Disclosures

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Interim Results of an International, Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Relapsed or Refractory Mantle Cell Lymphoma (MCL): Durable Efficacy and Tolerability With Longer Follow-up

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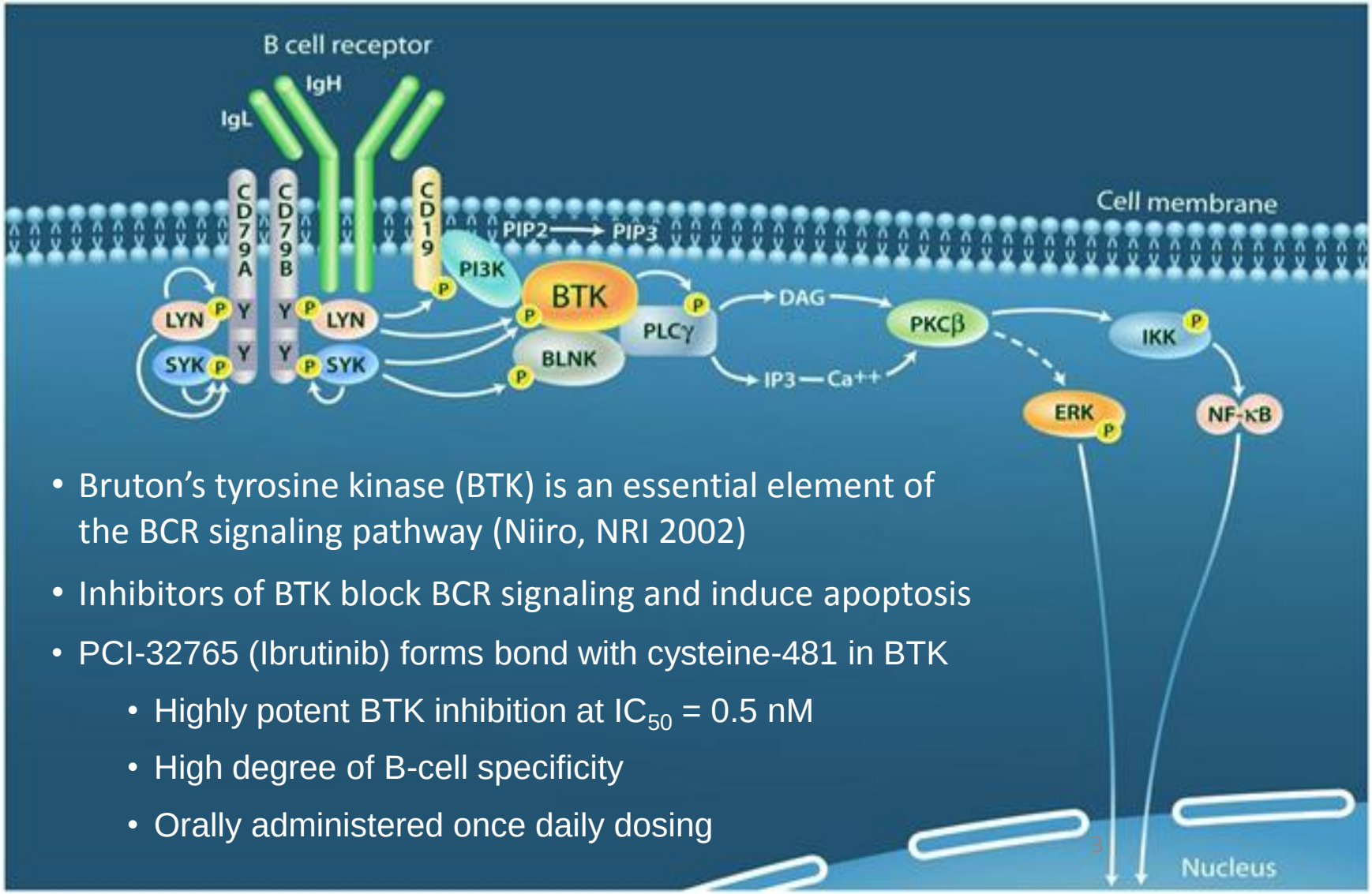
The safety and efficacy of the investigational use of this product has not been determined. There is no guarantee that the investigational uses listed will be filed with and/or approved for marketing by any regulatory agency.

Bruton's Tyrosine Kinase (BTK): A Critical Kinase for Lymphoma Cell Survival and Proliferation



- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway (Niiro, NRI 2002)
- Inhibitors of BTK block BCR signaling and induce apoptosis
- PCI-32765 (Ibrutinib) forms bond with cysteine-481 in BTK
  - Highly potent BTK inhibition at IC_{50} = 0.5 nM
  - High degree of B-cell specificity
  - Orally administered once daily dosing

Study Design: PCYC-1104-CA

- Ongoing International, multicenter, open-label, phase II single-agent study of ibrutinib in patients with relapsed or refractory MCL
- Treatment: 560 mg orally daily until progression (Cycle = 28 days)
- Objectives:
  - Overall response rate (ORR), duration of response (DOR), progression free survival (PFS), safety/tolerability
- Two cohorts enrolled in parallel:
  - Bortezomib-naïve (65 patients)
    - Totally-naïve: 58 patients (89.2%)
    - Minimally-treated: 7 patients (10.8%, less than 2 cycles)
  - Bortezomib-exposed (50 patients, at least 2 cycles)

