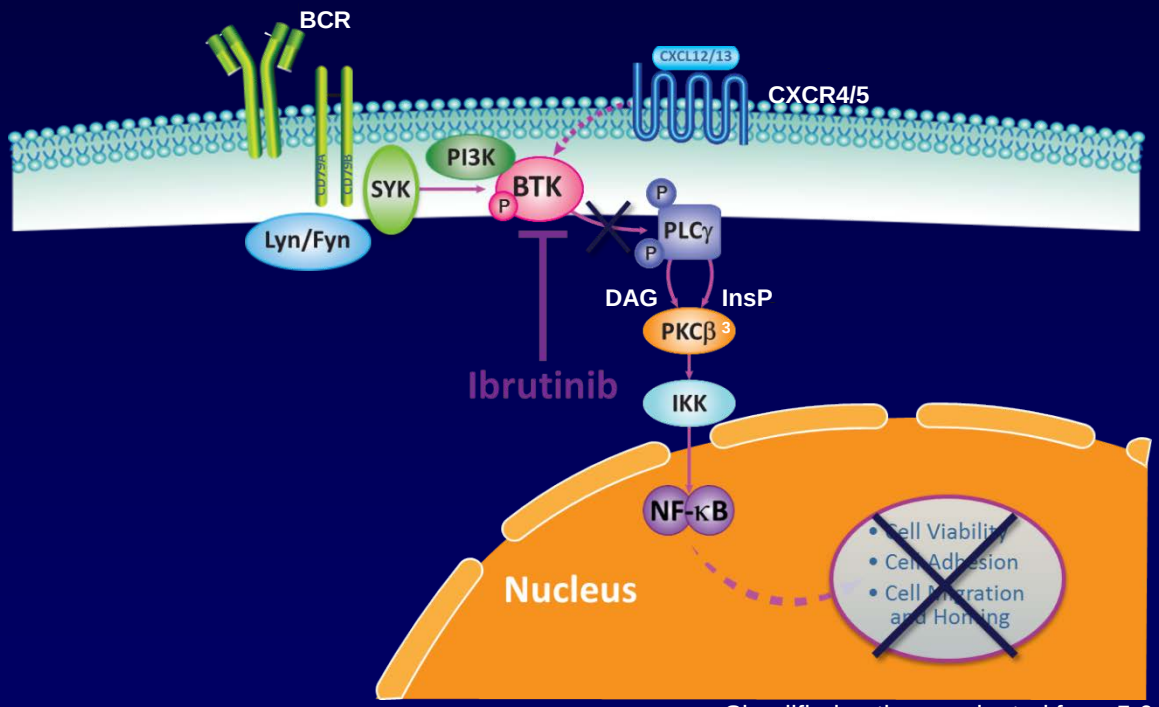
Ibrutinib, Single Agent or in Combination With Dexamethasone, in Patients With Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Preliminary Phase 2 Results

Abstract 31

Vij R, Huff CA, Bensinger WI, Siegel DS, Jagannath S, Berdeja JG, Lendvai N, Lebovic D, Anderson LD, Costello CL, Stockerl-Goldstein KE, Laubach JP, Elias L, Clow F, Fardis M, Graef T, Bilotti E, Richardson PG

Introduction

- MM remains an incurable disease in need of new therapies
- Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of BTK, an essential enzyme in B-cell receptor signaling[1,2]
- Ibrutinib has shown substantial clinical activity in CLL and MCL[2-4]
- In MM, ibrutinib may target both the MM cells and the microenvironment



Simplified pathway adapted from 5,6

1. Honigberg LA, et al. *Proc Natl Acad Sci U S A*. 2010:107(29):13075-13080; 2 .Byrd JC, et al. *N Engl J Med*. 2013;369(13):1278-1279; 3. Byrd JC, et al. *N Engl J Med.* 2014;371(3):213-223; 4. Wang ML, et al. *N Engl J Med.* 2013;369(6):507-516; 5. Buggy JJ, et al. *Int Rev Immunol*. 2012;31(2):119-132; 6. de Rooij MF, et al. *Blood*. 2012;119(11):2590-2594.

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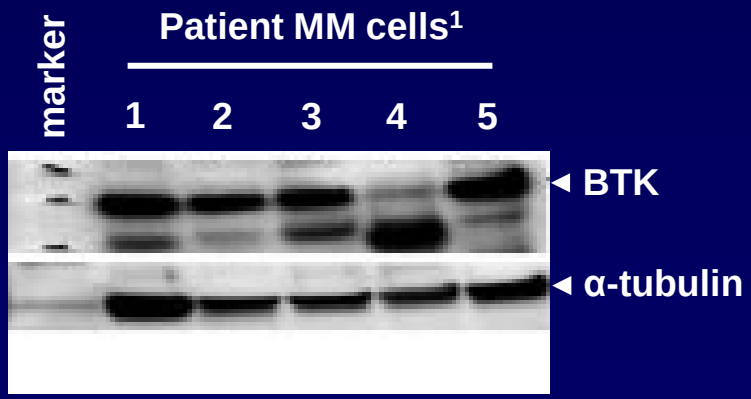
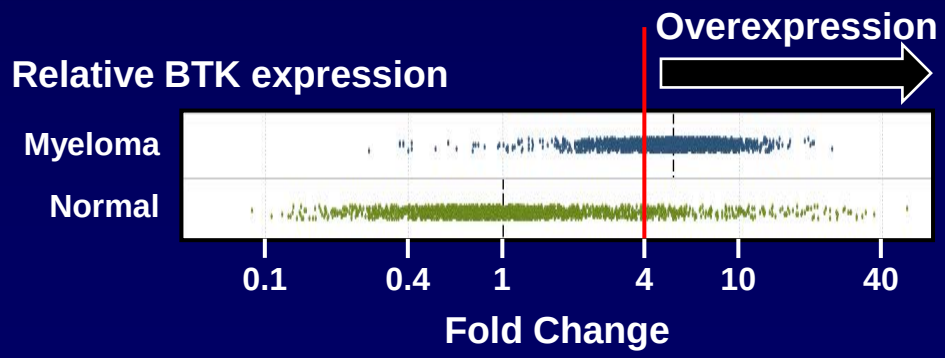
BTK Expression in MM Plasma Cells

