

**Safety and Efficacy of Subcutaneous-  
Administered Omacetaxine  
Mepesuccinate in Chronic Myeloid  
Leukemia Patients Who Are Resistant  
or Intolerant to Two or More Tyrosine  
Kinase Inhibitors – Results of  
A Multicenter Phase 2/3 Study**

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On behalf of the CML-203 Study Group

# Disclosures

<b>Research Support/P.I.</b>	<b>Chemgenex (JC)</b>
<b>Employee</b>	<b>No relevant conflicts of interest to declare</b>
<b>Consultant</b>	<b>Chemgenex (JC)</b>
<b>Major Stockholder</b>	<b>No relevant conflicts of interest to declare</b>
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<b>Scientific Advisory Board</b>	<b>No relevant conflicts of interest to declare</b>

# Omacetaxine after $\geq 2$ TKI Failure Background

- Frontline imatinib in CML CP:
  - 82% CCyR
  - 5-year EFS 60-80%
- Second line TKI in CML CP:
  - ~50% CCyR
  - 2-year EFS 70-80%
- Worse outcome in advanced stage
- Few transient responses to 3<sup>rd</sup> second generation TKI
- Treatment options needed for patients with multi-TKI resistance or intolerance

# Omacetaxine after $\geq 2$ TKI Failure

## Mechanism of Action

- First-in-class cetaxine, inhibitor of protein elongation<sup>1</sup>
- Potent inhibitory activity against leukemic cells, including T315I+ cells<sup>1</sup>
- Activity independent of Bcr-Abl binding
- Induces apoptosis by inhibiting the anti-apoptotic oncoprotein Mcl-1<sup>2</sup>
- Inhibits cell growth and induces apoptosis in CD34+ cells<sup>3</sup>
- Clinical activity in CML after imatinib failure<sup>4</sup>

<sup>1</sup>Chen et al. *Cancer Res* 2006; 66: 9059-66; <sup>2</sup>Tang et al. *Mol Cancer Ther* 2006; 5: 723-31; <sup>3</sup>Allan et al. *EHA* 2009 (Abstract# 1052); <sup>4</sup>Quintas-Cardama et al. *Cancer* 2007; 109: 248-55

# **Omacetaxine after $\geq 2$ TKI Failure Study Objectives**

- To evaluate the efficacy of subcutaneous omacetaxine in adult CML patients with resistance and/or intolerance to two or more TKIs**
- To determine the safety profile of subcutaneous omacetaxine in this patient population**

# **Omacetaxine after $\geq 2$ TKI Failure**

## **Key Inclusion Criteria**

- **CML, chronic, accelerated or myeloid blast phase**
- **Resistance or intolerance to imatinib and  $\geq 1$  additional TKI**
- **Prior TKI discontinued  $\geq 15$  days before enrollment**
- **Normal organ function**
- **T315I+ CML excluded**

# Omacetaxine after $\geq 2$ TKI Failure Treatment Plan

- **Induction Therapy**
  - 1.25 mg/m<sup>2</sup> BID SC x14 days every 28 d
- **Maintenance Therapy**
  - 1.25 mg/m<sup>2</sup> BID SC x7 days every 28 d
- Dose derived from phase I study<sup>1</sup>
- Self-administered at home
- Dosing adjustments by decreasing or increasing number of dosing days per cycle

<sup>1</sup>Quintas-Cardama et al. Cancer 2007; 109: 248-55

# **Omacetaxine after $\geq 2$ TKI Failure Evaluations on Study**

## **Every 3 Months**

- **Bone marrow aspiration**
- **Cytogenetic analysis based on a minimum of 20 metaphases**
- **Peripheral blood Bcr-Abl transcript levels by qRT-PCR**
- **Peripheral blood mutation analysis**
- **Periodic EKG**

# Omacetaxine after $\geq 2$ TKI Failure

## Baseline Characteristics

Characteristic	Median [range], or No. (%)		
	CP N=44	AP N=25	BP N=20
Age - years	59 [20-78]	48 [23-71]	58 [30-68]
Duration CML - mo	72 [3-221]	92 [20-197]	60 [1-176]
Baseline mutations	14 (32)	7 (28)	6 (30)
Baseline status			
CHR +	7 (16)		
Concurrent HU	2 (5)		
CHR -	37 (84)		
Concurrent HU	21 (57)		