Results

- Conducted at 18 sites (9 U.S. and 9 E.U.)
- Data cut on Sept 21, 2012
- Patient population (ITT) n = 115
  - Enrolled from Feb. 15, 2011 to Mar. 21, 2012
- Safety population (≥1 dose of ibrutinib) = 111 patients
- Efficacy population = 110 patients
  - Evaluable for response
  - At least one post-baseline tumor assessment
    - Bortezomib-naïve: n=63
    - Bortezomib-exposed: n=47

Patient Eligibility

- Confirmed MCL, with cyclin D1+, or t(11;14), and measurable disease
- Failure to achieve at least partial response (PR) to, or disease progression after, most recent treatment regimen
- At least 1, but not > 5 prior lines of therapy for MCL
- Adequate end-organ function
  - ANC ≥ 0.75 x 10^9/L*
  - Platelets ≥ 50 x 10^9/L*
  - ALT < 3.0 x ULN
  - Creatinine ≤ 2.0 x ULN
- ECOG Performance Status ≤ 2
- No clinically significant cardiovascular disease, malabsorption syndrome, or disease significantly affecting GI function

*unless bone marrow involvement

Patient Characteristics

	Bortezomib-Naïve (N=65)	Bortezomib-Exposed (N=50)	Total (N=115)
Median Age yrs (Range)	66 (46-83)	69 (40–84)	68 (40–84)
Gender: Male	48 (74%)	41 (82%)	89 (77%)
ECOG Status:			
0 - 1	55 (85%)	48 (96%)	103 (89%)
2	9 (14%)	2 (4%)	11 (10%)
>2	1 (1%)	0 (0%)	1 (1%)
Prior Regimens:			
Median (Range)	2 (1-6)	3 (1-5)	3 (1-6)
≥ 3 regimens	29 (45%)	32 (64%)	61 (53%)
Median Months Since Diagnosis (Range)	29 (3-214)	48 (7-224)	42 (3-224)

Disease History

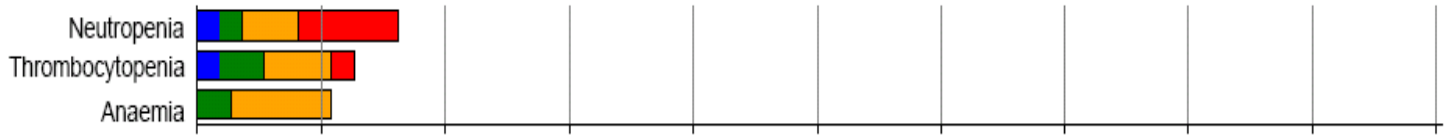
	Bortezomib-Naïve (N=65)	Bortezomib-Exposed (N=50)	Total (N=115)
Prior high intensity therapy			
Hyper CVAD	18 (28%)	15 (30%)	33 (29%)
Stem cell transplant	7 (11%)	4 (8%)	11 (10%)
Prior Lenalidomide	8 (12%)	19 (38%)	27 (23%)
MIPI Score			
Low risk	9 (14%)	6 (12%)	15 (13%)
Intermediate risk	23 (35%)	18 (36%)	41 (36%)
High risk	31 (48%)	26 (52%)	57 (49%)
Bulky Mass (≥10 cm)	6 (9%)	9 (18%)	15 (13%)
Refractory Disease*	27 (42%)	25 (50%)	52 (45%)

MIPI=MCL International Prognostic Index
* Refractory disease = failure to achieve at least PR to the last therapy prior to study entry