- BTK is a nonreceptor tyrosine kinase that is expressed in many hematopoietic lineages and plays a critical role in B-cell maturation[1,2]
- Increased BTK expression in MM plasma cells compared with normal plasma cells is not expected
- However, recent studies showed robust BTK expression in the majority of MM plasma cells in patients with MM[1,2]





1. Tai YT, et al. *Blood*. 2012;120(9):1877-1887. 2. Bam R, et al. *Am J Hematol*. 2013; 88(6):463-471.

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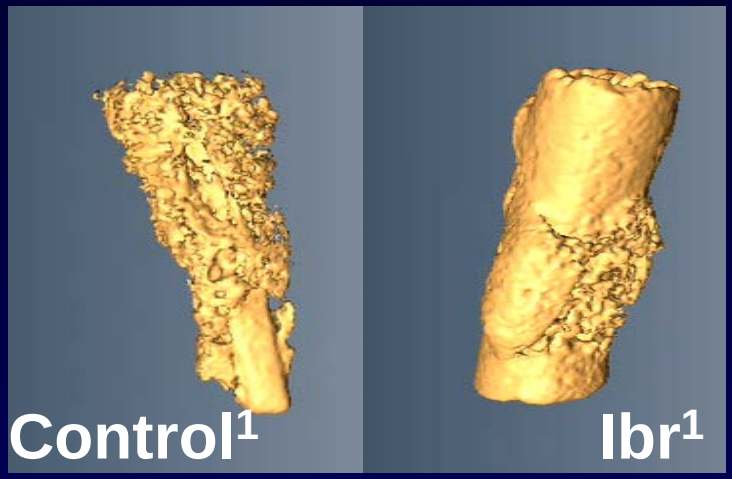
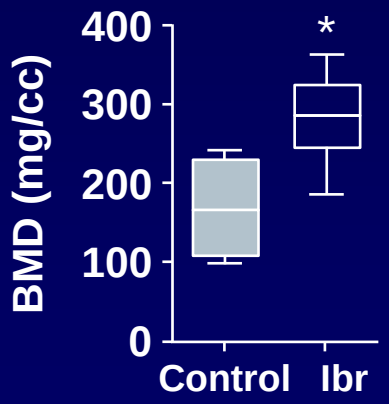
Impact of BTK Inhibition on Bone

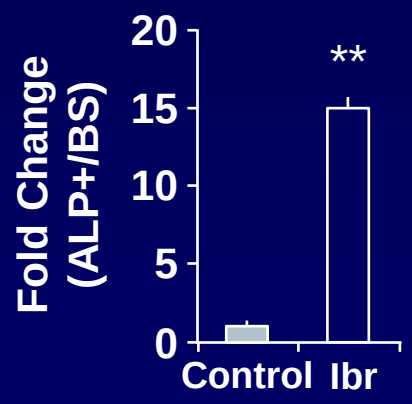
- **BTK is expressed on osteoclasts (OC) but not osteoblasts (OB)[1]**
- **BTK activation mediates osteoclastogenesis induced by M-CSF and RANKL[1,2]**
- **Ibrutinib inhibited osteolytic activity by OC in vitro and decreased OC cytokine secretion[1]**
- **Ibrutinib suppressed bone resorption activity by OC in SCID-hu animals implanted with MM cells[1]**



Bone Mineral Density[1]



Increase of OB[1]



***P* < .04; ****P* < .01**

1. Tai YT, et al. *Blood*. 2012;120(9):1877-1887. 2. Bam R, et al. *Am J Hematol*. 2013; 88(6):463-471.

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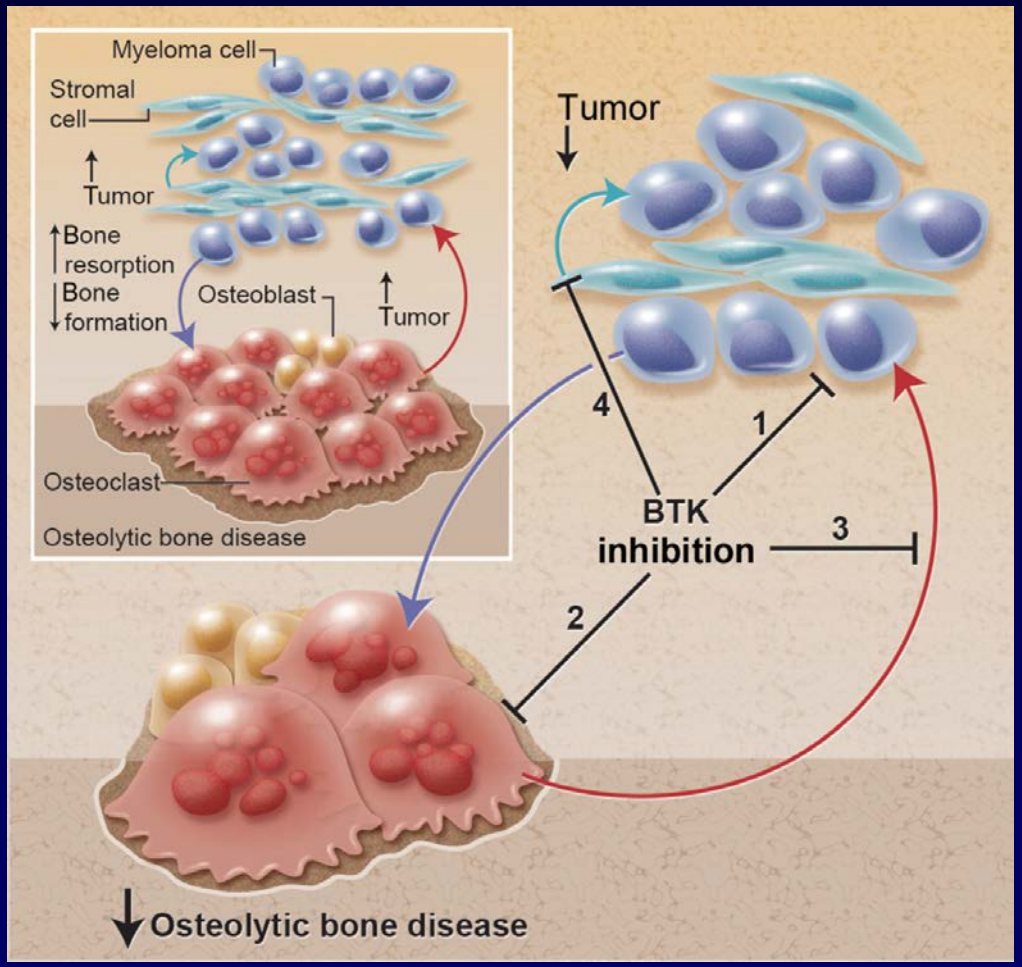
Effect of BTK Inhibition in the MM Microenvironment



