

Disclosures

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The Bruton's Tyrosine Kinase Inhibitor PCI-32765 is Highly Active As Single-Agent Therapy in Previously-Treated Mantle Cell Lymphoma (MCL): Preliminary Results of a Phase II Trial

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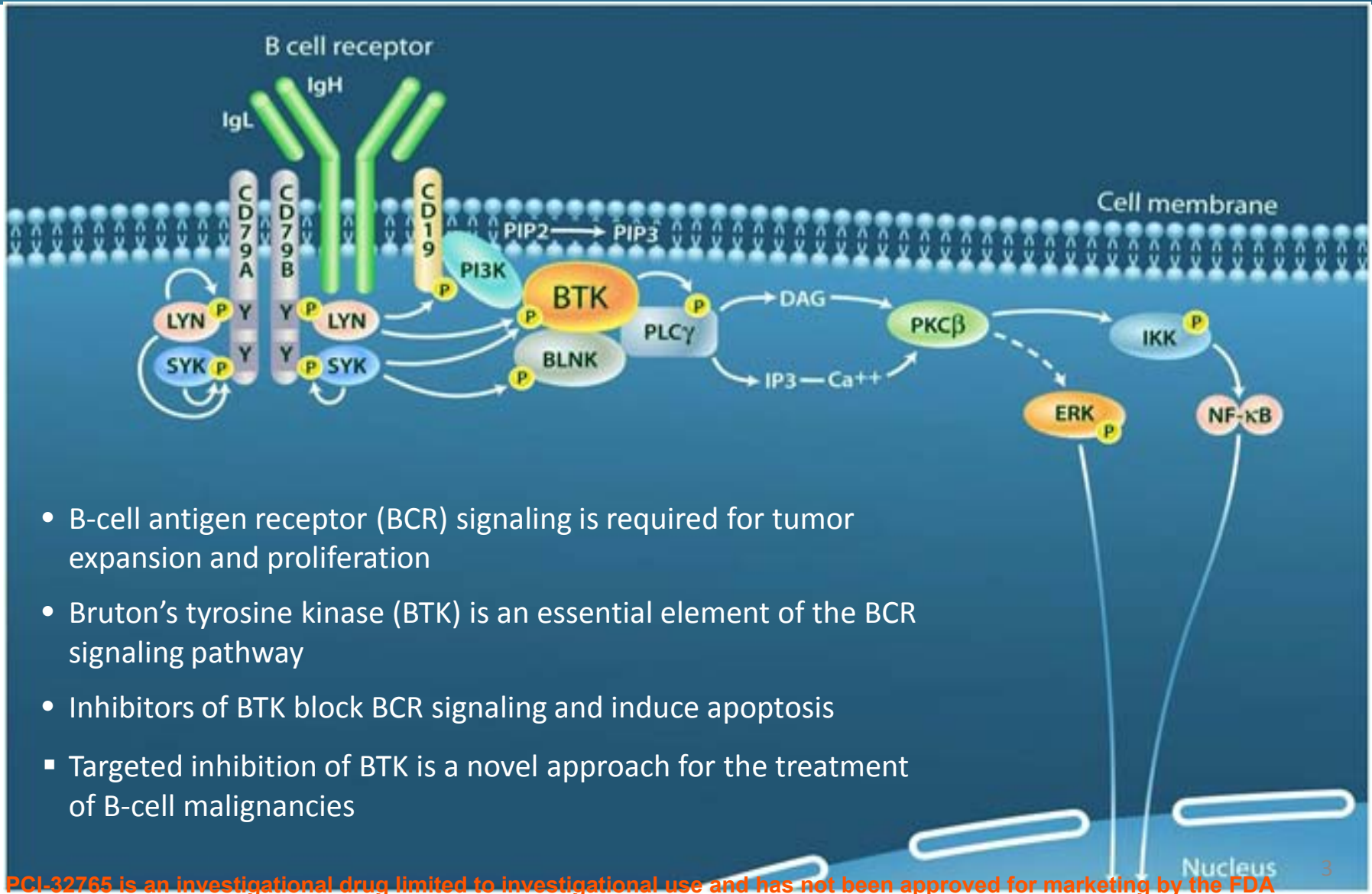
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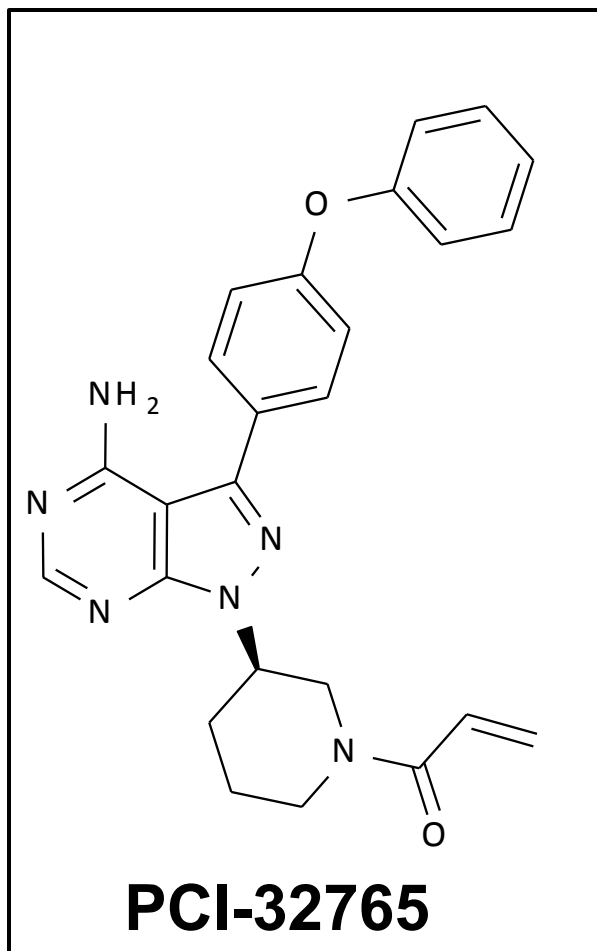
Bruton's Tyrosine Kinase (BTK)