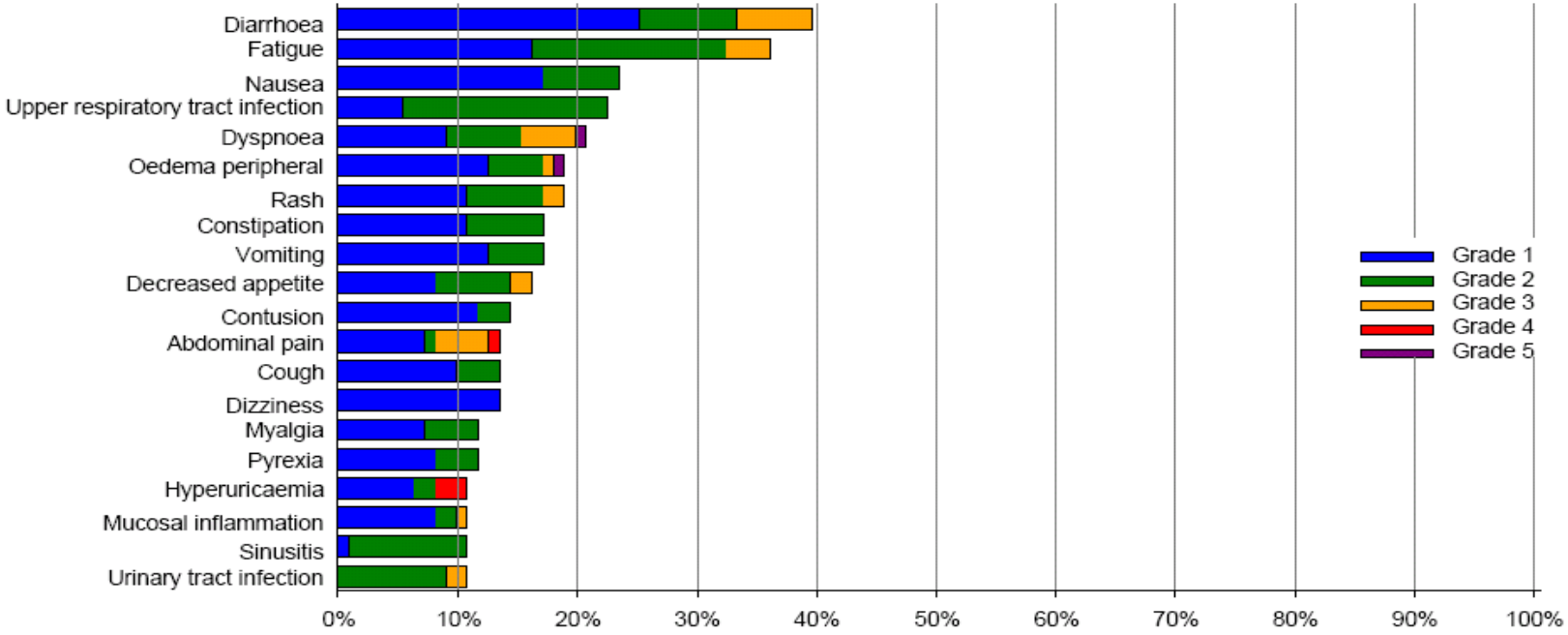
Treatment Emergent AEs in >10% of Patients Regardless of Relationship to Study Therapy

(1014 cycles administered to all pts)

Hematogenous AE:

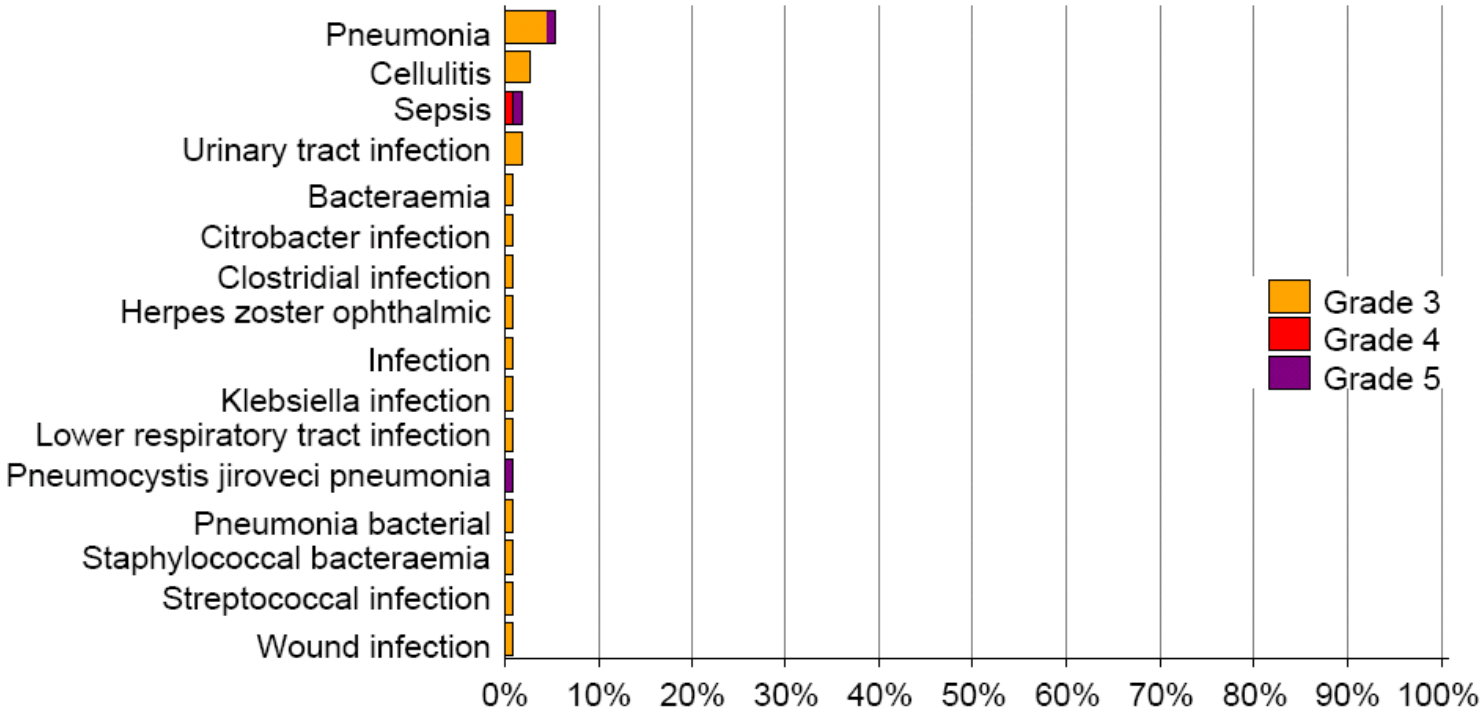


Non-Hematogenous AE:

