Medikamentstudier i Midt-Norge

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Hvorfor medikamentstudier ?

- Tilgang til medisin som ellers ikke er tilgjengelig

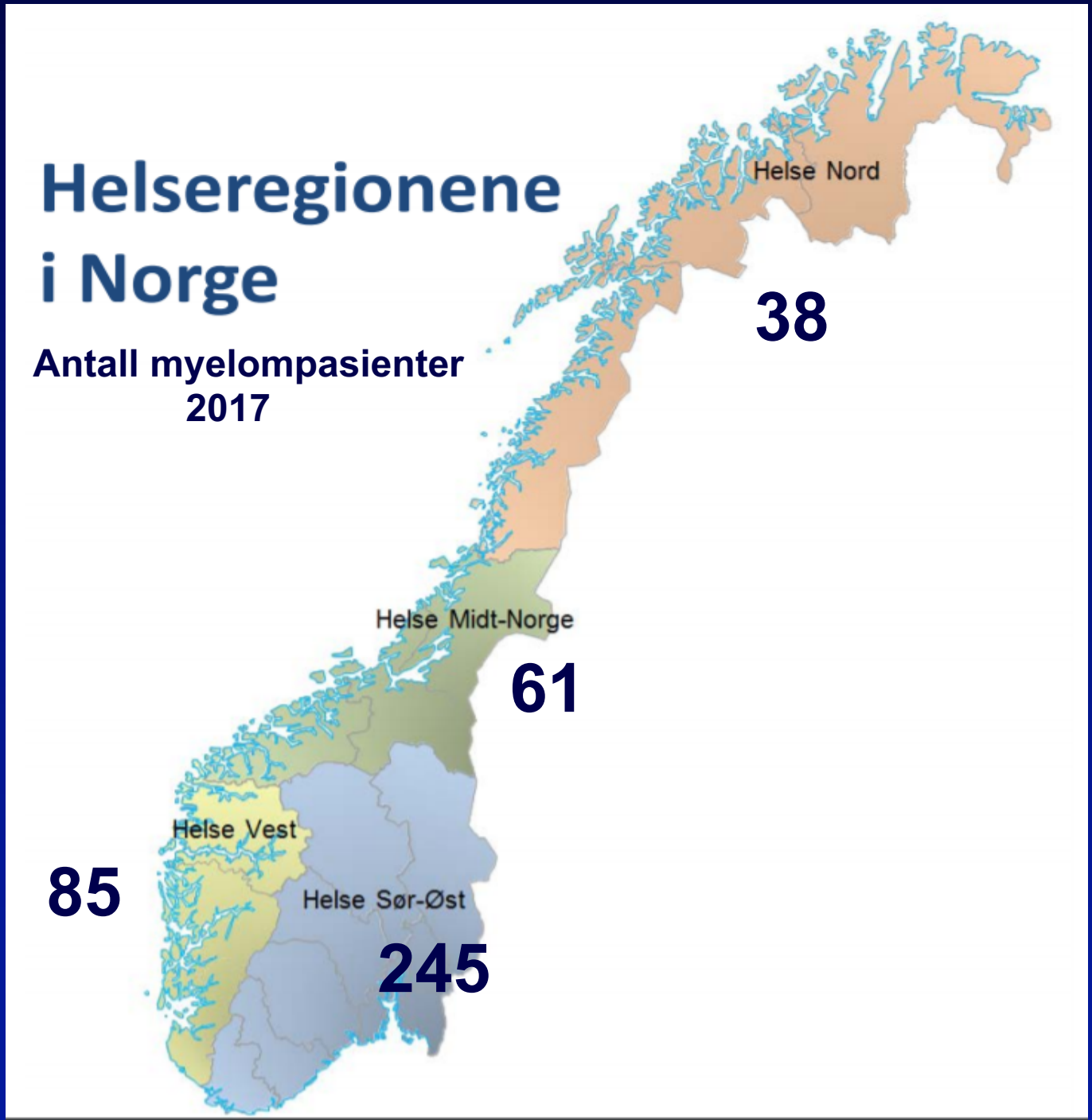
- Tilgang til enda et medikament når alle medikamentene er brukt opp

