The viewpoint of Scientific Groups: Part 2

Balkan Myeloma Group

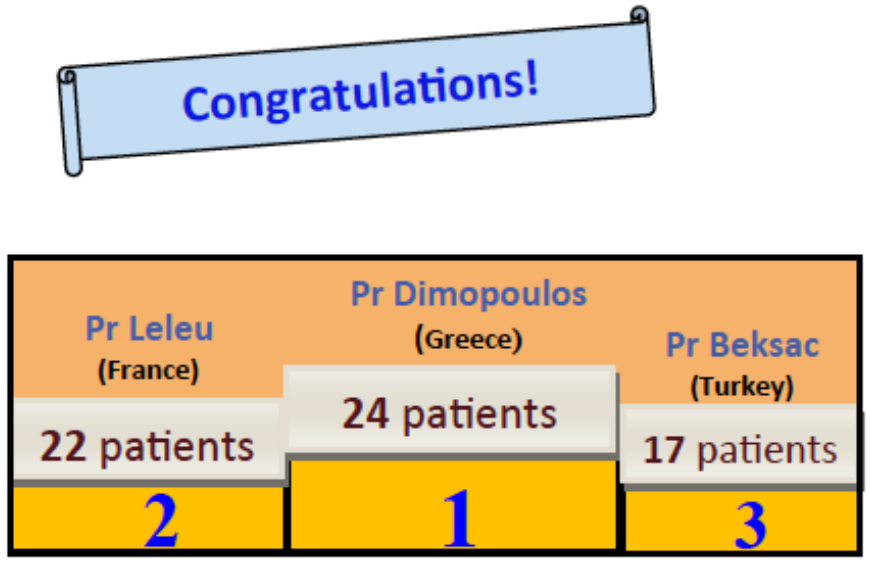
Meral Beksac
Ankara University

bjh research paper

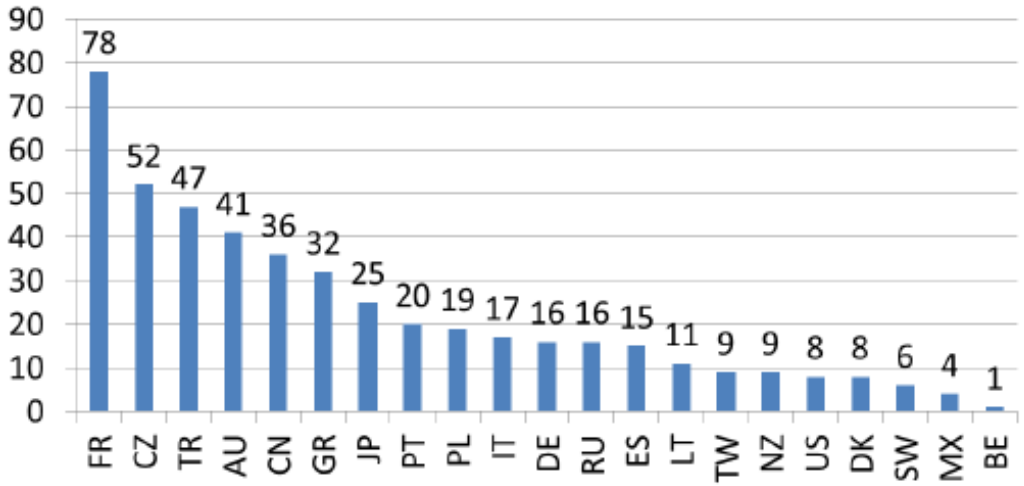
British Journal of Haematology, 2017, 178, 61–71

Effects of single-agent bortezomib as post-transplant consolidation therapy on multiple myeloma-related bone disease: a randomized phase II study

Orhan Sezer,[1,*] Meral Beksac,[2] Roman Hajek,[3,4] Gülsan Sucak,[5] Seckin Cagirgan,[6] Werner Linkesch,[7] Olga Meltem Akay,[8] Zafer Gülbas,[8,9] Hareth Nahi,[10] Torben Plesner,[11,12] John A. Snowden,[13,14] Ayşen Timurağaoğlu,[15] Tobias Dechow,[16] Alois Lang,[17] Tülin Tuğlular,[18] Johannes Drach,[19] Gabriele Armbrecht,[20] Anna Potamianou,[21] Catherine Couturier,[22] Robert A. Olie,[23] Caroline Feys,[24] Nathalie Allietta[22] and Evangelos Terpos[25]



