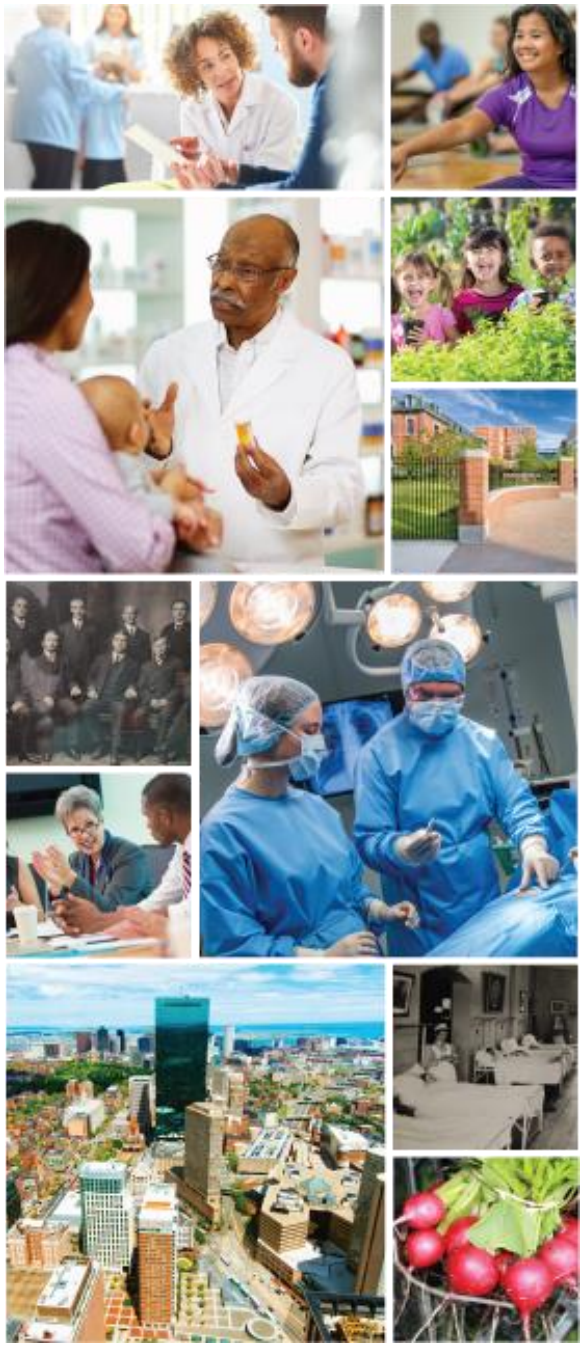


Bortezomib SubQ vs IV

Bhavesh Shah RPh, BCOP

Senior Director of Hematology Oncology and Specialty Pharmacy

June 2021

Boston Medical Center is a private hospital with a public mission

- **BMC** was formed in 1996 by a merger between two City of Boston public hospitals and a private, non-profit hospital affiliated with Boston University
- The merger created a **private non-profit corporation** charged with carrying on both Boston City Hospital's public and University Hospital's academic missions
- For more than 100 years, **BMC has been driven by a commitment to care for all people**, delivering not only traditional medical care, but also programs and services that provide wrap around care to enhance overall health
  - All of this supports **our mission** to provide *exceptional care, without exception*