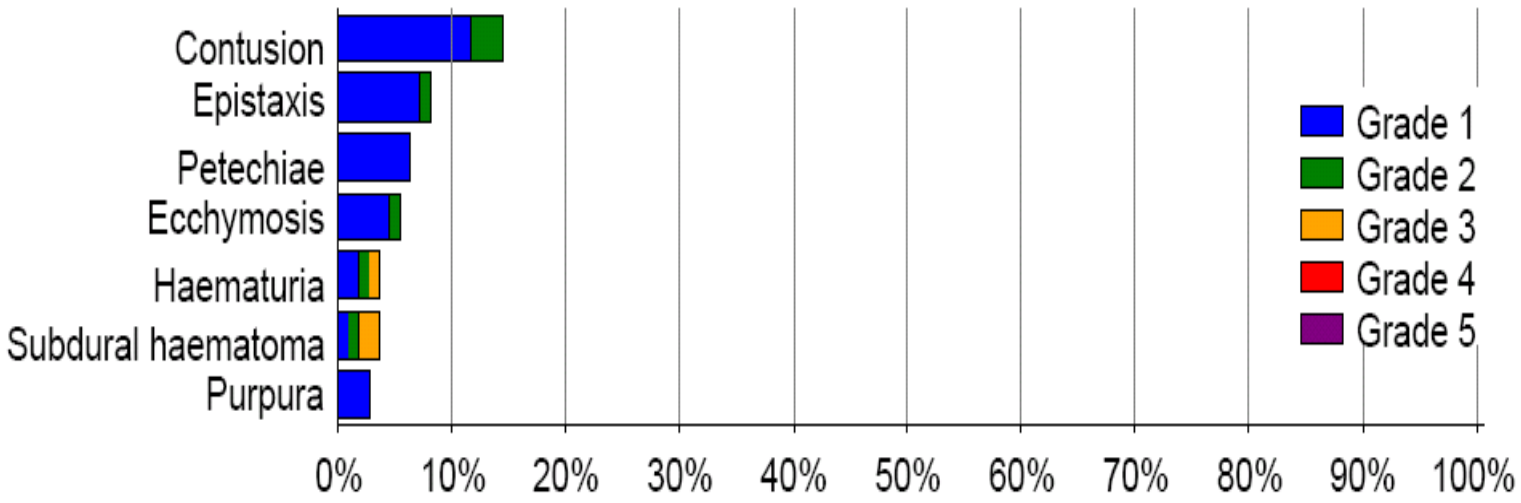


Treatment Emergent Infectious AEs ≥ Grade 3 Regardless of Relationship to Study Therapy

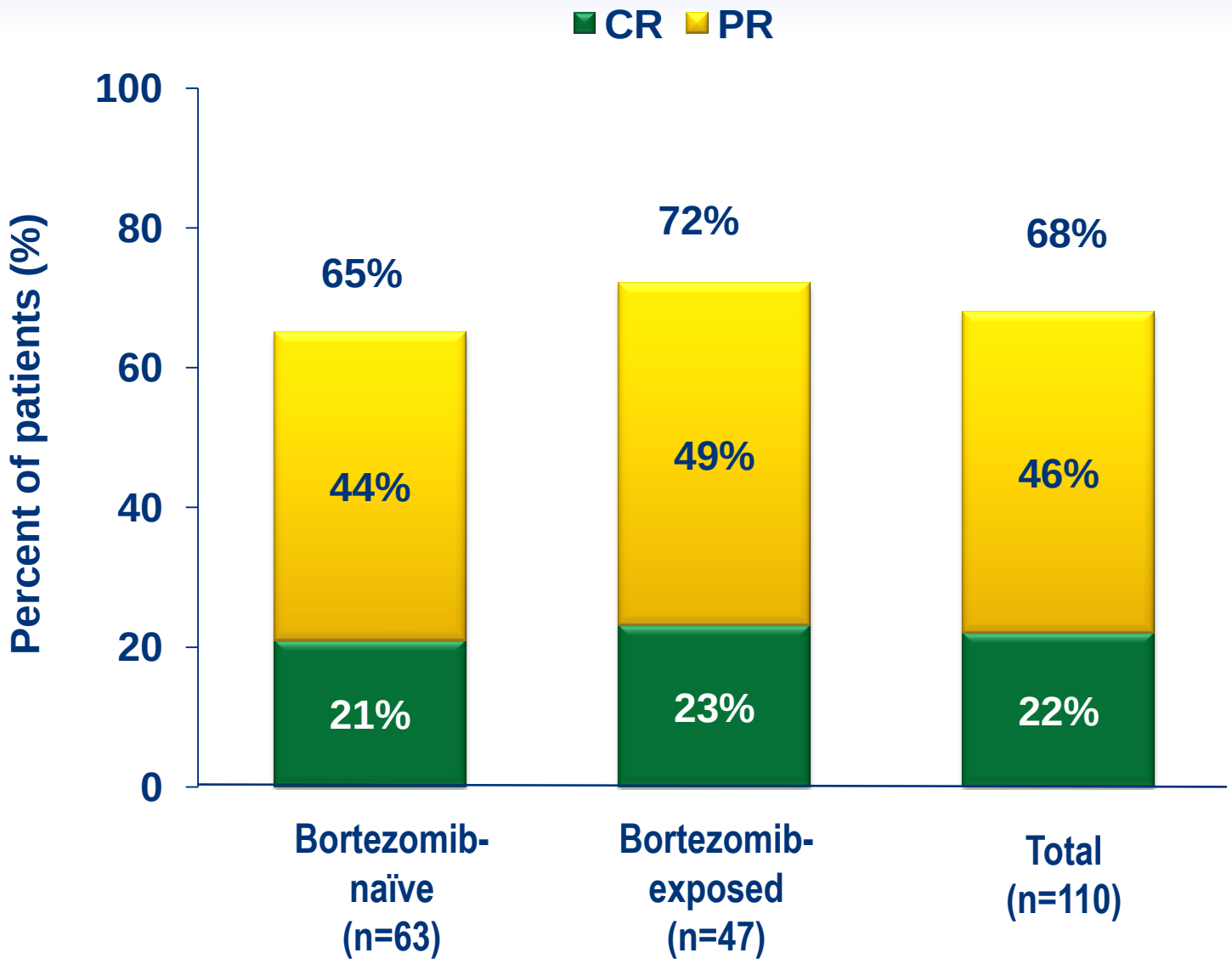
(1014 cycles administered to all pts)