A critical kinase for lymphoma cell survival and proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies

PCI-32765: First-in Class Inhibitor of BTK



- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at $IC_{50} = 0.5$ nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF- κ B pathways in mantle cell lymphoma lines.

Study Rationale

- In the Phase I, first-in-human, dose escalation study of PCI-32765
- 56 patients with recurrent B-cell malignancies enrolled (including 9 with MCL)
- Toxicity was modest and MTD not reached
- Pharmacodynamic studies revealed complete BTK active-site occupancy at doses of 2.5 mg/kg and above
- 7/9 MCL patients achieved a response to therapy including 3 complete responses (CR)
- 5 MCL patients remain on treatment with PCI-32765 (range 14-29 months)

Study Design: PCYC-1104-CA

- Multi-center, open-label, phase II single-agent study of PCI-32765 in two patient populations with relapsed or refractory Mantle Cell Lymphoma (MCL)
- Treatment: 560 mg PO daily until progression (cycle = 28 days)
- Objectives:
 - To determine the response rate, duration of response, PFS, PK/PD, safety/tolerability and patient reported quality of life
- Efficacy analyzed by 2 independent cohorts:
 - Bortezomib-exposed (27 patients, at least 2 cycles)
 - Bortezomib-naïve (41 patients)
 - Totally-naïve: 34 patients (83%)
 - Minimally-treated: 7 patients (17%)

Early Analysis of an Ongoing Trial

- Pharmacocyclics study database from investigators as of October 25, 2011
- Enrolled population: 68
- Safety population (>1 cycle): 61
- Efficacy (response rate) population patients had at least one post-baseline tumor assessment: 51
 - Bortezomib-naïve: n=31
 - Bortezomib-exposed: n=20

Subject Eligibility

- Pathologically confirmed MCL, with overexpression of cyclin D1 or t(11;14), and measurable disease on imaging
 - Failure to achieve at least partial response (PR) with, or documented disease progression after, most recent treatment regimen
 - At least 1, but no more than 5, prior treatment regimens for MCL
 - Adequate end-organ function
 - ANC $\geq 0.75 \times 10^9/L^*$ – Platelets $\geq 50 \times 10^9/L^*$
 - ALT $< 3.0 \times ULN$ – Creatinine $\leq 2.0 \times ULN$
- *unless bone marrow involvement*
- ECOG Performance Status ≤ 2
 - No clinically significant cardiovascular disease, malabsorption syndrome, or disease significantly affecting GI function