BMC is the *centerpiece of the city's public health network*

Over the years, BMC has grown into a multi-billion dollar health system

1855

BOSTON MEDICAL CENTER

BMC, formerly Boston City Hospital—the **first public hospital in the nation**

1994

BOSTON UNIVERSITY

Multi-specialty academic group practice with 18 clinical departments

1995

BostonHealthNet
Bringing Together the Best

Coordinated healthcare delivery network, including 13 CHCs

1997

BOSTON MEDICAL CENTER HEALTHNet PLAN

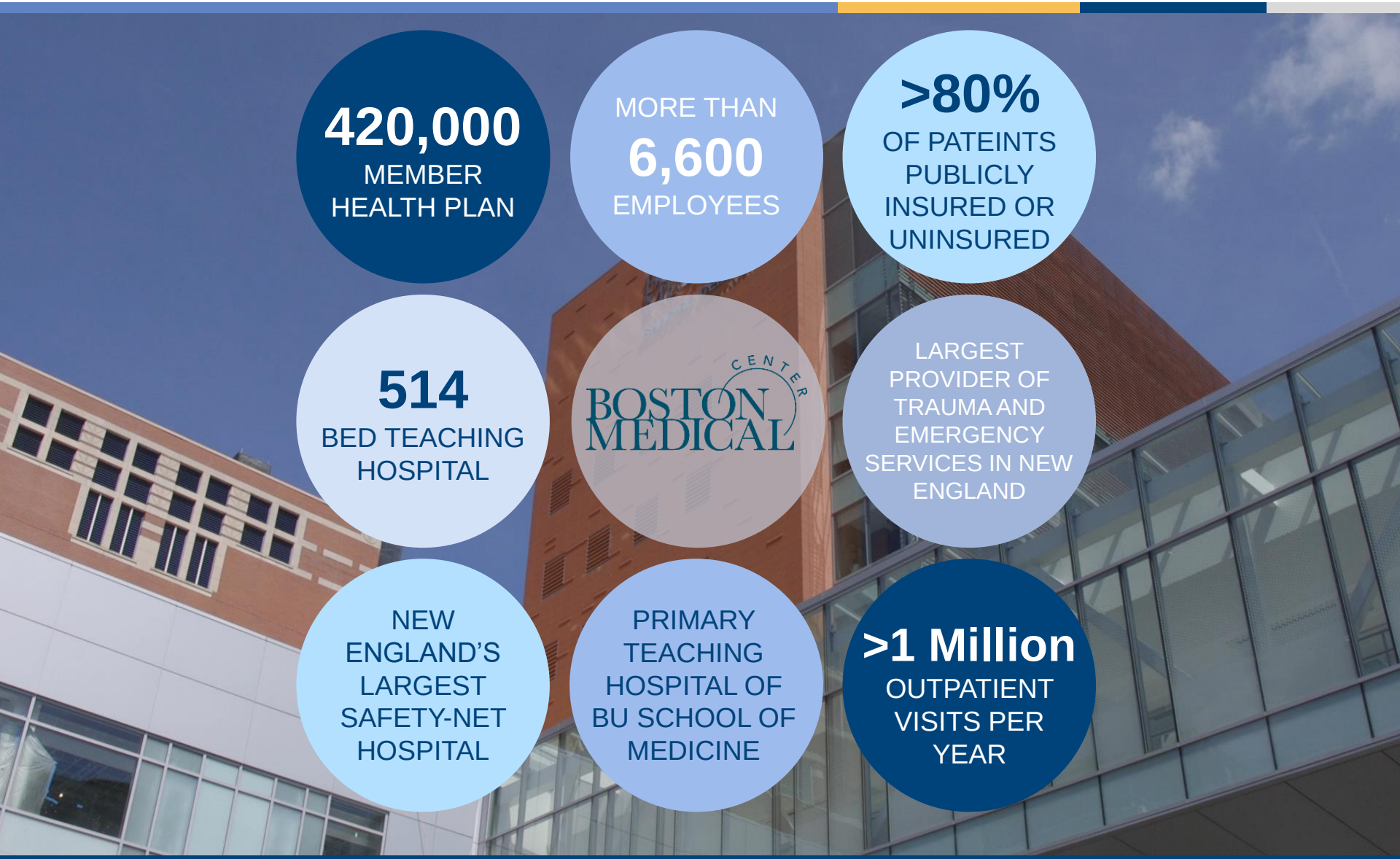
Largest Medicaid Managed Care Organization in Massachusetts