Top recruiters

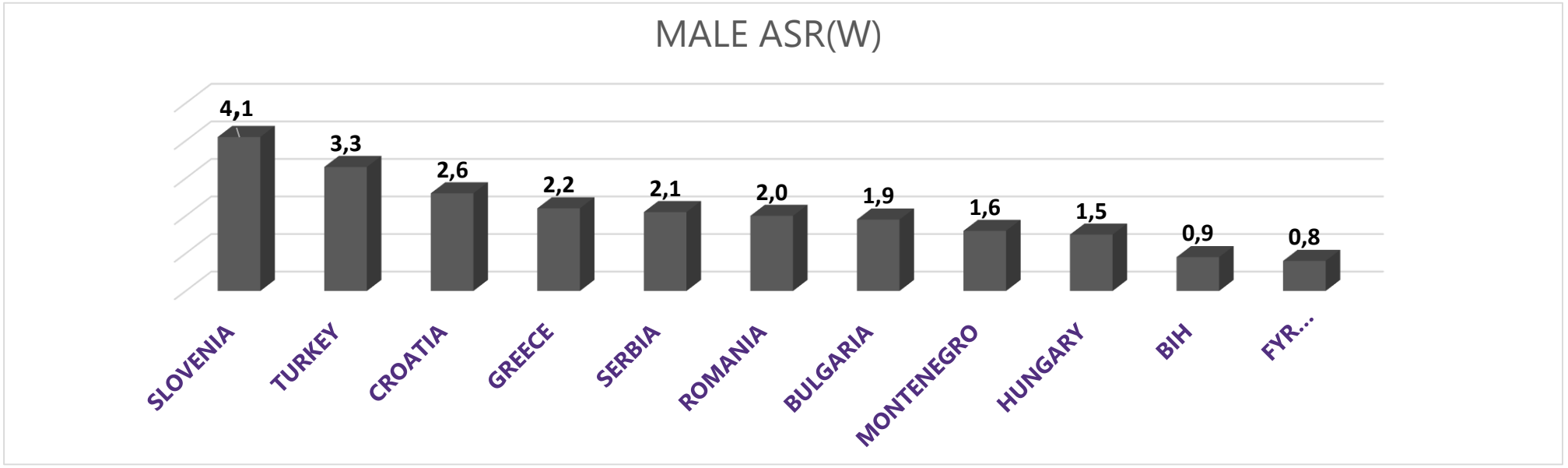


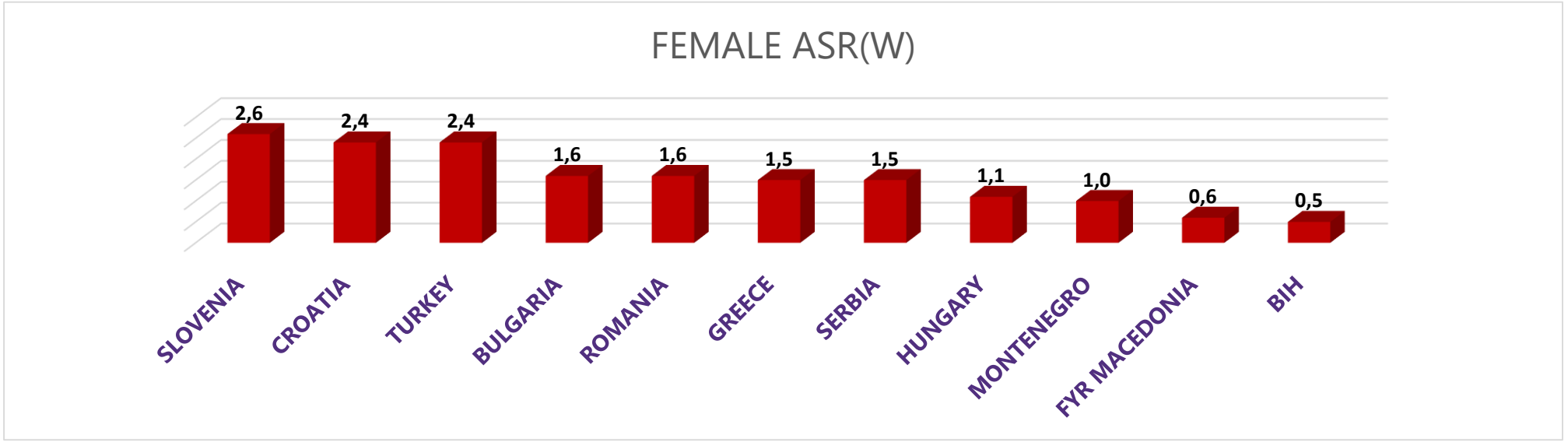
Number of patients randomized per country

MM Epidemiology

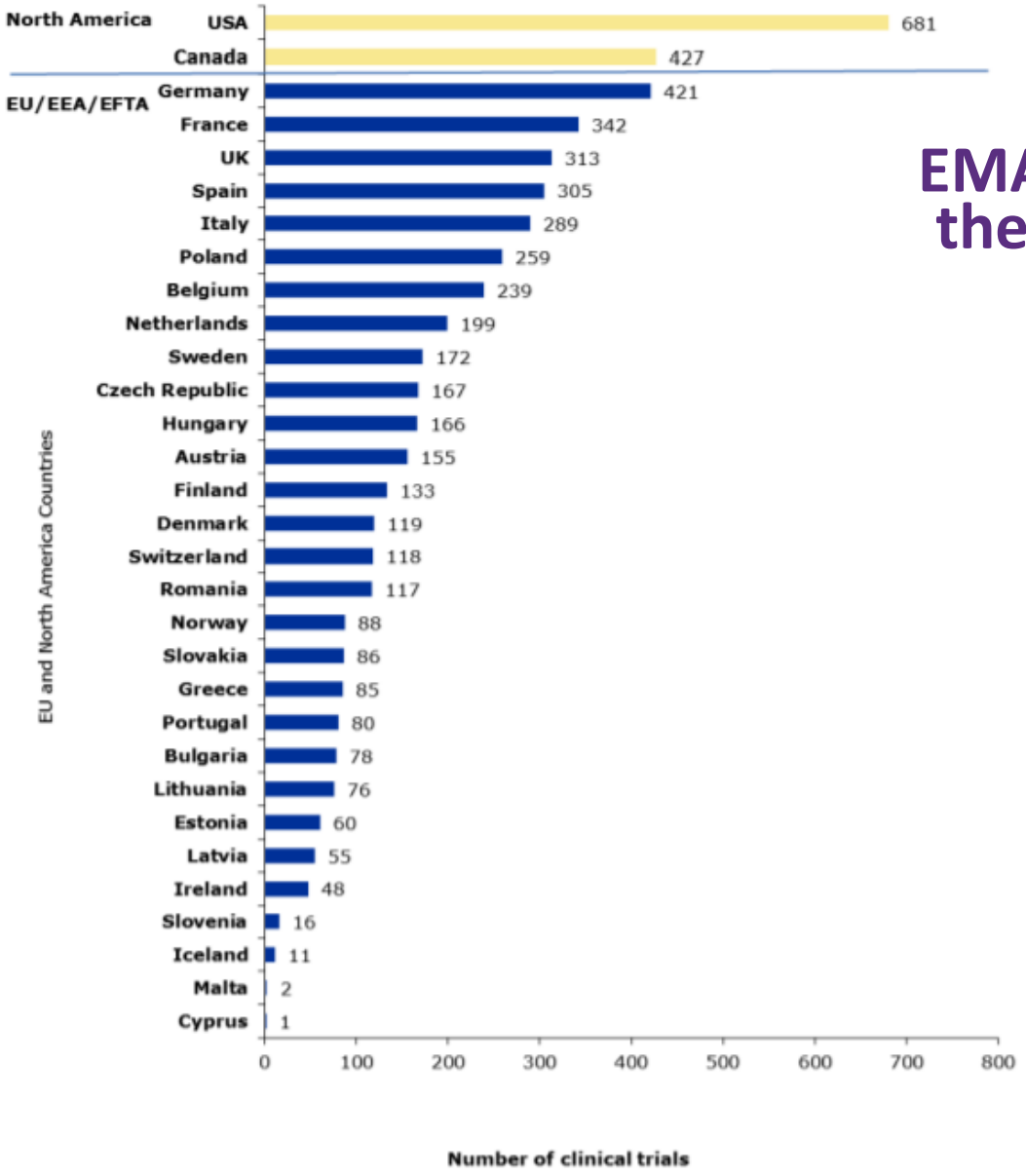
- 3500 newly diagnosed patients annually
- Total population of ≈ 11000 patients

GLOBOCAN (2012) – MM Age Standardized Rates (ASR)



