The viewpoint of Scientific Groups: Part 1

European Myeloma Group

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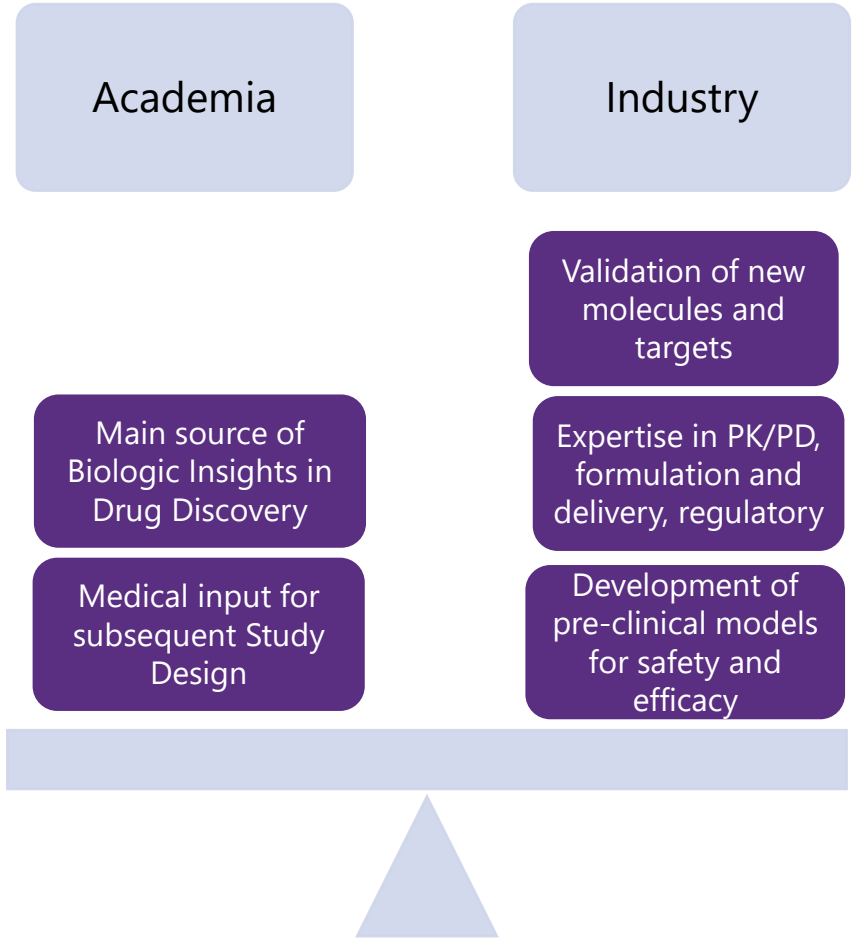
Discovery of New Molecules



The value of a close collaboration between Industry and Academia is evident even from the very beginning of a pharmaceutical agent's life cycle

Jeffrey S. Flier J Clin Invest. 2019;129(6):2172-2174

Late Clinical Development Landscape

Are pivotal trials enough?

Further need to:

1. Investigate the use of pharmaceutical compounds in
   - new indications
   - subset of approved populations
   - new dosages or regimen combinations
2. Provide Industry with additional insights for their compounds
3. Develop Evidence Based Medicine

Clinical research led by the Scientific Community is driven by a real world awareness of patient needs AND is crucial in establishing an evidence base for medical treatments

Which are the key benefits of collaborative research to the Scientific Community?