Betydelig oppbygging av studieaktiviteten i Midt-Norge

Myelomatose
Kronisk lymfatisk leukemi
Akutt myelogen leukemi
Kronisk myelogen leukemi

Helseregionene i Norge

Antall myelompasienter 2017



Medikamentstudier bør være tilgjengelig i hele Norge


Namsos
Levanger
Orkdal
St. Olavs Hospital
Universitetssykehuset i Trondheim
Kristiansund*
SØR-TRØNDELAG
Molde*
Ålesund
Volda

Myelomatose

1. behandling

    <70 år HMAS

    >70 år medikamenter

2-5. behandling Tilbakefall

Oversikt studier Midt-Norge

- IRd 1. behandling
- Perseus 1. behandling
- Magnolia 1. behandling
- Isatuximab 1. behandling
- Cobra 1. behandling
- Remnant Tilbakefall
- Carfilzomb + kloroquin Tilbakefall

Ixazomib/Revlimid/dex (IRd)/HMAS

- Ixazomib (Ninlaro)

- Proteasomhemmer (i slekt med Velcade)
- Tabletter
- Ikke refundert i Norge

Studien inkluderer aktivt nå

- Fordeler/ulemper:
- All behandling er tablettbehandling
- Lite bivirkninger

- Tilgang til nytt medikament (ixazomib)

Fase 1/2 studie

klorokvin og Karfilzomib

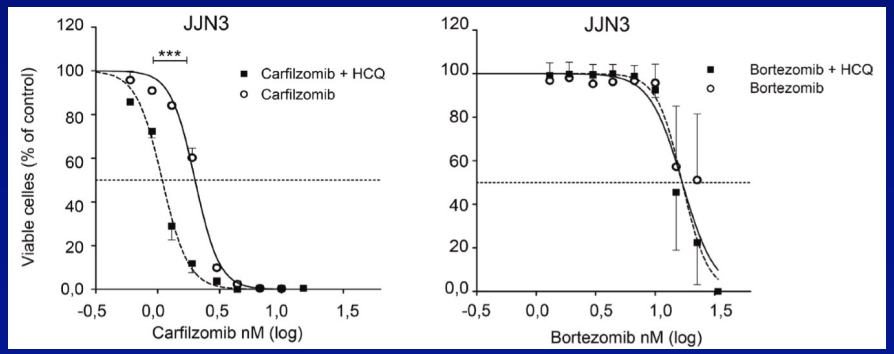
En studie som startet i laboratoriet i myelomgruppen i Trondheim

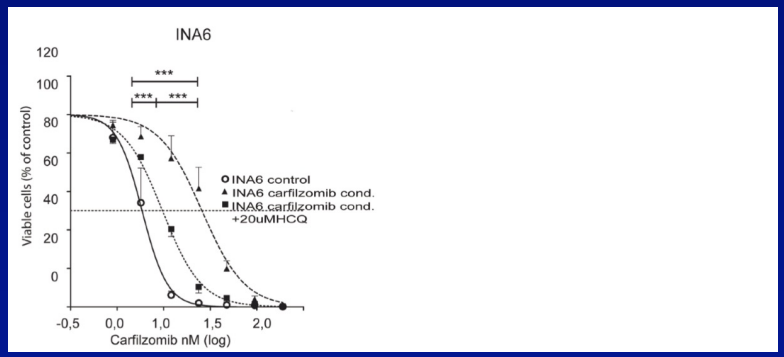
www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 43

Research Paper

Hydroxychloroquine potentiates carfilzomib toxicity towards myeloma cells

Katarzyna Baranowska[1,*], Kristine Misund[1,*], Kristian K. Starheim[1,2], Toril Holien[1], Ida Johansson[2,3], Sagar Darvekar[1], Glenn Buene[1], Anders Waage[1,4], Geir Bjørkøy[2,5], Anders Sundan[1,2]





Formål med studien

Fase 1
Etablere hvilken dose av klorokvin som er den beste

Få oversikt over bivirkninger

Fase 2
Virker medisinen på sykdommen ?