Patient Characteristics

	Bortezomib-Naïve (N=41)	Bortezomib-Exposed (N=27)	Total (N=68)
Age: Median:	66	69	67
Range:	47 – 83	54 – 83	47 – 83
Gender: Male	31 (76)	23 (85)	54 (79)
Time from Initial Diagnosis, # (%)			
< 3 yrs to 1 st dose	20 (49)	6 (22)	26 (38)
≥ 3 yrs to 1 st dose	21 (51)	21 (78)	42 (62)
ECOG Status: 0	24 (59)	13 (48)	37 (54)
1	12 (29)	12 (44)	24 (35)
2	5 (12)	2 (7)	7 (10)
Prior regimens, # (%)			
Median	2	3	2
Range	1 – 5	1 – 5	1 – 5
< 3 regimens	28 (68)	11 (41)	39 (57)
≥ 3 regimens	13 (32)	16 (59)	29 (43)

Patient Characteristics

	Bortezomib-Naïve (N=41)	Bortezomib-Exposed (N=27)	Total (N=68)
Prior high intensity therapy, # (%)			
HyperCVAD			
Stem cell transplant	17 (41)	11 (41)	28 (41)
Platinum-salvage therapy	5 (12)	2 (7)	7 (10)
	2 (5)	0 (0)	2 (3)
MIPI Score, # (%)			
Low risk	7 (17)	3 (11)	10 (15)
Intermediate risk	16 (39)	10 (37)	26 (38)
High risk	17 (41)	11 (41)	28 (41)
Bulky disease (mass ≥10 cm LD), # (%)	5 (12)	4 (15)	9 (13)
Stage IV Disease, # (%)	32 (78)	23 (85)	55 (81)
Refractory Disease*, # (%)	14 (34)	13 (48)	27 (40)

MIPI=MCL International Prognostic Index; LD=Longest Diameter

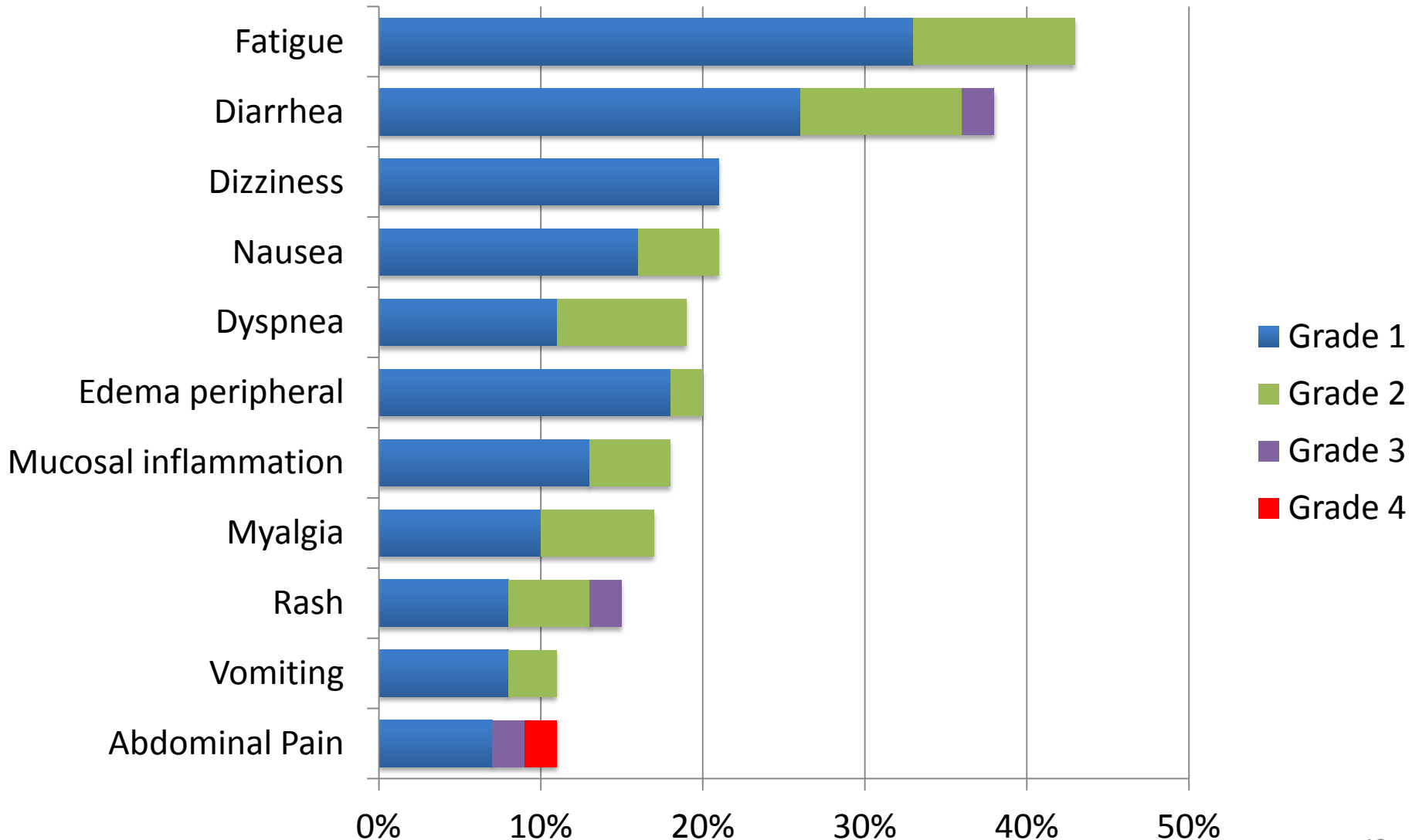
* Refractory disease = failure to achieve at least PR to the last therapy prior to study entry
 PCI-32765 is an investigational drug limited to investigational use and has not been approved for marketing by the FDA

