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ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

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Optimizing Dosing of Oncology Drugs

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Optimizing Dosing of Oncology Drugs

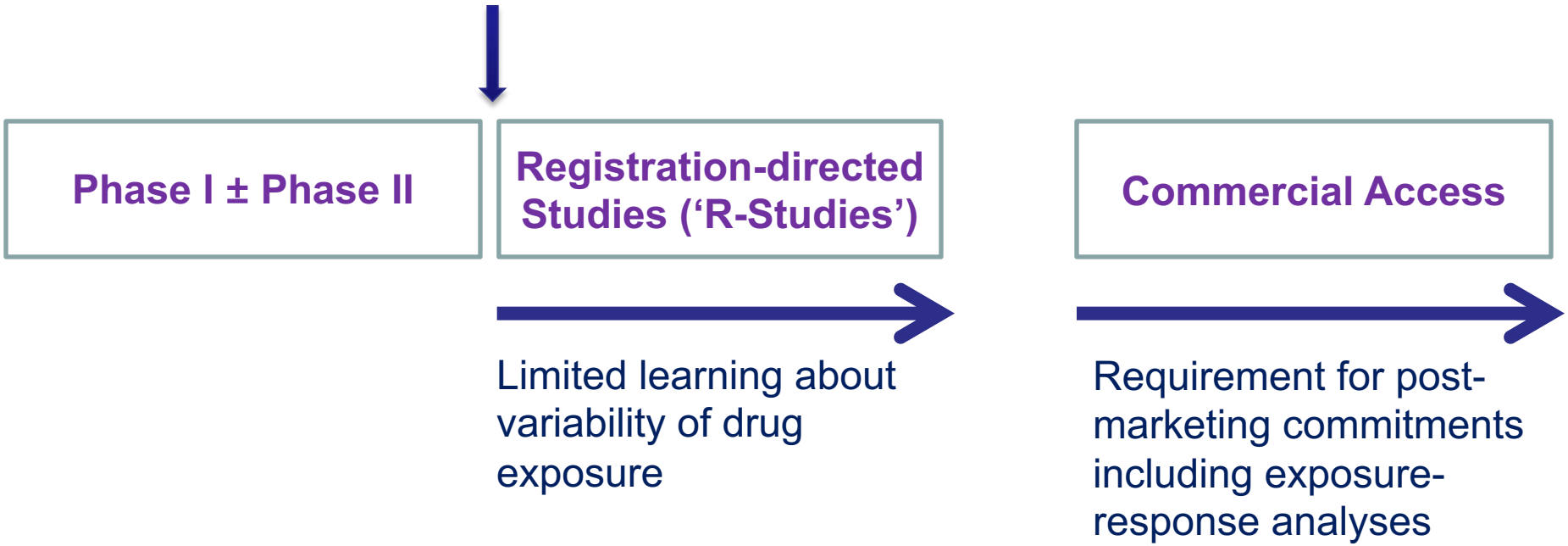
Richard L. Schilsky, M.D.
American Society of Clinical Oncology

Current Approach to Dose Determination in Oncology

- Aimed at the "maximum-tolerated dose" (MTD) to increase chance of obtaining an efficacy signal
- MTD is identified in phase 1 trials, often in heavily pre-treated patients
- MTD may be the only dose evaluated in phase 2 and phase 3 trials
- Clinical trials define a tolerable dose for a population, and adjusting dose for individual patients is done empirically

Traditional Approach to Dose Finding*

Determination of dose for registration-directed studies



*simplified for the purpose of illustration

Limitations of the Current Approach

- Dose (exposure)-response relationships are rarely well defined
- High rate of dose reductions in some clinical trials, recent examples in briefing document
- Failure to identify patients who may benefit from higher dose/exposure
- For some targeted agents, the “optimal biologic dose” may be that which results in saturation of a drug target, rather than the MTD
- Does not adequately evaluate late onset or cumulative toxicities or changes in tolerability over time

Many Factors Lead to Variable Drug Responses

- Genetic polymorphisms in drug transporters or drug-metabolizing enzymes
- Concomitant medications
- Age, body weight, hepatic and renal function
- Comorbidities
- “Food effect” on absorption of oral drugs
- Therefore, any dose chosen will be too high for some patients, too low for others.

Charge to the Panel

- Discuss **what** data needs to be collected to optimize dosing
- Discuss **how** this data can be used to optimize dosing
- Discuss **when** this data should be collected

Proposed Path

- Phase 1: Define a dose for future studies; preliminary characterization of pharmacokinetics (PK), include pharmacodynamic endpoints (PD) to assess target inhibition if possible
- Phase 2: Define drug activity and include exploration of dose variations, continued PK and PD measurements
- Phase 3: Incorporate population PK data to understand relationships between drug exposure and key clinical outcomes
- When subjective toxicities are identified, use validated tools (if available) to assess patient-reported outcomes (PROs)
- Post-market: Use data collected in phase 1-3 to modify doses based on observed exposure, efficacy and tolerability

How can this approach improve clinical outcomes?

- Definition of the ranges of toxic and therapeutic drug concentrations may, in some cases, enable monitoring of patient drug levels. This could be used to guide treatment decisions and may be particularly valuable for chronic treatment.
- Collection of drug exposure and clinical outcome data (i.e., tolerability, adverse events, efficacy) in the post-market setting could improve understanding of "real-world" patient experience with a drug and vulnerable populations

When should dose exploration be performed?

- Premarket (ideally, phase 2): Phase 2 dose exploration could inform dose selection for phase 3:
  - Less likely to choose a dose too high and observe excessive toxicity
  - Less likely to choose a dose too low and observe inadequate efficacy
- Challenges:
  - May slow the development of potentially important new drugs
  - May be excessively burdensome when there is uncertainty whether the drug will ultimately be approved
  - May be difficult to assess pharmacodynamic endpoints if drug target not well understood

When should dose exploration be performed?

- Post-market dose-exploration may be used to refine recommended dose when premarket dose exploration is unfeasible, but also poses challenges:
  - Patients may not want to participate in a trial of drug already on the market
  - Difficult to perform these studies in a timely manner
- Potential opportunity in the window of time between the completion of registration trials and marketing approval.

Speakers

- **Richard L. Schilsky, M.D.,** American Society of Clinical Oncology
- **Atiqur Rahman, Ph.D.**, Division of Clinical Pharmacology V, FDA
- **Daniel Auclair, Ph.D.,** Multiple Myeloma Research Foundation
- **Lori Minasian, M.D.,** National Cancer Institute
- **Oliver Rosen, M.D.,** Millennium: The Takeda Oncology Company
- **Richard Pazdur, M.D.,** Office of Hematology and Oncology Products, FDA

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Optimizing Dosing of Oncology Drugs

Atiqur Rahman, Ph.D.
Office of Clinical Pharmacology, FDA

Problem

- MTD based dose may not be appropriate for targeted therapy
- Dose selection based on MTD causing serious toxicities in phase 1b/2/3 and in post-marketing trials
- Doses used in Phase 2 and 3 often achieve concentrations that may substantially surpass concentrations needed to inhibit or stimulate the intended target (s)
  - not sufficiently specific to only hit the mechanistic/biologic target alone
  - off-target inhibition → toxicity?