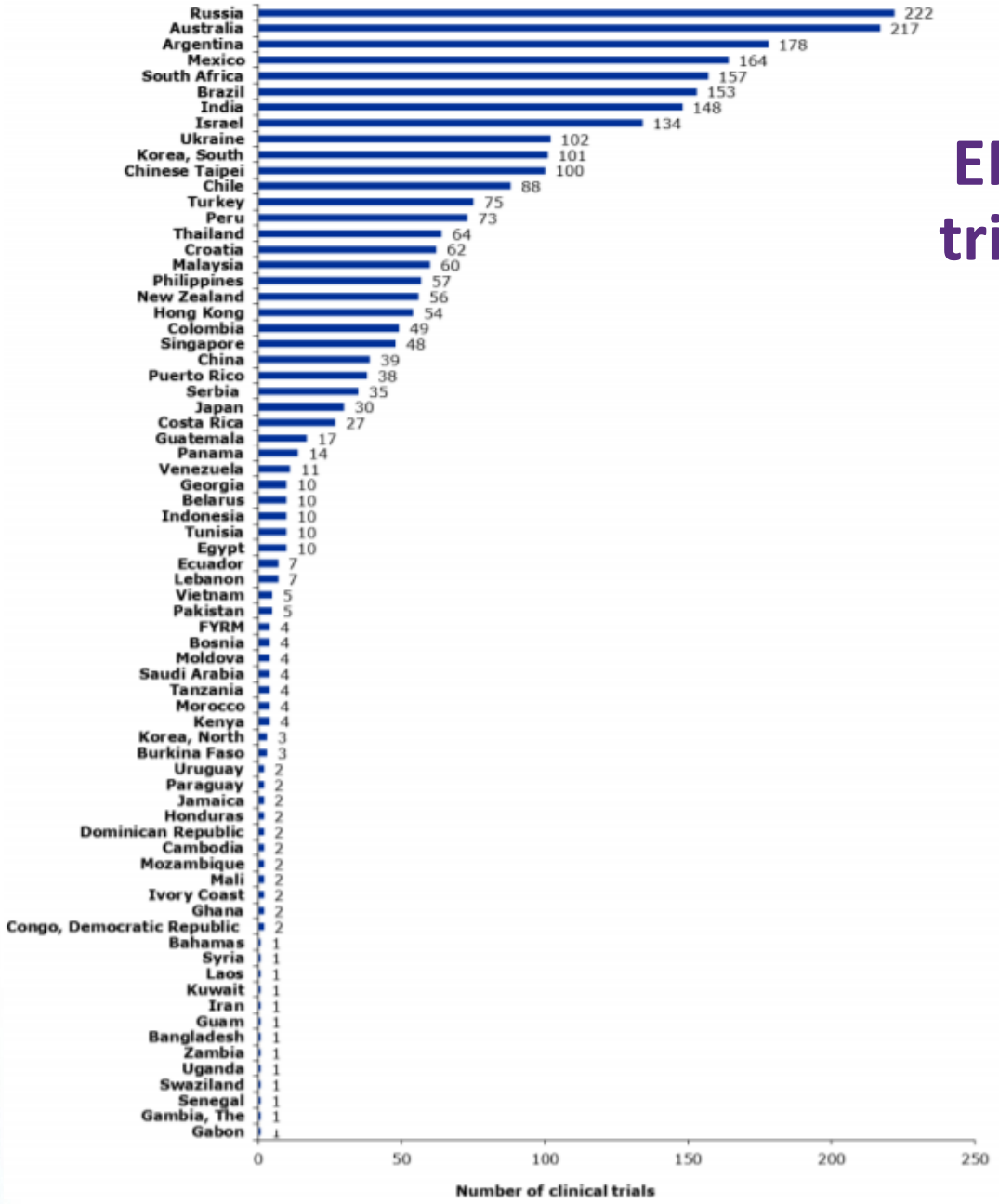


EMA: The number of pivotal clinical trials in the 2005-2011 period - North America and EU/EEA/EFTA



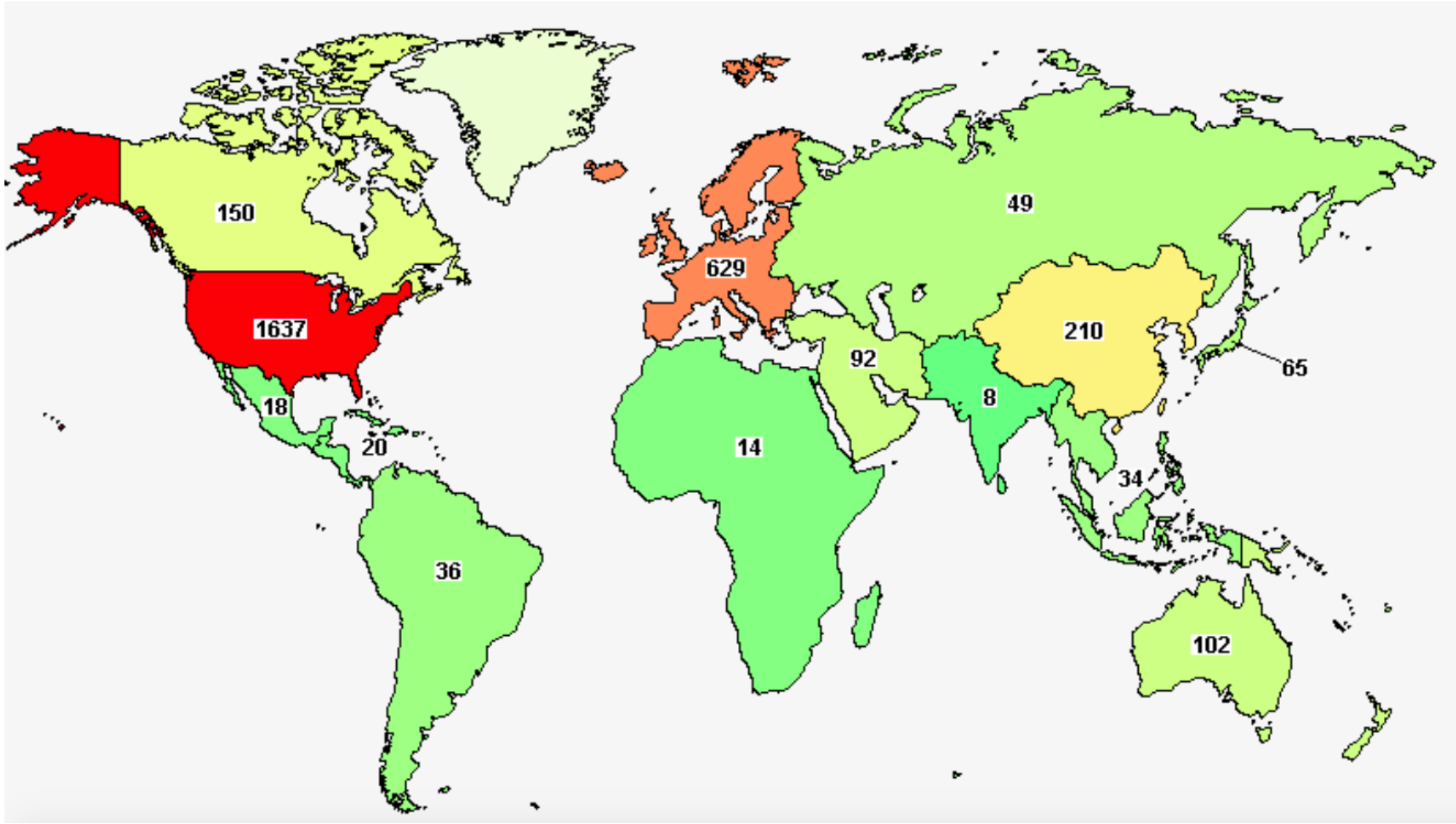
Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency EMA/INS/GCP/676319/2012 Page 19/39