Treatment Emergent Hemorrhagic AEs of All Grades in ≥2% of Patients Regardless of Relationship to Study Therapy (1014 cycles administered to all pts)



Best Response
(Efficacy Population n=110, Median Follow-up 9.2 mo)

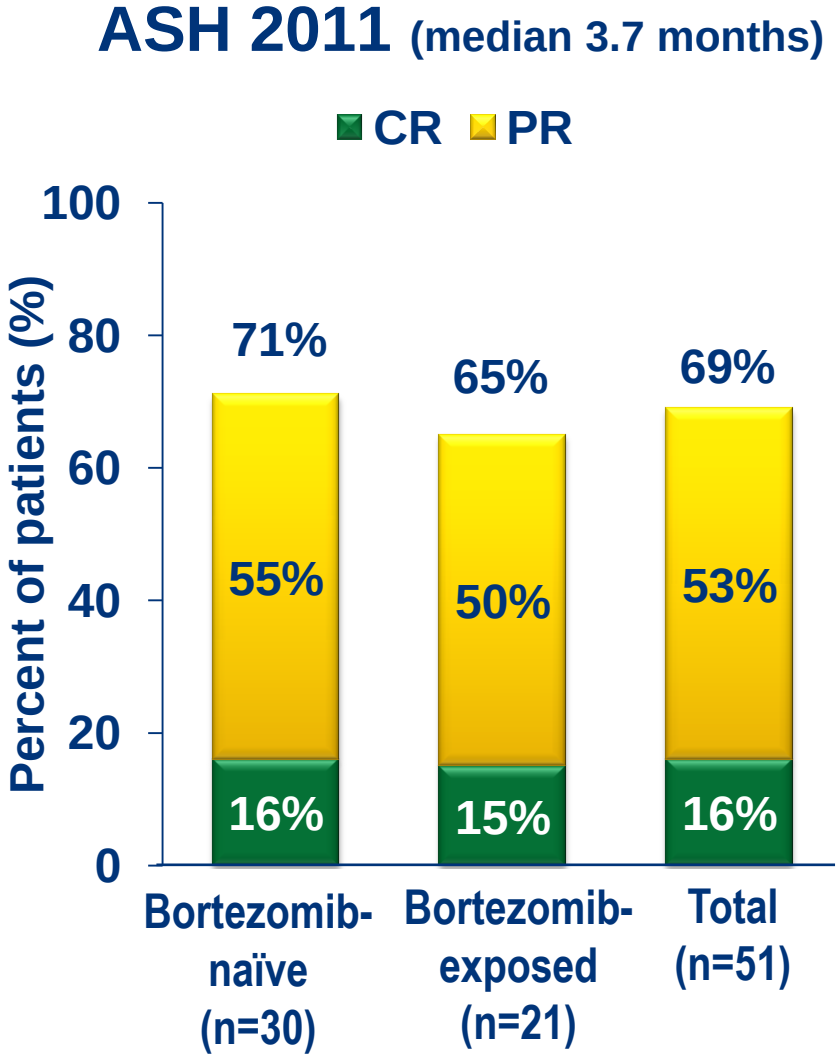


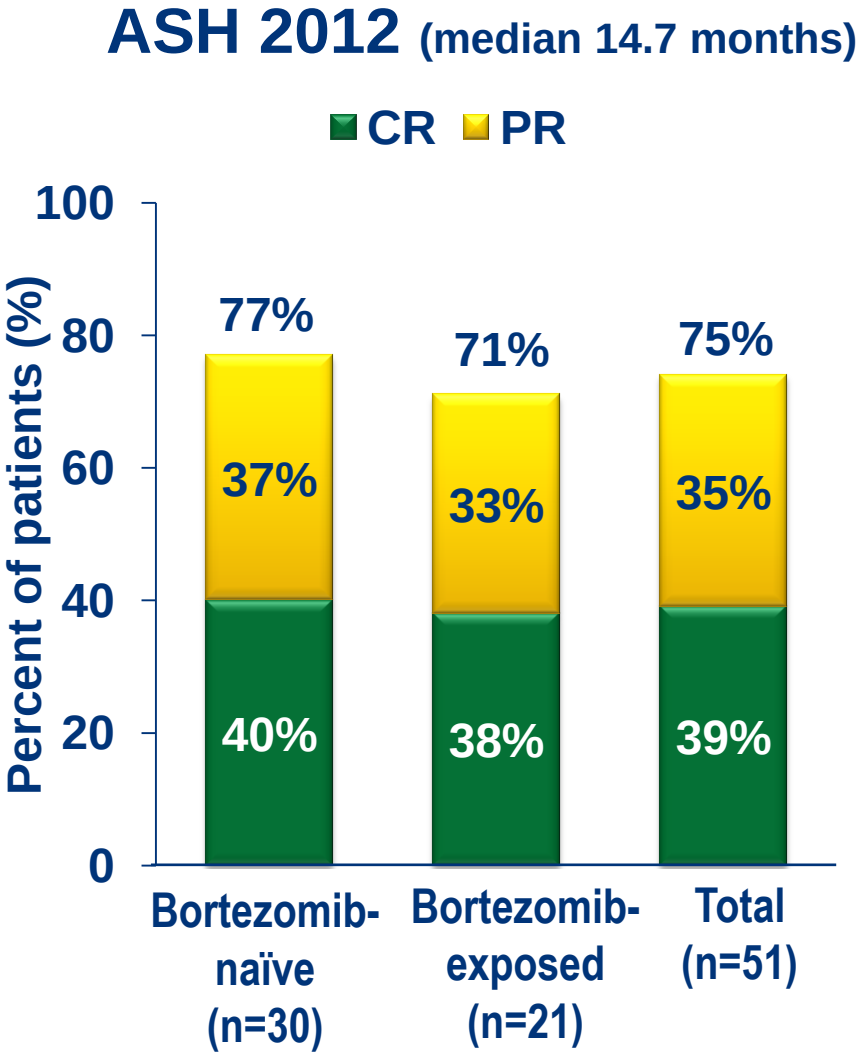
Best Response by Patient Characteristics

	n/N	ORR %
Bulky Disease (≥ 10 cm)	9/14	64%
Refractory		
Yes	32/49	65%
No	43/61	70%
Prior cancer treatments		
< 3 regimens	37/52	71%
≥ 3 regimens	38/58	66%
Prior high intensity therapy		
Yes	28/ 38	74%
No	47/ 72	65%
Prior Lenalidomide	19/25	76%
MIPI Score:		
Low Risk	11/15	73%
Intermediate Risk	25/40	63%
High Risk	39/53	74%

Best Response

(Longer Follow Up on Initial 51 Patients Presented at ASH 2011)





Time to Response: (Phenomenon of Incremental Response)

	Bortezomib – naïve (n=63)	Bortezomib-exposed (n=47)	Total (n=110)
Time to PR			
N	37	31	68
Median (months)	1.9	1.8	1.9
Range (months)	1.4-8.1	1.5-9.1	1.4-9.1
Time to CR			
N	13	11	24
Median (months)	5.6	3.9	5.5
Range (months)	1.7-16.4	1.7-11.0	1.7-16.4