2018

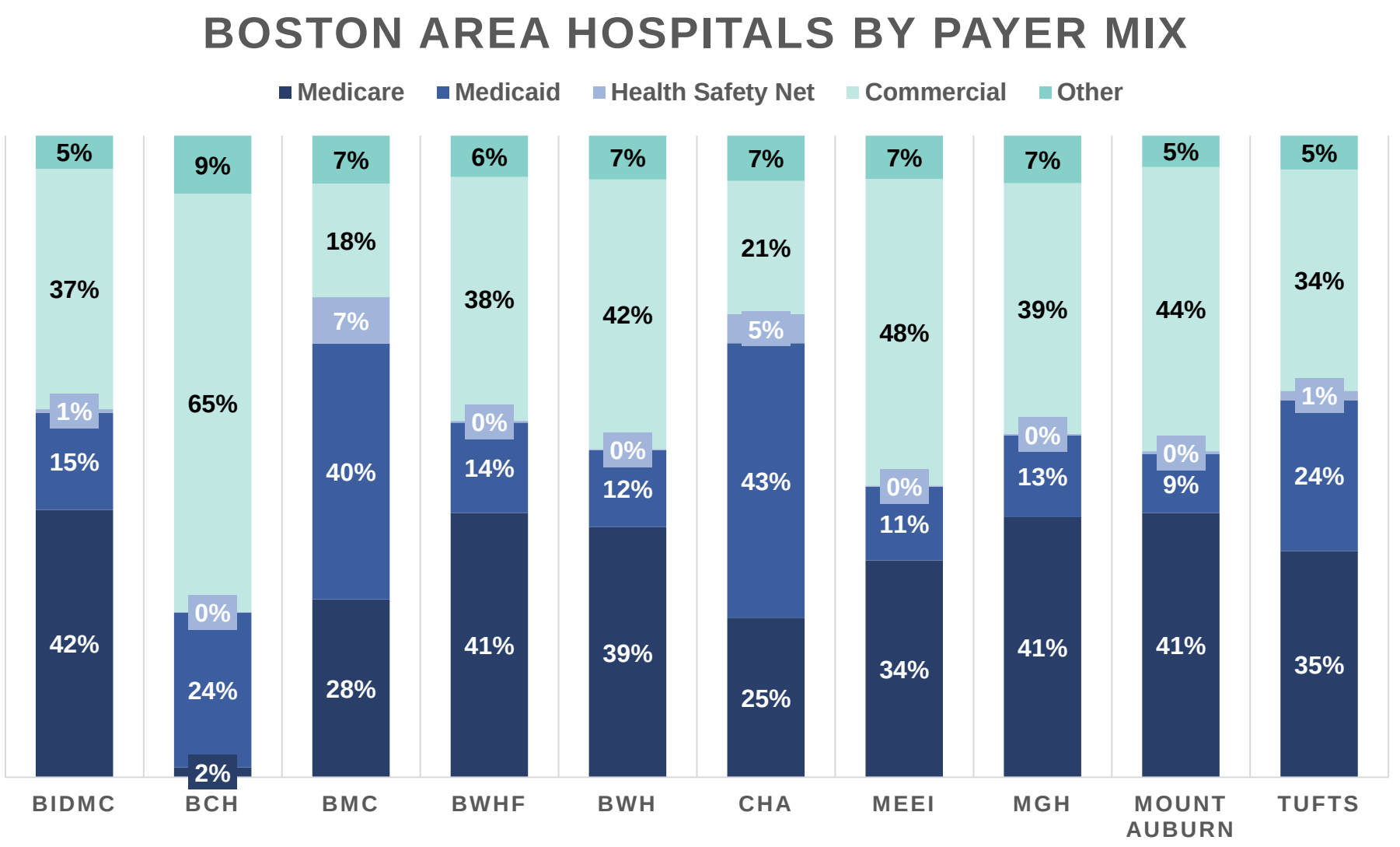
Boston Accountable Care Organization

Largest of the 4 BMC Health System MassHealth ACOs

We are a $4B Health System providing over 1M visits annually and insurance for more than 400K members

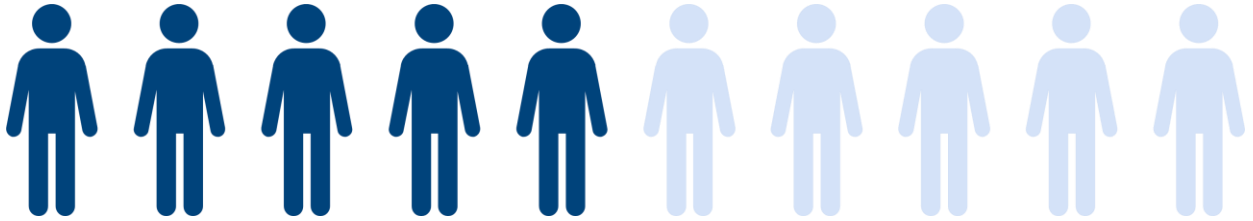


Compared to other Boston hospitals, BMC cares for a disproportionate number of low income patients—many of whom are covered by MassHealth

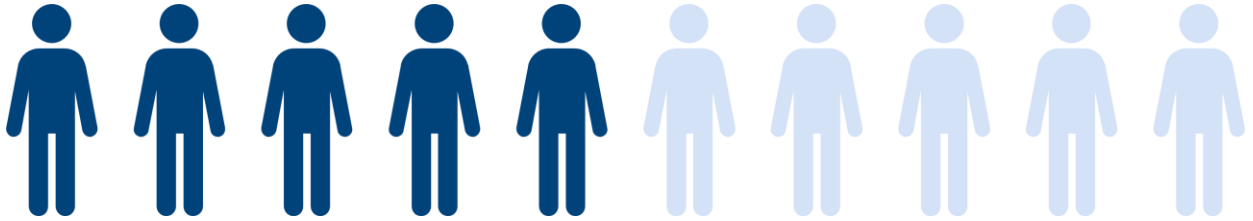


Our patient population is racially, culturally, and linguistically diverse—making the promotion of health equity a system imperative