Increased motivation

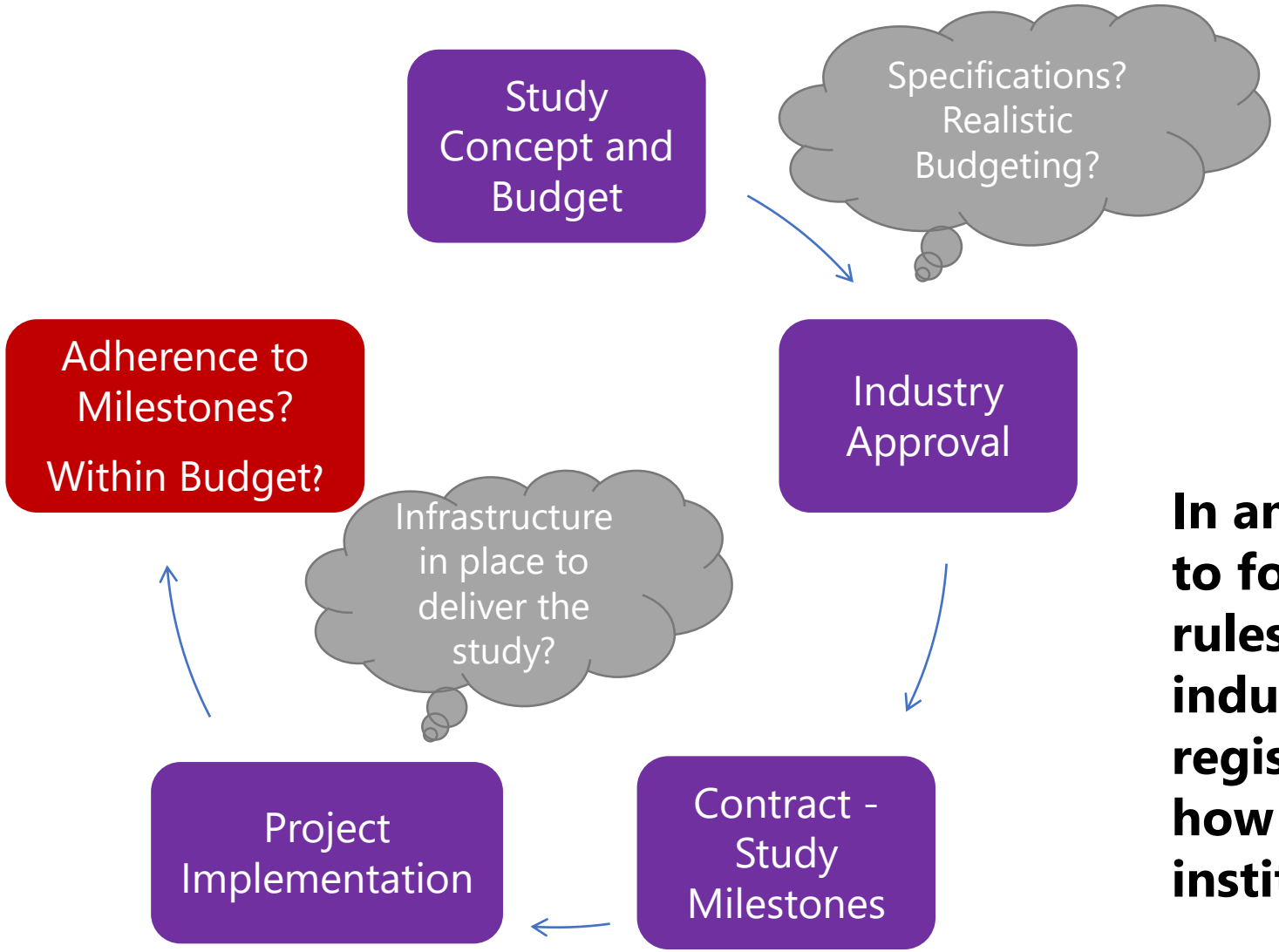
- Platform to enable the pursuit of niche research interests

Gains in infrastructure and technical expertise

- Increased experience with administration of advanced therapies
- Increasing availability of advanced techniques (e.g. FISH, MRD, DSIFE) at the clinic level

Definite advancements in medical treatments and overall patient management

The Collaborative Framework so far



In an era where IITs have to follow the same rules/requirements as industry sponsored registrational studies, how ready are single institutions/clinics?

Strength in Numbers

- In the new era of clinical research there are strict specifications and requirements in all types of clinical trials, irrespective of sponsor type
- Single Institutions by definition cannot be experts in all aspects of clinical study design and execution
- Aggregation of expert knowledge and resources from multiple institutions under Scientific Groups is the first step towards expanding clinical research within the scientific community

The European Myeloma Network (EMN)

an umbrella organization for collaborative groups and projects

European Myeloma Network: Brief Introduction

EMN: History and Goals

Important dates

- 2005 creation of the network with a small group
- 2017 new Bylaw of the EMN
- 2019 inclusion of other relevant collaborative groups under the EMN

Our goals

- Perform large, international trials in myeloma and related conditions
- Perform trials in rare plasma cell disorders (plasma cell leukemia)
- Uniform standards for correlative studies
- Quality control
- Consensus, guidelines and recommendations in Europe
- Platform for analyses and meta-analyses
- Spread knowledge through workshops and meetings

Organization

Board:

Prof. Sonneveld (Chairman)

Prof. Boccadoro (Secretary)

Prof. Dimopoulos (Member)

Prof. Einsele (Member)

Prof. Ludwig (Member)

Prof. San Miguel (Member)

Board expanding in 2019:

Prof. Cook (Member)

Prof. Hajek (Member)

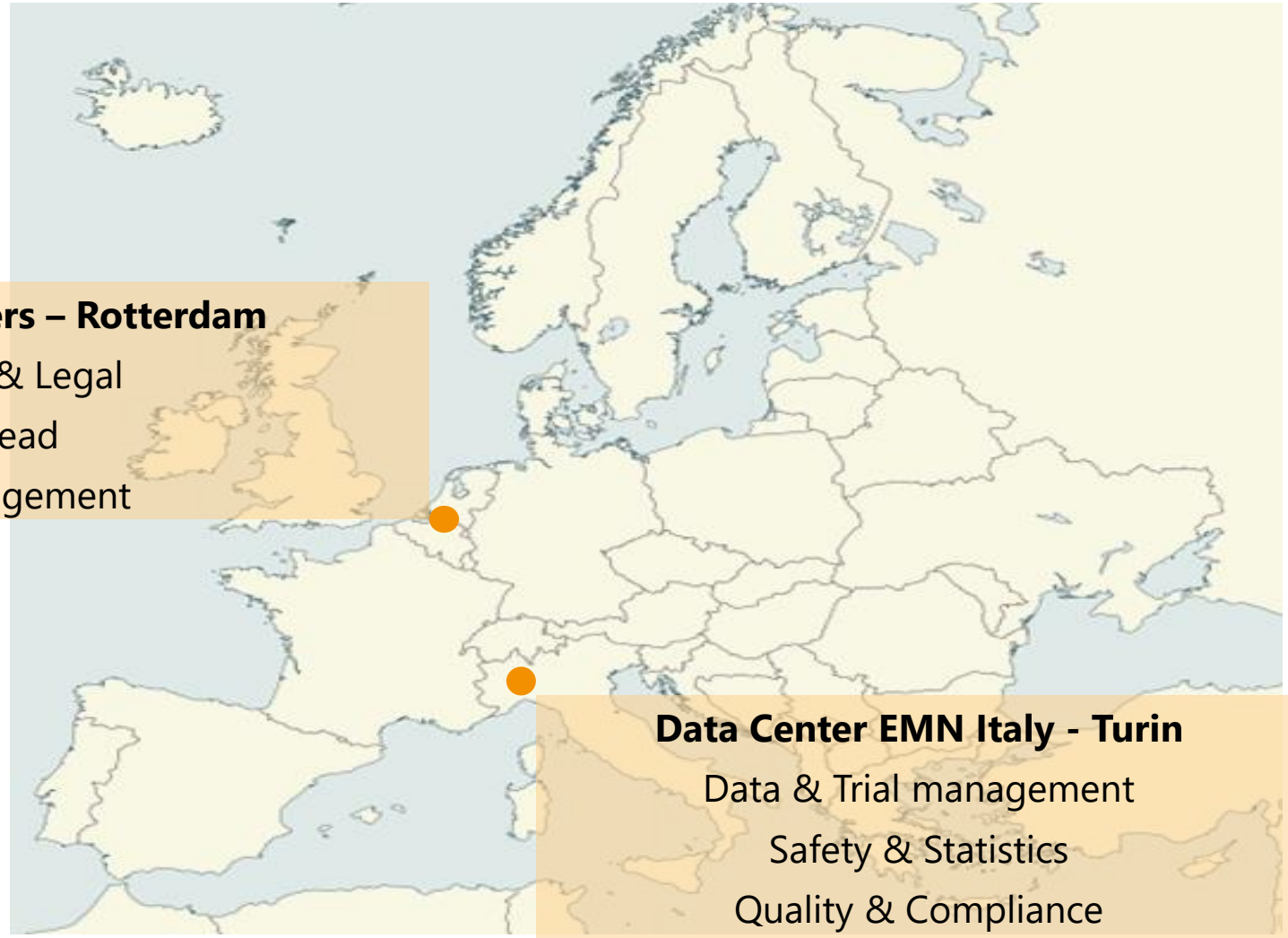
Prof. Moreau (Member)

Prof. Vangsted (Member)

Participants:

Open registration to EMN to be included in the projects and trials of the network. Registration online is required www.myeloma-europe.org

