Available Data on Pediatric Exposure Response a Clinician's Perspective

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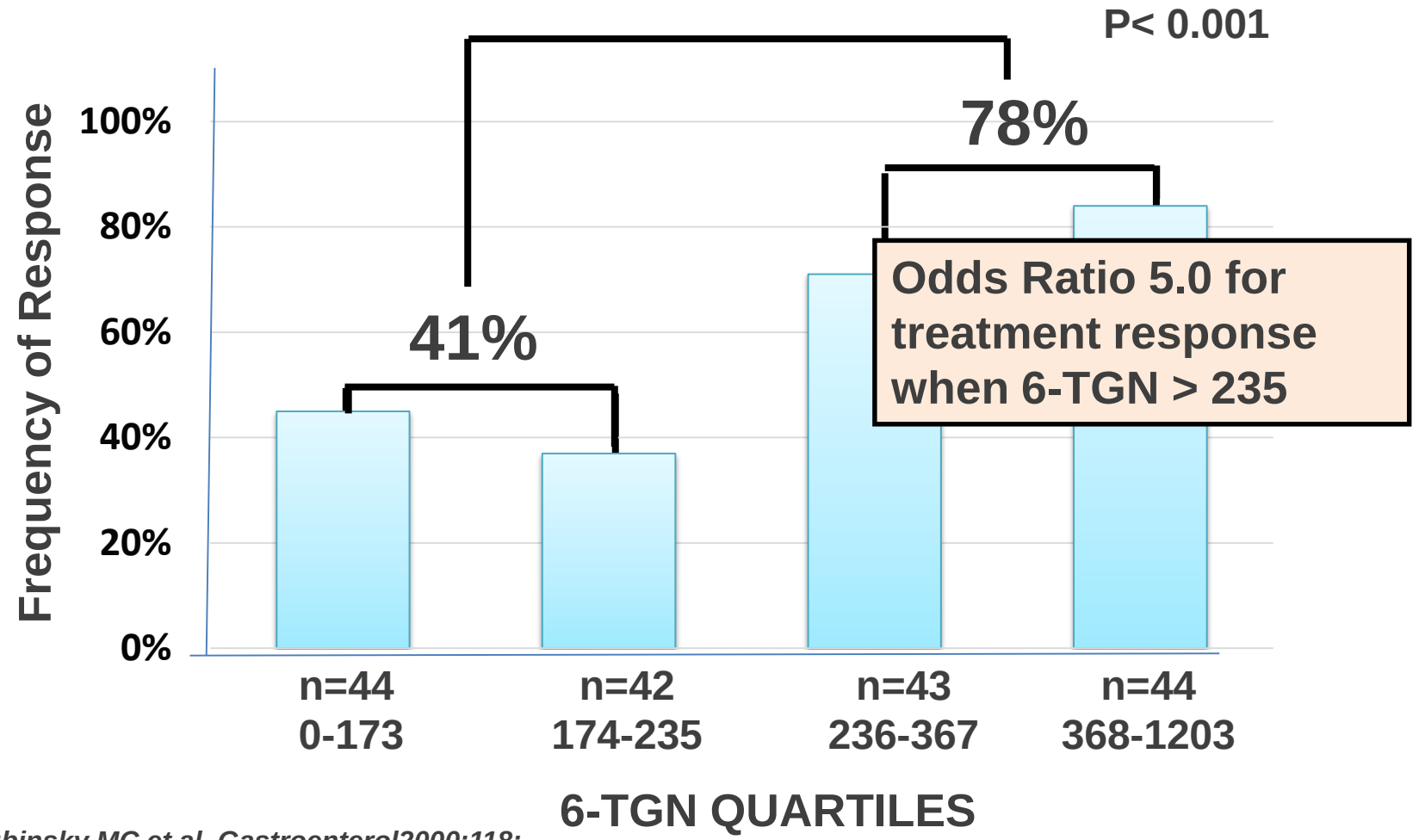
Disclosures

