A novel approach to analyzing toxicity in lymphoma clinical trials

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Presentation Objectives

- Introduce and demonstrate a novel method of AE assessment that includes duration as well as grade of toxicity: Toxicity over Time (ToxT) analysis

- Propose application of ToxT analysis to a completed Alliance lymphoma clinical trial: CALGB 50401 (Alliance)

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Current Approach: Max Grade Only

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Table 3. Toxicity Grade ≥ 3 and Second-Line Treatment

Toxicity Grade ≥3	Oxaliplatin and Irinotecan (n = 256)	Oxaliplatin and Fluorouracil Plus Leucovorin (n = 258)	P‡
Nausea	19	6	.001
Vomiting	22	3	.001
Diarrhea	24	12	.001
Febrile neutropenia	11	4	.002
Dehydration	6	4	.41
Paresthesias	7	18	.001
Neutropenia	36	50	.002

Table 4. Adverse Events Deemed Related to Panobinostat (≥ 10% any grade) As of June 11, 2010

	Any Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%
Thrombocytopenia	110	85	102	79
Diarrhea	85	66	4	3
Nausea	77	60	1	1
Anemia	49	38	27	21
Fatigue	49	38	12	9
Vomiting	42	33	4	3
Neutropenia	34	26	27	21
Decreased appetite	32	25	4	3
Dysgeusia	19	15	1	1
Constipation	15	12	—	
Asthenia	14	11	3	2
Leukopenia	13	10	7	5
Hypothyroidism	13	10	—	

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National Cancer Institute. CTCAE v.4.0. Bethesda, MD: Us. Department of Health and Human Services; 2009
Goldberg et al. J Clin Oncol 2004;22:23-30.
Younes et al. J Clin Oncol 2012;30:2197-203.

Conventional AE Evaluation is Inadequate

- Does not account for the time profile of AEs
  - When do they arise?
  - How long will they last?
  - When will they be worst?
- Does not capture the impact of chronic, low grade toxicity on the ability to continue treatment
- Does not incorporate patient reported outcomes (PRO)

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Basch E. N Engl J Med 2013; 369;5:397-400
Trotti A. J Clin Oncol 2007;25:5121-5127
Thanarajasingam G et al. J Natl Cancer Inst 2015. 107(10)

Lymphoma therapy has changed

- Rapid expansion of *continuously administered* therapies against lymphoma
  - Targeted agents
  - Immunotherapy
  - Maintenance regimens
- Continuous therapies make AE evaluation more problematic

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Toxicity over Time (ToxT) Analytic Approach

- Standardized package of statistical tools that are more comprehensive and involved that conventional methods for AE analysis
- Uncovers aspects of toxicity that are clinically relevant and missed in traditional analyses
- A novel way to explore the impact of time-dependent AEs on lymphoma patients
- Previously demonstrated in a phase III GI trial and phase II symptom control trial (Alliance/NCCTG N9741 and 979254)

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Thanarajasingam G et al. Lancet Oncol. 2016 Apr 12. doi: 10.1016/S1470-2045(16)00038-3. [Epub ahead of print]