EMA: The number of pivotal clinical trials in the 2005-2011 period - ROW



Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency EMA/INS/GCP/676319/2012 Page 19/39

Myeloma studies worldwide



Daratumumab containing study accrual

- Slovenia (SVN) - 0
- Croatia (HRV) - 2
- Bosnia & Herzegovina (BIH) - 0
- Serbia (SRB) - 11
- Montenegro (MNE) - 0
- Turkey (TUR) - 76
- Greece (GRC) - 112
- Bulgaria (BGR) - 6
- Romania (ROU) - 10
- North Macedonia (MKD) - 1
- Albania (ALB) – 0

TOTAL: 218

Balkan Myeloma Initiative

Balkan Myeloma Initiative

www.balkanmyelomainitiative.org

Belgrade, 25th February 2017

Chair Professor dr Meletios Dimopoulos

Hosting organizer Associate Professor dr Jelena Bila

On behalf of the Serbian Myeloma Group

Serbian Myeloma Group

Balkan Myeloma Study Group: General Assembly

President: Meletios A. Dimopoulos (Greece)

Vice President: Meral Beksac (Turkey)

General Secretary: Jelena Bila (Serbia)

Treasurer: Evangelos Terpos (Greece)

Members of the Assembly

SLOVENIA
Samo Zver (Ljubljana)

CROATIA
Dražen Pulanić (Zagreb)
Sanda Basic Kinda (Zagreb)
Josip Batinic (Zagreb)

BOSNIA & HERZEGOVINA
Alma Sofo (Sarajevo)
Lejla Ibrićević Balić (Sarajevo)
Jadranka Mirjanic (Banja Luka)
Tanja Drljaca (Banja Luka)

SERBIA
Biljana Mihaljevic (Belgrade)
Olivera Markovic (Belgrade)
Predrag Djurdjevic (Kragujevac)

MONTENEGRO
Anka Popovic (Podgorica)
Milena Dapcevic (Podgorica)

TURKEY
Hayri Ozsan (Izmir)
Ali Unal (Kayseri)

GREECE
Efstathios Kastritis (Athens)

BULGARIA
Margarita Guenova (Sofia)
Veselina Goranova (Plovdiv)

ROMANIA
Daniel Coriu (Bucharest)
Radu Niculescu (Bucharest)
Sorina Badelita (Bucharest)

FYROM
Sonja Genadieva Stavric (Skopje)
Oliver Karanfilski (Skopje)

ALBANIA
Arben Ivanaj (Tirana)

Balkan Myeloma Initiative

Balkan Myeloma Study Group (BMSG)

An independent association consisting of experts who deal with **diagnostics, treatment, research and education in the field of multiple myeloma and associated plasma cell disorders**.

The work of BMSG is based on a unique diagnostic and therapeutic principles and is a reflection of the exchange of professional experiences and **intensive cooperation of participating haematological centers in Balkan countries**.

Since its founding on **25th February 2017**, BMSG is **expanding intensive cooperation with similar national and international associations** to exchange knowledge, experience, personnel and scientific achievements

Objectives

The BMSG will pursue the following objectives:

- Promote experience, technology and innovation through the exchange of knowledge between scientists and scholars, between the members of the BMSG
- Favour collaboration, including joint research and development projects, between scientists, scholars, and non-profit, for-profit and governmental organizations in the members of the BMSG
- Promote the flow of scientists and scholars between the members of the BMSG
- Design and performance of clinical trials according to the law of each member country
- Promote, provide information about, and administer fellowships for the exchange of scientists and scholars
- Identify significant research opportunities - with specific regard to European Union Framework Programmes - for individuals, organizations, institutions, academia and high-tech industry, and stimulate their development
- Provide advice about the capabilities and merits of individuals and organizations – non-profit, for-profit, and governmental –for scientists, scholars, and entrepreneurs from the member states of the BMSG
- Advocate the improvement of scientific and scholarly activity and organizations within the members of the BMSG
- Promote and coordinate the activities of other organizations and associations that link scientists, scholars and professionals in the members of the BMSG

Constituent Bodies and Membership

- BMSG constituent bodies are the General Assembly and Steering Committee, which consists of eminent experts in the field of multiple myeloma and associated disorders of plasmacytoid lineage from different haematological centres in Balkan countries.

- Membership in the BMSG is voluntary and it is acquired by fulfilment of necessary conditions with written statement of accession. Members of the BMSG are specialists in dealing with the diagnosis and therapy of multiple myeloma and associated plasma cell dyscrasias. Furthermore, BMSG membership includes selected individuals from other professions that deal with basic, pharmacological or other research in the field of multiple myeloma and related plasma cell disorders.

Educational Workshop

October 26-27, 2018 | Royal Olympic Hotel | Athens, Greece

PROGRAM CO-CHAIRS:

Meletios A. Dimopoulos, MD
National and Kapodistrian University of Athens

Evangelos Terpos, MD
National and Kapodistrian University of Athens

PROGRAM COMMITTEE:

Meral Beksac, MD
University of Ankara, Turkey

Jelena Bila, MD
University of Belgrade, Serbia

Daniel Coriu, MD
University of Bucarest, Romania

Margarita Guenova, MD
University of Sofia, Bulgaria

Moshe Gat, MD
Hadassah University, Jerusalem, Israel

Efstathios Kastritis, MD
N. K. University of Athens, Greece

Samo Zver, MD
University of Ljubljana, Slovenia

Sandra Bašić-Kinda, MD
University of Zagreb, Croatia

Join us for an educational workshop on the diagnosis, treatment and monitoring of plasma cell malignancies, including current practices and opportunities for improvement.

The workshop will include lectures plus roundtable discussions around the most hot and controversial topics, featuring point-counterpoint conversations between invited speakers and local hematologists based on both challenging questions and clinical cases.

Numerous networking opportunities will also be available in order to establish potential collaborations among speakers and participants.