Hvem kan være med ?

- Må ha mottatt 2 tidligere behandlinger inkludert bortezomib og IMIDS
- Må ikke være resistent mot karfilzomib
- Må ha tilbakefall

Når starter studien ?

- Desember 2019
- Inklusjon i 15 måneder
- Oppfølgingstudie fase 2 i 2020

NMSG-studie: hvor lenge skal vi bruke benbeskyttende behandling ?

Bisfosfanat i 2 eller 4 år ?

- Alle pasienter som starter 1. behandling
- Pasienter som har fått Zometa i 2 år og ikke har fått tilbakefall

- Loddtrekning etter 2 år: slutte eller fortsette med Zometa i 2 år til

Studier som ikke har startet enda

COBRA
Nylig diagnostisert myelomatose
KRd vs. VRd

Karfilzomib Len, Dex (KRD)

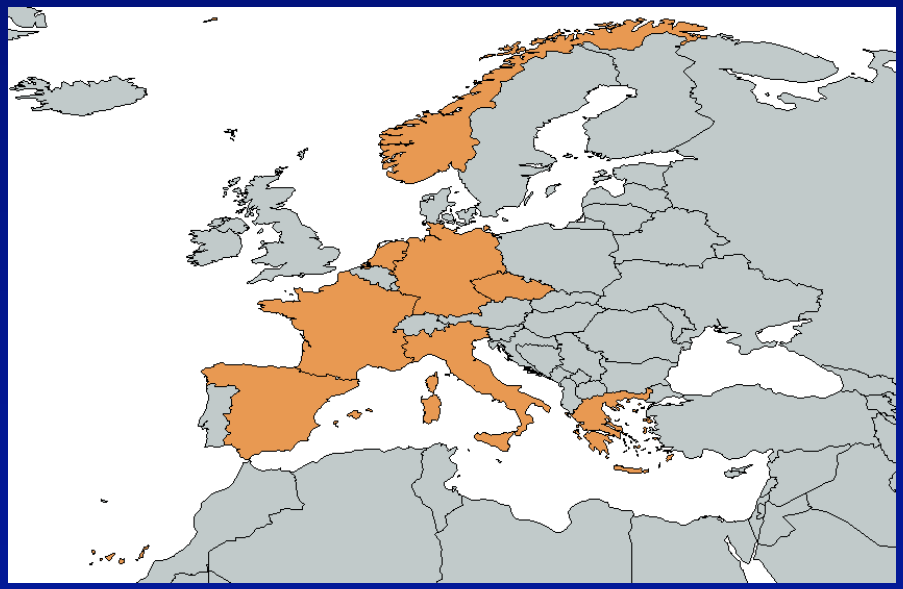
versus

Velcade, Len, Dex (VRD)