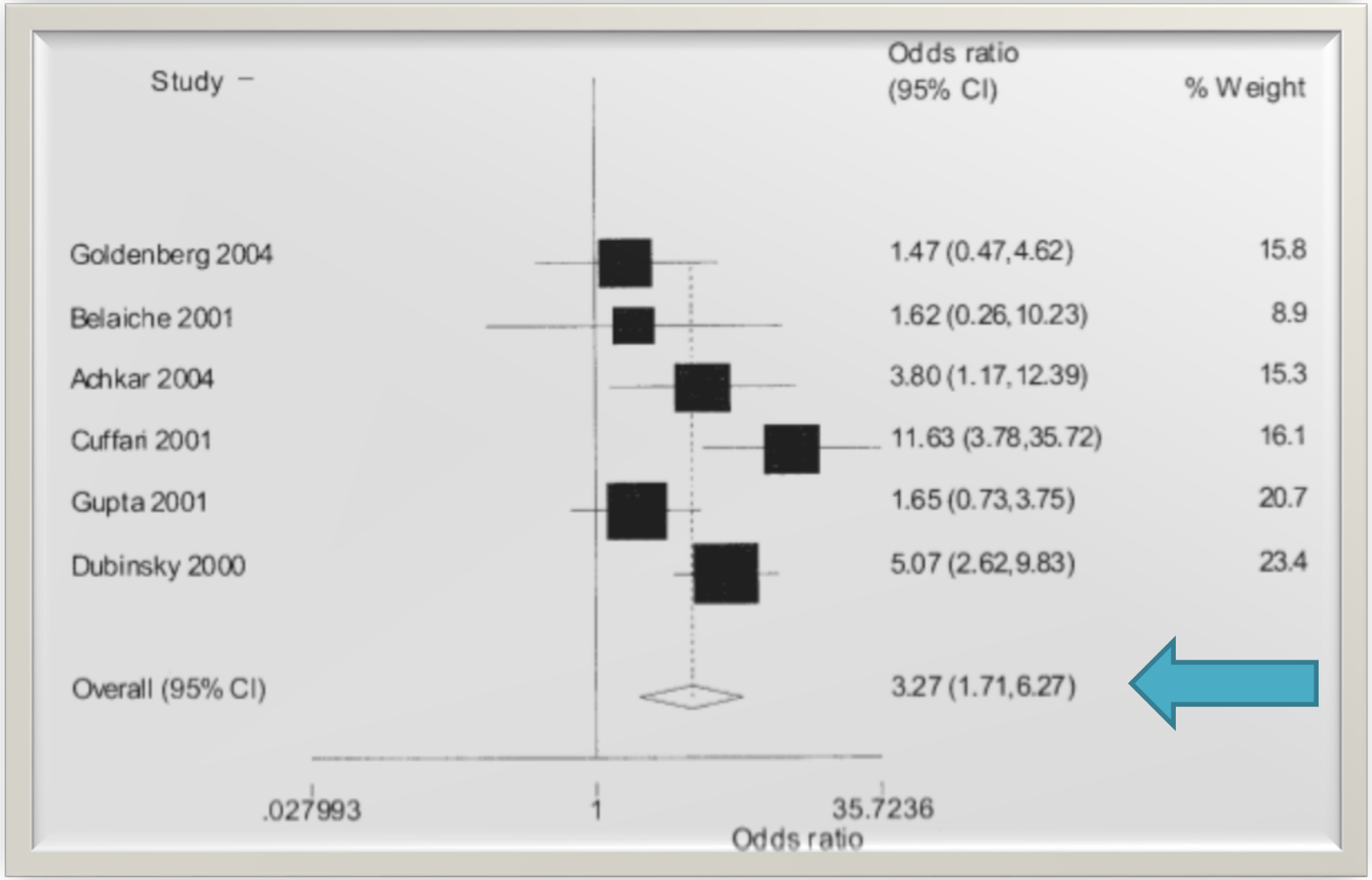
- Consultant: Janssen, Abbvie, Takeda, Prometheus Labs, Celgene, Pfizer, Genentech, UCB, Salix, Arena, Eli Lilly
- Research Support: Janssen, Abbvie, Pfizer, Prometheus Labs
- Co-Founder: Mi Test Health
- Co founder: Cornerstones Health

Thiopurine metabolite levels: our first understanding of exposure vs response



Dubinsky MC et al. Gastroenterol2000;118:

Association of 6-thioguanine nucleotide levels and IBD activity: a meta-analysis



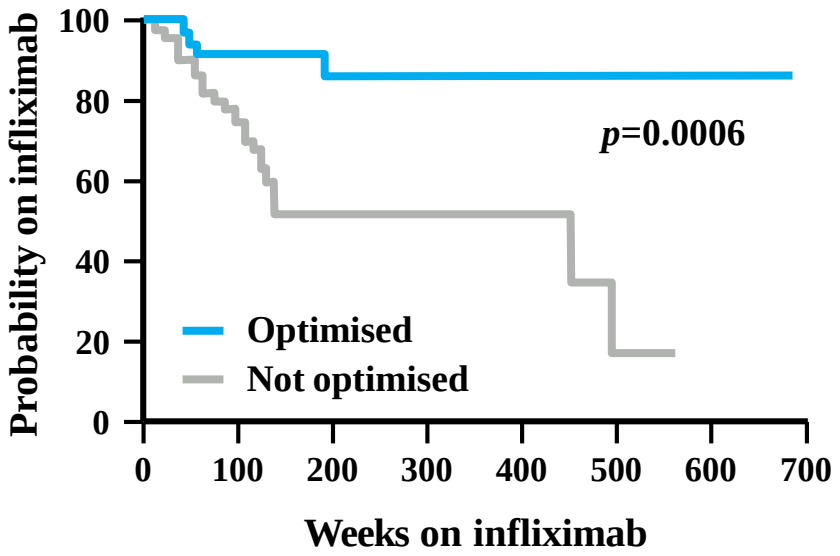
Osterman MT. Gastroenterology 2006;130:1047-53.

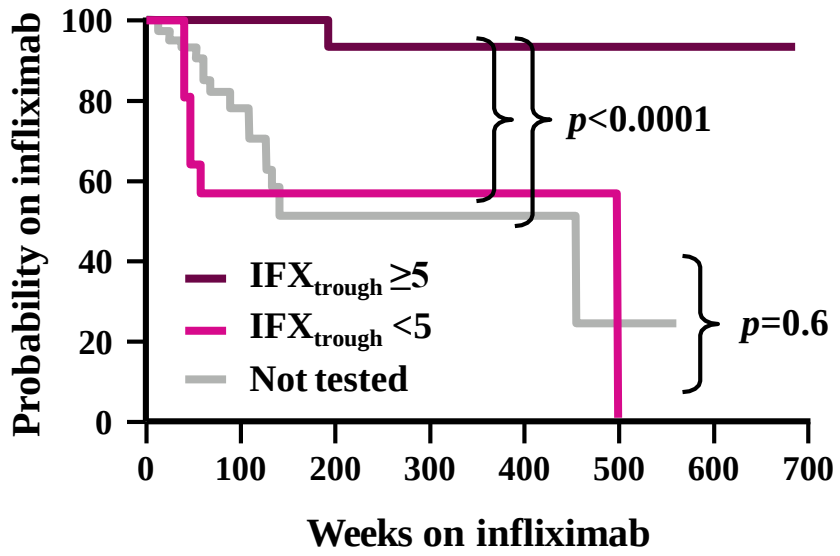
Anti-TNF concentrations correlate with outcome: Cohort studies and post-hoc analysis

Disease	Drug	Concentration	Clinical outcome	Notes
CD (Maser CGH 2006)	IFX	Detectable	Clinical remission, CRP, Endoscopic remission	Trough assessed after 1 year (range after 6-37 infusion)
CD (Cornillie GUT 2014)	IFX	> 3.5	Sustained response	Post hoc analysis of ACCENT I
CD (Bortlik JCC 2013)	IFX	> 3	Sustained response	Week 14 or 24 trough
CD (Lamblin JCC 2012)	IFX	> 5.6	Reduced CRP	
CD (Drobne Gastro 2011)	IFX	Undetectable	Loss of response	
UC (Arias JCC 2012)	IFX	> 7.19	Sustained response	
UC (Seow GUT 2010)	IFX	Detectable	Higher rates of remission, Endoscopic improvement	Undetectable serum IFX associated with colectomy
CD/UC (Yanai AJG 2011)	IFX	> 3.8	Failed to respond to increase in IFX or change to another anti-TNF	Population was patients with LOR
CD/UC (Roblin CHG 2014)	ADA	> 4.9	Mucosal healing	Higher trough concentrations associated with clinical remission and mucosal healing
CD/UC (Yanai AJG 2011)	ADA	> 4.5	Failed to respond to increase in ADA or change to another anti-TNF	Population was patients with LOR
CD/UC (Roblin AJG 2014)	ADA	< 4.9 ug/ml	Clinical response to ADA dose intensification	Prospective trial with ADA demonstrating benefit of dose optimization for low trough concentration
UC (Velayos CGH 2013)	ADA	> 4.58 ug/ml	Week 12 clinical response	Week 2-4 concentration predicts week 12 response
CD (Colombel CGH 2014)	CTP	Higher quartile (mean value for highest quartile: 30.1 ug/ml)	Endoscopic and clinical response and remission	