FEATURED SPEAKER:

SATURDAY 12:30-13:00

Minimal Residual Disease: How and when to do it?
Jesús San Miguel, MD

Projects

Retrospective/Prospective

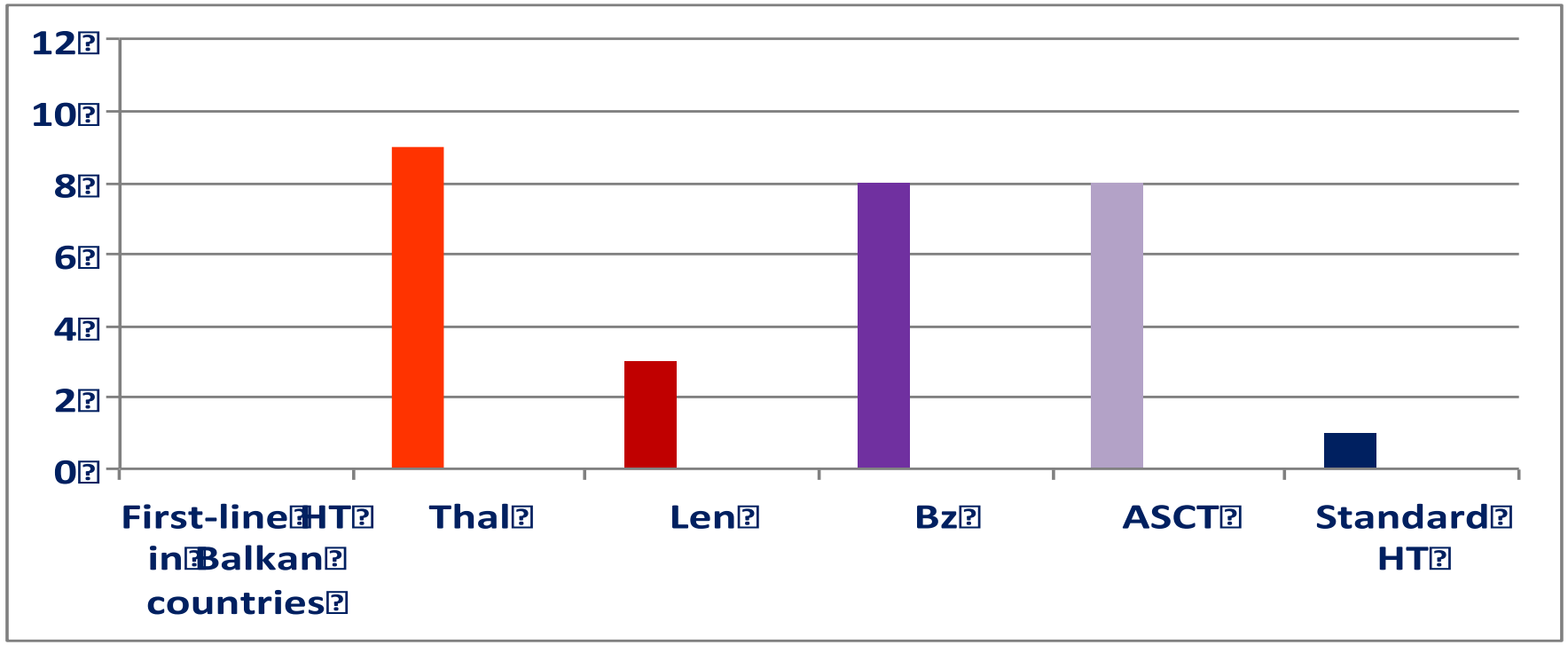
- Drug accessibility in the Balkan region
- Outcomes of Extramedullary disease
- Clinical profile and outcomes of plasma cell disorders in the Balkan region, a multi-national database

CURRENT TREATMENT OPTIONS FOR MULTIPLE MYELOMA PATIENTS AND THEIR IMPLEMENTATION IN THE REAL-WORLD CLINICAL PRACTICE IN THE BALKAN REGION: A REPORT OF THE BALKAN MYELOMA STUDY GROUP

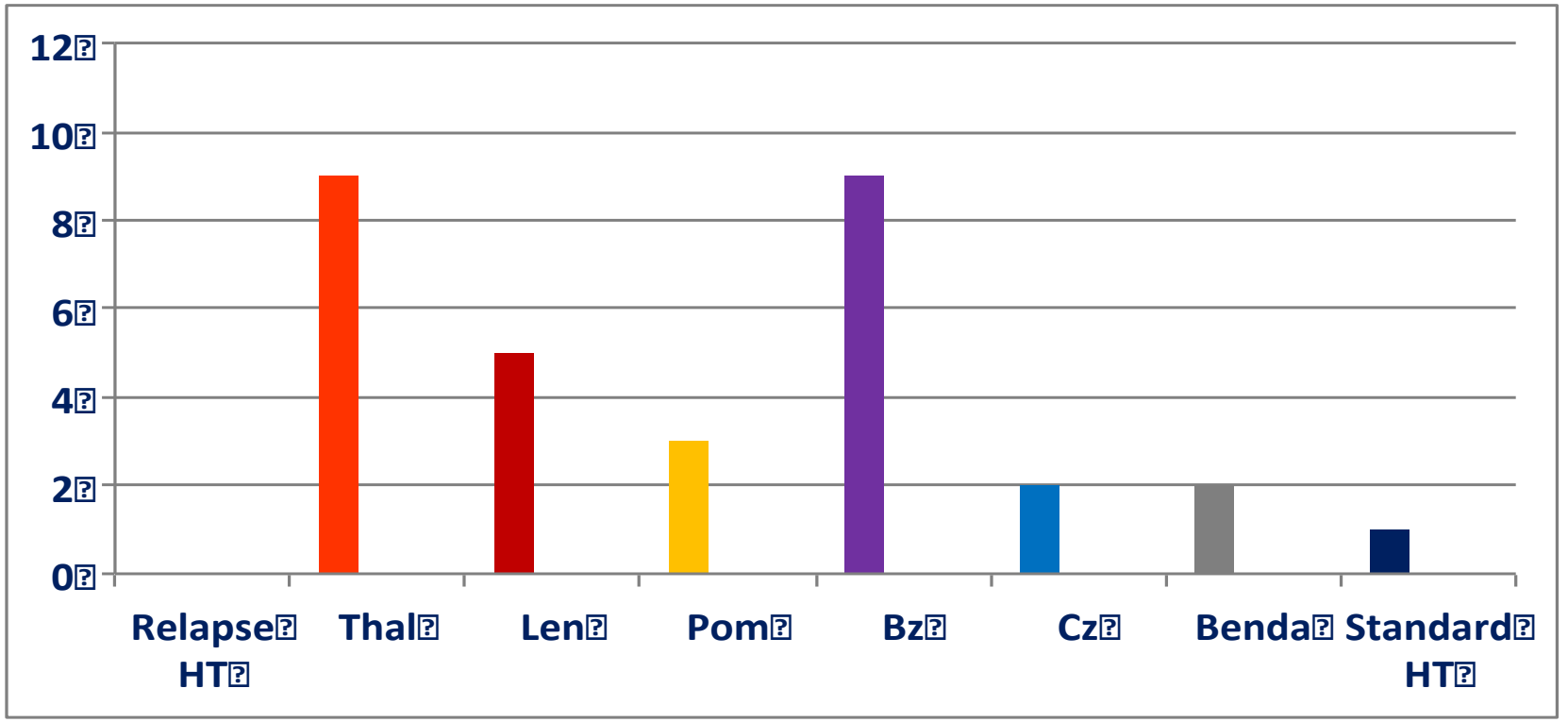
Jelena Bila[1], Evangelos Terpos[2], Efstathios Kastritis[2], Sorina Badelita[3], Sandra Basic-Kinda[4], Josip Batinic[4], Daniel Coriu[3], Milena Dapcevic[5], Tatjana Drljaca[6], Predrag Djurdjevic[7], Maria Gavriatopoulou[2], Sonja Genadieva Stavric[8], Vesselina Goranova[9], Margarita Guenova[10], Lejla Ibricevic-Balic[11], Arben Ivanaj[12], Oliver Karanfilski[8], Olivera Markovic[13], Biljana Mihaljevic[1], Jadranka Mirjanic[6], Radu Niculescu[3], Hayri Ozsan[14], Anka Popovic[5], Drazen Pulanic[4], Alma Sofo-Hafizovic[11], Ali Unal[15], Samo Zver[16], & Meral Beksac[17*], Meletios A.Dimopoulos[2*]