Dose-Exposure Relationship

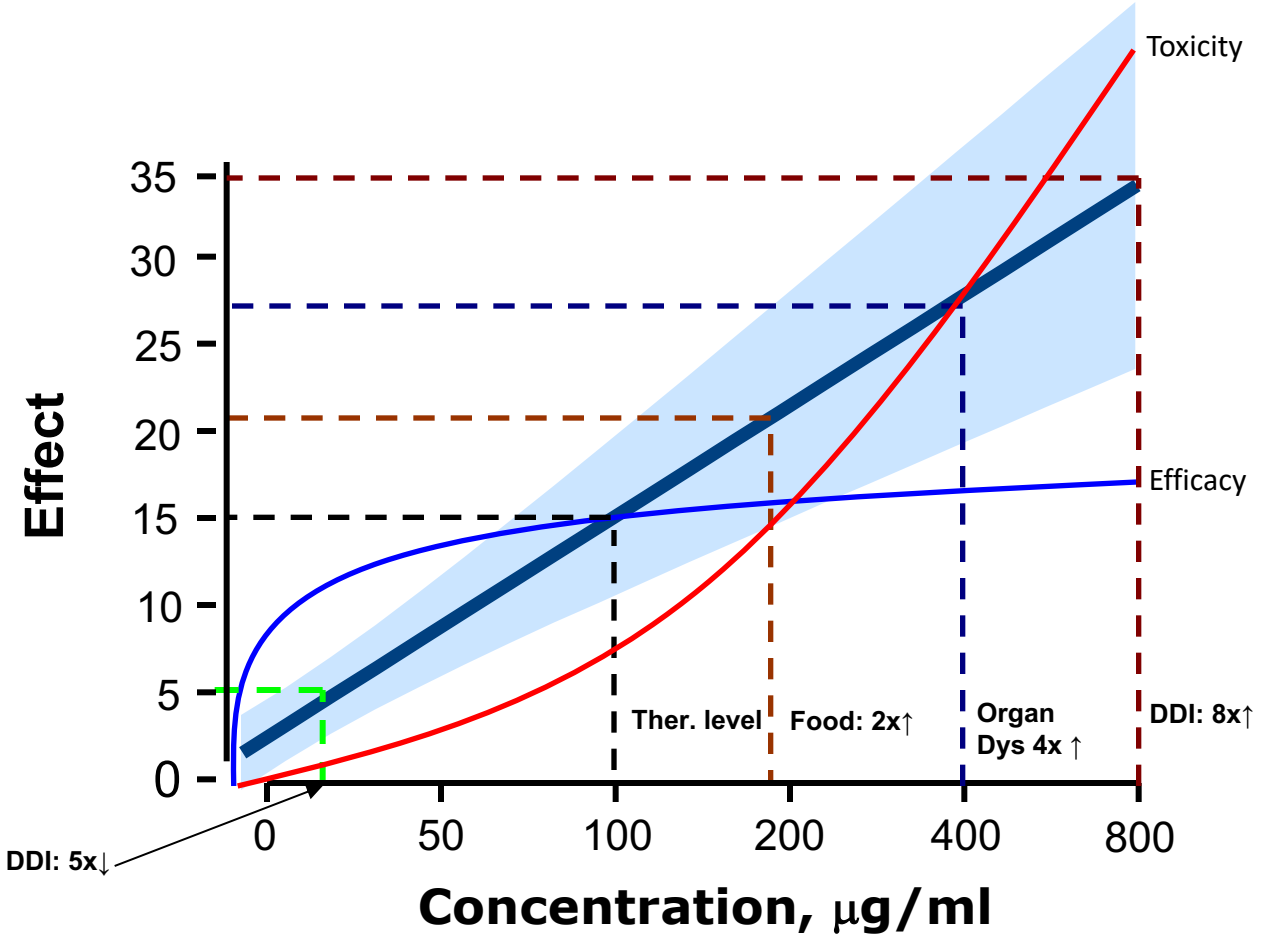
- Why is understanding exposure (PK/PD) important for dose optimization?

- How can exposure (PK/PD) help in optimizing the dose in drug development?

Exposure Effect Relationship

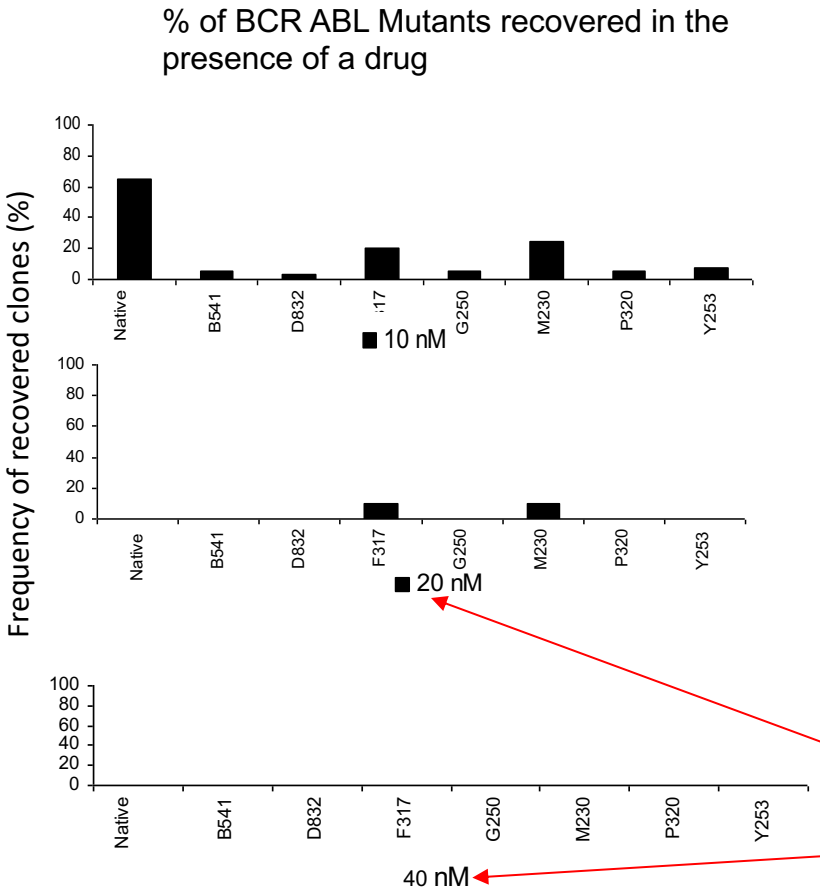
Influence of intrinsic and extrinsic factors on drug levels and therapeutic effects

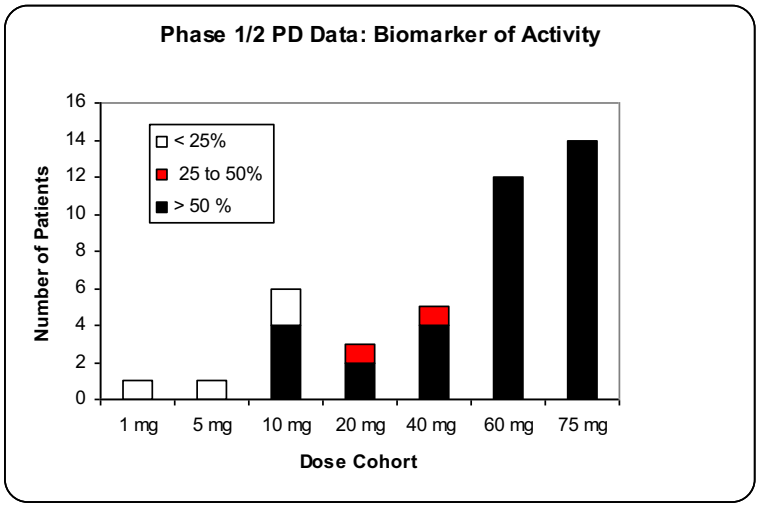
Dose → Exposure → Target → Effect

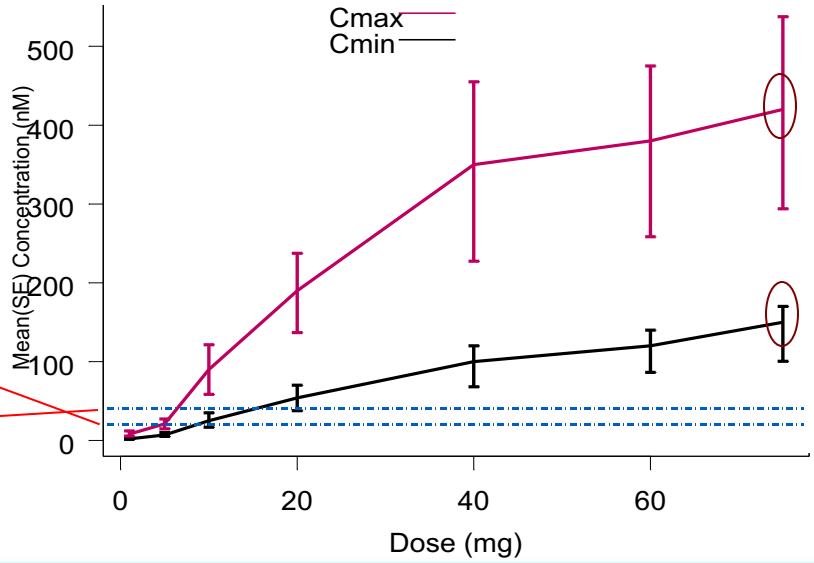


How can PK/PD help in optimizing dose in drug development?