Patient Disposition

	Bortezomib-Naïve (N=41)	Bortezomib-Exposed (N=27)	Total (N=68)
Time on Study (mos), #			
N	36	25	61
Median	3.7	3.7	3.7
Range	0.9 – 7.0	0.7 – 7.5	0.7 – 7.5
Patients Still on Study Treatment , # (%)	29 (71)	19 (70)	48 (71)
Patients Discontinued Treatment , # (%)	12 (29)	8 (30)	20 (29)
Primary Reasons for Discontinuation, # (%)			
Disease Progression	7 (17)	6 (22)	13 (19)
Adverse event	2 (5)	1 (4)	3 (4)
Sponsor decision	1 (2)	0 (0)	1 (1)
Investigator decision	2 (5)	1 (4)	3 (4)
Death on study¹, # (%)	0 (0)	1 (4)	1 (2)

Common Non-Hematologic AEs

(Events in > 10% of Patients Regardless of relationship to PCI-32765)



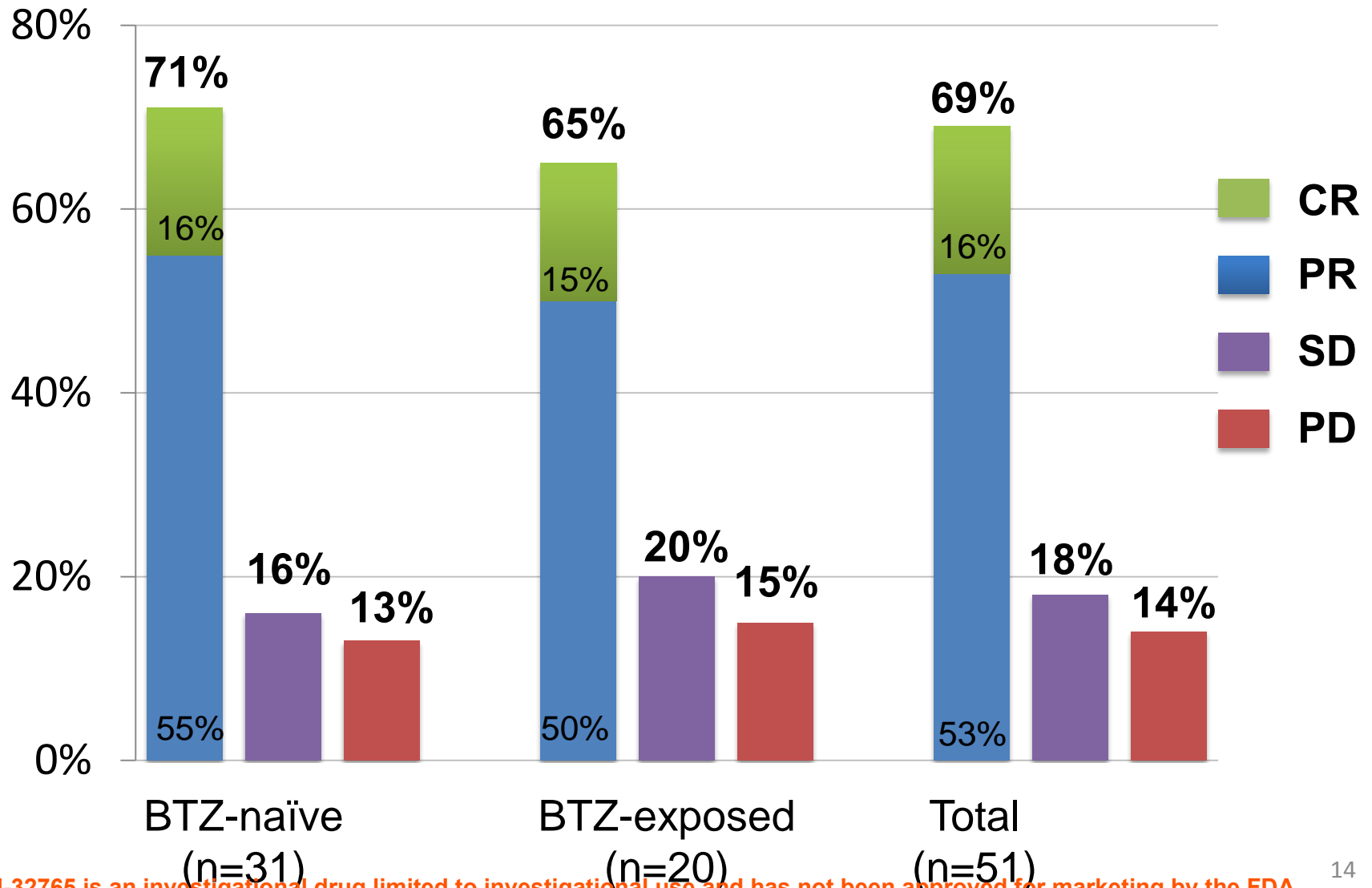
Grade 3/4 Hematologic Toxicity

(regardless of relationship to PCI-32765)