[1] University of Belgrade, Serbia, [2] University of Athens, Greece[2] ,[3] Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [4] University Hospital Centre Zagreb, Zagreb, Croatia , [5] Clinical Center of Montenegro, Podgorica, Montenegro , [6] University Clinical Center of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina , [7] University of Kragujevac, Kragujevac, Serbia , [8] University of Skopje, Former Yugoslav Republic of Macedonia , [9] Clinic of Haematology, Higher Medical Institute, Plovdiv, Bulgaria, [10] National Specialised Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria, [11] University Clinical Center of Sarajevo, Sarajevo, Bosnia and Herzegovina, [12] University Medical Center „Mother Teresa", Tirana, Albania, [13] University of Belgrade, Belgrade, Serbia, [14] Dokuz Eyul University, Izmir, Turkey, [15] Erciyes University Medical School, Kayseri, Turkey, [16] University Medical Centre Ljubljana, Ljubljana, Slovenia, [17] University of Ankara, Turkey

Drugs approved at first line: April 2017



Drugs approved for RRMM-April 2017



A REAL WORLD MULTICENTER RETROSPECTIVE STUDY ON EXTRAMEDULLARY DISEASE FROM BALKAN MYELOMA STUDY GROUP AND BARCELONA UNIVERSITY: ANALYSIS OF PARAMETERS THAT IMPROVE OUTCOME

Beksac M[1], Seval GC[1], Kanellias N[2], Coriu D[3], Rosiñol L[4], Ozet G[5], Goranova-Marinova V[6], Unal A[7] Bila J[8], Ozsan H[9], Ivanaj A[10] , Balić LI[11], Kastritis E[2], Bladè J[4], Dimopoulos MA[2]

[1]Department of Hematology, School of Medicine, Ankara University, TURKEY;

[2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, GREECE;

[3]University of Medicine and Pharmacy "Carol Davila", Fundeni Clinical Institute, Bucharest, ROMANIA ;

[4]Hospital Clinic, IDIBAPS, BARCELONA;

[5]Clinic of Hematology, Ankara Numune Education and Research Hospital, TURKEY;

[6]University Hospital "Sv. Georgi" and Medical University Plovdiv, BULGARIA;

[7]Department of Hematology, School of Medicine, Erciyes University, TURKEY;

[8]Faculty of Medicine, University of Belgrade, Belgrade, SERBIA;

[9]Department of Hematology, School of Medicine, Dokuz Eylül University, TURKEY;

[10]University of Medicine Tirana, ALBANIA;

[11]Clinical Center of Sarajevo University, Sarajevo, BOSNIA and HERZEGOVINA;

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Clinical characteristics of patients

Characteristics (n=226)	**Results**
Age, years, *Median (range)*	62 (34-87)
Age, years, Median (range)	EMP: 64 (34-87) PO: 59 (36-83) p=0.01
Age ≤45 vs. >45 (**at diagnosis**)	EMP: 13 vs. 79 PO:2 vs. 36
Age ≤45 vs. >45 (**at relapse**)	EMP: 3 vs. 81 PO:1 vs. 11
ISS stage (at myeloma diagnosis)	
Stage I, *n (%)*	76 (33.6 %)
Stage II, *n (%)*	68 (30.1 %)
Stage III, *n (%)*	76 (33.6 %)
Unknown	6 (2.7%)
Number of FISH abnormalities	
No abnormalities, *n (%)*	57 (51.3 %)
1 abnormality, *n (%)*	28 (25.2 %)
2 abnormalities, *n (%)*	12 (10.8 %)
≥3 abnormalities, *n (%)*	12 (10.8 %)
Del17p, *n (%)*	10 (9 %)
Del13q, *n (%)*	20 (18 %)
t (4;14), *n (%)*	8 (7.2 %)
t (14;16), *n (%)*	2 (1.8 %)
t (11;14), *n (%)*	4 (3.6 %)
Anatomical locations of EMP	
Soft tissue (muscle/skin) , *n (%)*	55 (24.3 %)
Lymph nodes, *n (%)*	23 (10.2 %)
Pleural, *n (%)*	27 (11.9 %)
Liver, *n (%)*	21 (9.3 %)
Central nervous system, *n (%)*	14 (6.2 %)
Abdominal, *n (%)*	9 (4.0 %)
Oropharynx, *n (%)*	8 (3.5 %)
Lung, *n (%)*	7 (3.1 %)
Testis, *n (%)*	4 (1.8 %)
Others, *n (%)*	4 (1.8 %)

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Clinical characteristics of patients

Initial therapy for EMD (all patients)	At initial diagnosis	At relapse
Only radiotherapy, *n (%)*	9 (6.9 %)	-
Systemic chemotherapy (without novel agent)	34 (26.2%)	23 (24%)-
Thalidomide combinations*, *n (%)*	13 (10%)	2 (2.1%)
PI combinations*, *n (%)*	63 (48.5%)	40 (41.7%)
Len/Pom combinations*, *n (%)*	5 (3.8%)	8 (8.3%)
PI+IMID combinations:		
VDT, *n(%)*	-	4 (4.2%)
VRD, *n(%)*	6 (4.6%)	12 (12.5%)
Monoclonal Antibodies, *n(%)*	-	7 (7.3%)
Lines of therapy after EMD diagnosis		
1-2 lines, *n (%)*	121 (53.8 %)	
>2 lines, *n (%)*	104 (46.2 %)	
Autologous stem cell transplantation, *n (%)*	100 (44.2 %)	

