patients with previously treated multiple myeloma

November 16, 2015

Release:

Today the U.S. Food and Drug Administration granted accelerated approval for Darzalex (daratumumab) to treat patients with multiple myeloma who have received at least three prior treatments.

Darzalex is the first monoclonal antibody approved for treating multiple myeloma.

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