~70% of our hospital patients identify as **people of color**



~50% of our hospital patients live at or **below the federal poverty level**



~50% of our Health Plan members have a **mental health and/or substance use disorder**

As a point of comparison, the low income patient population at Brigham and Women's Hospital and Beth Israel Deaconess is less than 15%

Bortezomib Background and Cost Savings Case Example

- 2003 Bortezomib IV first approved by the FDA
- 2012 Bortezomib Subcutaneous route approved
- 2017 Fresenius Kabi formulation approved for Intavenous use only
- 2019 Dr. Reddy's laboratory formulation approved for Intravenous use only
- FY 2019 $1.1 Billion sales from Bortezomib

A Phase 3 Prospective, Randomized, International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma

Philippe Moreau,[1] Halyna Pylypenko,[2] Sebastian Grosicki,[3] Evgeniy Karamanesht,[4] Xavier Leleu,[5] Maria Grishunina,[6] Grigoriy Rekhtman,[7] Zvenyslava Masliak,[8] Tadeusz Robak,[9] Anna Shubina,[10] Jean-Paul Fermand,[11] Martin Kropff,[12] James Cavet,[13] Dixie-Lee Esseltine,[14] Huaibao Feng,[15] Donna Skee,[15] Helgi van de Velde,[16] William Deraedt,[16] Jean-Luc Harousseau[17]

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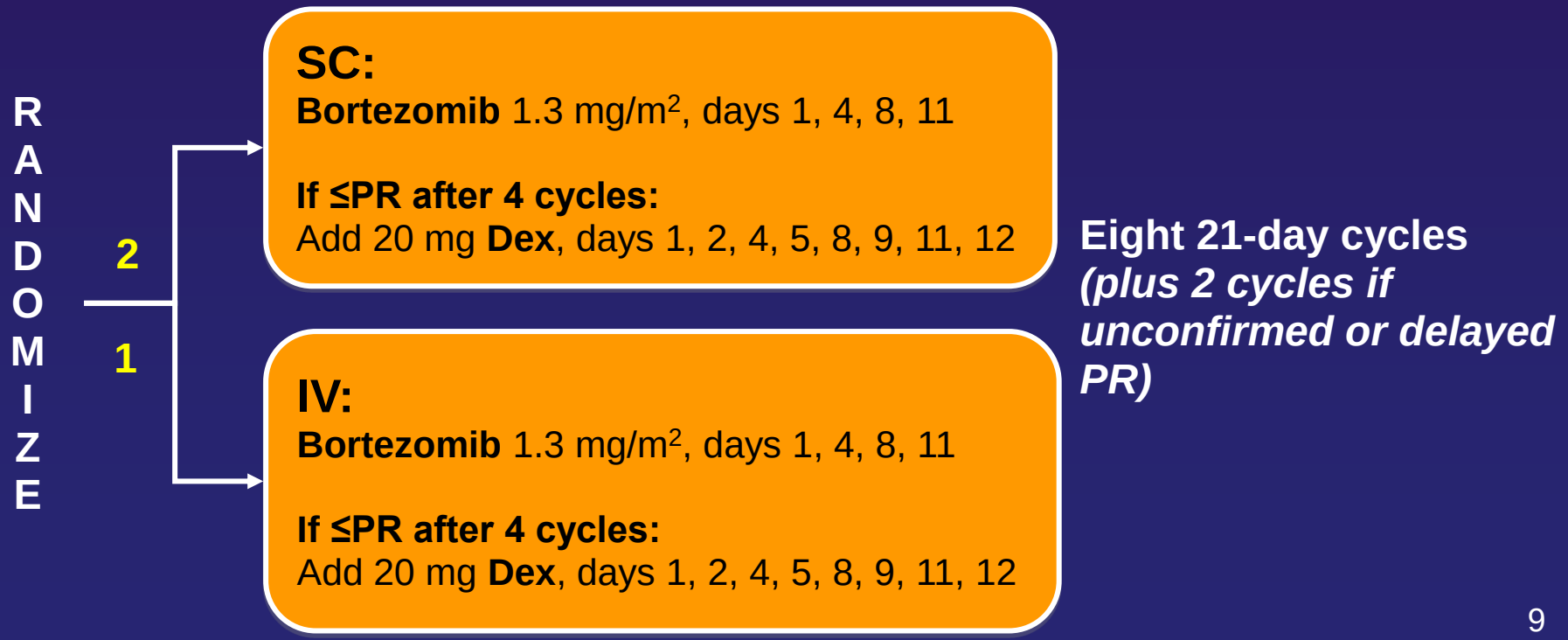
Study Design