HU - hydroxyurea

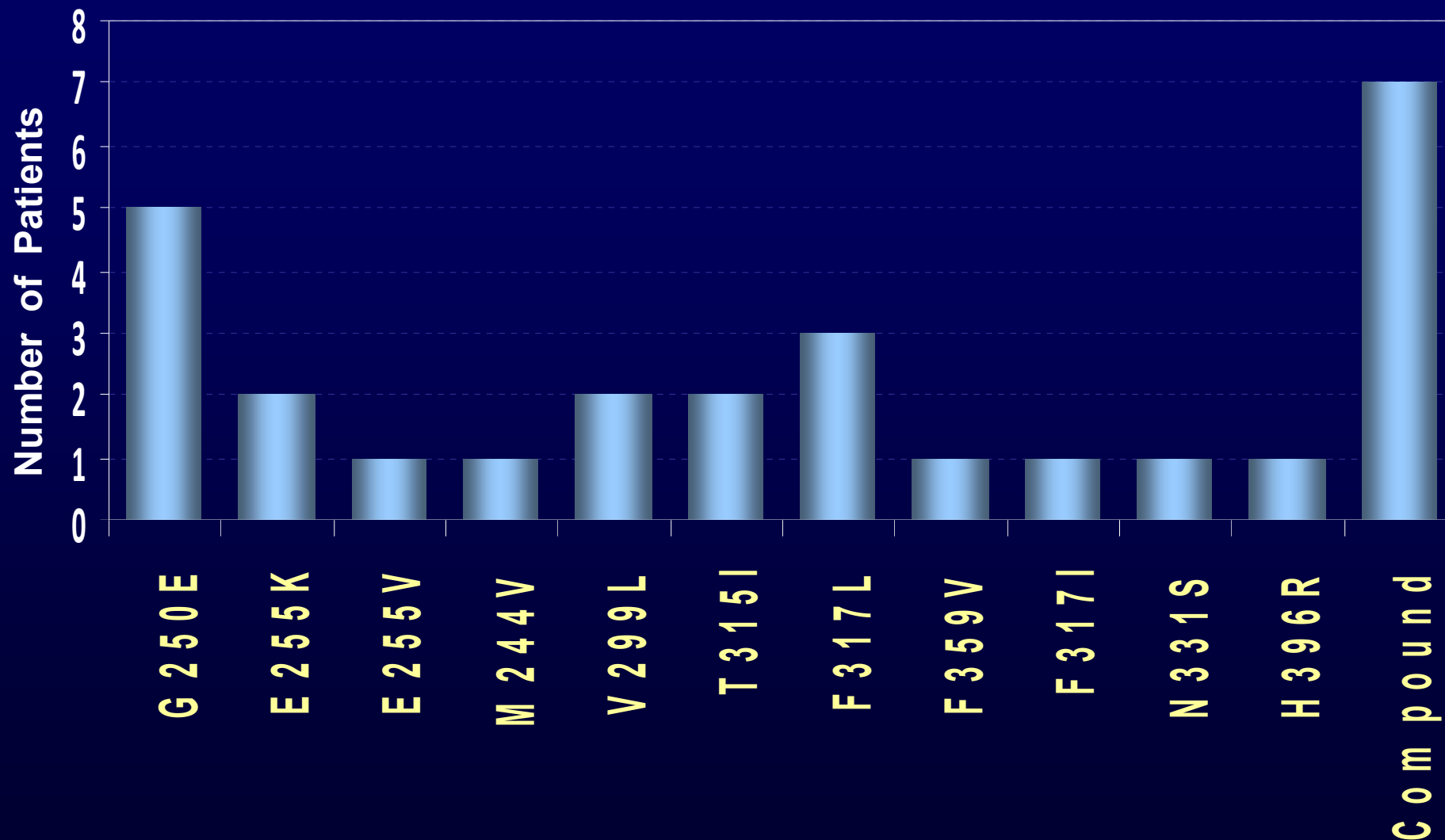
# Omacetaxine after $\geq 2$ TKI Failure

## Prior Treatments

	No. (%)		
	CP N=44	AP N=25	BP N=20
<b>Prior TKI failure</b>			
1 TKI <sup>1</sup>	5 (11)	7 (28)	0
2 TKIs	12 (27)	8 (32)	7 (35)
3 or more TKIs	27 (61)	10 (40)	13 (65)
<b>Time off most recent TKI</b>			
< 1 mo	18 (41)	7 (28)	7 (35)
1-3 mo	12 (27)	6 (24)	8 (40)
> 3 mo	14 (32)	12 (48)	5 (25)