Prospective therapeutic drug monitoring to optimise infliximab maintenance therapy in IBD

- Retrospective cohort of patients in clinical remission, single physician practice
  - Infliximab dose optimisation to trough concentrations 5–10 µg/mL (n=48)
  - No infliximab dose optimisation (n=78)
- Evaluated probability of remaining on infliximab, for up to 5 years

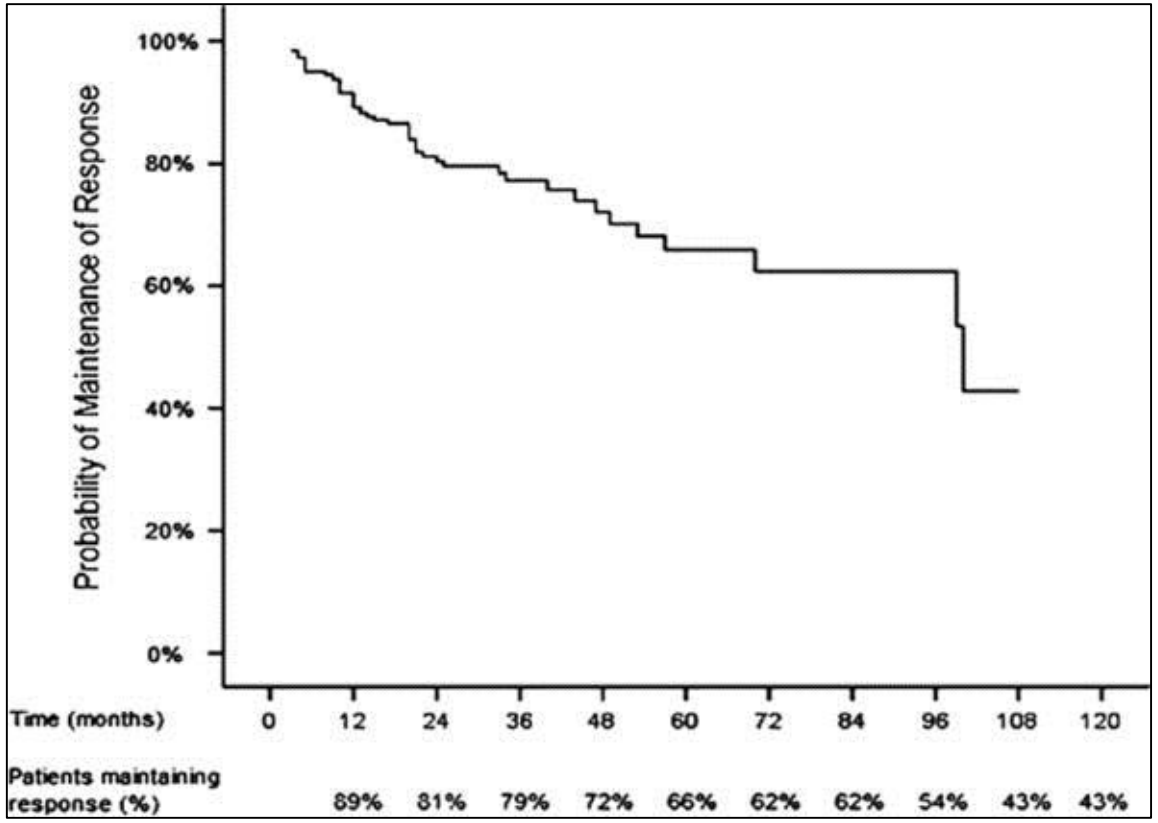




Dose optimisation increases probability of remaining on infliximab up to 5 years

Vaughn BP et al. Inflamm Bowel Dis 2014

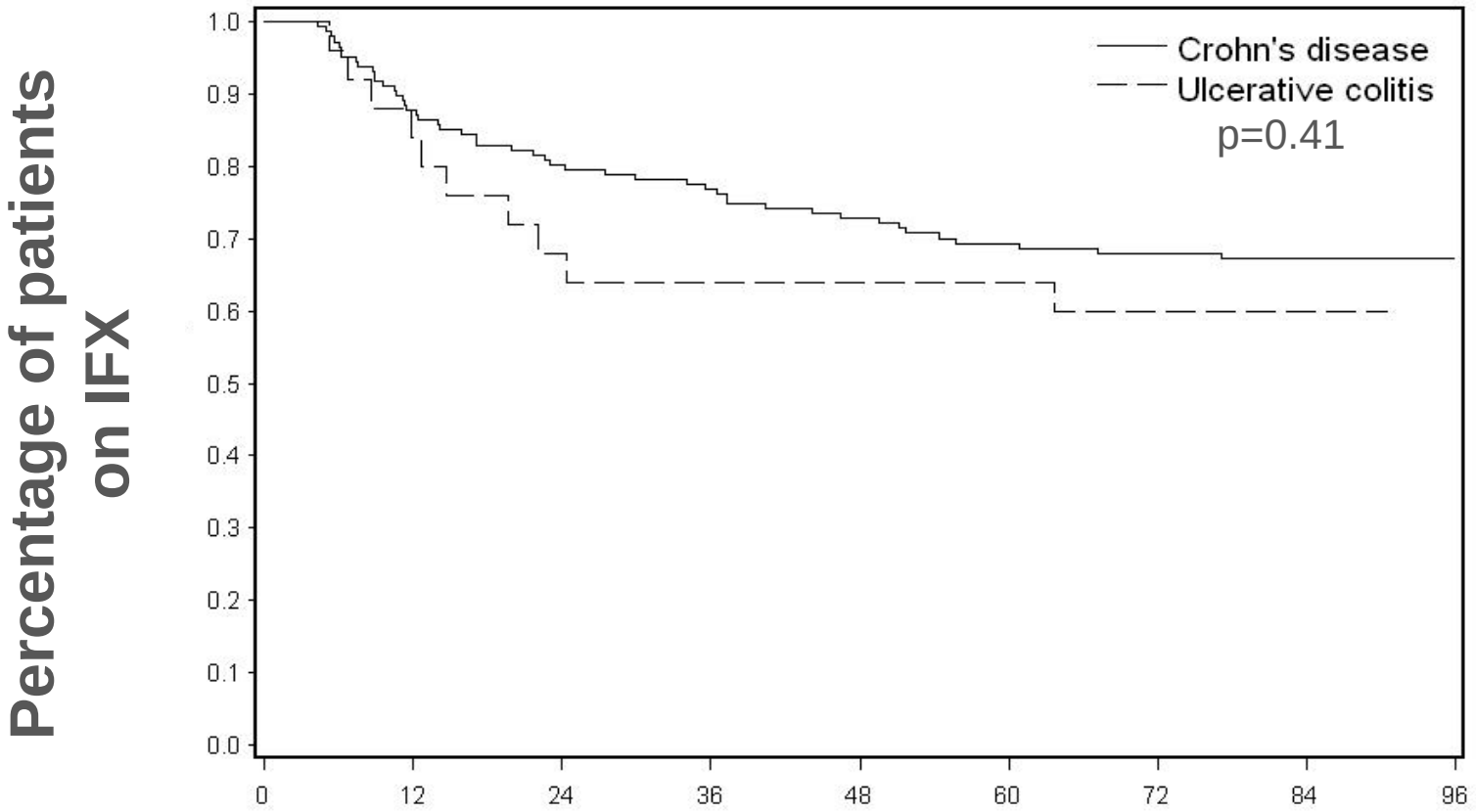
Loss of Response Over Time to Biologics



- Cohort of 309 CD patients who responded to induction with IFX
- Annual risk of loss of response to IFX was 12% per patient-year

Chaparro M et al. J Clin Gastro 2011

IFX Durability in Pediatric IBD



Vahabnezhad E et al IBD 2014

Week 14 Infliximab Levels and Outcomes

Week 54 Outcome (Yes Versus No)	IFX14 Median Level, µg/mL	P^a
PR	**4.7 versus 2.6**	**0.03**
Clinical remission	3.2 versus 2.2	0.07
Clinical and laboratory remission	4.2 versus 3.0	0.07
SDR14	**5.5 versus 3.1**	**0.05**
SDR22	**5.1 versus 3.0**	**0.04**

[a]*P* value: Wilcoxon rank sum test.
Bold text indicates significant *P* values.