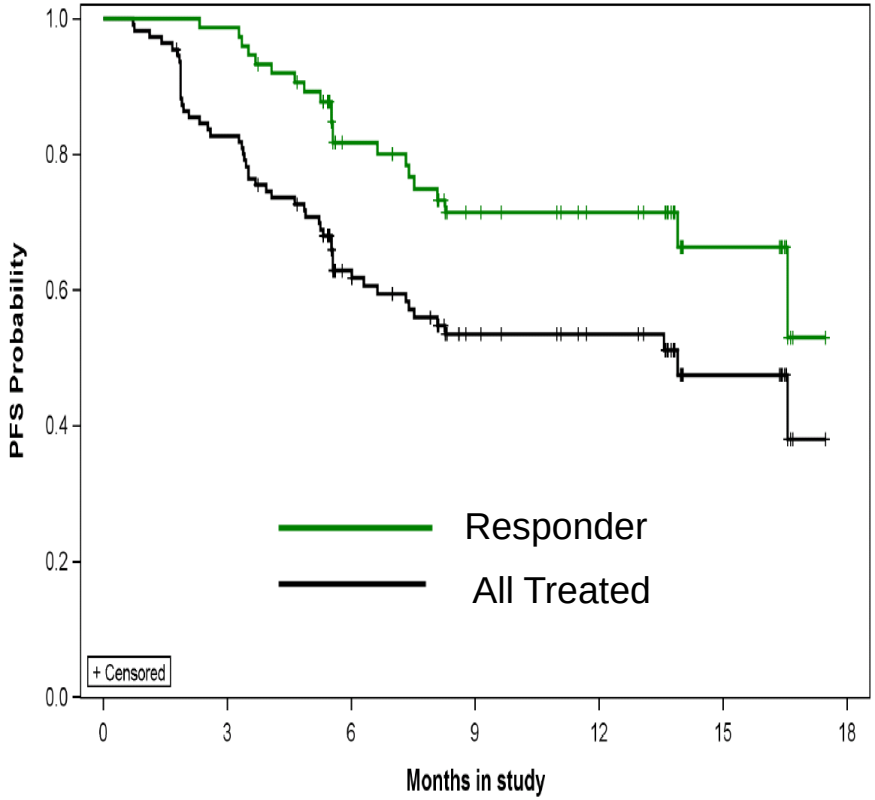
Phenomenon: Incremental Response
M.D. Anderson Sub-site Analysis

Accrue#	C3	C5	C7	C10	C13	C16	C19	Best Response
1	SD-PD							SD
2	SD	PD						SD
3	SD	SD	PD					SD
4	SD	CR	CR	CR	CR	CR	CR	CR
5	PR	PR	CR	CR	CR	CR	CR	CR
6	SD	SD	SD					SD
7	PR	PR	CR	CR	CR	CR	CR	CR
8	SD	SD	SD	PR	PR	PR	PD	PR
9	SD	SD	SD	PR	PR	PR	PR	PR
10	PR	PD						PR
11	PR	CR	CR	CR	CR		CR	CR
12	SD	PR	PR	PR	CR	CR	CR	CR
14	PR	CR	CR	CR	CR	CR		CR
15	PR	CR						CR
16	SD	PR	PR	CR	CR	CR		CR
17	PR	PR	PD					PR
18	PR	PR	PR	PR	PR	PR		PR
19	PD							PD
20	SD	SD	SD	SD	CR	CR		CR
21	SD	PR	CR					CR
22	SD	SD	SD	SD				SD
23	PR	PR	PR	PR	PR	PR		PR
24	PR	PR	PR	PR	CR	PR		CR
25	PR	PR	CR	CR	CR	CR		CR
26	CR	CR	PD					CR
27	PR	PR	PR	PR	CR	CR		CR
29	SD					PD		SD
30	PR	PR	PR	PR	PR			PR
31	PR	PR	PR	PR	CR			CR
32	PR	PR	CR					CR

Data cut on Sept 21, 2012

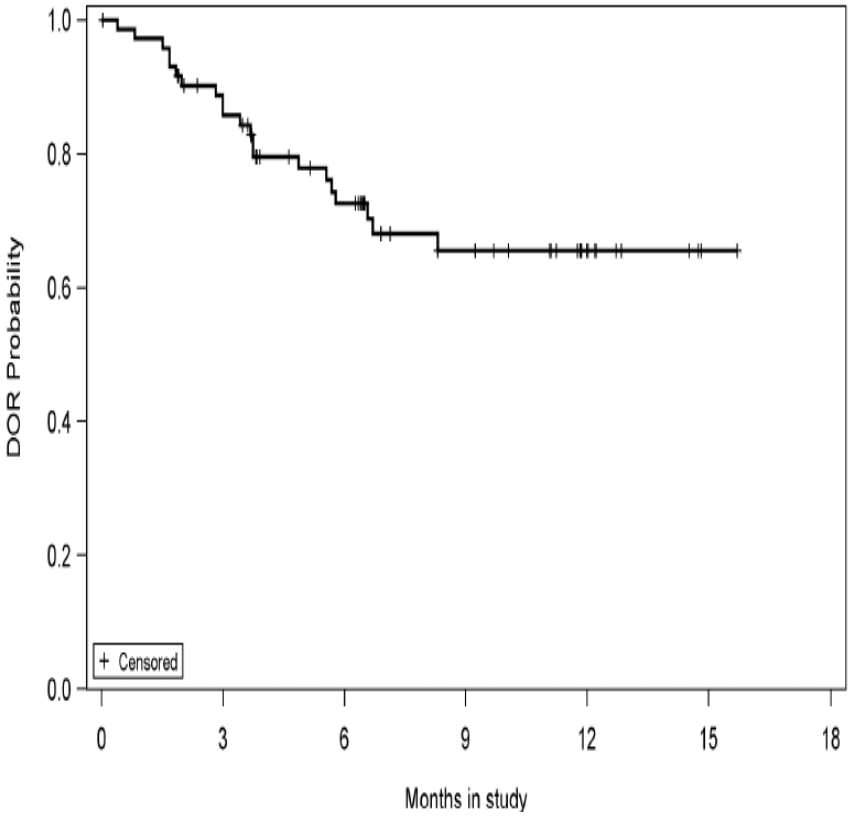
Kaplan-Meier Progression-Free Survival and Duration of response