Edwards CM, et al. *Blood.* 2012;120(9):1757-1759.

1. **Inhibits tumor growth**
   - **Reduced downstream NF-κB and STAT3**
   - **ERK1/2 and AKT signaling**
2. **Directly inhibits osteoclastic bone resorption and OC formation**
3. **Inhibits the release of osteoclast-derived tumor growth factors**
4. **Prevents adhesion to bone marrow stromal cells (BMSCs) and release of BMSC-derived growth factors**
   - **Reduced IL-6, SDF-1, BAFF, IL-8, M-CSF, and MIP-1**

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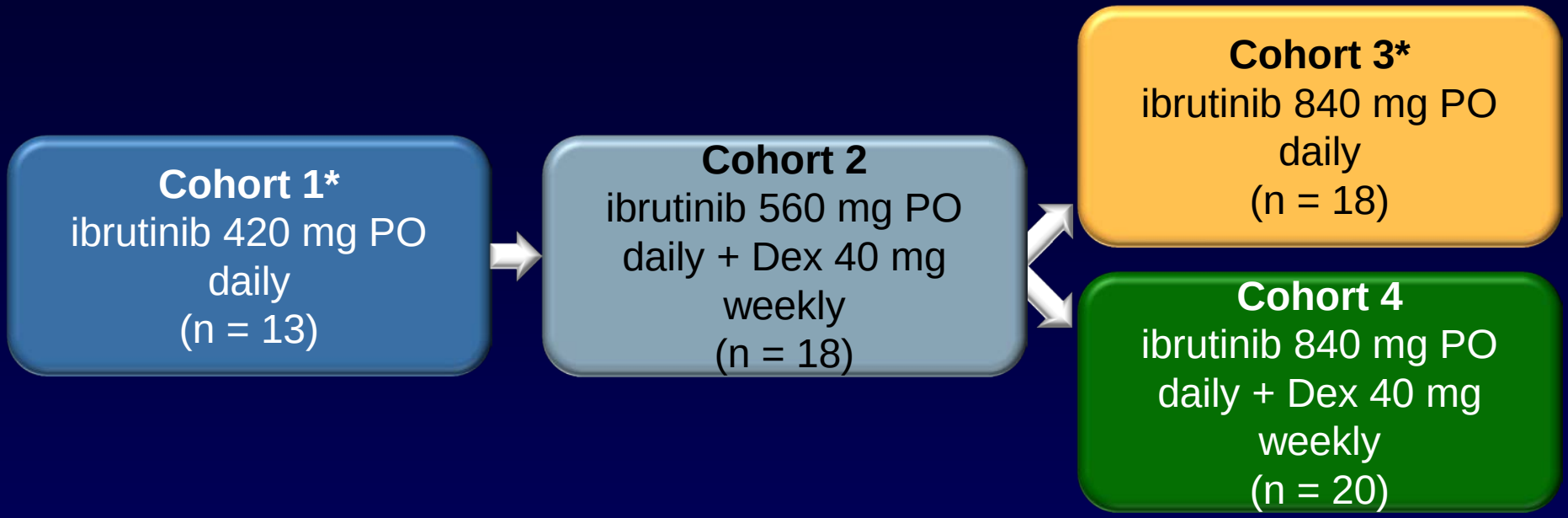
PCYC-1111 Study Design



*For cohorts 1 and 3, addition of Dex 40 mg weekly permitted at disease progression per investigator discretion.

- **Phase II, open-label, nonrandomized, multicohort, multicenter study**
- **Primary objective: clinical benefit rate defined as ≥MR by IMWG criteria[1]**
- **Secondary objectives: duration of clinical benefit, ORR (≥PR), duration of objective response, safety, and pharmacokinetics**

1. Rajkumar SV, et al. *Blood.* 2011;117:4691-4695.

Vij R, et al. *Blood.* 2014;124: Abstract 31.