AE Incidence/Grade by Cycle

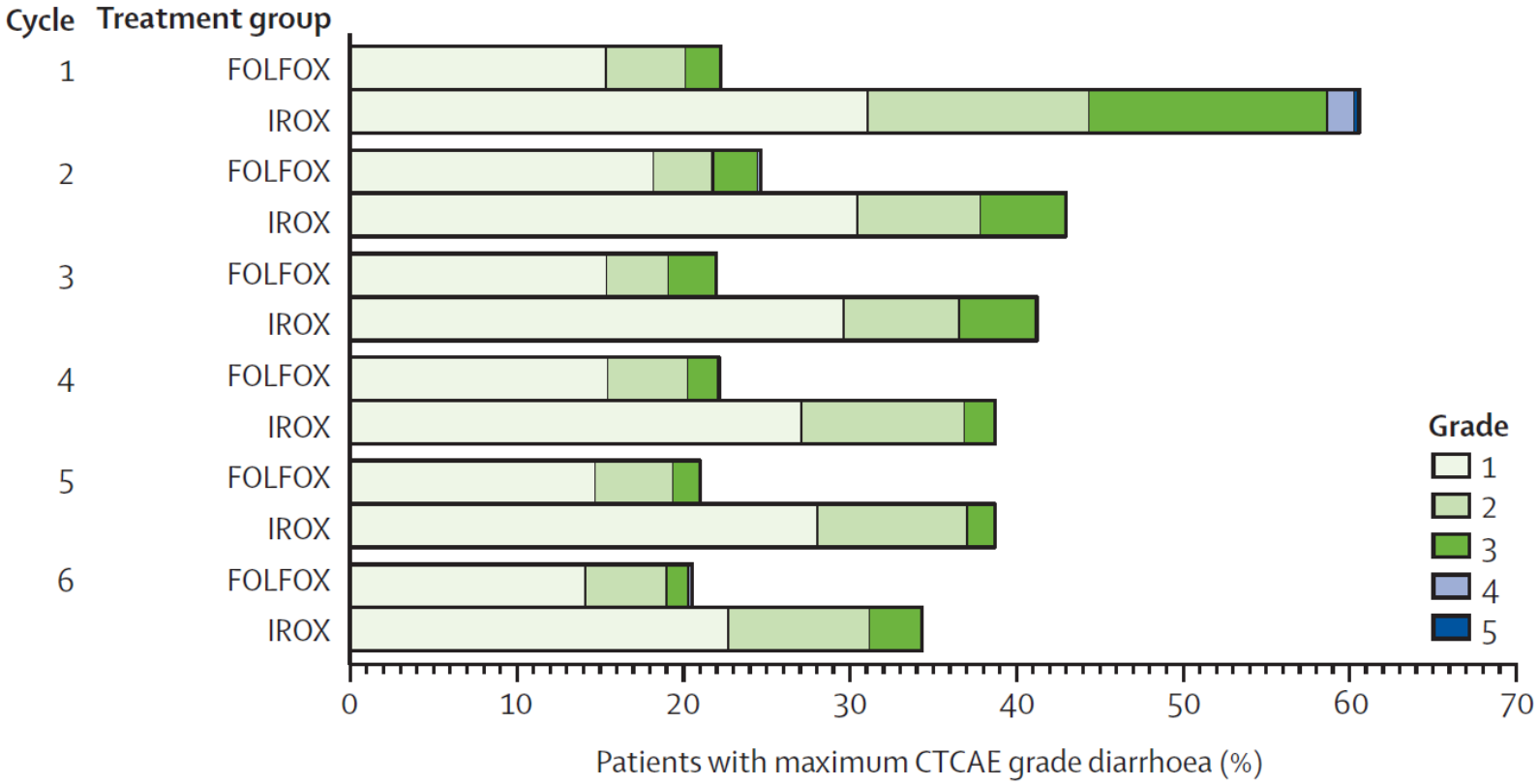

Figure 1: **Incidence of diarrhoea in patients given FOLFOX and IROX in NCCTG N9741 by drug cycle and adverse event grade**

FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. CTCAE=Common Terminology Criteria for Adverse Events.

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Stream Plot: AEs by Cycle (one study arm)