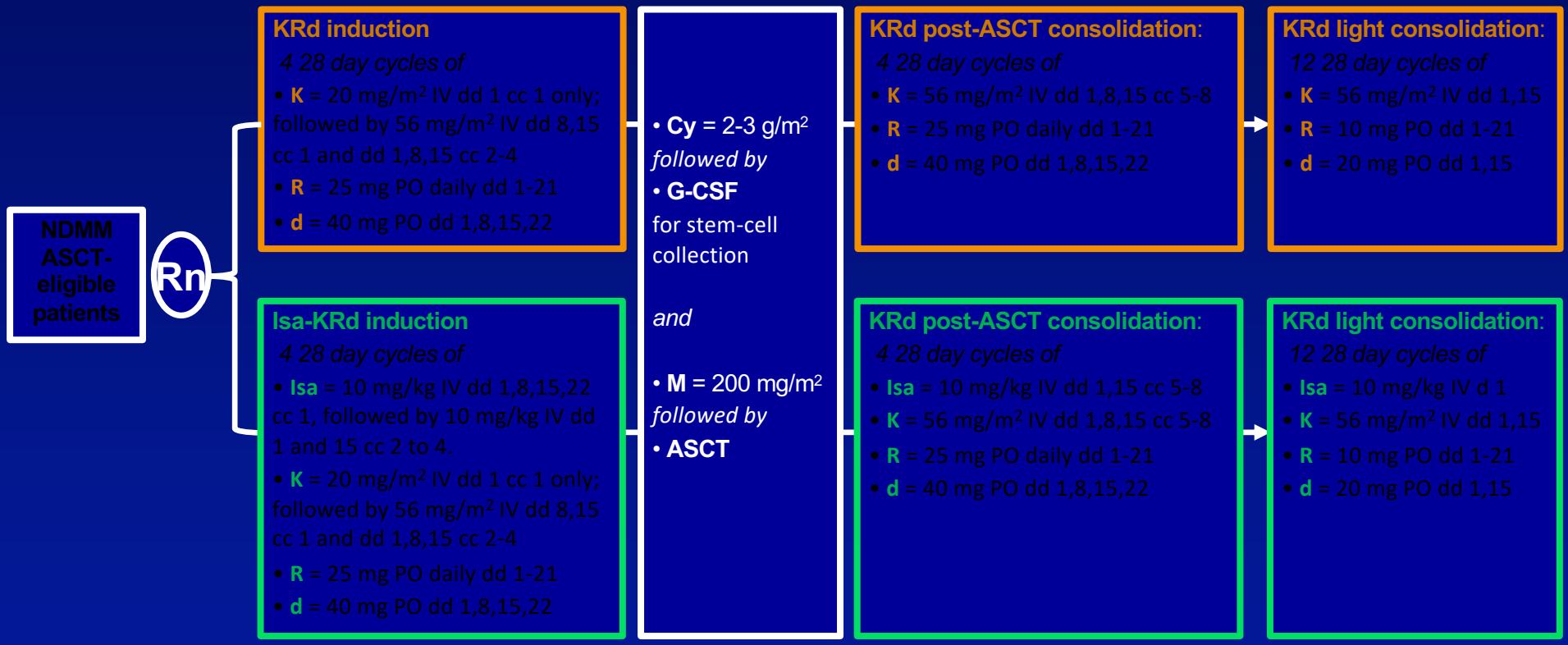
- Samarbeid: USA (Chicago) – Polen – NMSG
- Pasient antall 400
- 150 patienter i NMSG, 150 i Polen sites, 100 i US
- Inklusjon
  - 1. HMAS

upcoming EMN trials (EMN 24- ISKIa)

EMN24	
Other identifying number/names	-
Setting	NDMM
Study Phase	III
Drug/s	Isa-KRd vs KRd
Principal Investigator	Dr Brojl Dr Gay
Number of participating sites	50/60 under discussion
First patient in	Q1 2019
Last patient in	Q4-2020/Q1 2021
Number of patients needed	300



Isatuximab-KRD vs KRD



Rn, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; Cy, cyclophosphamide; M, melphalan; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem-cell transplantation; dd, days; cc, cycles; G-CSF, Granulocyte-Colony Stimulating Factor PO, orally; IV, intravenous.