Integration of Information Target inhibition, PK and PD







Path Forward

- Early Drug development
  - Identify targets
  - Identify optimal concentrations (IC_{50}, IC_{90}) for target effects
  - Determine correlation of human PK to
    - in vivo biomarker
    - in vitro target concentrations
- Phase 2 Development
  - Adaptive design to explore more than one dose
    - Optimal biologic dose
    - Near MTD dose
    - Collect PK and evaluate exposure activity and safety relationships
- Phase 3 Development
  - Sparse PK samples in all patients
    - Evaluate relationships between covariates influencing exposure and key clinical outcome (including biomarkers)
    - Develop rationale for dose escalation or reduction for approval and labeling
- Post-Marketing Trials
  - Refine dose if not optimized during development (difficult to do)
  - Sparse PK sampling in all patients
    - Evaluate relationships between exposure and **long term toxicity**

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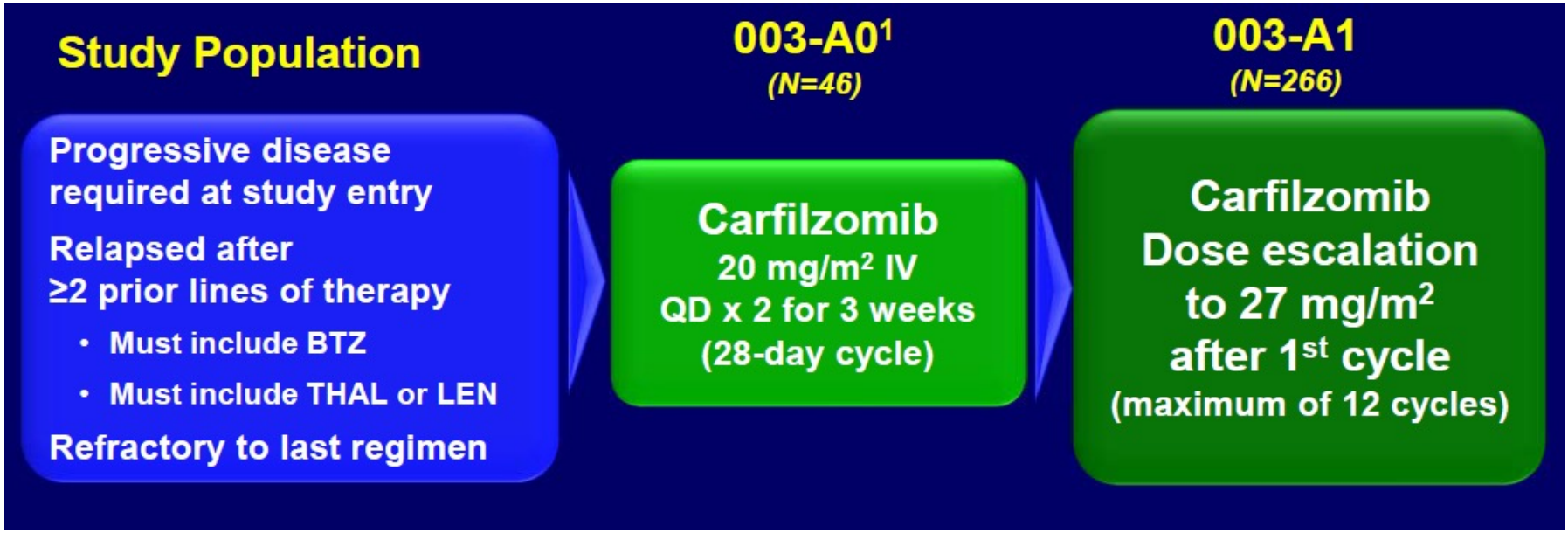
Optimizing Dosing of Oncology Drugs

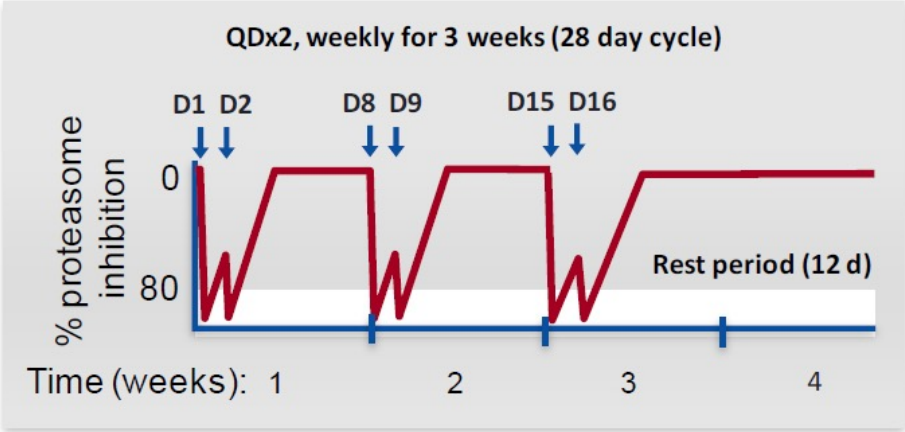
Daniel Auclair, Ph.D.
Multiple Myeloma Research Foundation

Carfilzomib PX-171-003 Studies



Jagannath *et al.* ASH 2009; Siegel *et al.* Blood 2012

Carfilzomib Dosing Schedule & PD



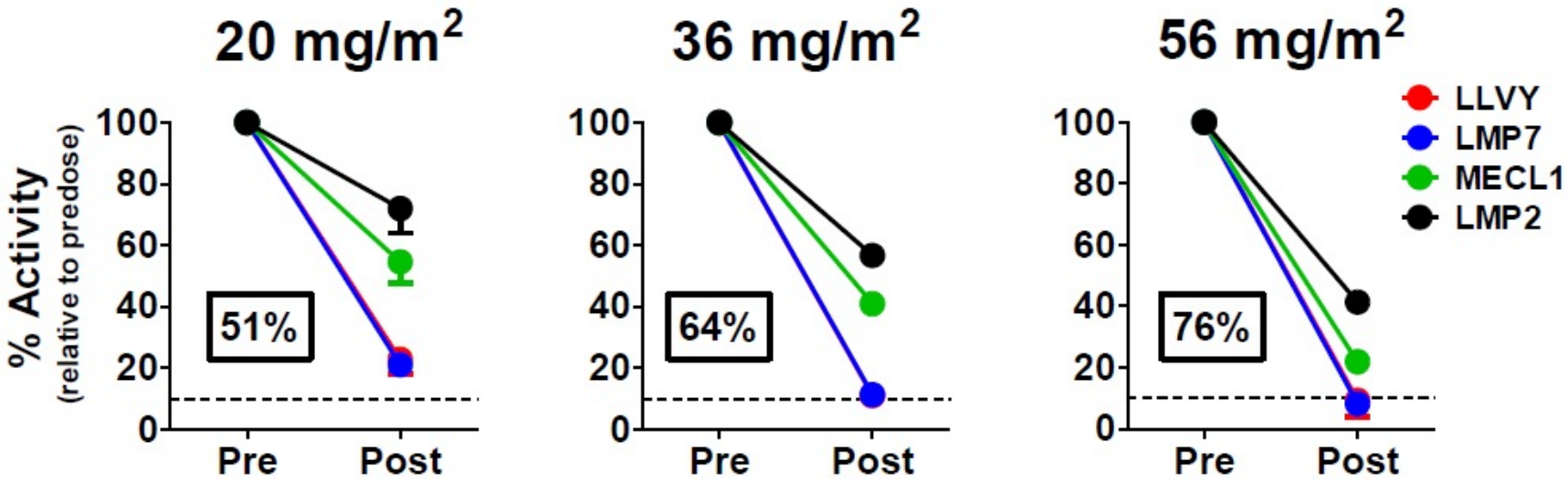
	CD138+ (Bone Marrow)	Blood	PBMC
LLVY	CT-L	CT-L	CT-L
ProCISE	Beta5 LMP7 MECL1	Beta5 Beta2 Beta1	LMP7 LMP2 MECL1
# Patients Analyzed	40	74	71