Key Eligibility Criteria

Inclusion Criteria

- Measurable symptomatic MM
  - SPEP ≥0.5 g/dL
  - UPEP ≥200 mg/24 hours
  - sFLC: involved FLC level ≥10 mg/dL (≥100 mg/L)
- Rel or Rel/Ref MM after receiving ≥2 lines of therapy, including an immunomodulatory agent
  - Refractory defined as nonresponsive (failure to achieve MR) while on treatment or PD within 60 days of last treatment
- ECOG PS ≤1

Exclusion Criteria

- Inadequate BM function
  - ANC <750 cells/μL
  - Platelets <50,000 cells/μL
- Creatinine >2.5 mg/dL
- Currently active, clinically significant cardiovascular disease (ie, uncontrolled arrhythmias, recent MI, NYHA class 3 or 4)
- Peripheral neuropathy grade ≥2
- Requires warfarin or other vitamin K antagonist (eg, phenprocoumon) or strong CYP3A4/5 inhibitors

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Patient Characteristics

Characteristic	Cohort 1 (n = 13)	Cohort 2 (n = 18)	Cohort 3 (n = 18)	Cohort 4 (n = 20)
Median age, y (range)	62 (49-74)	66 (46-77)	66 (54-81)	65 (43-78)
Male, %	62	50	72	55
ECOG PS 0/1, %	54/46	33/67	44/56	35/65
Median time since Dx, y	3.9	5.0	6.0	6.0
Measurable disease, %				
SPEP/UPEP	85	78	89	85
sFLC	15	22	11	15
Disease status to last Tx, %				
Relapsed	31	17	11	20
Relapsed and refractory*	69	83	89	80

*Refractory defined as either no response or progression on or within 60 days of the completion of therapy.

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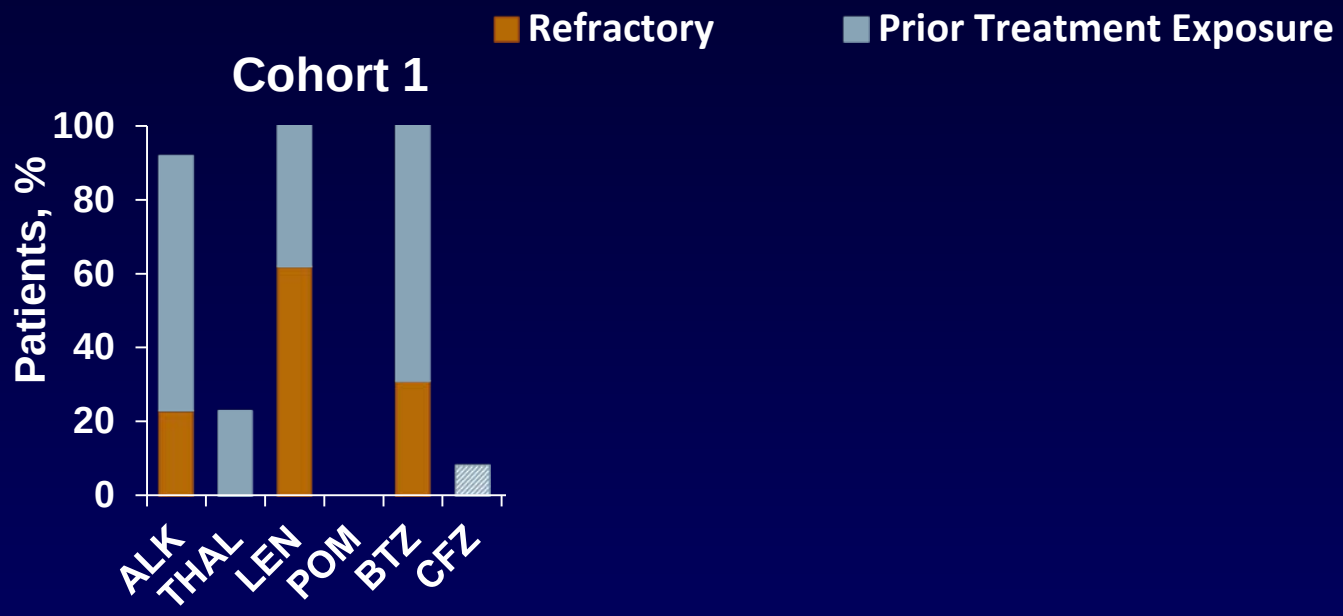
Prior Treatment Exposure



Median prior Tx (range)	4 (2-10)
SCT, %	92

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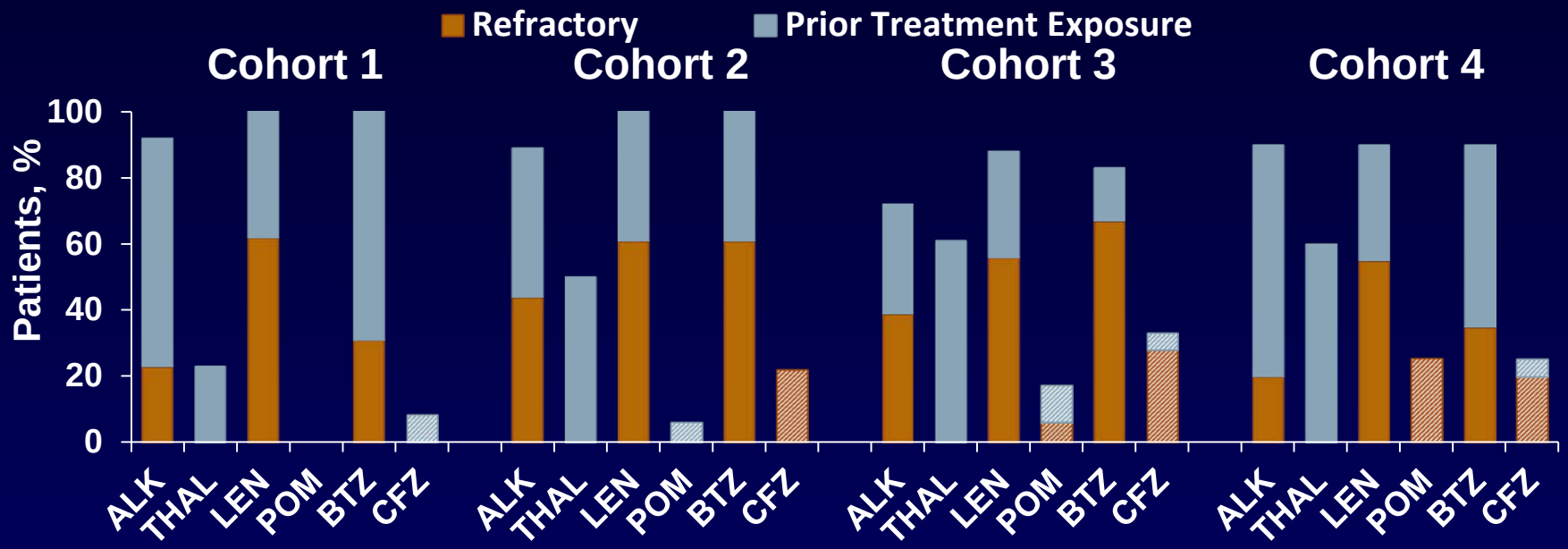
Prior Treatment Exposure