Singh and Dubinsky et al Inflamm Bowel Disease 2014;20: 1708-1713

Clinical Utility of Week 14 levels Predicting Durability

IFX14 Cut Point, μg/mL	Sensitivity	Specificity	PPV, %	NPV, %	AUC (95% CI)
≥1	80	45	69	60	0.63 (0.49–0.80)
≥2	70	45	66	50	0.58 (0.44–0.72)
≥3	60	50	64	46	0.55 (0.41–0.69)
≥4	53	75	76	52	0.64 (0.51–0.78)
≥5	50	85	83	53	0.68 (0.55–0.80)
≥5.5	47	90	88	53	0.68 (0.57–0.80)
≥6	37	95	92	50	0.66 (0.56–0.76)
≥7	33	100	100	50	0.67 (0.58–0.75)

NPV, negative predictive values; CI, confidence interval.

Singh and Dubinsky et al Inflamm Bowel Disease 2014;20: 1708-1713

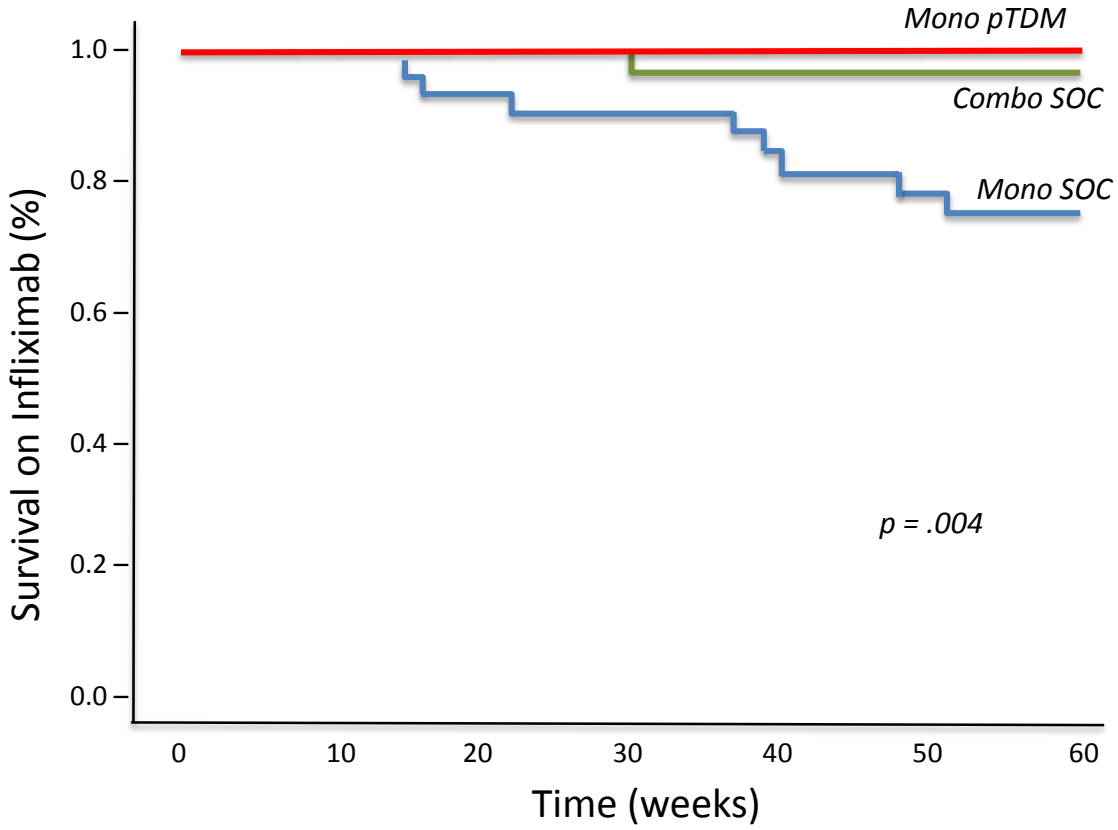
Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

	Impact on Pharmacokinetics
Presence of ADAs	• Decreases serum mAbs • Threefold-increased clearance • Worse clinical outcomes
Concomitant use of IS	• Reduces formation • Increases serum mAbs • Decreases mAb clearance • Better clinical outcomes
High baseline TNF-α	• May decrease mAbs by increasing clearance
Low albumin	• Increased clearance • Worse clinical outcomes
High baseline CRP	• Increased clearance
Body size	• High BMI may increase clearance
Gender	• Males have higher clearance

ADA, antidrug antibody; mAB, monoclonal antibody

Ordas I et al. Clin Pharmacol Ther. 2012.