<sup>1</sup>Single country-specific amendment allowed patients with multiple prior therapies and 1 prior TKI to enroll

# Omacetaxine after $\geq 2$ TKI Failure Baseline Mutations



Compound mutations: M244V/M351T; V299L/F359C; V299L/F359V; L248V/M351T/F359V;  
E255Q/M244V; M244V/G250E; M244V/E255Q (1 each)

# Omacetaxine after $\geq 2$ TKI Failure

## Drug Exposure

Median [range] or No. (%)

CP  
N=44

AP  
N=25

BP  
N=20

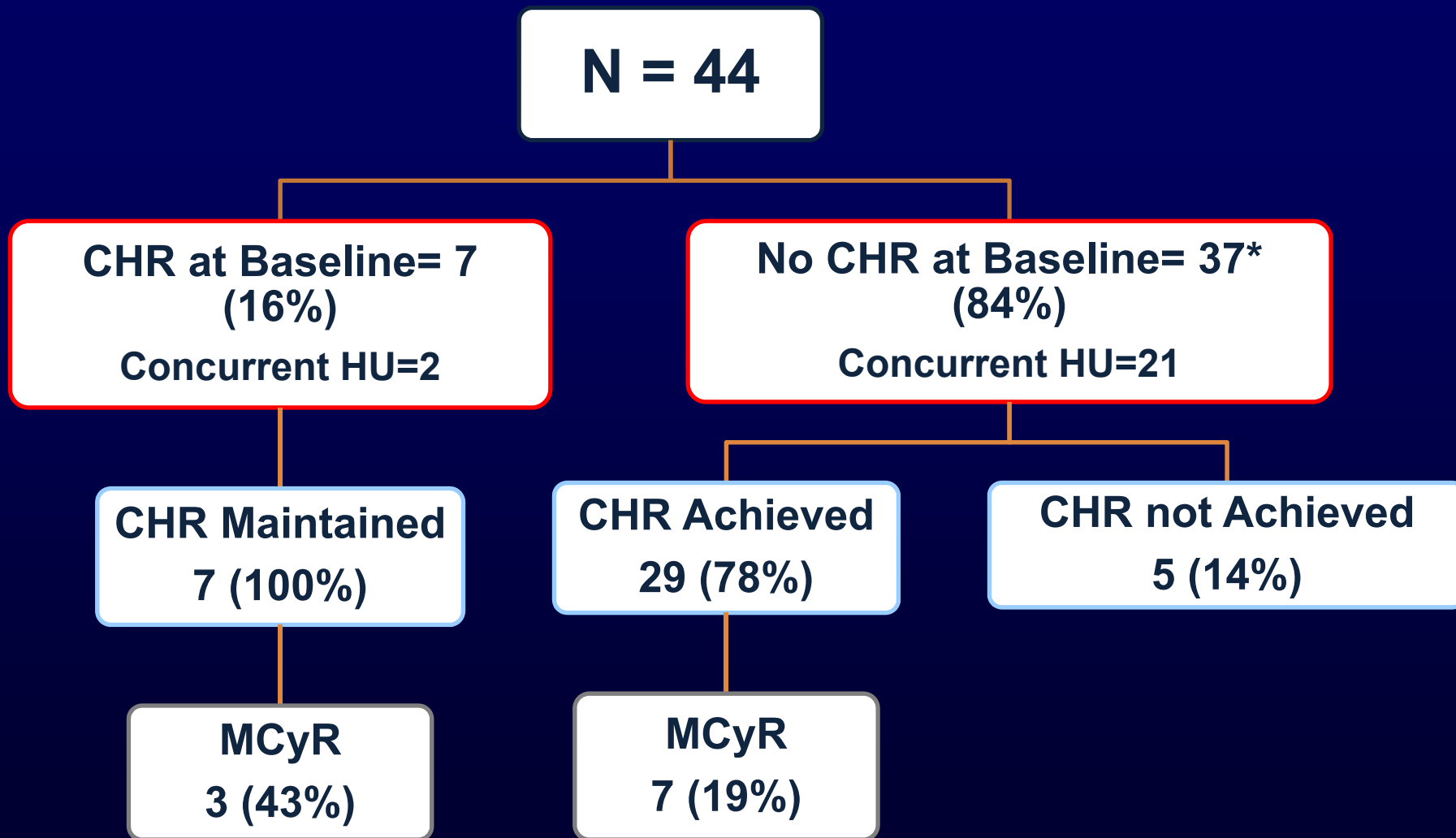
<b>Cycles received</b>	<b>4.0 [1-20]</b>	<b>2 [1-16]</b>	<b>2 [1-12]</b>
<b>Patients with dose delays</b>	<b>30 (68)</b>	<b>12 (48)</b>	<b>7 (35)</b>
<b>Duration of dose delays (days)</b>	<b>8 [1-79]</b>	<b>9 [3-68]</b>	<b>12 [2-51]</b>