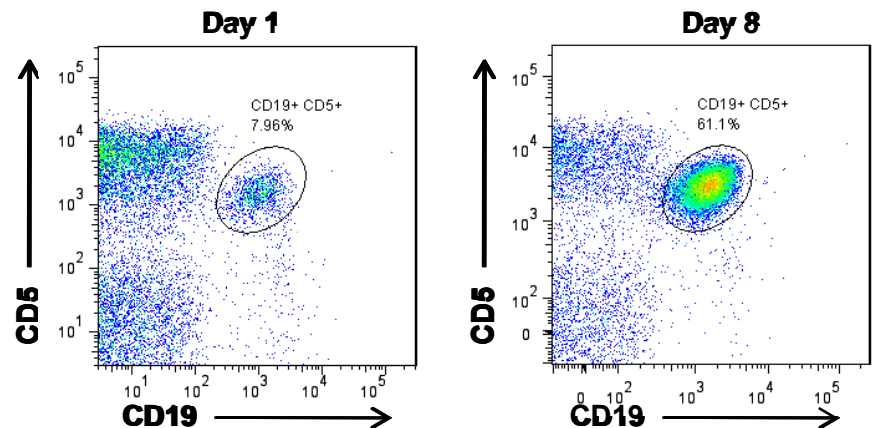
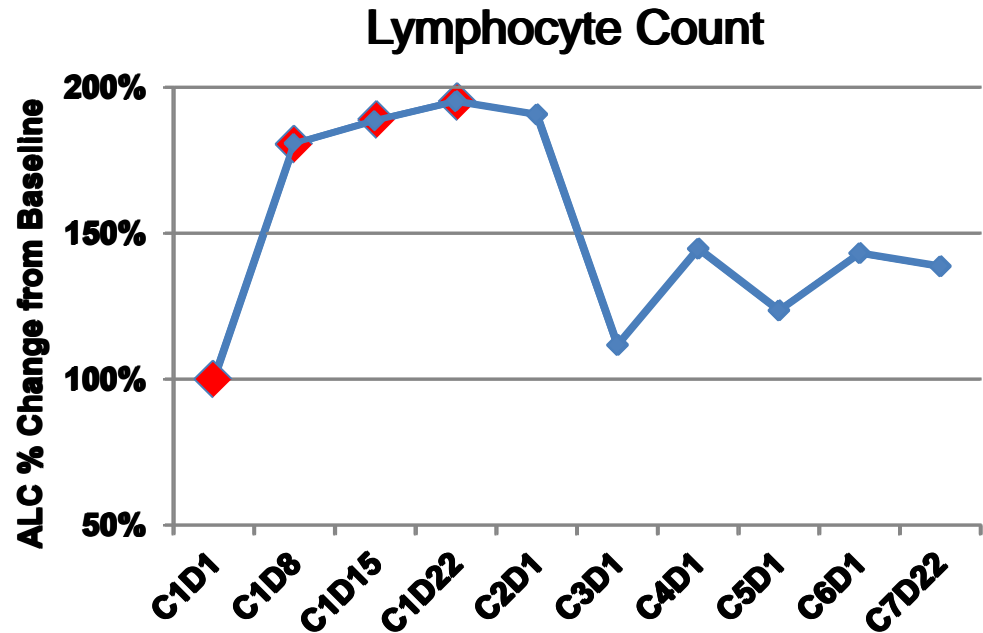
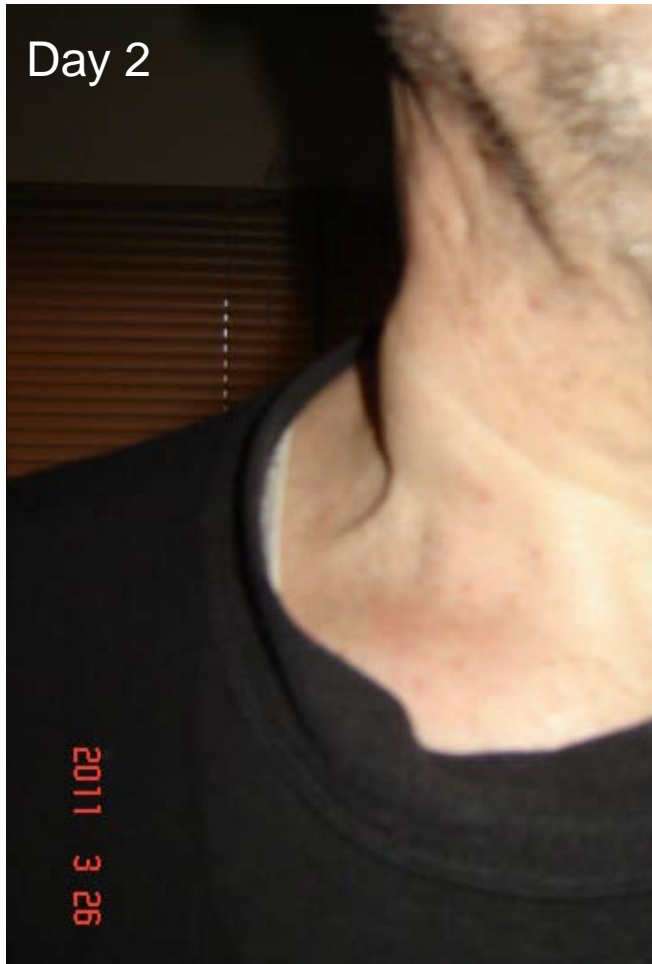
Grade 3/4 Hematology toxicity ¹	Total (n=61)	
	Grade 3	Grade 4
Neutropenia	2%	3%
Febrile neutropenia	3%	0%
Anemia	3%	0%
Thrombocytopenia	3%	0%
Pancytopenia	0%	2%