- Non-inferiority design
  - 60% retention of the IV treatment effect as measured by overall response rate (ORR) after 4 cycles of treatment
  - 2:1 randomization SC vs IV (N=222)
  - Stratification factors: ISS stage, number of prior lines of therapy (1 vs >1)
- 53 centers in 10 countries (Europe, Asia, and South America)



Peripheral Neuropathy (PN)

	Bortezomib IV (N=74)	Bortezomib SC (N=148)	P-value*
Any PN event, %	**53**	**38**	**0.04**
Grade ≥2, %	**41**	**24**	**0.01**
Grade ≥3, %	**16**	**6**	**0.03**
Risk factors for PN, %			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	

*P-values are based on 2-sided Fisher's exact test

Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib-melphalan-prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy

María-Victoria Mateos,[1] Sara Bringhen,[2] Paul G. Richardson,[3] Juan Jose Lahuerta,[4] Alessandra Larocca,[2] Albert Oriol,[5] Mario Boccadoro,[2] Ramón García-Sanz,[1] Francesco Di Raimondo,[6] Dixie-Lee Esseltine,[7] Helgi van de Velde,[8] Avinash Desai,[9] Anil Londhe,[10] Jesús F. San Miguel,[11] and Antonio Palumbo[2]

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ABSTRACT

Substantial efficacy has been demonstrated with bortezomib-melphalan-prednisone in phase III studies in transplant-ineligible myeloma patients using various twice-weekly and once-weekly bortezomib dosing schedules. In VISTA, the regimen comprised four 6-week twice-weekly cycles, plus five 6-week once-weekly cycles. In the GIMEMA MM-03-05 study, the bortezomib-melphalan-prednisone regimen was either per VISTA ('GIMEMA twice-weekly'), or comprised nine 5-week once-weekly cycles ('GIMEMA once-weekly'). In the GEM2005MAS65 study, the regimen comprised one 6-week twice-weekly cycle, plus five 5-week once-weekly cycles. We evaluated the cumulative bortezomib dose administered during bortezomib-melphalan-prednisone, as well as efficacy and tolerability, using patient-level study data. Over all bortezomib-melphalan-prednisone cycles (nine in VISTA/GIMEMA; six in GEM2005MAS65), the median cumulative bortezomib dose administered was 38.5, 42.1, 40.3, and 32.9 mg/m^2 in VISTA, GIMEMA twice-weekly, GIMEMA once-weekly, and GEM2005MAS65, respec-

Table 1. VMP regimens and post-VMP maintenance therapy used in the phase III studies.

	VISTA / GIMEMA BIW*	GIMEMA QW*	GEM2005MAS65
Bortezomib 1.3 mg/m^2			
Early cycles	4 x 6-week BIW†	4 x 5-week QW‡	1 x 6-week BIW
5 x 5-week QW			
Doses, n / weeks, n	32 / 24	16 / 20	28 / 31
Dose intensity, mg/m^2/week	1.39	1.04	1.17
Later cycles	5 x 6-week QW¶	5 x 5-week QW	NA#
Doses, n / weeks, n	20 / 30	20 / 25	–
Dose intensity, mg/m^2/week	0.87	1.04	–
Melphalan	9 mg/m^2, Days 1–4, all cycles		
Prednisone	60 mg/m^2, Days 1–4, all cycles		
Bortezomib-based maintenance post-VMP	None	None	1 x 3-week BIW, every 3 months for up to 3 years§

**In the GIMEMA study, bortezomib was given either per the VISTA study (GIMEMA BIW, n=63) or, after protocol amendment, on a weekly schedule (GIMEMA QW, n=190). †Six-week cycles of BIW bortezomib comprised dosing on Days 1, 4, 8, 11, 22, 25, 29, and 32. ‡5-week cycles of QW bortezomib comprised dosing on Days 1, 8, 15, and 22. ¶6-week cycles of QW bortezomib comprised dosing on days 1, 8, 22, and 29. #In these analyses, all 6 cycles of VMP in GEM2005MAS65 were considered as 'early' induction cycles. §Plus either prednisone 50 mg every other Day or thalidomide 50 mg/day; BIW: twice-weekly; NA: not applicable; QW: once-weekly; VMP: bortezomib-melphalan-prednisone.*

Table 4. Rates of peripheral neuropathy and treatment discontinuation with the different VMP regimens (excluding maintenance therapy) (data derived from patient-level data from each study database).