# Omacetaxine after $\geq 2$ TKI Failure Response to Therapy

Response	No. (%)		
	CP N=44	AP N=25	BP N=20
<b>Hematologic</b>	<b>36 (82)</b>	20 (80)	10 (50)
CHR	36 (82)	13 (52)	7 (35)
HI	NA	3 (12)	1 (5)
RCP	NA	7 (28)	3 (15)
<b>Cytogenetic</b>	<b>12 (27)</b>	5 (20)	1 (5)
MCyR	10 (23)	1 (4)	-
CCyR	3 (7)	-	-
PCyR	7 (16)	1 (4)	-
<b>Minor/Minimal</b>	<b>2 (4)</b>	4 (16)	1 (5)

Data independently adjudicated by Data Monitoring Committee

# Omacetaxine after $\geq 2$ TKI Failure Baseline CHR and Response in CP



*HU - hydroxyurea*

\*One patient unevaluable

# Omacetaxine after $\geq 2$ TKI Failure Response to Therapy

Response	N(Percent)		
	Mutation	No Mutation	Unknown
<b>CP</b>	<b>N=14</b>	<b>N=18</b>	<b>N=12</b>
MCyR	2 (14)	6 (33)	2 (17)
CHR	12 (85)	15 (83)	9 (75)
<b>AP</b>	<b>N=7</b>	<b>N=10</b>	<b>N=8</b>
MCyR	0 (0)	1 (10)	0 (0)
CHR	4 (57)	6 (60)	3 (38)
RCP	2 (29)	1 (10)	4 (50)
<b>BP</b>	<b>N=6</b>	<b>N=6</b>	<b>N=8</b>
CHR	2 (33)	2 (33)	3 (38)
RCP	2 (33)	1 (17)	0 (0)