Remnant-studien
Alle som har fått HMAS

- Tidlig eller sen behandling ved tilbakefall

Oversikt studier Midt-Norge

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- Perseus 1. behandling
- Magnolia 1. behandling
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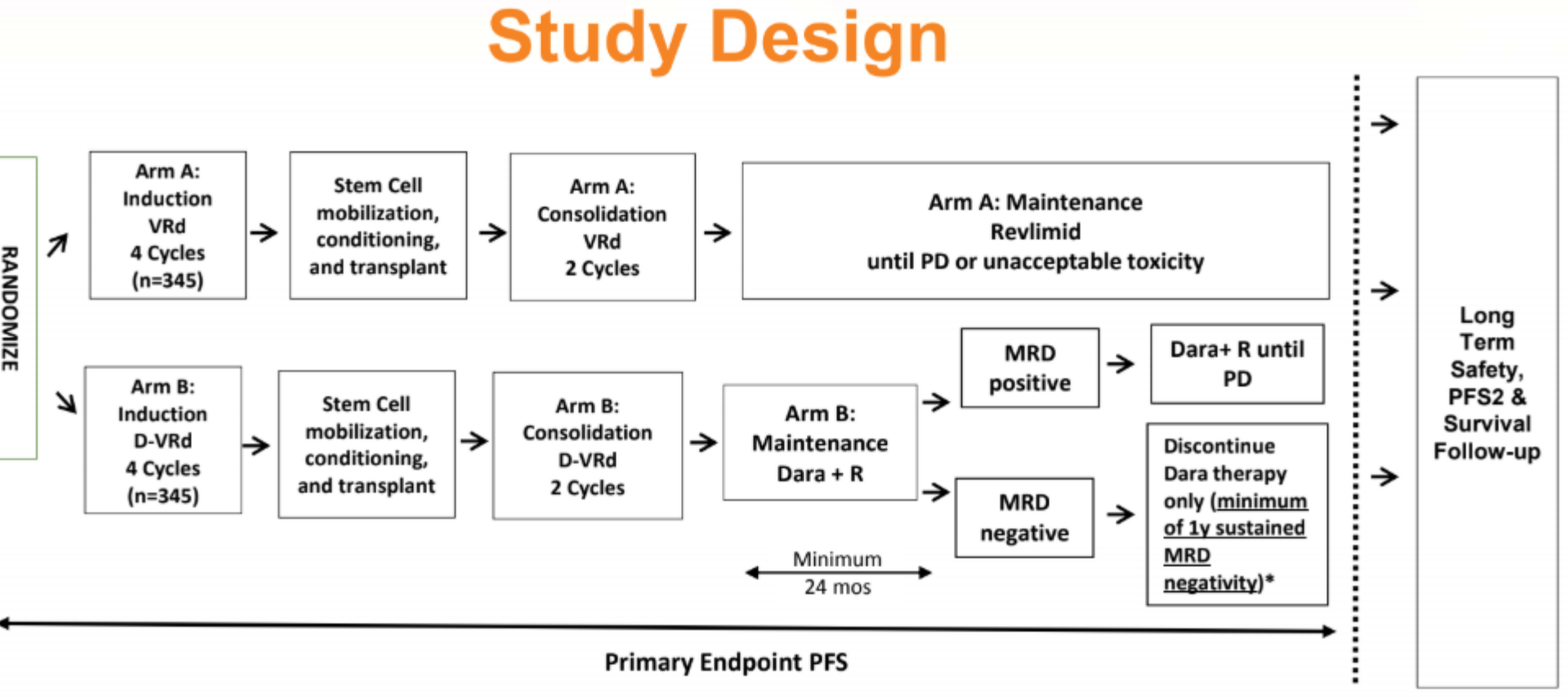
- Cobra 1. behandling
- Remnant Tilbakefall
- Carfilzomb + klorokvin Tilbakefall

Betydelig opptrapping av studieaktiviteten i Midt-Norge

Det er også god behandling utenom studier

44

Studie som avsluttes nov 2019
Dara-VRD vs VRD



COBRA

Carfilzomib x1/uke

upcoming EMN trials (EMN 24- ISKIa)

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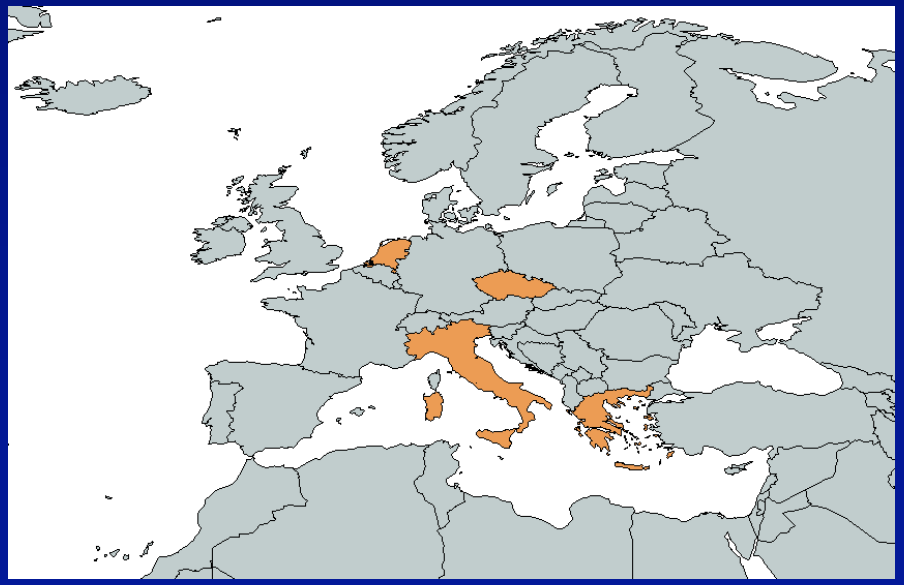