Lee *et al.*, ESMO-TAT Meeting 2011

Carfilzomib EAP

- Single arm study in relapse refractory patients
- Same 20 -> 27 mg/m^2 design as PX-171-003-A1
- Almost 350 patients enrolled over an 11 months period

Higher doses Carfilzomib PD



Lee *et al.*, ESMO-TAT Meeting 2011

MMRF CoMMpass Study

National Cancer Institute
at the National Institutes of Health

We Can Answer Your Questions
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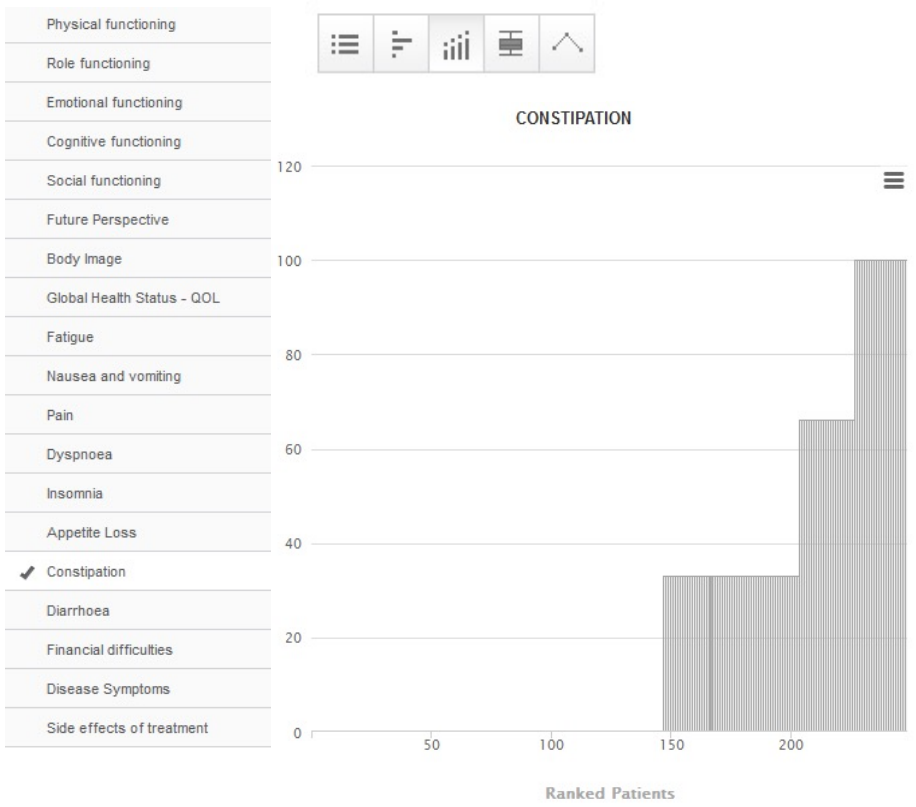
Help Using the NCI Clinical Trials Search Form
How to Find a Cancer Treatment

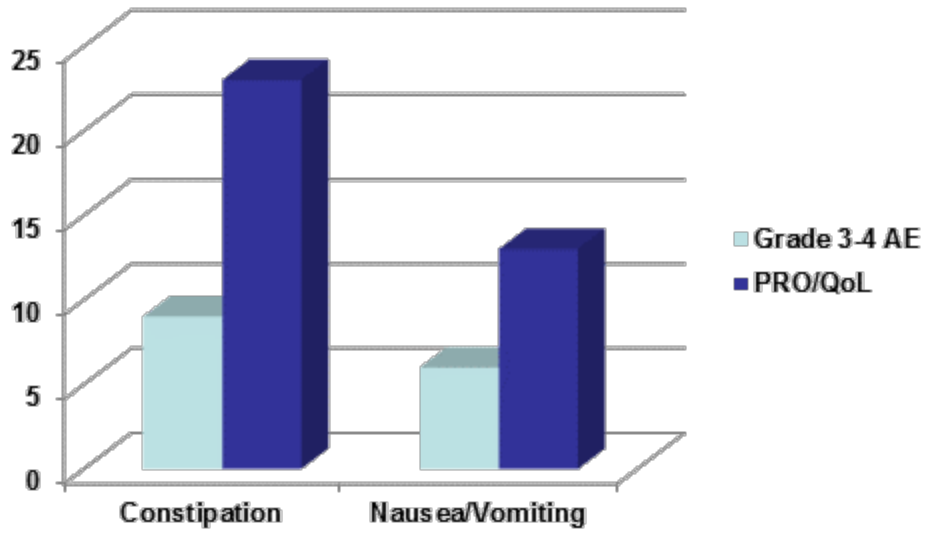
Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile

Basic Trial Information

Phase	Type	Status	Age	Sponsor	Protocol IDs
No phase specified	Biomarker/Laboratory analysis, Natural history/Epidemiology, Supportive care	Active	18 and over	Other	**MMRF-11-001** NCT01454297

CoMMpass Grade 3-4 AEs versus PROs/QoL





MMRF Gateways

https://research.themmrf.org

https://community.themmrf.org

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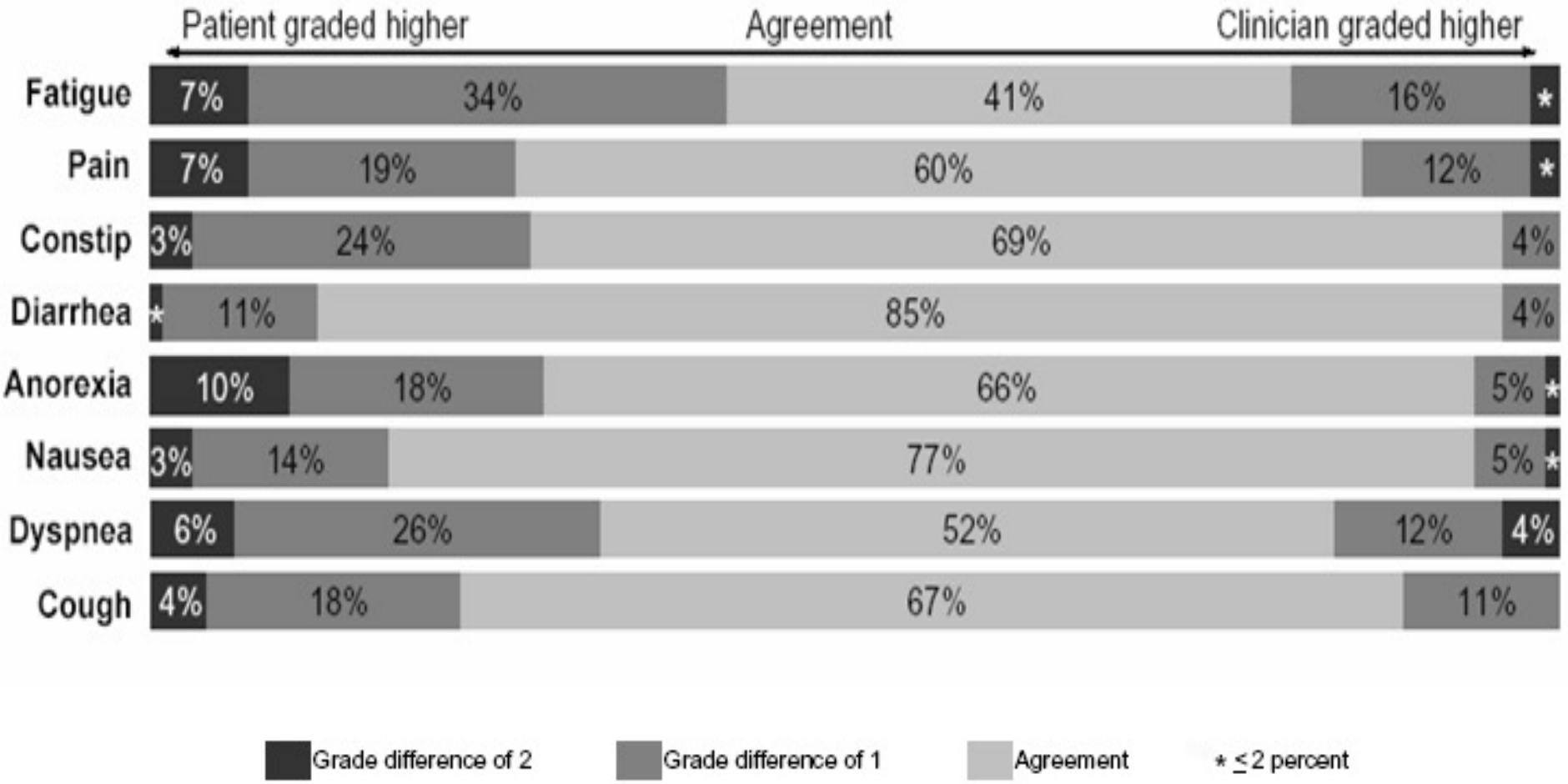
Subjective Toxicities & (PRO-CTCAE) Patient Reported Outcomes version of CTCAE