	VISTA	GIMEMA BIW	GIMEMA QW	GEM2005MAS65
Peripheral neuropathy, %				
Overall rate (all grades)	47	44	22	25
Grade 2–4	32	27	6	15
Grade 3–4	13	14	2	7
Discontinuations, %				
Due to AEs, all cycles	14.7 / 18.5*	22.2	13.2	12
Due to AEs, early cycles	12.1	14.3	8.9	NA
Due to peripheral neuropathy	3/11†	16	4	5
Dose reductions, %				
Due to peripheral neuropathy	22	40	14	NR
Deaths during treatment, %	6	1.5	4.2	5
Treatment-related	2	NR	NR	4

**14.7% discontinued VMP, and an additional 18.5% selectively discontinued bortezomib due to AEs. †3% discontinued VMP, and an additional 11% selectively discontinued bortezomib due to peripheral neuropathy. AEs: adverse events; BIW: twice-weekly; NA: not applicable; NR: not recorded; QW: once-weekly.*

Efficacy and safety of once-weekly bortezomib in multiple myeloma patients

Sara Bringhen,[1] Alessandra Larocca,[1] Davide Rossi,[2] Maide Cavalli,[3] Mariella Genuardi,[1] Roberto Ria,[4] Silvia Gentili,[5] Francesca Patriarca,[6] Chiara Nozzoli,[7] Anna Levi,[8] Tommasina Guglielmelli,[9] Giulia Benevolo,[10] Vincenzo Callea,[11] Vincenzo Rizzo,[12] Clotilde Cangialosi,[13] Pellegrino Musto,[14] Luca De Rosa,[15] Anna Marina Liberati,[16] Mariella Grasso,[17] Antonietta P. Falcone,[18] Andrea Evangelista,[19] Michele Cavo,[20] Gianluca Gaidano,[2] Mario Boccadoro,[1] and Antonio Palumbo[1]

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Table 6. Comparison between efficacy and safety data reported for different VMP regimens

Parameter	This study		GEM05>65[24]	VISTA[2,3,7]
	VMP (9 once-weekly cycles)*	VMP (4/5 twice-/once-weekly cycles)†	VMP (1/5 twice-/once-weekly cycles)‡	VMP (4/5 twice-/once-weekly cycles)†
n	191	66	130	344
Median age, y (range)	71 (56-86)	72 (65-85)	73 (65-83)	71 (57-90)
Overall response rate (≥PR), %	79#	86#	80 (98 on maintenance)	71§/74#
CR rate, %	23	27	20 (44 on maintenance)	30/33
CR/nCR rate, %	NA	NA	32 (59 on maintenance)	NR
Median follow-up, mo (range)	20.9 (0.3-48.6)	35.3 (0.1-48.0)	24 (12-43)	36.7 (NR)
Median PFS, mo	27	26	34	22
3-y PFS rate, %	46	39	NR	NR
3-y OS rate, %	87	89	80	68.5
Median no. cycles, n	9	9	NR	9
Sensory PN (any grade), %	22	44	NR	44
Grade 3/4, %	2	14	5 (2/5 on VP/VT maintenance)	13
Discontinuation caused by PN, %	4	16	NR	15 (3.2 VMP, 11.8 V only)
Bortezomib dose reductions caused by PN, %	14	40	NR	22
Bortezomib planned dose intensity, mg/m²/wk	1.04	1.73 (cycles 1-4) 0.87 (cycles 5-9)	1.73 (cycle 1) 1.04 (cycles 2-6)	1.73 (cycles 1-4) 0.87 (cycles 5-9)

CR indicates complete response; NA, not applicable; nCR, near-complete response; NR, not reported; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response; TNT, time to next therapy; VMP, bortezomib, melphalan, prednisone; VP, bortezomib plus prednisone; and VT, bortezomib plus thalidomide.

*Bortezomib 1.3 mg/m² on days 1, 8, 15, and 22 for 9 5-week cycles.