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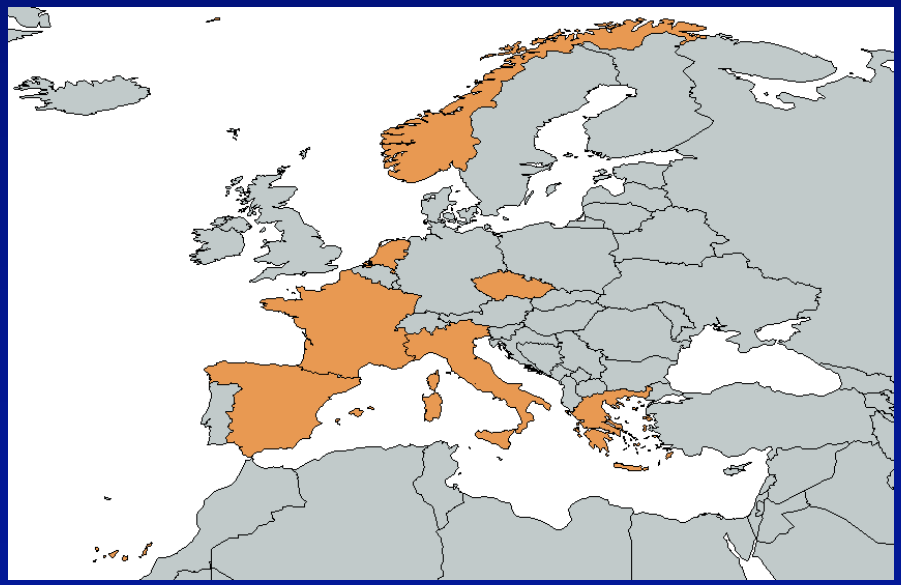

Phase III EMN24 IsKia study

Inclusion criteria

- documented MM:
  - **CRAB criteria**:
  - **Biomarkers of Malignancy**:
- Patient **18-70 years old** and **ASCT-eligible**
- **Measurable disease**
- **ECOG** status ≤2
- **Clinical laboratory values** :
  - **Adequate hepatic function**, ALT/AST ≤2.5 times the ULN
  - **Serum direct bilirubin** ≤1.5 ULNLN (except in subjects with congenital bilirubinemia, direct bilirubinemia ≤1.5 ULN)
  - **Absolute neutrophil count** (ANC) ≥1.0 × 109/L
  - **Platelet count** ≥75×109/L (≥50× 109/L if MM involvement in the bone marrow >50%)
  - **Creatinine clearance** (CrCl) ≥30 mL/minute.
  - **Corrected serum calcium** ≤13.5 mg/dL (3.4 mmol/L)
  - **LVEF** ≥40%.

Phase III EMN24 IsKia study

Exclusion criteria I

•• **Non-secretory MM** (unless serum free light chains with abnormal ratio or plasmacytoma with D>2 cm).

•• **Plasma cell leukemia, amyloidosis, Waldenstrom disease, POEMS syndrome**.

•• **Meningeal involvement** of MM.

•• **Acute active infection** requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to randomization.

•• **Significant neuropathy** (G3-4, or G2 with pain).

•• Known human immunodeficiency virus infection (HIV).

•• Active hepatitis B or C infection.

•• **Allergy to Captisol® or** any of the components of **study treatments or H2 blockers**.