Lori Minasian, M.D.
National Cancer Institute

Adverse Event Reporting

- Clinicians Trained to Recognize Serious Effects
  - Accurately Capture SAEs
  - Clinicians Tend to Under-report Bothersome Effects
- Patients' Report of Side Effects Correlates Better with Function and Overall Health Status
  - May Better Reflect Tolerability over Time
  - Chronic Bothersome Side Effects May Reduce Adherence
- Optimal to Capture Both in Integrated Fashion

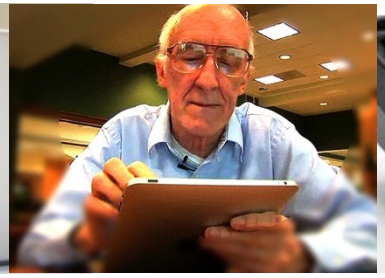
Clinician & Patient Reports are Discrepant



Basch, Lancet Oncol, 2006

PRO-CTCAE Measurement System

1. Symptom Library	2. System for Survey Administration
• 78 symptomatic adverse events drawn from CTCAE • PRO-CTCAE questions evaluate symptom occurrence, frequency, severity, and interference	• Web-based system to customize surveys and manage survey administration • Patient responds to surveys using web, tablet or interactive voice response (IVRS) telephone system • Conditional branching (skip patterns) • Write-ins with automatic mapping to standardized terminology


CTCAE vs. PRO-CTCAE Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

Current Status & Ongoing Activities

- Standard Analytic Validation for Patient Reported Outcome Measure Nearly Completed
  - Reliability, Validity, Mode Equivalence, Group Differences
  - PRO-CTCAE Can Be Used For Descriptive Information

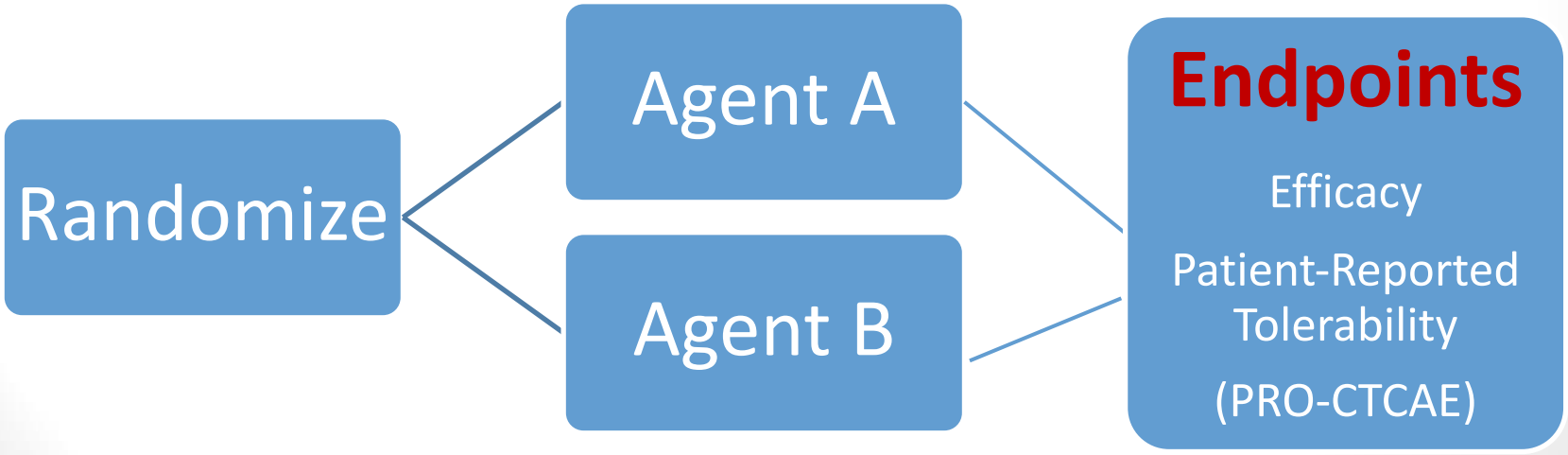
- Understanding Clinical Validity, Interpretation, & Clinical Utility is Evolving
  - Incorporation of PRO-CTCAE Scores into Clinician Grading
  - Integration of Information into Study Conduct
  - Use in Analyzing Tolerability

Potential Utility of PRO-CTCAE

- **Phase I:** Exploratory
  - Gauge side effects relative to dose escalation; refine measurement approaches (items, timing) for later phase studies
- **Phase II:** Describe Toxicity in Depth
  - Assess tolerablility of the recommended phase II dosing
  - Identify chronic symptomatic toxicities that may impair adherence
  - Explore approaches (schedule/dosing, supportive care) to reduce symptomatic adverse effects
- **Phase III:** Assess Overall Benefit/Risk for Regimen
  - Evaluate efficacy and tolerability on a wider scale
  - Assess impact of dosing modifications to reduce chronic symptomatic toxicities on overall benefit/risk
- **Phase IV:** Efficacy → Effectiveness
  - Optimize tolerability
  - Tailor regimens for vulnerable sub-populations (comorbidities, frail, older adults)

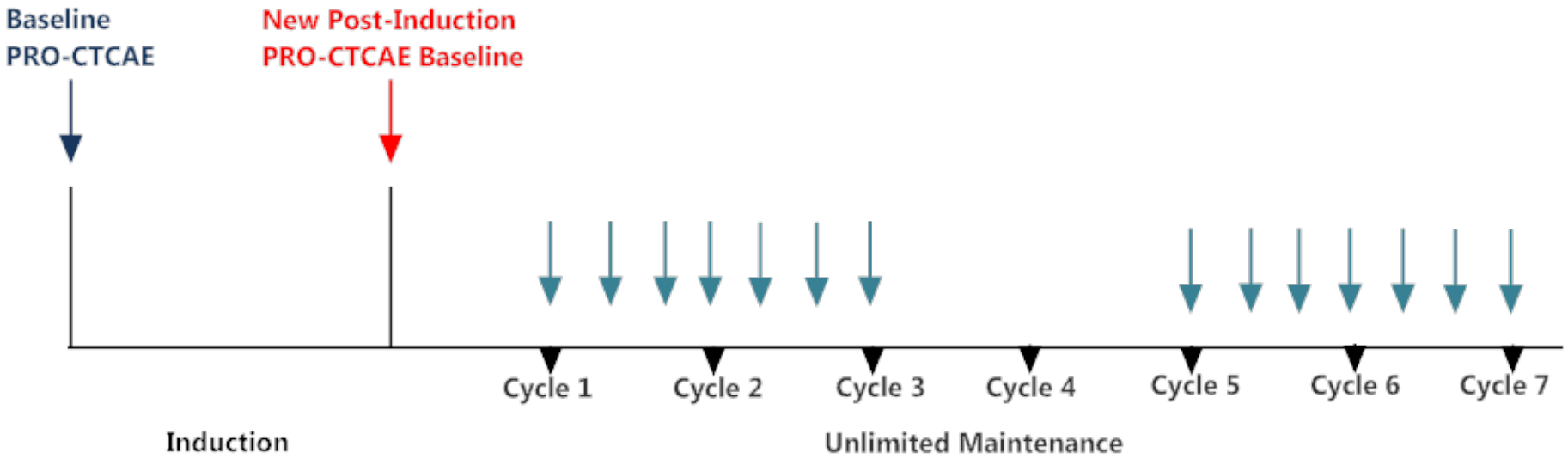
Phase 2 B Comparative Tolerability

- Two oral agents with comparable efficacy and clinician-rated toxicity in Phase II trials
  - Research Question: Are there subtle tolerability differences between the two agents that might become important in Phase III and which can be detected with inclusion of PROs in Phase II?
- Randomized phase II study with efficacy and patient-reported tolerability as the primary endpoints



Tolerability of Maintenance Therapy

Research Question:
What is the chronic tolerability of bortezomib maintenance therapy in multiple myeloma in remission after induction?