†Bortezomib 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 for 4 6-week cycles, and on days 1, 8, 22, and 29 for 56-week cycles.

‡Bortezomib 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 for 1 6-week cycle, and on days 1, 8, 15, and 22 for 55-week cycles; followed by maintenance including bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 every 3 months, for up to 3 years.

#International Myeloma Working Group uniform criteria.[17]

§European Group for Blood and Marrow Transplantation criteria.

RESEARCH ARTICLE

Subcutaneous Bortezomib in Multiple Myeloma Patients Induces Similar Therapeutic Response Rates as Intravenous Application But It Does Not Reduce the Incidence of Peripheral Neuropathy

Jiri Minarik[1]*, Petr Pavlicek[2], Ludek Pour[3], Tomas Pika[1], Vladimir Maisnar[4], Ivan Spicka[5], Jiri Jarkovsky[6], Marta Krejci[3], Jaroslav Bacovsky[1], Jakub Radocha[4], Jan Straub[5], Petr Kessler[7], Marek Wrobel[8], Lenka Walterova[9], Michal Sykora[10], Jarmila Obernauerova[11], Lucie Brozova[6], Evzen Gregora[2], Dagmar Adamova[12], Jaromir Gumulec[13], Zdenek Adam[3], Vlastimil Scudla[1], Roman Hajek[13], for the Czech Myeloma Group

1 Department of Hemato-oncology, University Hospital Olomouc and Medical Faculty of Palacky University Olomouc, Olomouc, Czech Republic, **2** Department of Clinical Hematology, University Hospital Kralovske Vinohrady, Praha, Czech Republic, **3** Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic, **4** Department of Clinical Hematology, University Hospital, Hradec Kralove, Czech Republic, **5** Department of Internal Medicine, University Hospital, Praha, Czech Republic, **6** Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic, **7** Department of Hematology and Transfusion, General Hospital, Pelhrimov, Czech Republic, **8** Department of Oncology, Hospital Novy Jicin, Novy Jicin, Czech Republic, **9** Department of Clinical Hematology, General Hospital Liberec, Liberec, Czech Republic, **10** Department of Clinical Hematology

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Citation: Minarik J, Pavlicek P, Pour L, Pika T, Maisnar V, Spicka I, et al. (2015) Subcutaneous Bortezomib in Multiple Myeloma Patients Induces Similar Therapeutic Response Rates as Intravenous

	SC bortezomib (N = 85)		IV bortezomib (N = 177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Anemia	65 (81.4%)	19 (23.8%)	151 (85.8%)	28 (15.9%)
Thrombocytopenia	41 (51.3%)	12 (15.0%)	111 (63.1%)	26 (14.8%)
Fatigue	39 (48.8%)	3 (3.8%)	92(52.3%)	4 (2.3%)
Neutropenia	40 (50%)	12 (15.0%)	90 (51.2%)	32 (18.2%)
Infection	37 (46.3%)	10 (12.5%)	82 (46.6%)	28 (15.9%)
Peripheral sensory neuropathy	32 (40.5%)	3 (3.8%)	84 (48%)	10 (5.7%)
Nausea	28 (35.1%)	1 (1.3%)	35 (19.9%)	1 (0.6%)
Diarrhoea	21 (26.3%)	5 (6.3%)	41(23.3%)	6 (3.4%)
Anorexia	18 (18.8%)	1 (1.3%)	25 (14.2%)	3 (1.7%)
Constipation	11 (13.8%)	2 (2.5%)	27(15.3%)	2 (1.1%)
Thrombosis/Embolism	0 (0%)	0 (0%)	11 (6.3%)	10 (5.7%)

Fig 3. Rates of adverse events in SC and IV aplication routes of bortezomib.