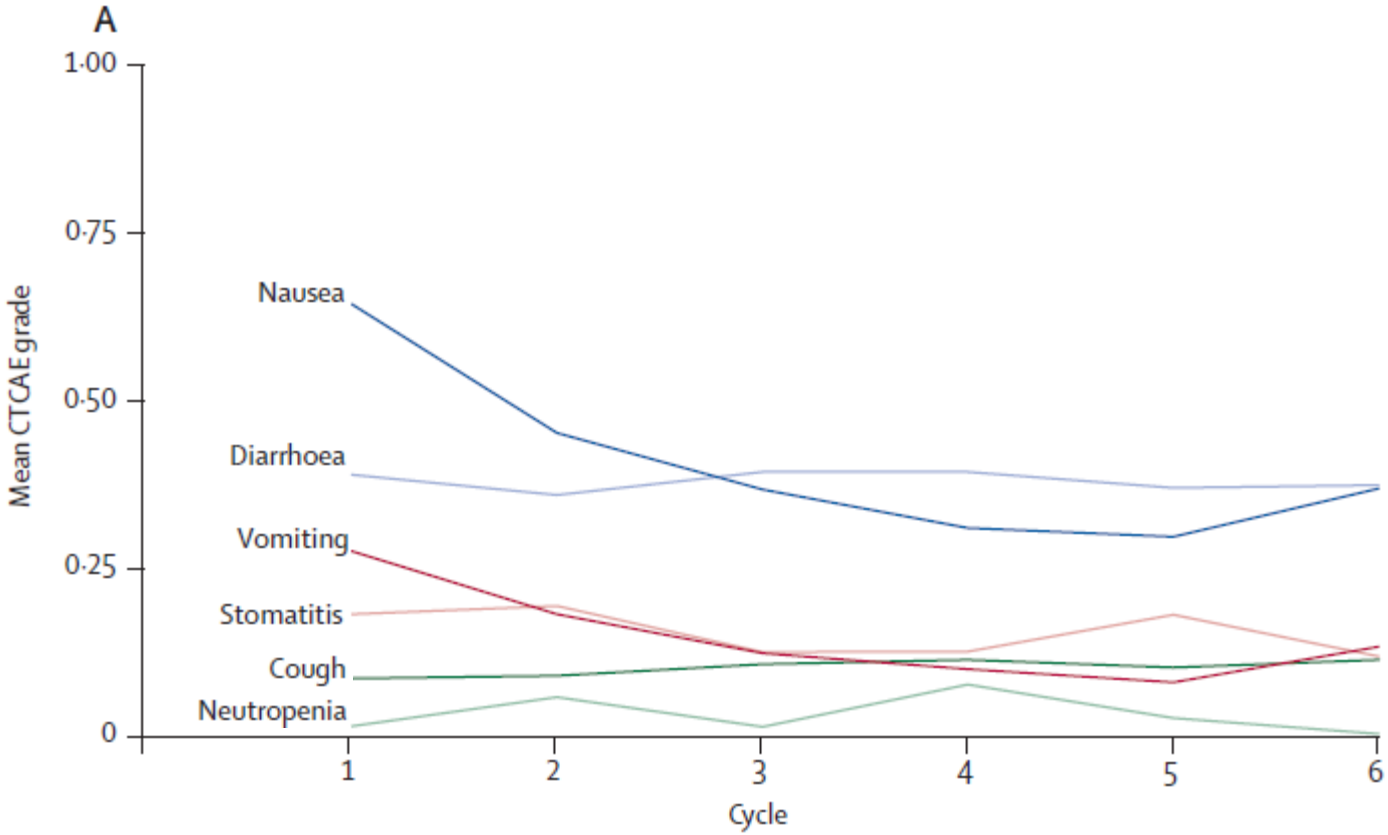

Figure 2: Adverse event trajectory over time
CTCAE=Common Terminology Criteria for Adverse Events. FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. (A) Stream plot of toxic effects of FOLFOX by cycle in NCCTG N9741.