NCI PRO-CTCAE Study Group

Supported through NCI contracts HHSN261200800043C and HHSN261201000063C

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	Cori Couture	Edward Korn	Lauren Rogak
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Suneel Allareddy	Jana Eisenstein	Suzanne Lechner	Daniel Satele
Benjamin Arnold	Maria Fawzy	Lauren Lent	Martin Schoen
Pamela Atherton	Shanda Finnigan	Yuelin Li	Deborah Schrag
Thomas Atkinson	Steve Friedman	Carol Lowenstein	Ann Setser
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Paul Baumgartner	Vinay Gangoli	Michael Mejia	Mary Shaw
Lauren Becker	Marcha Gatewood	Tito Mendoza	Marwan Shouery
Antonia Bennett	Araceli Garcia-Gonzalez	Lori Minasian	Laura Sit
Nancy Breen	Cindy Geoghegan	Michael Montello	Jeff Sloan
Deborah Bruner	Maria Gonzalez	Hannah O'Gorman	Diane St. Germain
Laurie Burke	Mehul Gulati	Ann O'Mara	Ann Marie Trentascosti
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David Cella	Jennifer Hay	John Payne	Andy Trotti
Alice Chen	Madeline Hernandez-Krause	Frank Penedo	Andrea Vinard
Ram Chilukuri	Jessica Hess	Barbara Perez	Vish Viswanath
Steven Clauser	Lori Hudson	Richard Piekarz	Gordon Willis
Charles Cleeland	Norval Johnson	Liora Pollick	Jennifer Wind

- Organizational Affiliations: NCI Community Cancer Centers Program (NCCCP), RTOG, Alliance, FDA
- We gratefully acknowledge our study participants and patient representatives!

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Optimizing Dosing of Oncology Drugs

Oliver Rosen, M.D.
Millennium: The Takeda Oncology Company

A New Window of Opportunity

- Promising data from registration-directed studies trigger the desire for early drug access
- **Time from data presentation until the commercial launch represents a window of opportunity for additional data collection**
  - Expanded access programs usually the only way for early access
  - Dosing optimization study attractive due to lack of placebo arm
- Timing of dosing optimization studies is important
- Collaborative assessment of dosing optimization data will be based on surrogate endpoints e.g. response rate

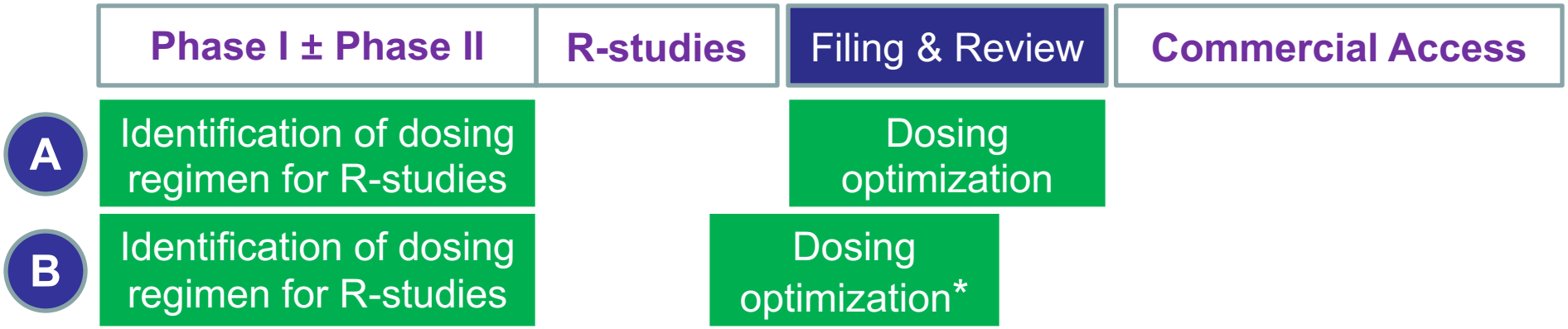
What does it take for such an approach to succeed?

- Approach requires a close collaboration between FDA and a sponsor
- Review of supplemental dosing data should not lead to
  - A delay of the PDUFA date
  - Require a supplemental BLA
- Two approaches are conceivable regarding timing of dosing optimization studies

The Two Potential Approaches

- After (high-level) release of promising data e.g. press release of promising data a registration-directed study
  - Not realistic to provide exposure data in time without delaying the PDUFA date
  - Will most likely require a supplemental BLA
- Earlier activation e.g. following an milestone of a registration-directed study to ensure consideration of data during FDA review process
  - Will ensure a review of exposure data in time without delaying the PDUFA date

Second Window of Opportunity … Two Possibilities



*would need to allow for consideration in initial product label

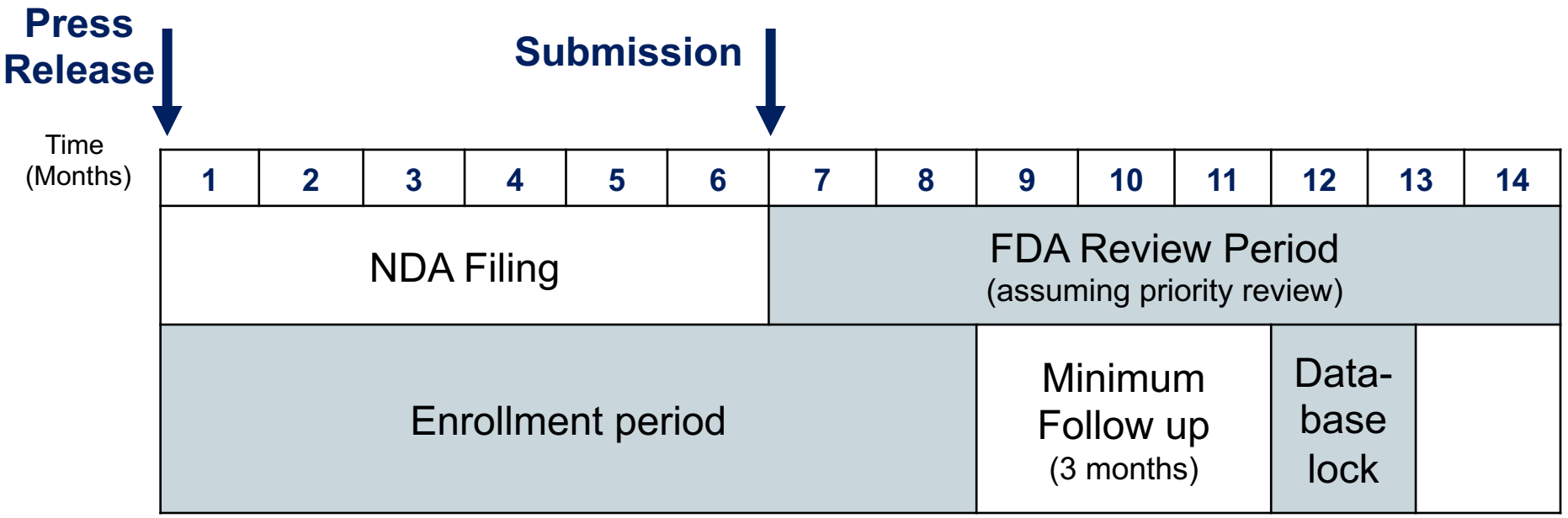
Second Window of Opportunity … Two Possibilities

Phase I ± Phase II	R-studies	Filing & Review	Commercial Access
A: Identification of dosing regimen for R-studies		Dosing optimization	
B: Identification of dosing regimen for R-studies		Dosing optimization*	

*would need to allow for consideration in initial product label

Compared to the traditional approach

Phase I ± Phase II	R-Studies	Commercial Access
Identification of dosing regimen for R-studies		Dosing optimization as Post-Marketing commitments