Infliximab durability Decreased with Monotherapy IFX and Reactive TDM

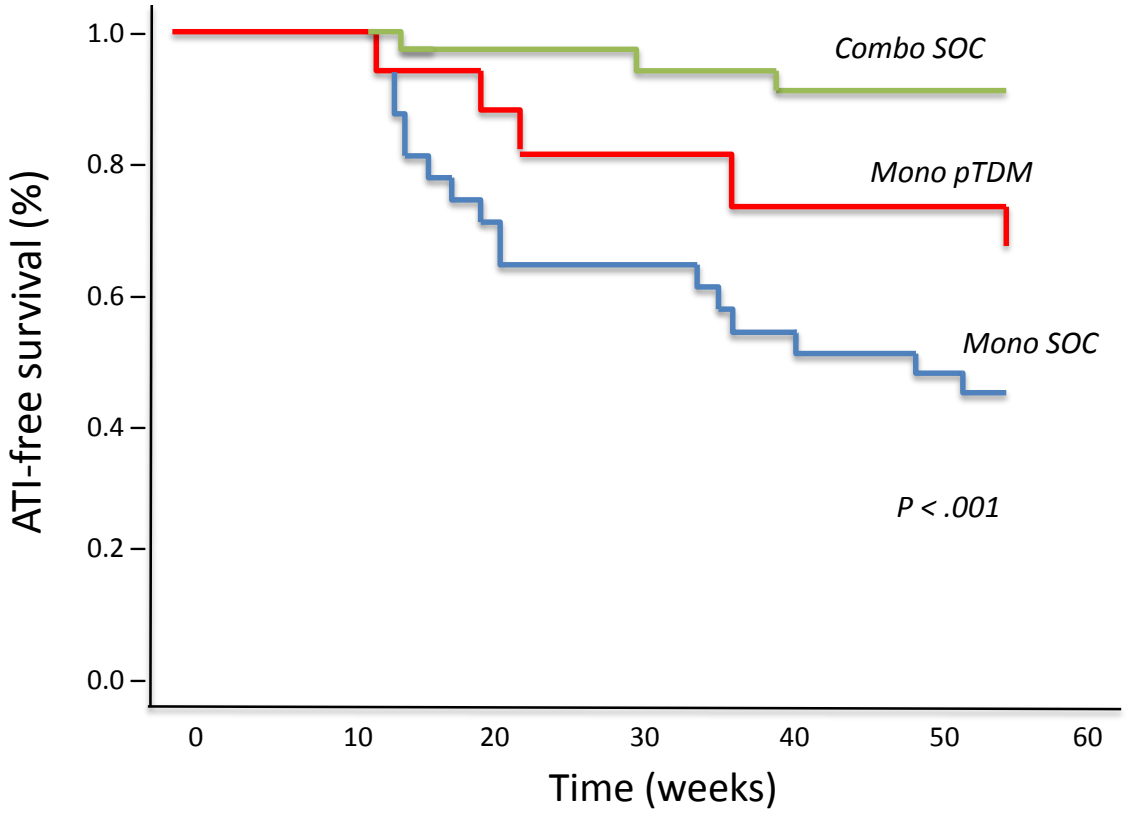


Number at risk

Mono pTDM	16	16	16	16	16	16
Mono SOC	32	30	29	27	25	24
Combo SOC	35	35	35	34	34	34