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Time-to-Event Analysis

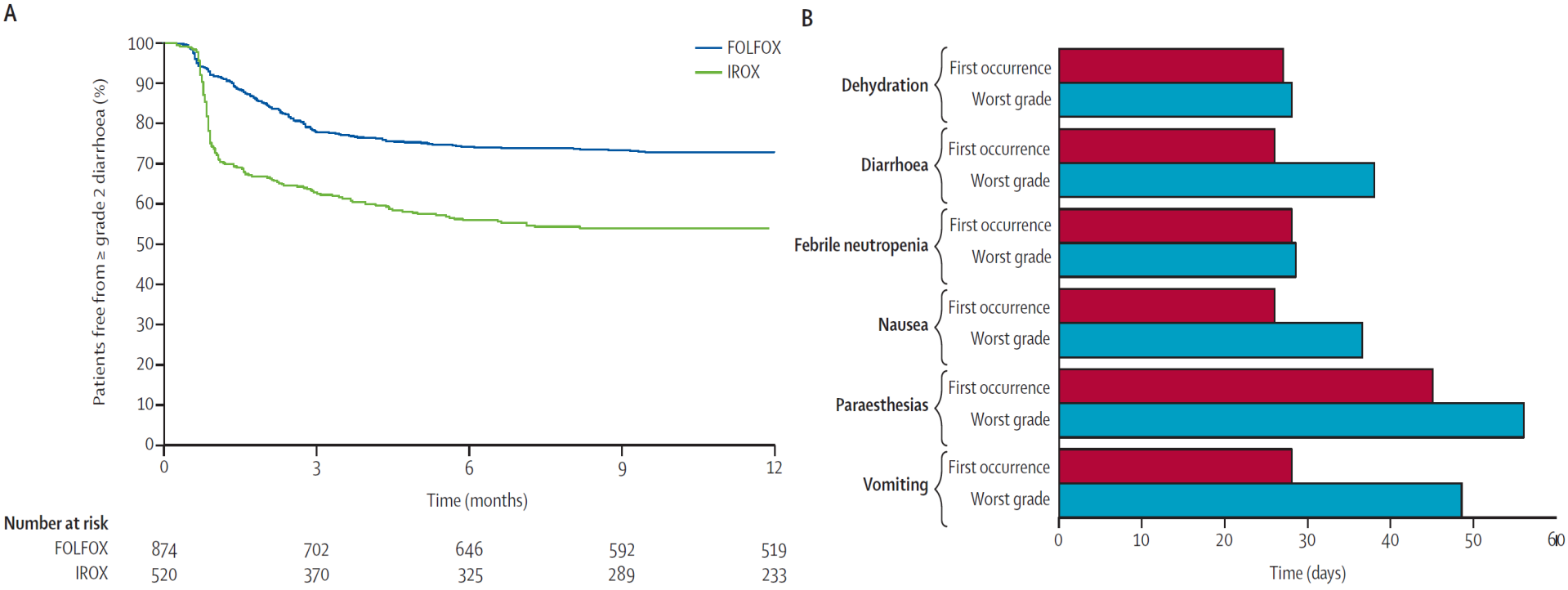

Figure 4: **Time-to-event analyses for onset of adverse events**
FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. (A) Time to grade 2 or worse diarrhoea in patients given FOLFOX and IROX in NCCTG N9741. (B) Median time to first occurrence and worst grade toxic effect in patients given IROX in NCCTG N9741.

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Area Under Curve (AUC)