Press Release
Submission
Time (Months)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
NDA Filing
FDA Review Period
(assuming priority review)
Enrollment period
Minimum Follow up
(3 months)
Data-base lock


Phase I ± Phase II
R-studies
Filing & Review
Commercial Access
A
Identification of dosing regimen for R-studies
Dosing optimization

Conclusion

- As outlined by Dr Rahman, several recently approved oncology drugs are indicated for the use with suboptimal doses
- Both approaches for additional data collection during second window of opportunity have its pro's & con's
- Benefits of the option of delayed dosing optimization studies
  - Increased flexibility for sponsors due to a second, later window of opportunity for dose comparisons
  - Opportunity to further refine the dosing & administration section of a product label while pivotal studies are ongoing
  - Dose or scheduling comparisons could be based on surrogate endpoints and not the primary endpoint of ongoing pivotal studies
  - Reduction in post-marketing commitments

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Office of Hematology and Oncology Products, FDA

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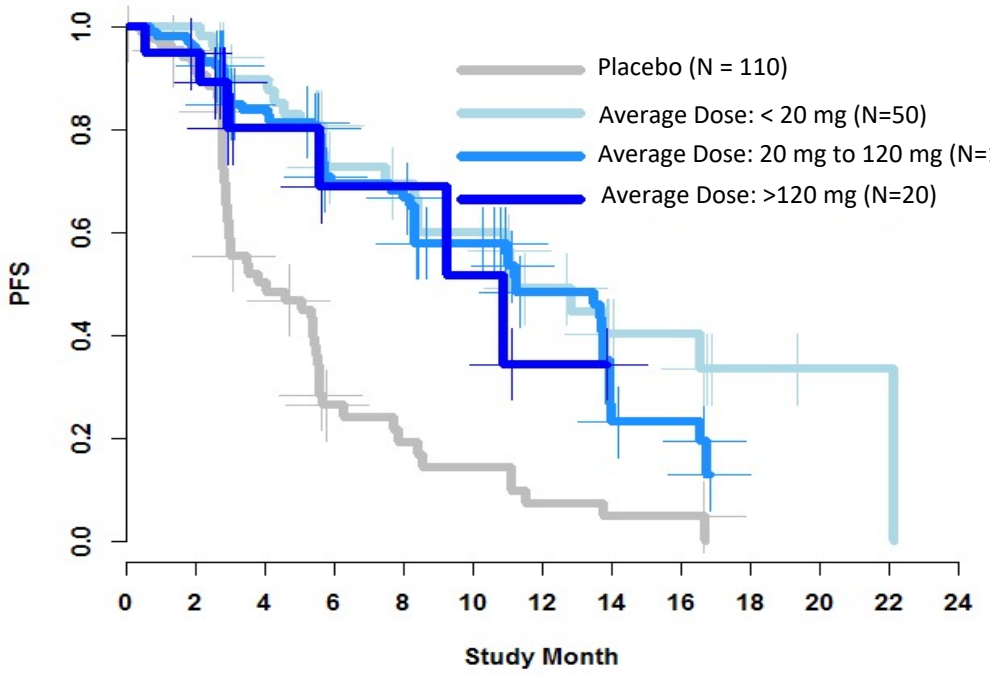
Dose selection for a targeted therapy

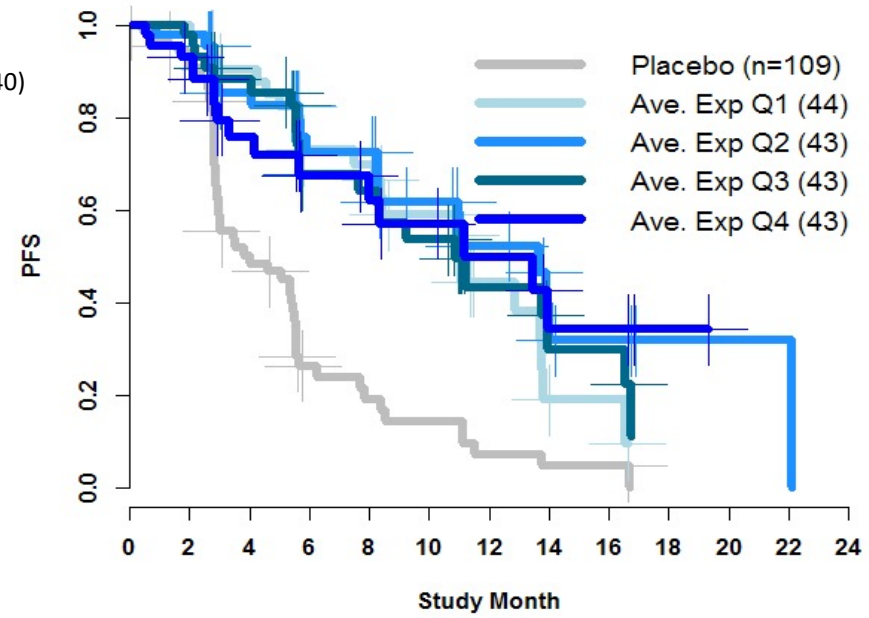
- Potent target inhibition (IC_{50}) occurred at 10 nM concentration in vitro
- MTD dose selected based on "3+3" rule in a Phase 1 trial
  - 21 patients treated at MTD: 80% of patients suffered grade 3 or 4 toxicities and 83% dose reduced.
  - Steady State concentration ranged from 3500 nM to 4500 nM
- MTD dose further tested in Phase 2 in another patient population
  - 46 patients treated at MTD: 85% of patients suffered grade 3 or 4 toxicities and 80% patients required dose modification.
- MTD taken forward in pivotal registration trial
  - Grade 3 or 4 toxicities: 69% patients
  - Dose modifications: 85% patients

	TRT (N=309)	Placebo (N=151)
• 1-Level dose reduction • 2-Level dose reduction • Discontinuation	79% 41% 16%	9.2% 0.9% 8.3%
Frequent AEs leading to dose modification		
PPE (Palmar-plantar erythrodysaesthesia syndrome)	25%	0
Diarrhea	19.2%	1.8%
Fatigue	13%	2.8%
Weight decreased	12.6%	0
Decreased appetite	11.7%	0.9%

Efficacy is not altered at lower concentration

- Average dose not associated with PFS reduction
- Average exposure not associated with PFS reduction





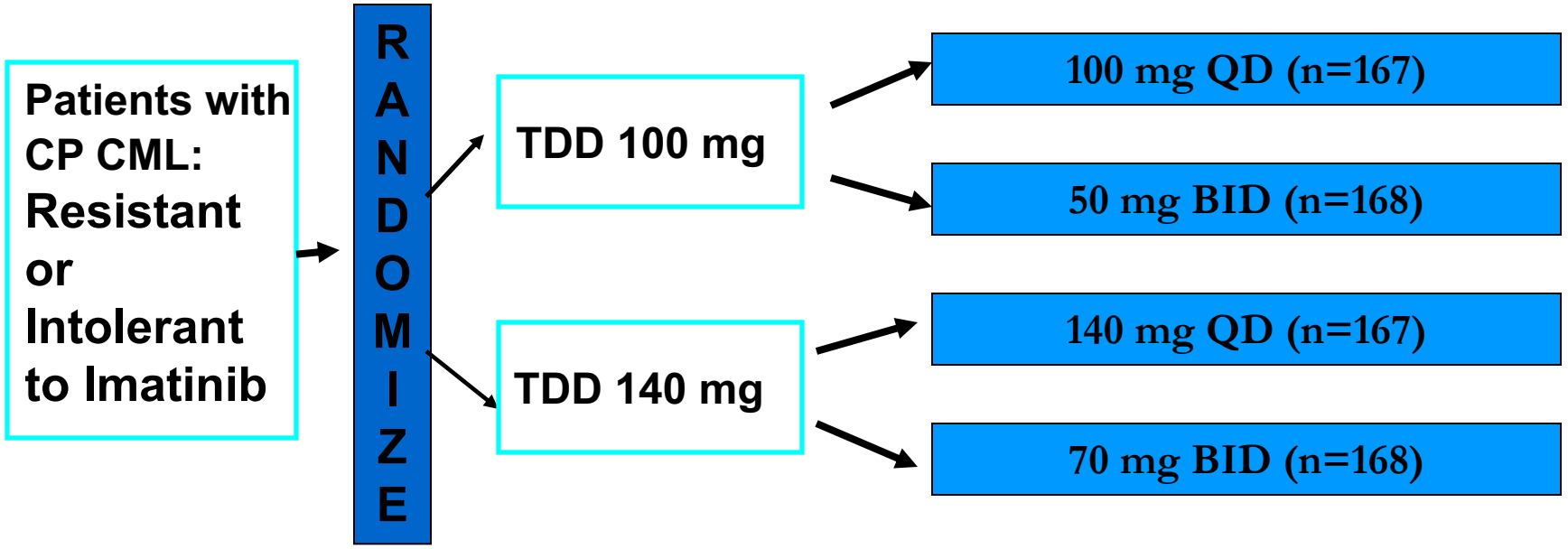
Dose Modifications

Approved Products Evaluating Alternate Dose in Post Marketing Trials	
Product	Approved Dose
Trastuzumab	6-8 mg/kg
Vandetanib	300 mg
Omacetaxine	1.25 mg/m^2
Cabozantinib	140 mg
Ponatinib	45 mg
Radium RA-123	50 kBq/kg
Ado-trastuzumab	3.6 mg/kg