Headquarters and Data Center



EMN Headquarters – Rotterdam

Financial & Legal

Trial Lead

Trial Management

Data Center EMN Italy - Turin

Data & Trial management

Safety & Statistics

Quality & Compliance

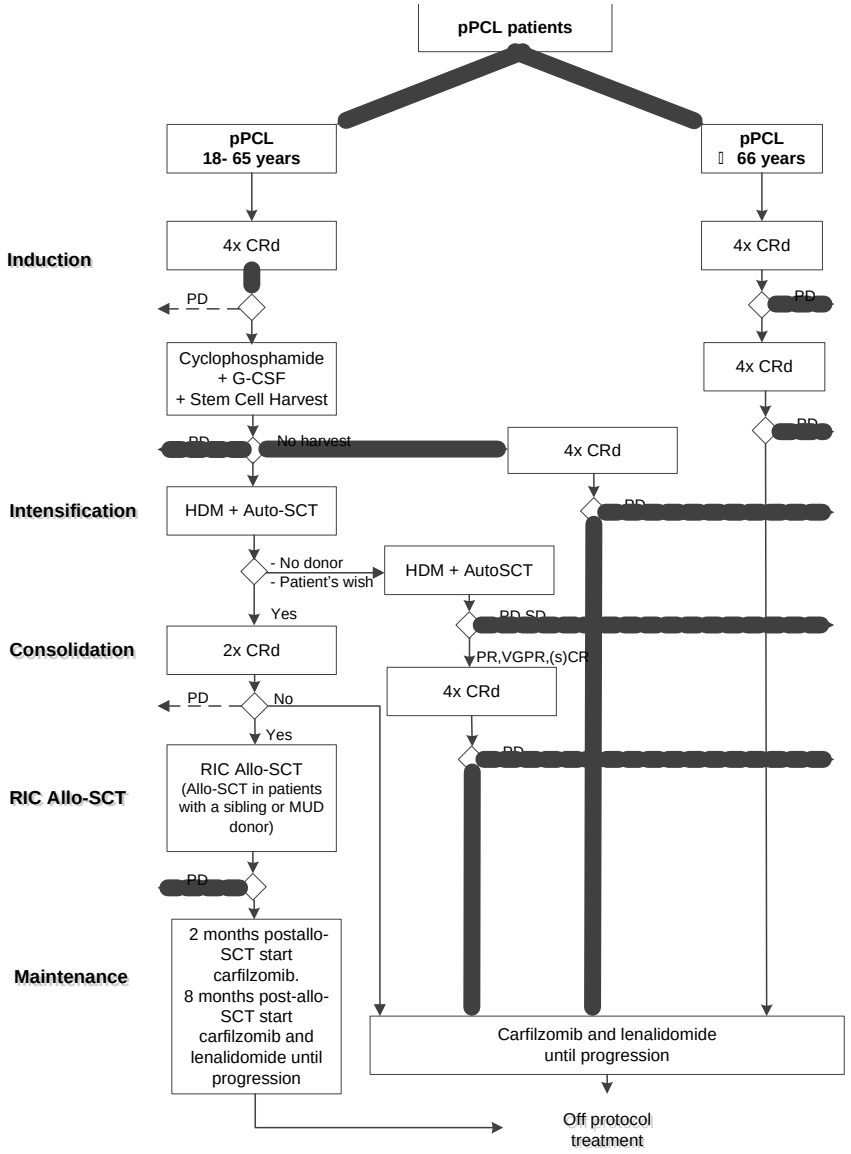
Communication & ICT

Clinical Program

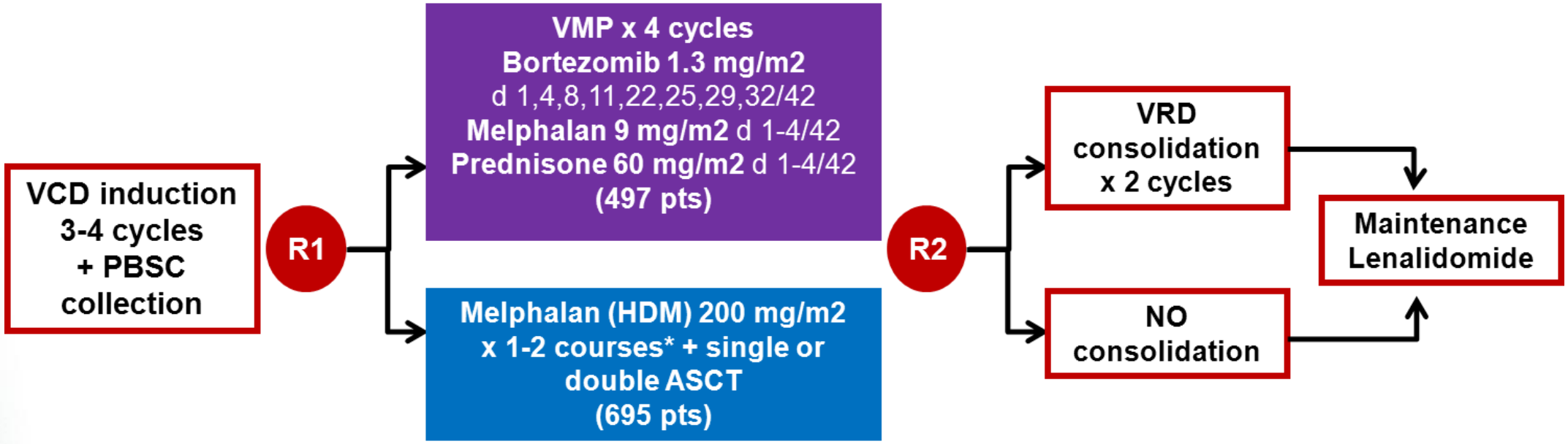
EMN has been actively running large Phase III/pivotal studies in:

- **Newly Diagnosed Multiple Myeloma**