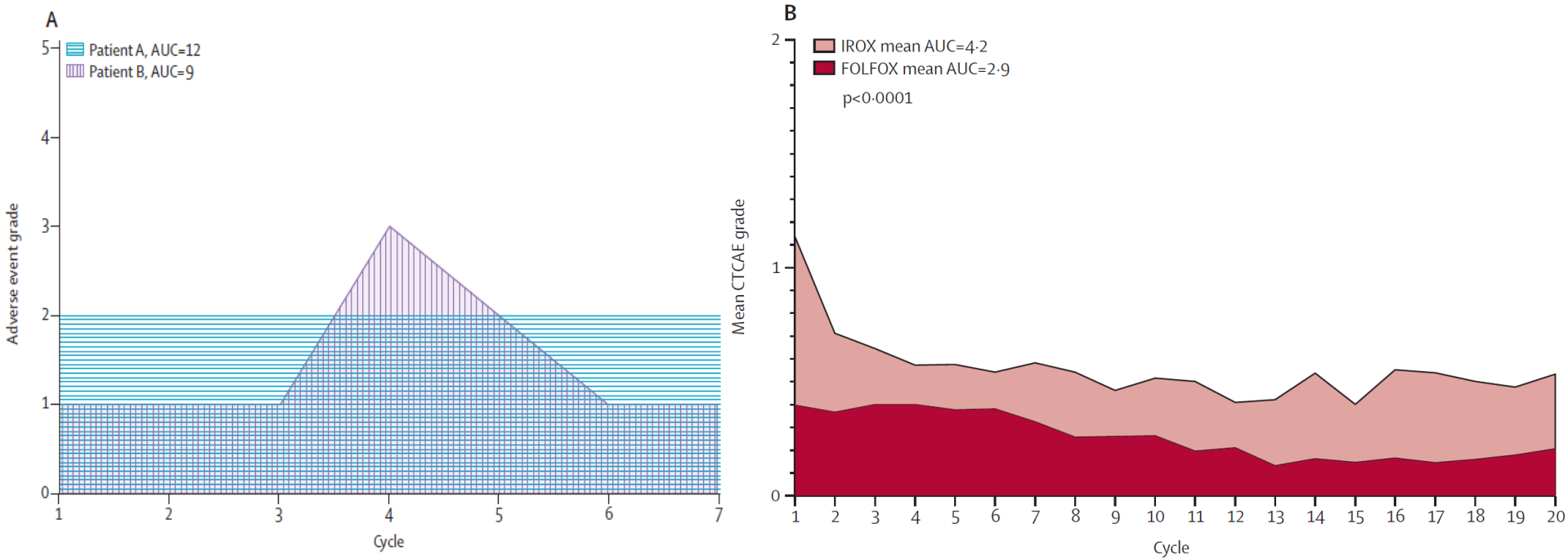

Figure 6: **AUC analysis to compare adverse events over time**
AUC=area under the curve. FOLFOX=5-fluorouracil plus oxaliplatin. IROX=irinotecan plus oxaliplatin. (A) Conceptual example of AUC analysis. (B) Application of AUC analysis, mean diarrhoea grade over time in patients given FOLFOX and IROX in NCCTG N9741.

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Application to lymphoma

Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance)

John P. Leonard, Sin-Ho Jung, Jeffrey Johnson, Brandelyn N. Pitcher, Nancy L. Bartlett, Kristie A. Blum, Myron Czuczman, Jeffrey K. Giguere, and Bruce D. Cheson

More time-dependent, low grade toxicity data to assess

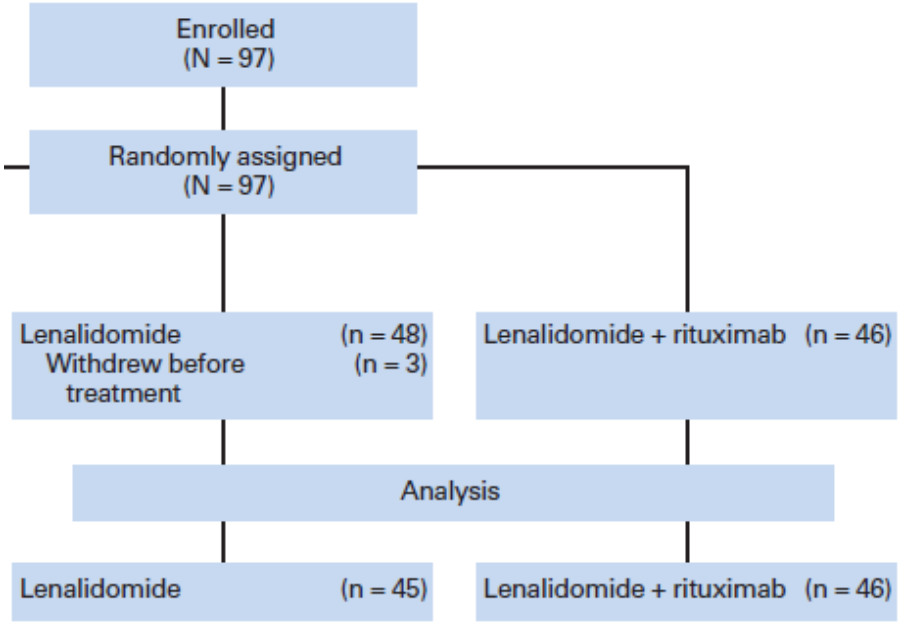

Table 2. Grade 3 to 4 Hematologic Adverse Events Occurring in > One Patient

	% of Patients			
	L (n = 45)		LR (n = 46)	
Adverse Event	Grade 3	Grade 4	Grade 3	Grade 4
Lymphopenia	1	0	3	0
Neutrophils	16	0	16	4
Platelets	0	0	4	0
Fatigue	9	0	11	2
Rash	2	2	4	0
AST	4	0	0	0
Infection (with neutropenia)	4	0	2	0
Thrombosis	9	7	2	2

Abbreviations: L, lenalidomide; LR, lenalidomide plus rituximab.