Dose Escalation in Oncology/Hematology Drug Labels	
Product	Approved Dose
Dasatinib	50 mg BID → 100 mg BID
Axitinib	5 mg bid → 10 mg BID
Ruxolitinib	20 mg BID → 25 mg BID
Mitotane	2 g/day → 16 g/day

Dasatinib

Design of CA 180034



Endpoints:

Primary: MCyR rate QD vs BID after a minimal 6 m follow-up

Secondary: McyR rate between the two TDDs, durability and time to MCyR, safety, etc.

Assessments:

Bone Marrow CyR after 3 & 6 months and then q 6 mos; CBC

Treatment:

until disease progression or intolerable toxicity

Response Analyses

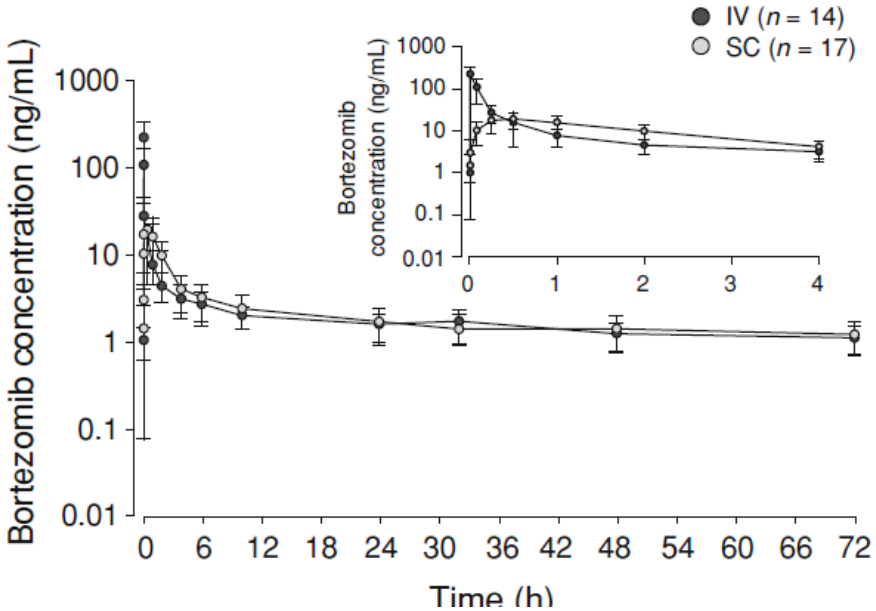
	100 mg QD (N=167)	50 mg BID (N=168)	140 mg QD (N=167)	70 mg BID (N=168)
MCyR				
All Patients	59%	54%	56%	55%
Imatinib-Resistant	53%	47%	50%	51%
Intolerant to Imatinib	74%	73%	70%	61%
CHR				
All Patients	90%	92%	86%	87%
Imatinib-Resistant	86%	91%	85%	87%
Intolerant to Imatinib	100%	93%	86%	85%

FDA Review http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021986_s001_s002.pdf

Laboratory Abnormalities

	100 mg QD (N=165)	50 mg BID (N=167)	140 mg QD (N=163)	70 mg BID (N=167)
Grade 3/ 4	% of patients			
Neutropenia	34%	46%	43%	43%
Thrombocytopenia	22%	34%	40%	38%
Anemia	10%	18%	19%	17%

Bortezomib PK and PD



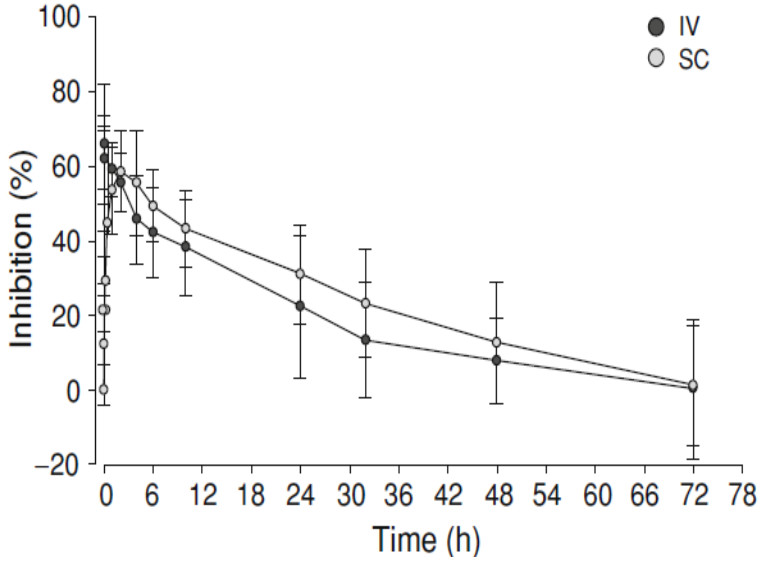


Table 1 Summary of mean (standard deviation) pharmacokinetic and blood 20S proteasome inhibition pharmacodynamic parameters of bortezomib following subcutaneous or intravenous injection of 1.3 mg/m^2 on day 11 of cycle 1 in the MMY-3021 and CAN-1004 studies

Parameter	MMY-3021		CAN-1004	
	SC 2.5 mg/mL	IV 1.0 mg/mL	SC 1.0 mg/mL	IV 1.0 mg/mL
Pharmacokinetic				
AUC_{last}, ng·h/mL	155 (56.8)	151 (42.9)	195 (51.2)	241 (82.0)
C_{max}, ng/mL	20.4 (8.87)	223 (101)	22.5 (5.36)	162 (79.9)
t_{max}, min[a]	30 (5–60)	2 (2–5)	30 (15–60)	2 (2–30)
Pharmacodynamic				
$AUEC_{72}$, %·h	1,714 (617)	1,383 (767)	1,619 (804)	1,283 (595)
E_{max}, %	63.7 (10.6)	69.3 (13.2)	57.0 (12.8)	68.8 (6.49)
Time to E_{max}, min[a]	120 (30–1440)	5 (2–30)	120 (60–240)	3 (2–30)

Moreau et al. Clin Pharmacokinet (2012) 51:823-829

Bortezomib for Relapsed/Refractory Myeloma

Efficacy Estimates	Subcutaneous	Intravenous	Statistics
TTP (months, 95% CI)	9.7 (8.5, 11.7)	9.6 (8.0, 11.0)	HR: 0.872 (0.605, 1.257) P = 0.462
PFS (months, 95% CI)	9.3 (8.1, 10.7)	8.4 (6.7, 10.0)	HR: 0.846 (0.608, 1.176) P = 0.319
1-year survival	76.4% (68.5, 82.5)	78% (66.7, 85.9)	P = 0.788
Median Overall survival (months, 95% CI)	28.7 (23.2 – NA)	NA (21.5 – NA)	NA

Arnulf et al. Haematologica (2012) 97(12): 1925-1928

SC vs IV Bortezomib for Relapsed/ Refractory Myeloma

EQUIVALENT EFFICACY Peripheral Neuropathy	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

Ken Anderson: AACR Presentation at the FDA, 2013