Data independently adjudicated by Data Monitoring Committee

# Omacetaxine after $\geq 2$ TKI Failure

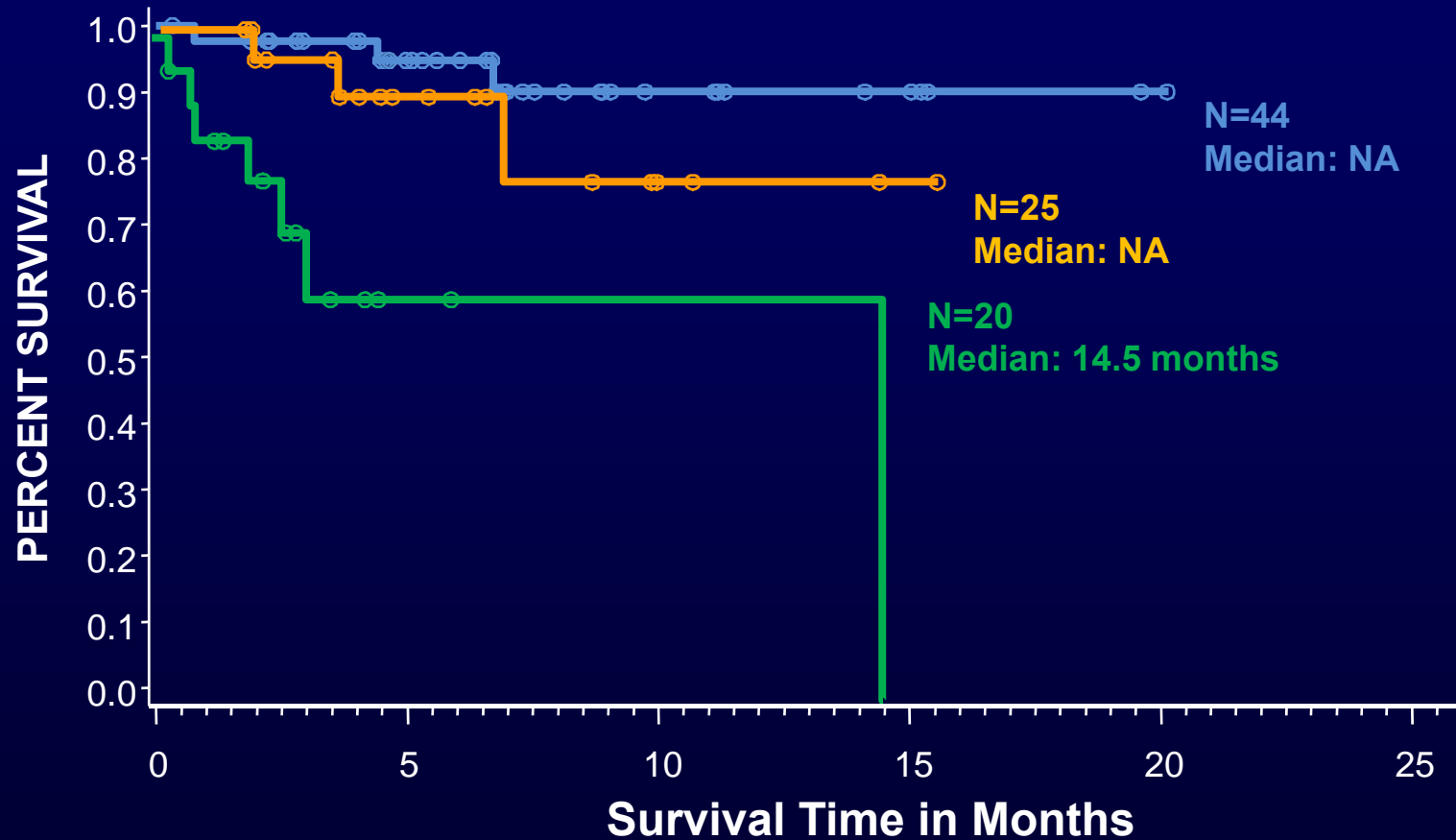
## Duration of Response

Median Duration in Months

Response	CP	AP	BP
	N=44	N=25	N=20
Hematologic	4.8	3.1	2.5
Range	1.15-19.38	0.72-10.53	0.66-10.95
MCyR	2.31	0	-
Range	0.03-9.34	-	-

# Omacetaxine after $\geq 2$ TKI Failure

## Overall Survival



— Chronic Phase    — Accelerated Phase    — Blast Phase

# Omacetaxine after $\geq 2$ TKI Failure Grade 3-4 Non-Hematologic AE\*

Adverse Event	Percentage							
	CP N=44		AP N=25		BP N=20		Total N=89	
	Any	G $\geq 3$	Any	G $\geq 3$	Any	G $\geq 3$	Any	G $\geq 3$
Diarrhea	34	0	44	16	40	5	38	6
Fatigue	23	2	28	16	20	5	24	7
Pyrexia	21	0	44	4	30	5	29	2
Headache	11	0	24	4	20	5	17	2
Nausea	27	0	24	4	25	0	26	1
Asthenia	18	2	20	4	15	0	18	2
Epistaxis	18	0	8	0	20	0	16	0

\*Present in at least 15% of patients, regardless of relationship to omacetaxine treatment

# Omacetaxine after $\geq 2$ TKI Failure Grade 3-4 Hematologic Adverse Events\*

Adverse Event	Percentage			
	CP N=44	AP N=25	BP N=20	Total N=89
Thrombocytopenia	52	40	25	43
Neutropenia	50	8	15	30
Anemia	25	28	15	24
Febrile neutropenia	7	12	10	9

\*Regardless of causality

# Omacetaxine after $\geq 2$ TKI Failure

## Patient Disposition

Patient Disposition	Number (%)		
	CP N=44	AP N=25	BP N=20
Treatment ongoing	14 (32)	5 (20)	0
Treatment discontinued	30 (68)	20 (80)	20 (100)
Disease progression	10 (23)	7 (28)	8 (40)
Lack of response	4 (9)	5 (20)	2 (10)
Adverse event	3 (7)	3 (12)	2 (10)
Death on study	3 (7)	2 (8)	5 (25)
PI/patient request	6 (14)	1 (4)	3 (15)
Other	4 (9)	2 (8)	0 (0)

# Omacetaxine after $\geq 2$ TKI Failure

## Conclusions

- Subcutaneously administered omacetaxine is well tolerated
- Most common toxicity: myelosuppression
- Safe self-administration
- Durable hematologic & cytogenetic responses (82% CHR, 27% cytogenetic response in CP)
- Overall survival at 20 months is 90% in CP
- Omacetaxine may be an option for CML patients with multi-TKI resistance

# Omacetaxine after $\geq 2$ TKI Failure

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