  - Young
  - Elderly
- **Relapsed/Refractory Multiple Myeloma**
- **Rare Plasma Cell Disorders**

EMN12: Primary Plasma Cell Leukemia

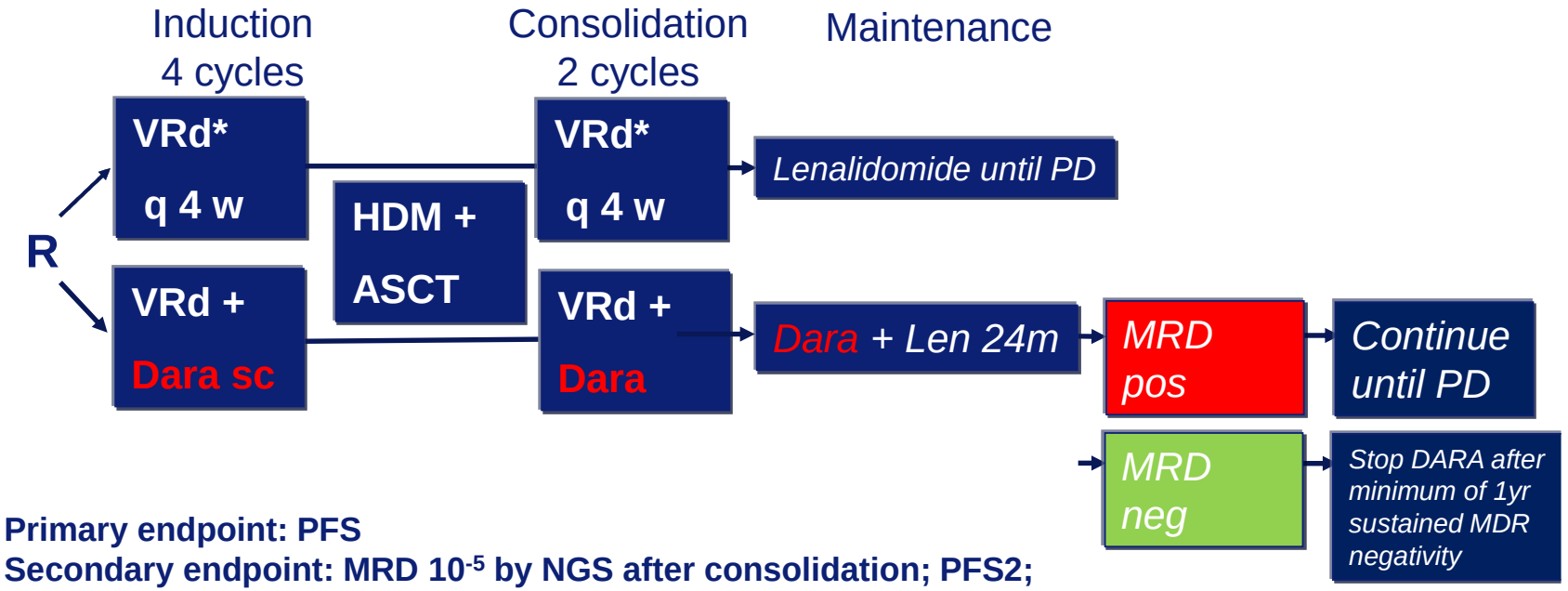


EMN 02: NDMM - young



- **Stratification according to center and ISS disease stage (I vs. II vs. III)**
- **Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy**
- **Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy**