PFS



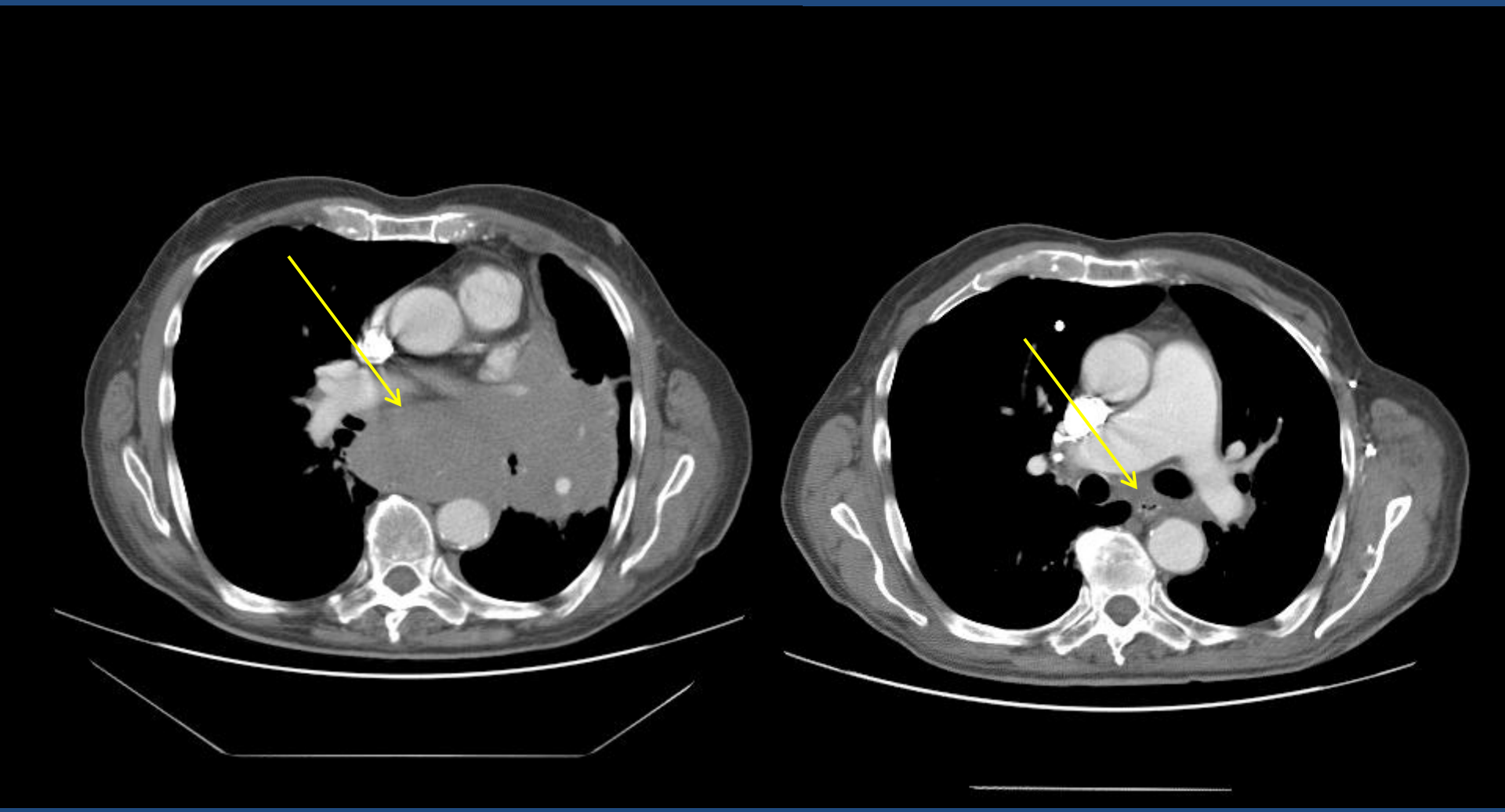
All Treated Population	**111**
Median PFS (CI 95%) months	**13.9 (6.64, NR)**

DOR



All Responded Population	**75**
Median DOR (CI 95%) months	**NR (NR, NR)**

Response after 2 Cycles of Ibrutinib



Patient #15: on 4/28/11 subcarinal LAD: 83 x 54 mm 7/15/11 subcarinal LAD: 21 x 13 mm

PCYC-1104-CA: Conclusions

- Ibrutinib demonstrated in this study:
  - unprecedented single agent overall response rate in relapsed or refractory MCL
  - high CR rate
- Responses have been durable.
  - median duration of response not reached
  - median PFS of 13.9 months
- Response improved with longer follow-up with phenomenon of "Incremental Response".
- Ibrutinib has a favorable safety profile and is well tolerated. The treatment-emergent AEs were consistent with safety data previously reported.
- Additional studies in MCL patients have been initiated in multiple clinical settings.

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