	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Median prior Tx (range)	4 (2-10)	4.5 (2-11)	3 (2-14)	4.5 (2-7)
SCT, %	92	78	78	90

- **74% of patients received steroids in most recent therapy (all previously exposed)**
- **Of 43 patients refractory to most recent Tx, 32 had steroids included in the regimen**

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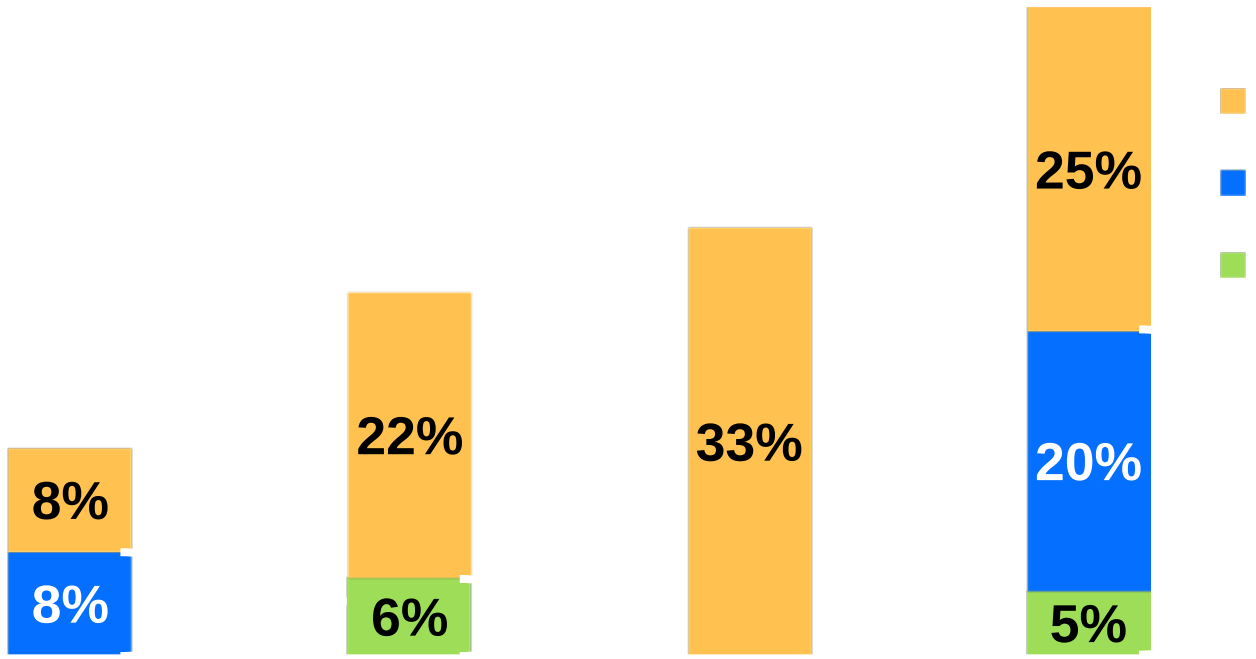
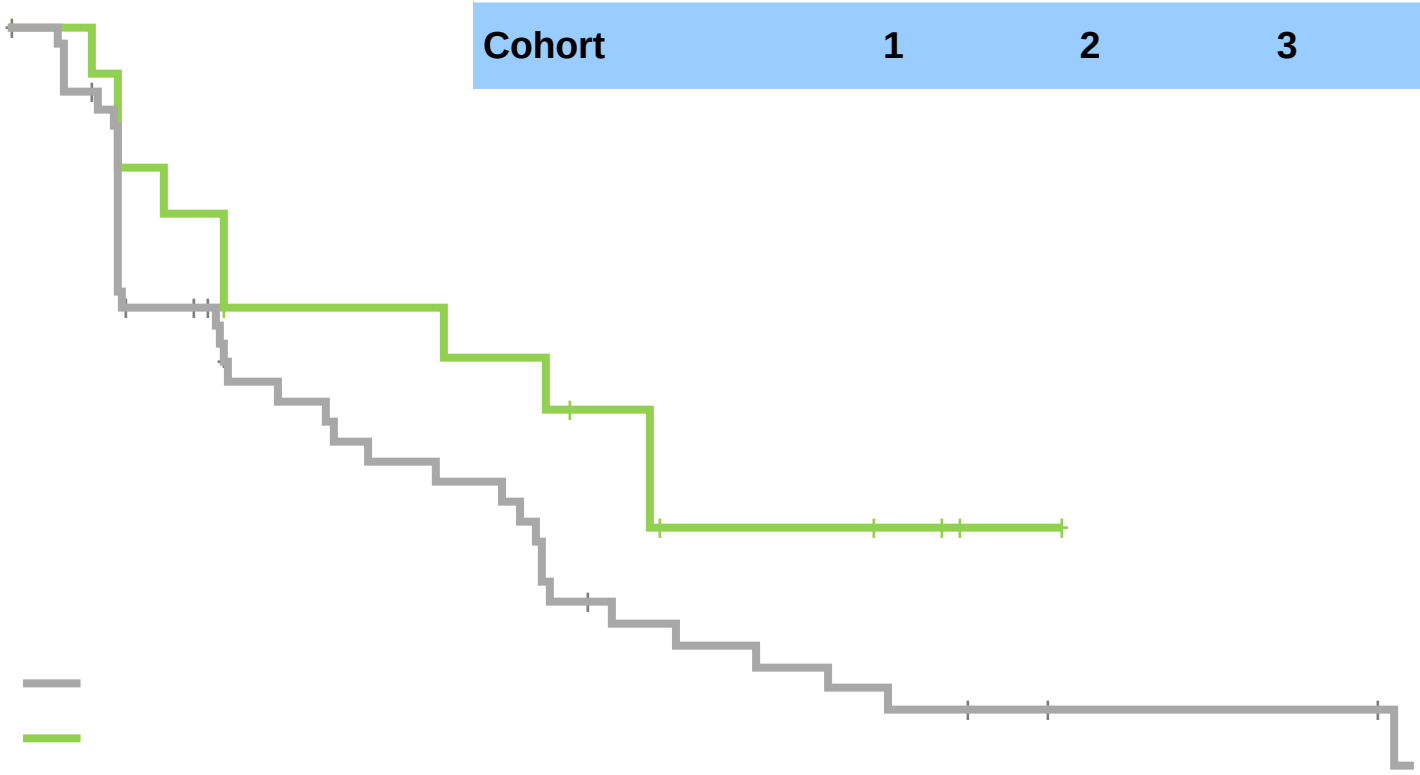
Overall Response