•• **Contraindication to any of the required concomitant drugs or supportive treatments**,

•• **Significant medical disease or condition** that may interfere with protocol adherence or informed consent.

•• **Cardiovascular comorbidities**:
Unstable angina or myocardial infarction ≤4 months prior to randomization; NYHA Class III or IV heart failure; uncontrolled angina; uncontrolled hypertension; pulmonary embolia; history of severe coronary artery disease; severe uncontrolled ventricular arrhythmias; sick sinus syndrome; or electrocardiographic evidence of acute ischemia or G3 conduction system abnormalities unless subject has a pacemaker.

•• **Non-hematologic malignancy ≤3 years**, with the exception of:

a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer;
b) carcinoma in situ of the cervix or breast
c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels
d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, (e.g. localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas).

MM, multiple myeloma; D, diameter; ASCT, autologous stem-cell transplantation; G, grade; POEMS, polyneuropathy, organomegaly, endocrinopathy of various forms, production of a monoclonal [M] component, and skin changes.

Phase III EMN24 IsKia study

Statistical methods I

Primary Endpoint:

ITT population

•• post ASCT consolidation **MRD**:

- α= 0.05 (two sided)
- β= 0.10
- Allocation ratio: 1:1
- MRD negativity (NGS, 10^{-5}) rate ARM A (Isa-KRd): 64%
- MRD negativity (NGS, 10^{-5}) rate ARM B (KRd): 45%

Total number of patients required: 300 (by the X2 test with Yates' continuity correction).

ITT, intention to treat population; MRD, minimal residual disease; ASCT, autologous stem-cell trnsplantation; NGS, next-generation sequencing; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; HR, hazard ratio.

Secondary Endpoints:

Hierarchical testing procedure for the key secondary endpoints to achieve control of the overall familywise Type I error rate at a two-sided significance level of 0.05.

•• **MRD negativity rate after induction**:

- α= 0.05 (two sided)
- β= 0.15
- Allocation ratio: 1:1
- MRD negativity (10^{-5}) (NGS) rate ARM A (Isa-KRd): 30%
- MRD negativity (10^{-5}) (NGS) rate ARM B (KRd): 15%

•• **PFS**:

- α= 0.05 (two sided)
- β= 0.06
- Allocation ratio: 1:1
- 60 months PFS ARM A (Isa-KRd): 80%
- 60 months PFS ARM B (KRd): 60% (HR:0.44

Opptrapping av studieaktiviteten i Midt-Norge

- Hvem kan være med?
- Ved hvilke sykehus kan behandlingen gis
- Tabletter versus i sprøyte
- Reisevei

- Forbehandling: Ixazomib/rev/dex
- Høydosebehandling
- 2 kurer med IRd
- Vedlikeholdsbehandling:
  - Høyrisiko: ixazomib/Revlimid
  - Standardrisiko: Revlimid

Tabletter

- Melfalan
- Cyklofosfamid
- Thalidomid
- Lenalidomid
- Imnovid
- Ixazomib
- Panobinostat

- Venetoclax
- Selinexor

Iv

- Daratumumab
- Carfilzomib
- Elotuzumab

- **sc**
- Bortezomib
- (daratumumab)

Noen huskeregler 3. linje og utover

- Umulig å forutsi respons på det enkelte medikament
- Umulig å si hvilken rekkefølge som er best
- Alle pasienter bør ha prøvd 80% av medikamentene. Det 5. medikamentet kan være det beste
- Tenk hele behandlingsforløpet, ikke bare den aktuelle behandlingen
- Praktiske forhold, preferanser, reisevei, komorbiditet spiler stor rolle

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- 3 Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B, Carlson K, Dahl IM, Forsberg K, Gulbrandsen N, Haukås E, Hjertner Ø, Hjorth M, Karlsson T, Knudsen L, Nielsen JL, Linder O, Mellqvist UH, Nesthus I, Rolke J, Strandberg M, Sørbø JH, Wisløff F, Juliusson G, Turesson I,for the Nordic Myeloma Study Group. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 116:1405-12,2010..