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Comparison of response and survival outcomes of EMP or PO patients either at diagnosis or relapse

		CR (%)		PFS (mos)		OS (mos)	
EMP	diagnosis (n=92)	19.3	p=0.034	38.9 (95% CI: 23.6-54.2)	p<0.001	46.5 (95% CI: 25.5-67.5)	p<0.001
	relapse (n=84)	9		13.6 (95% CI: 11.6-15.6)		11.4 (95% CI:*.6-16.2)	
PO	diagnosis (n=38)	34.2	p=0.001	51.7 95% CI: 13.5-89.9)	p=0.005	NR	p<0.001
	relapse (n=12)	54.5		20.9 (95% CI: 10.3-31.5)		39.8 (95% CI: 12.7-66.9)	

p=0.002

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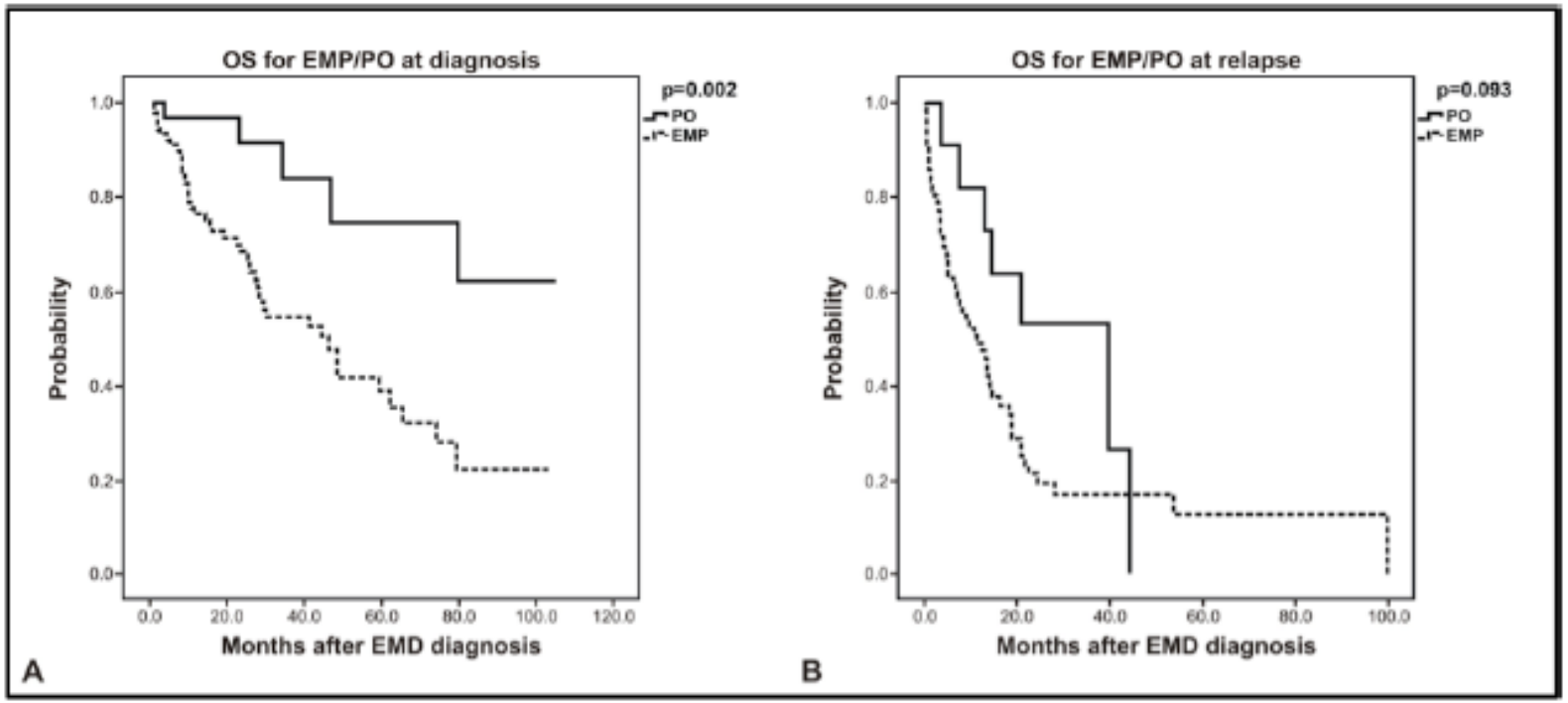
Overall Survival



OS estimate comparing patients with EMP to those with PO lesions at diagnosis (A) and relapse (B)