ASH 2014, PCYC-1111, Vij R, et al.

Progression-Free Survival

Cohort	1	2	3	4



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Progression-Free Survival

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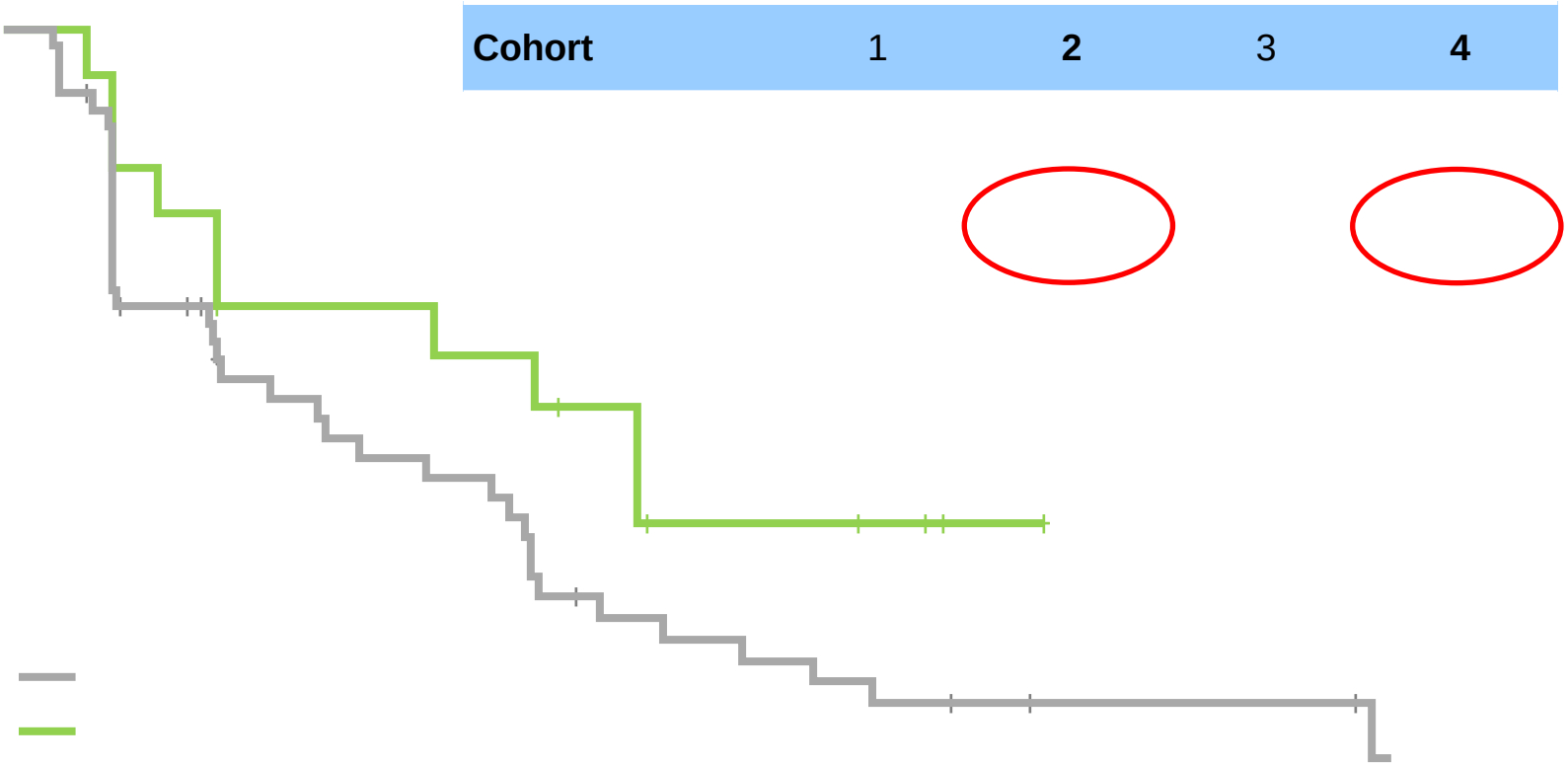