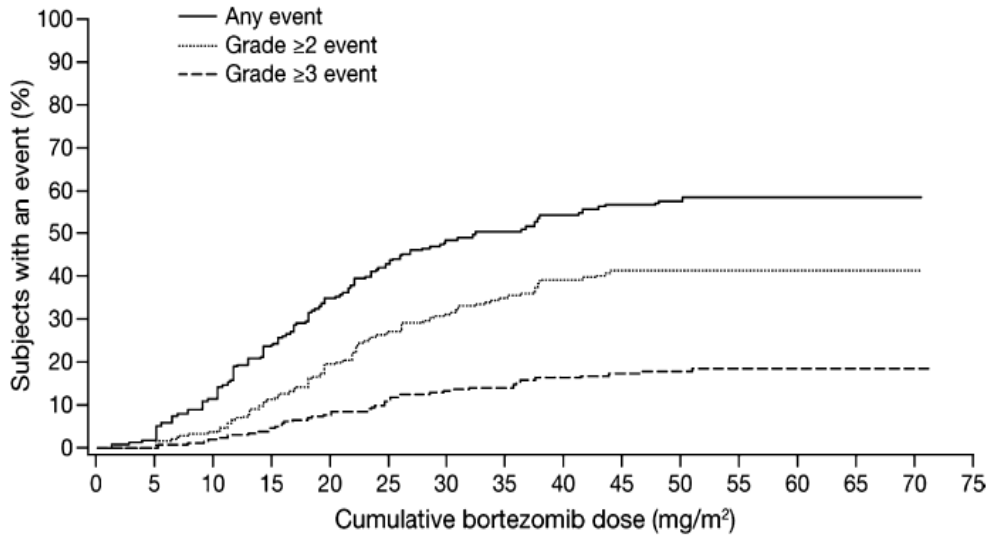
doi:10.1371/journal.pone.0123866.g003

Risk factors for peripheral neuropathy

Rates of PN according to patient baseline characteristics and medical history are shown in Table 3. By univariate, multivariate, and stepwise Cox regression analyses, a history of neuropathy appeared to be the only consistent strong risk factor for any PN [hazard ratio (HR) 1.785, $P = 0.0065$] and both grade ≥2 (HR 2.205, $P = 0.0032$)

Correlation of peripheral neuropathy with response and outcome

In the response-evaluable VMP population ($N = 337$ the incidence of PN was 53%, 57%, and 26% in patien who achieved CR, partial response (PR), or no respons (NR), respectively (Table 5). Similar trends were seen i the incidence of grade ≥2 and grade ≥3 PN (Table 5



Number of subjects at risk

Any event	340	326	271	211	174	146	128	112	97	82	68	55	39	17	2	0
Grade ≥2 event	340	331	295	250	220	191	172	148	129	109	89	68	46	23	2	0
Grade ≥3 event	340	331	299	262	242	221	200	179	156	129	104	76	49	25	3	0

Figure 1 Cumulative bortezomib dose to first onset of a peripheral neuropathy event.

Risk Factors for PN (peripheral neuropathy) and Lessons learned

- PN incidence is dose related and plateau at 45mg/m2
- Median time to onset 2.3 months
- Bortezomib associated PN is reversible
- 79% of events improved by 1 grade with in 1.9 months
- 60% complete resolution within 5.7 months
- Baseline neuropathy was the only risk factor for any PN
- Age, pre-existing DM, ISI stage, Obesity, Race, CrCl did not affect rate of PN
- Once weekly IV Bortezomib has comparable incidence of PN vs once weekly SubQ

Successful Transition from Bortezomib Subcutaneous (SubQ) to Generic Intravenous (IV) Bortezomib: Cost Savings Initiative with Global Economic Impact

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Blood (2019) 134 (Supplement_1): 4758.

https://doi.org/10.1182/blood-2019-128992

Background:

It is estimated that the U.S. will spend $370 billion in 2019 on pharmaceuticals and by 2020 the cost of cancer care will be approximately 158 billion. Cost containment strategies for high cost drugs are needed. In 2019 global sales from subcutaneous (SubQ) bortezomib manufactured by Takeda® will exceed $1 billion. There exists an opportunity to decrease overall cost related to bortezomib by $300-400 million across the globe by switching patients to bortezomib intravenous (IV) (manufactured by Fresenius Kabi®). Generic bortezomib was first approved by the FDA in January 2018 but it can only be administered intravenously. A phase 3 randomized controlled trial of twice weekly SubQ vs IV bortezomib showed no difference in time to progression or 1 year overall survival, however rate of Grade 3 peripheral neuropathy doubled in the IV arm compared to SubQ (Moreau et al, 2011). Although twice weekly bortezomib has fallen out of favor and there are retrospective data suggesting that neuropathy from weekly subQ and weekly IV bortezomib may be similar, there exist no prospective data to date to confirm this. Bortezomib induced peripheral neuropathy (BIPN) typically occurs by cycle 4 of twice weekly therapy, and the majority of cases are partially reversible (Dimopolous et al, 2011). We hypothesized that patients who have not developed neuropathy after or during 4 cycles of subcutaneous bortezomib could be switched to IV bortezomib without greatly increasing neuropathy.