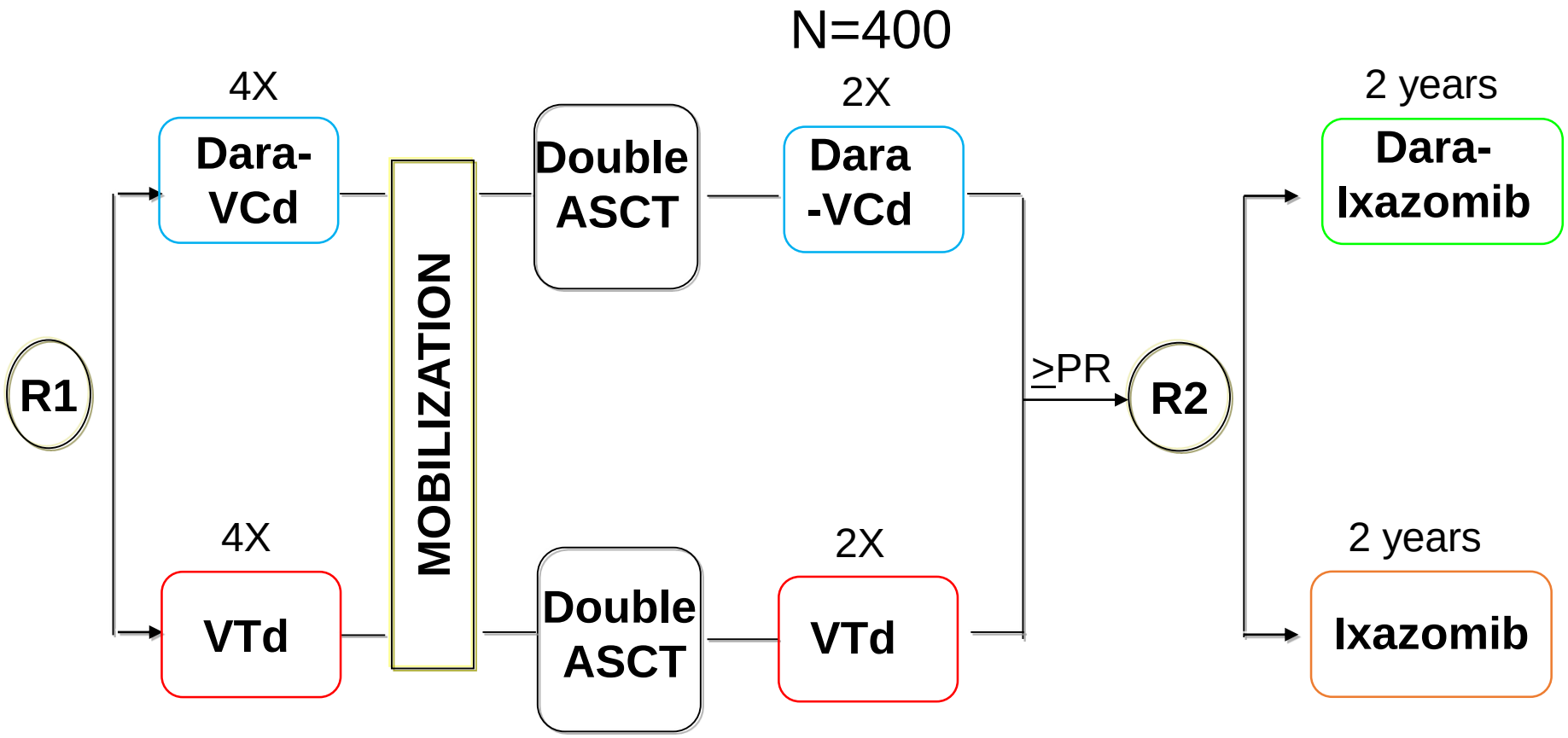
EMN 17 (PERSEUS): NDMM - young



Primary endpoint: PFS
Secondary endpoint: MRD 10^{-5} by NGS after consolidation; PFS2; OS
Patients: NDMM, 18-70 yr, n=690