Leonard et al. J Clin Oncol 2015;33(31):3635-40

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Project Hypothesis/Aim

Hypothesis: ToxT method uncovers more time-dependent toxicity from LR than R that is missed by conventional AE reporting methods that use only maximum grade

Specific Aim: To demonstrate that a time-dependent measure of toxicity, AUC, is superior to conventional maximum grade AE reporting at predicting clinical outcomes:

- Time to dose reduction
- Time to treatment discontinuation
- Quality of life (QOL)

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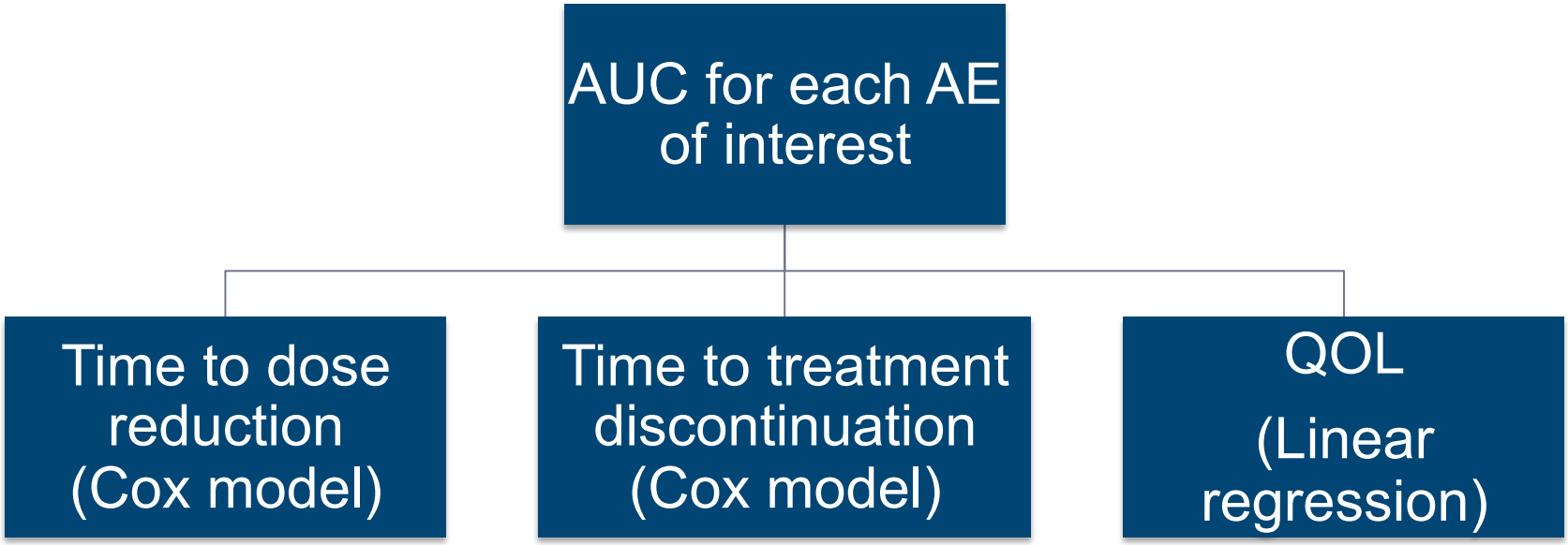
Methods



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Timeline for Achievement

- **Summer 2016**: Obtain toxicity CALGB 50401 toxicity data. Reformat and reorganize data for compatibility to ToxT.

- **Fall 2016:** Review outputs with Alliance statistics team and isolate clinically relevant time-dependent toxicity demonstrated by ToxT analysis.

- **Winter 2017:** Perform further analyses of time-dependent toxicity as a predictor of clinical outcome. Submit abstract to American Society of Clinical Oncology (ASCO) demonstrating longitudinal AE analysis and relevance to clinical outcome in lymphoma.

- **Spring 2017**: Review preliminary data with Alliance Health Outcomes leadership. Write and submit finalized manuscript.

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Summary

- Current methods of AE assessment are inadequate in the era of chronically administered lymphoma therapy
- The ToxT approach can capture time-dependent toxicity and chronic low grade AEs
- We propose application of longitudinal toxicity analysis to CALGB (Alliance) 50401

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Thank you

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- Thomas Witzig, MD
- Alliance Health Outcomes Committee

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Q & A

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