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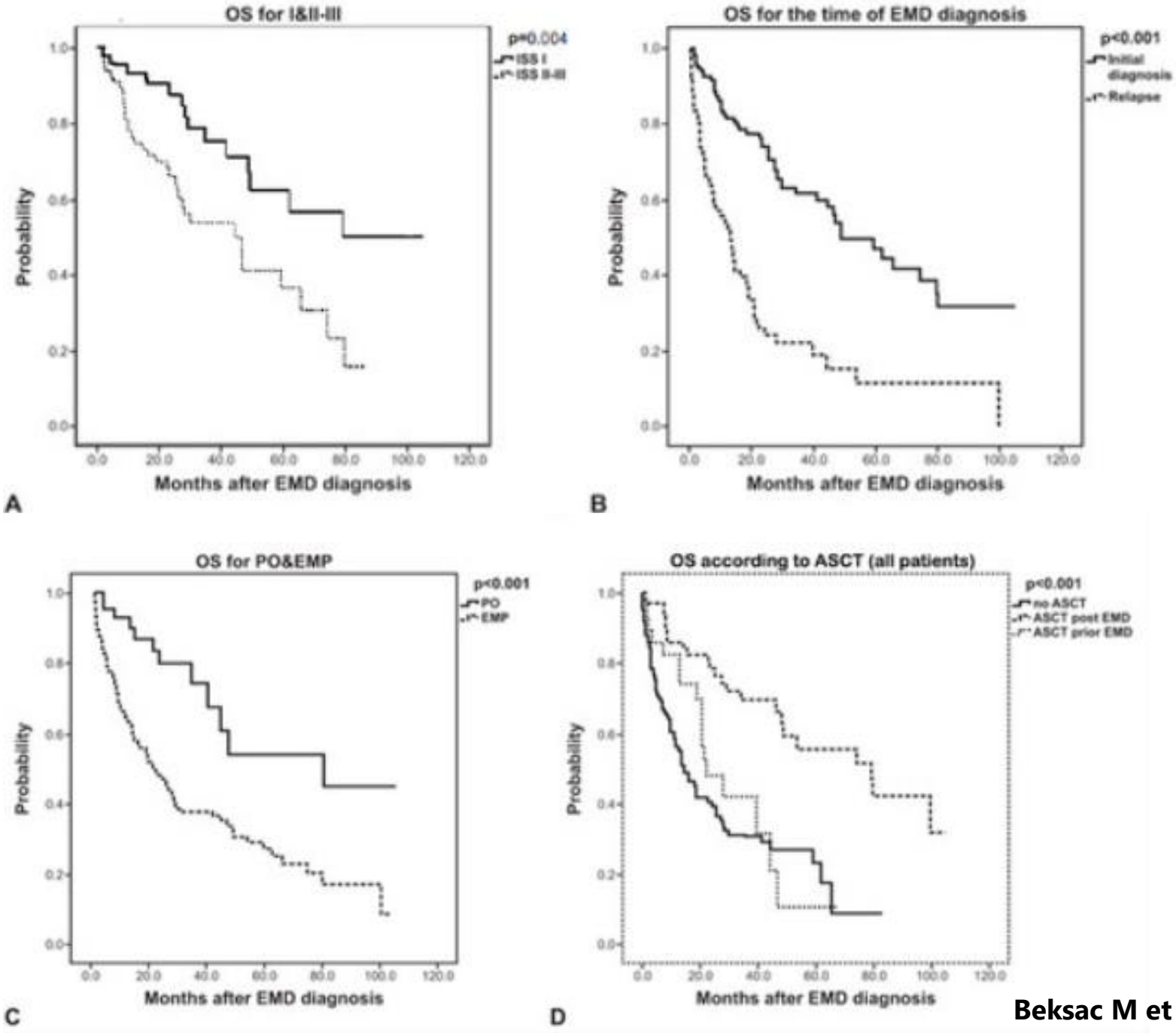

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Univariate and multivariate analysis for overall survival in myeloma patients with EMD

Factors	Median OS (months)	Univariate HR (95 % CI)	p value	Multivariate HR (95 % CI)	p value
Age in years, >45 <45 >45	 68.3 months 28.4 months	 0.77 (0.36-1.6) 1.00	NS		
Extramedullary involvement type PO EMP	 Not reached 19.2 months	0.44 (0.21-0.93) 1.00	0.032	0.44 (0.21-0.92) 1.00	0.029
Timing of EMD At initial diagnosis At relapse	 59.2 months 8.4 months	0.33 (0.21-0.50) 1.00	<0.001	0.34 (0.23-0.51) 1.00	<0.001
ISS ISS stage I ISS stage II-III	 Not reached 16.1 months	 0.45 (0.28-0.72) 1.00	0.001	0.45 (0.28-0.73) 1.00	0.001
Previous lines of therapy 1-2 previous line 2+ previous lines	 33.4 months 28.6 months	1.00 1.26 (0.84-1.89)	NS		
ASCT (all patients) Yes No	 79.5 months 34.7 months	 0.61 (0.39-0.94) 1.00	0.026	0.58 (0.38-0.89) 1.00	0.013

EMD is a high risk feature - an unmet need

Daratumumab combined with Bortezomib, Cyclophosphamide and Dexamethasone for the Treatment of Multiple Myeloma Patients Presenting with Extramedullary Disease

Protocol

The ANTARES Study

Principal Investigator	:	**Professor Meral Beksac**
Sponsor	:	**European Myeloma Network (EMN)**
Protocol Identifying Number	:	**EMN19**
Protocol Version Number	:	**1.0**
EudraCT number	:	**2019-000991-41**

Study design

Key Eligibility Criteria

1. Newly Diagnosed or 1st relapse MM patients with EMD (paraskeletal plasmacytomas ONLY are not eligible)
2. ECOG PS ≤ 2. Note: for subjects with CNS involvement, an ECOG PS >2 is also acceptable
3. Measurable Disease (Serum, Urine or sFLC MM)
4. Non refractory to Bortezomib based regimens
5. No prior treatment with anti-CD38 or anti-CS1 MoAB
6. Adequate Bone Marrow function (minimum laboratory requirements)
7. No ASCT within 12 weeks of C1D1
8. No prior allo-SCT (regardless of timing)

Sponsor Approval

D-VCd (n=40)

Until PD or unacceptable toxicity (max. 36 months)*

Daratumumab (D) 16 mg/kg IV

- QW in Cycles 1-2, Q2W in Cycles 3-6, Q4W in Cycles 7+

Bortezomib (V) 1.5 mg/m² SC

- QW in every cycle

Cyclophosphamide (C) 300 mg/m² IV or PO

- QW in every cycle

Dexamethasone (d) 20 mg PO or IV

- Days 1, 2, 8, 9, 15, 16, 22, 23 of every cycle

Objectives

Primary

- CR rate

Secondary

- DoR
- PFS
- ORR
- TnT
- OS
- Safety (Adverse Events)

Exploratory

- GEP in BM and EMD site(s)
- Circulating Tumor Cell characterization
- Clinical and biological biomarker characterization
- Immune Profiling of BM and EMD site(s)

Study Objectives

Primary Objectives

- **To evaluate the Complete Response (CR) rate**

Secondary Objectives

- **To evaluate Duration of Response (DoR)**
- **To evaluate the Progression Free Survival (PFS)**
- **To evaluate the Overall Response Rate (ORR)**
- **To evaluate Time to next Therapy (TnT)**
- **To evaluate the Overall Survival (OS)**
- **To assess the safety (adverse events) of DaraVCD treatment**

Exploratory objectives

- **To describe the gene expression profile of marrow vs. extramedullary sites of MM with EMD**
- **To describe the circulating tumor cell (CTC) status in MM with EMD**
- **To explore the suitability of clinical and biological disease characteristics as prognostic markers**
- **To describe the immune profiling of bone marrow and EMD site(s)**

Key Eligibility Criteria

- Newly Diagnosed or 1st relapse MM patients with EMD (paraskeletal placmatocytomas ONLY are not eligible)
- ECOG PS ≤ 2. NOTE: For subjects with CNS involvement, an ECOG PS>2 is also acceptable
- Measurable Disease (Serum, Urine or sFLC MM)
- Non refractory to Bortezomib based regimens
- No prior treatment with anti- CD38 or anti-CS1 MoAB
- Adequate Bone Marrow function (minimum laboratory requirements)
- No ASCT within 12 weeks of C1D1
- No prior allo-SCT (regardless of timing)

EMN

EMN

Balkan Myeloma Initiative

Thank You!