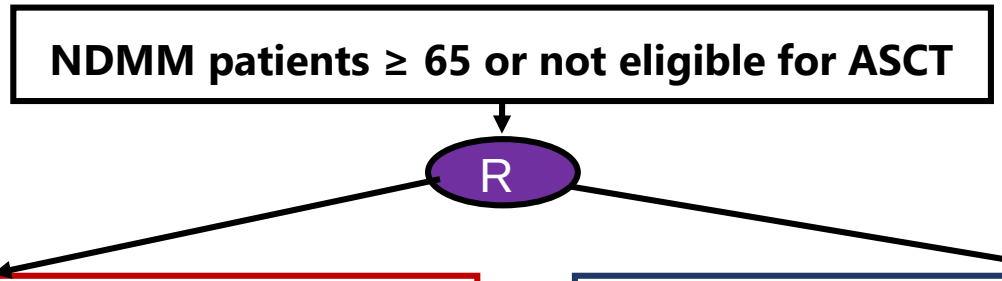
- **Registration trial for VRd-Dara EMA and FDA**
- **Future standard of care**
- **Investigator sponsored EMN**
- **Inclusion time 12-16 months**
- **15 participating countries: EU, AUSTRALIA**
- **Central lab for MRD, Genetics, Immunomonitoring, ME**

EMN 18: NDMM - young



R: randomization; Dara-VCd: Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone; VTd:Bortezomib, Thalidomide, Dexamethasone; ASCT: autologous stem cell Transplant: Dex: Dexamethasone

EMN 20: NDMM - elderly



ARM A: until PD or intolerance*

Carfilzomib (K):

- 20 mg/m² IV on day 1 of cycle 1;

- 56 mg/m² IV on days 8 and 15 in cycle 1;

- 56 mg/m² IV on days 1, 8 and 15 in cycles 2-12;

- 56 mg/m² on days 1 and 15 from cycle 13 and onwards.

Lenalidomide (R):

- 25 mg orally on days 1-21 of each cycle.

Dexamethasone (d):

- 40 mg orally on days 1, 8, 15 and 22 of each cycle.

Each cycle is a 28-day cycle.

ARM B: until PD or intolerance

Lenalidomide (R):

-25 mg orally on days 1-21 of each cycle.

Dexamethasone (d):

-40 mg orally on days 1, 8, 15 and 22 of each cycle.