¹Reported as Adverse Events

Best Response



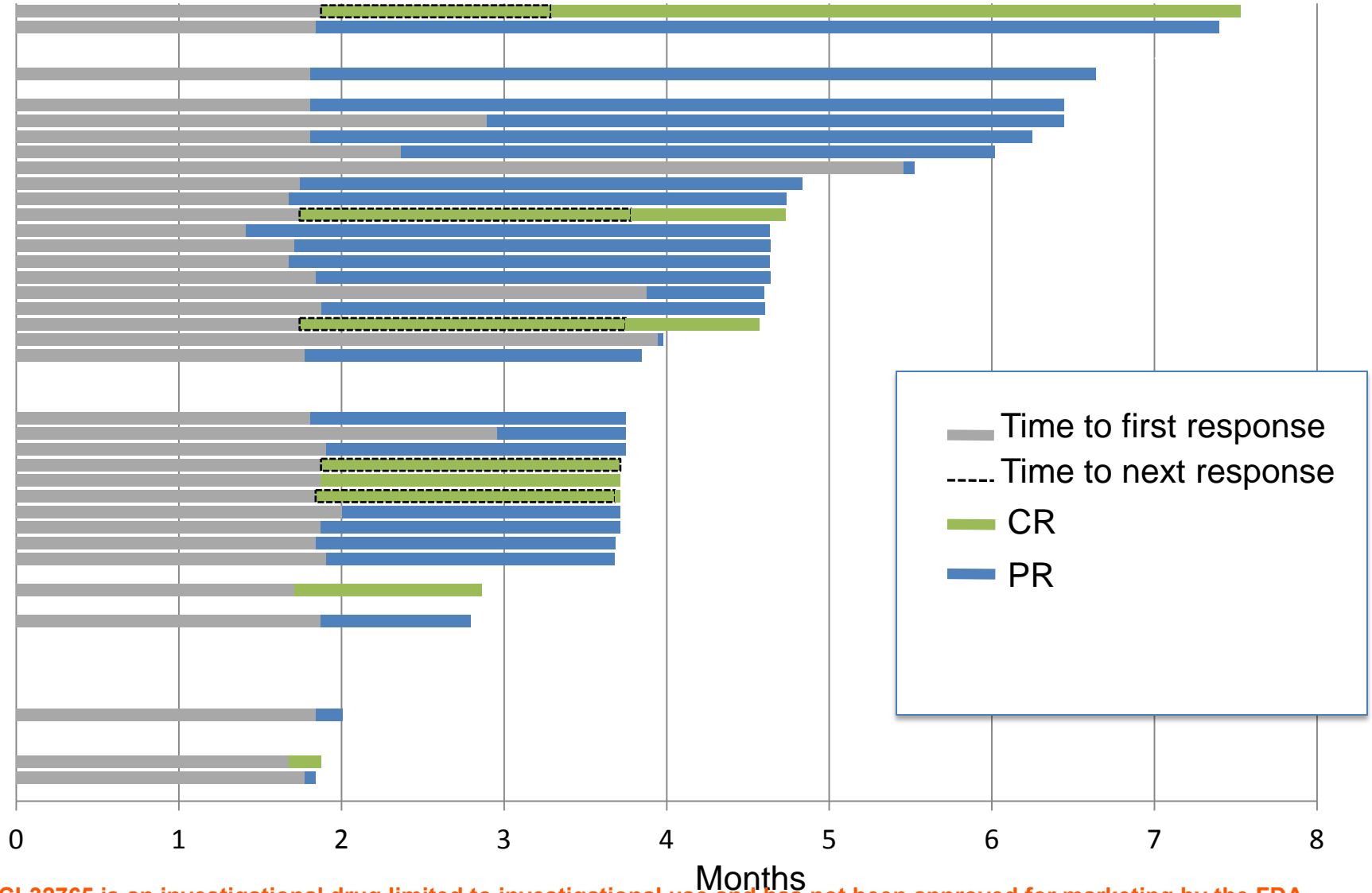
Rapid Nodal Response Accompanied by “Compartmental Shift” of CD19/CD5+ B-cells



Best Response by Patient Characteristics

	n/N	ORR %
All Patients	35/51	69
Bulky Disease	4/7	57
Refractory		
Yes	14/21	67
No	21/30	70
Prior cancer treatments		
< 3 regimens	23/30	77
≥ 3 regimens	12/21	57
Prior high intensity therapy		
Yes	22/31	71
No	13/20	65
MIPI Score: Low Risk	6/8	75
Intermediate Risk	13/20	65
High Risk	15/20	75

Time on Study and to Best Response



Conclusions

- PCI-32765, a selective irreversible inhibitor of BTK, induced a very high response rate as a single oral agent for relapsed or refractory MCL.
- PCI-32765 is associated with a favorable safety profile.
- There was no significant myelosuppression.
- This is an ongoing study and accurate determination of duration of response and PFS requires longer follow-up.
- More clinical trials are warranted to study PCI-32765 in MCL.

Acknowledgement

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Colleagues from Pharmacyclics.