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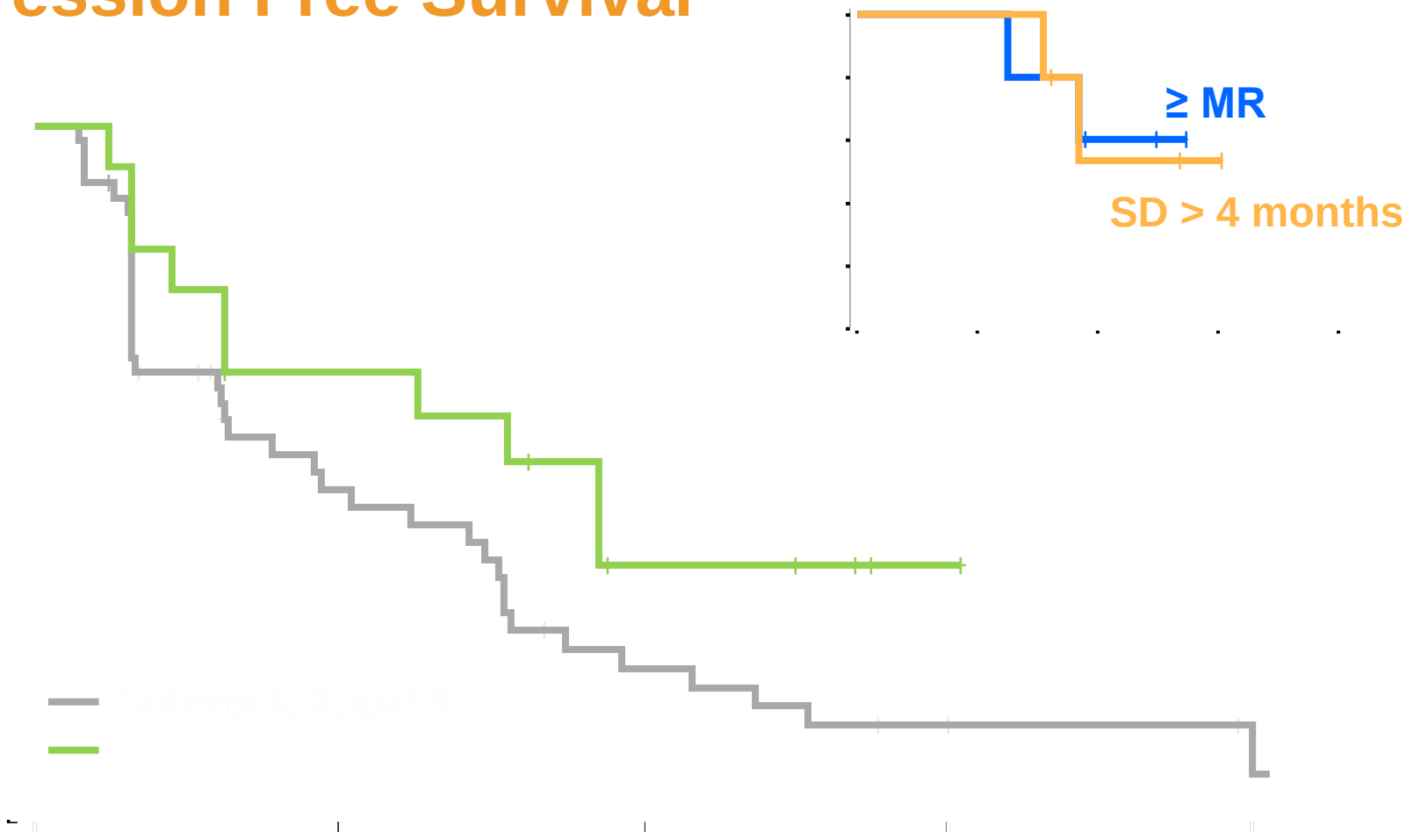
Progression Free Survival



Cohort 4: Efficacy Summary

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Safety Summary

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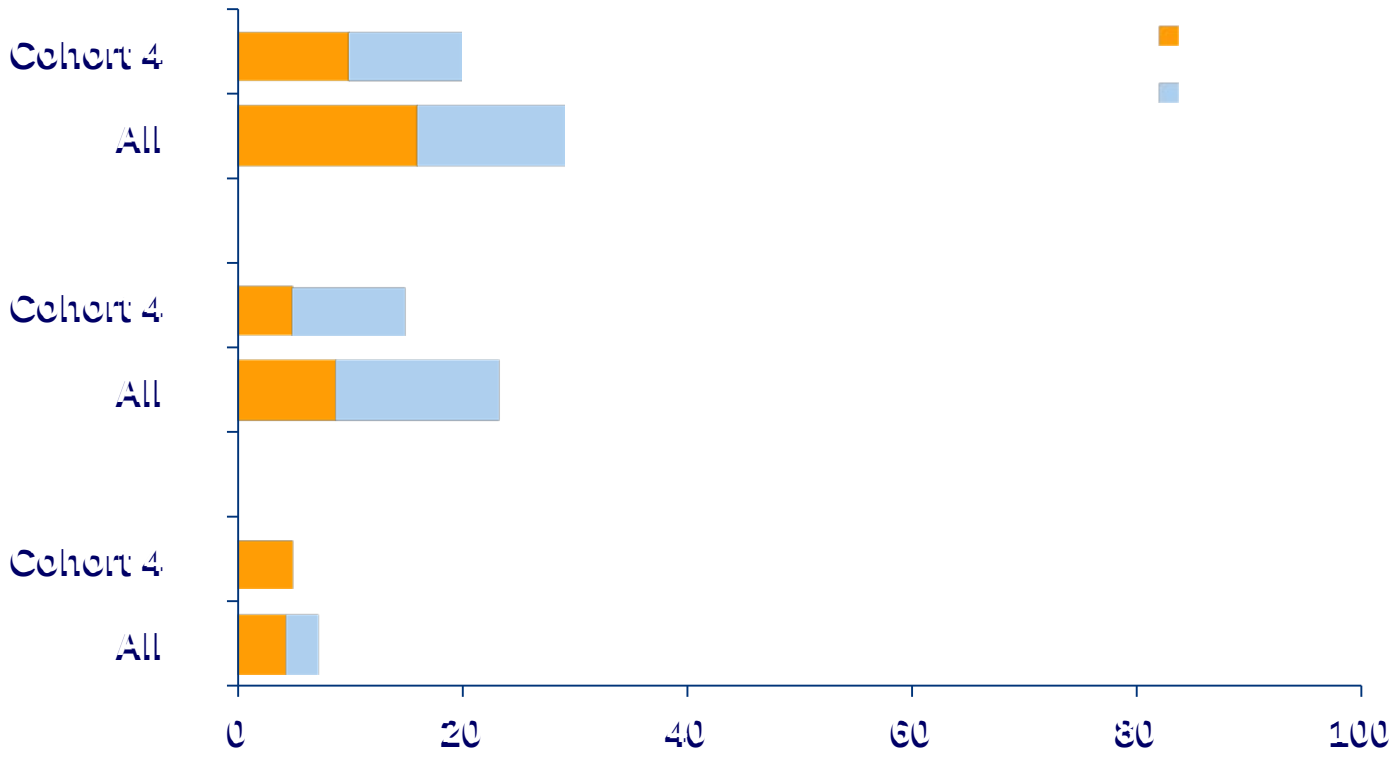
Hematologic Adverse Events