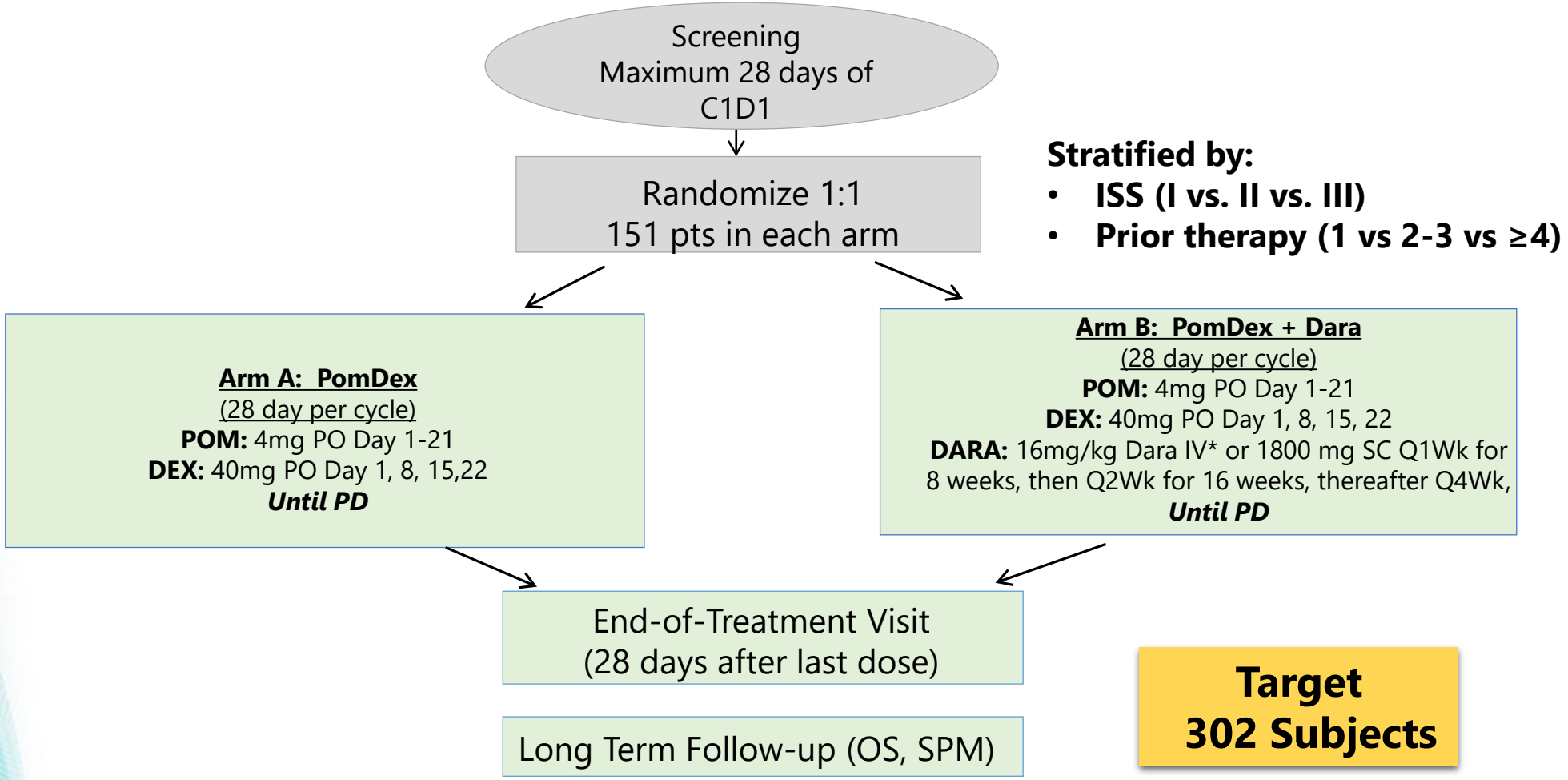
Each cycle is a 28-day cycle.

*Only patients that achieve at least a VGPR within the first year of treatment and in sustained MRD negativity (MRD negative at least at 10^{-5} after 1 and 2 years of therapy) will stop Carfilzomib after 2 years of treatment, and will continue with lenalidomide and dexamethasone administration.

Stratification for ISS risk (1 or 2 vs 3) and **frailty status** (fit vs intemediate)

NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplantation; ASCT, autologous stem cell transplantation; PD, progressive disease; VGPR, very good partial response; MRD, minimal residual disease; ISS, International Staging System.

EMN 14 (APOLLO): RRMM



* Only for patients that were enrolled with version 1.0 of the Study Protocol. These 4 patients have switched to Daratumumab SC

Papers: Guidelines and Meta-analyses

- Bone disease in Myeloma (Terpos et al., Leukemia 2014)
- Myeloma complications (Terpos et al., Haematologica 2015)
- Cellular therapies (Gay et al., Haematologica 2018)
- Elderly Myeloma patients (Larocca et al., Leukemia 2018)
- Management of adverse events (Lugwig et al., Leukemia 2018)
- Tools to monitor Myeloma (Caers et al, Haematologica 2018)
- Maintenance treatment (Gay et al., JAMA Oncology 2018)
- Cardiovascular adverse events (Bringhen et al., Haematologica 2018)
- Rare plasma cells disorders ir (Gavriatopoulou et al., Haematologica 2018)

Which are the Challenges of Collaborative Research for a Scientific Group?

1. **Data Ownership**
   - **Collaborative Agreements:** Need clear specifications as to what type of access to the data is allowed to the collaborative partner
2. **Publication Rights**
   - Need a robust publication policy in place to avoid conflicts down the line
3. **Establishment and continuous expansion of Infrastructure**
4. **Differing viewpoint and levels of flexibility compared to Pharma Industry**
   - Industry's standard processes may require significant time before an action may be initiated

Moving Forward: How can we improve our collaboration with the Industry partner?

1. **Continuous investment in Scientific Group's Infrastructure and resources**
2. **Create preferred vendor lists to ensure a quick and reliable vendor selection process**
3. **Set expectations from the start:**
   - Request clear specifications from the Industry early in the collaborative project
4. **Clear contractual agreements with realistic milestones are key to a smooth project execution**

Thank You!