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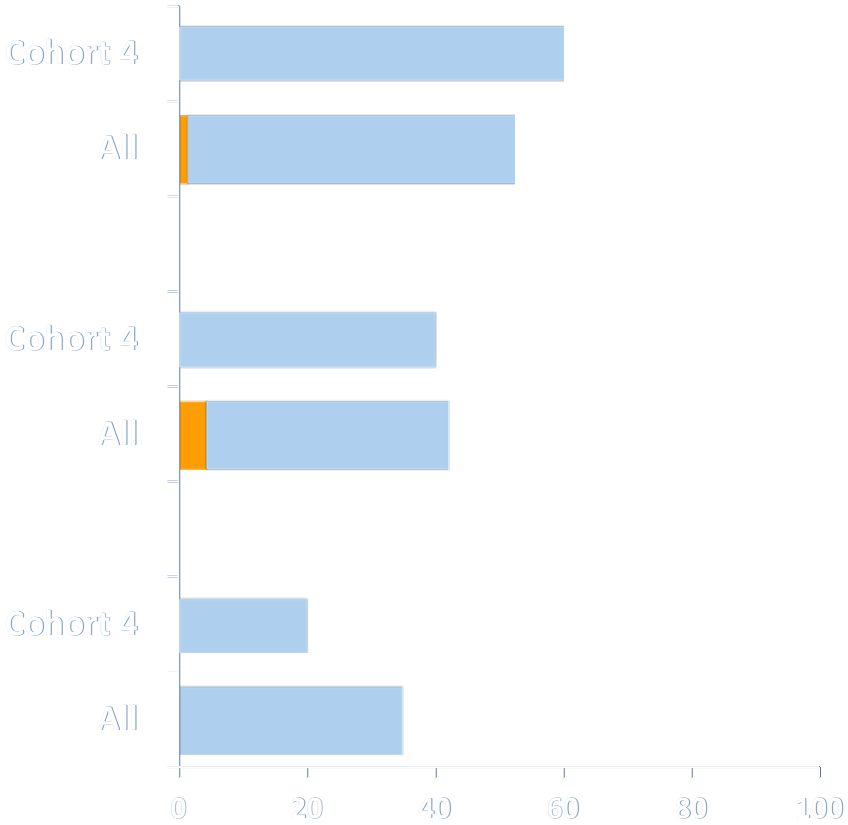
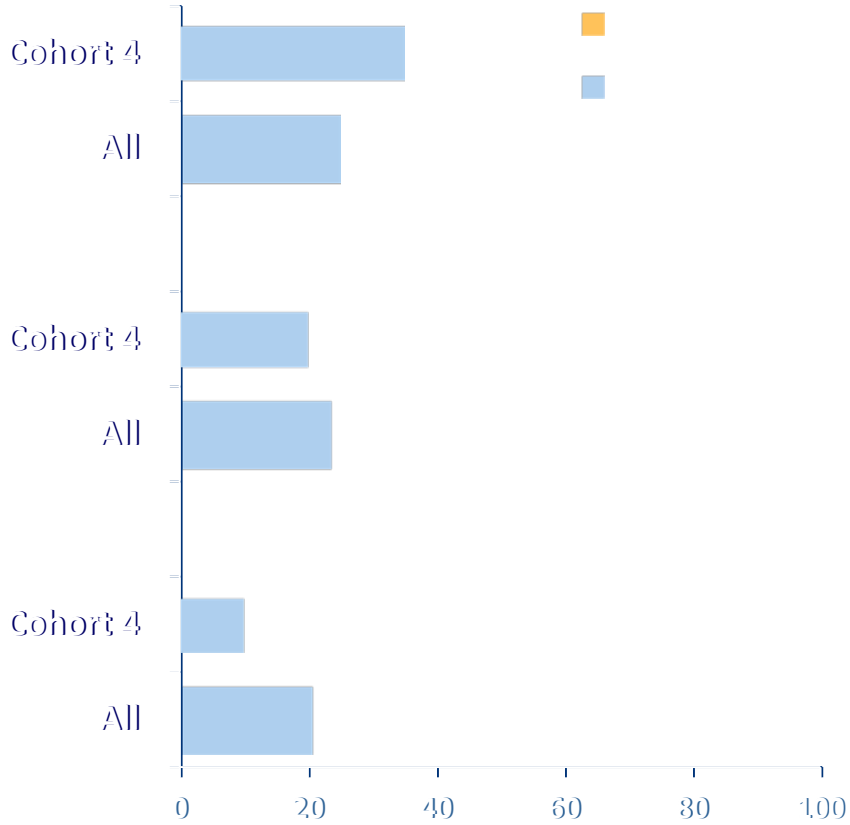
Nonhematologic Adverse Events (>20%)





ASH 2014, PCYC-1111, Vij R, et al.

Patient Disposition

Disposition	Cohort 1 (n = 13)	Cohort 2 (n = 18)	Cohort 3 (n = 18)	Cohort 4 (n = 20)

Conclusions

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Future Directions

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