Lega S et al Inflamm Bowel Dis. 2018 epub ahead of print

Antibodies to Infliximab increased with monotherapy IFX and reactive TDM



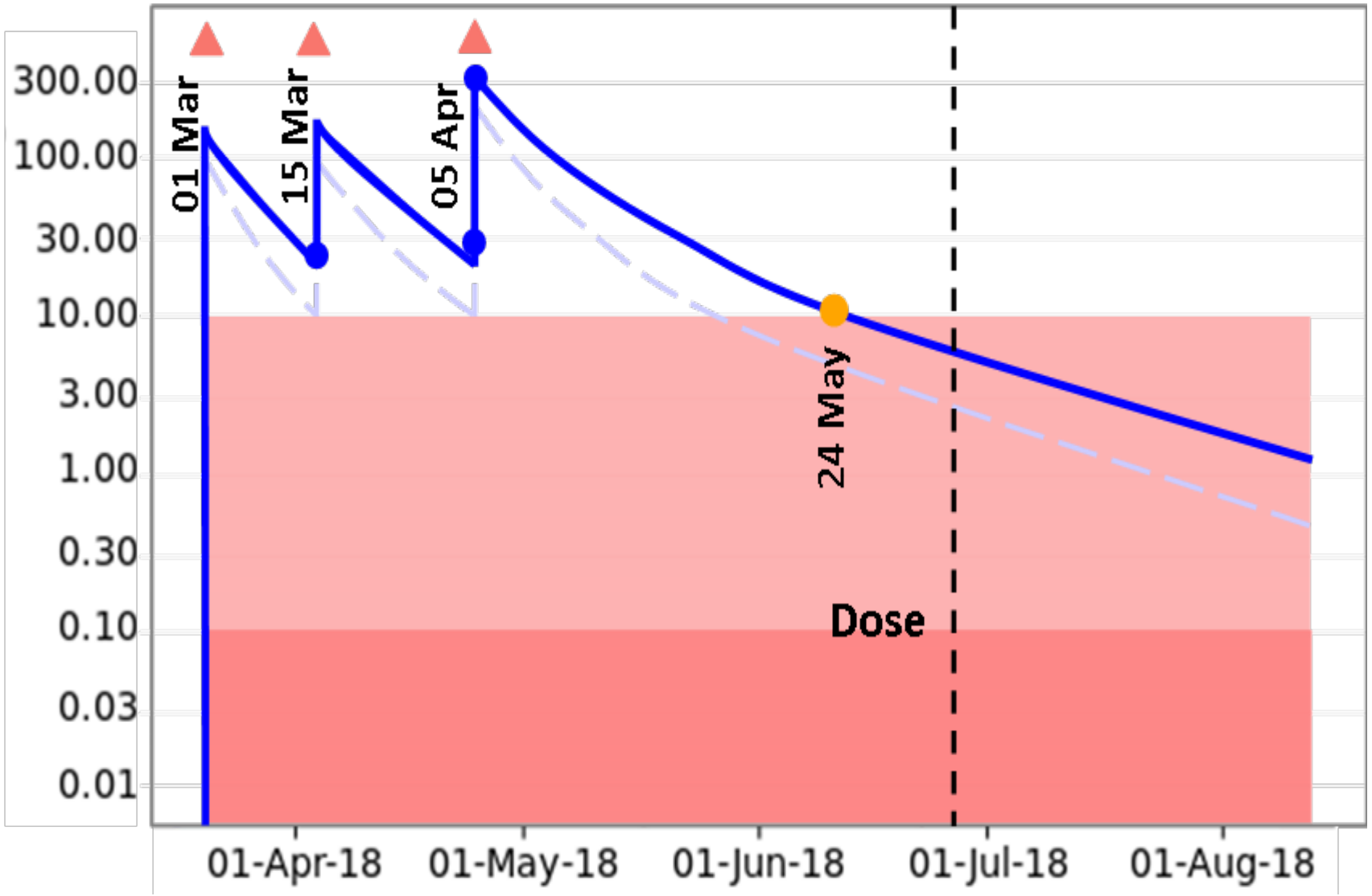
Number at risk

Mono pTDM	16	15	13	12	12	11
Mono SOC	32	24	21	18	16	15
Combo SOC	35	34	34	32	32	32

Lega S et al Inflamm Bowel Dis. 2018 epub ahead of print

THE FUTURE: THE MAGIC OF INDUCTION
PK DASHBOARDS AND EARLY OPTIMIZED MONOTHERAPY

Figure 1. Example of "Precision IFX" *i*Dose Dashboard Forecast (Projections Research) Bayesian Dashboard System



STUDY POPULATION

Patient Population

114
ENROLLED
& Rec'd 2 Doses

45
IFX 10 MG/KG
Weeks 0

46
IFX 10 MG/KG
Weeks 2

69
IFX 5 MG/KG
Week 0

61*
IFX 5 MG/KG
Week 2

58‡
INFUSION #3

50§
INFUSION #4

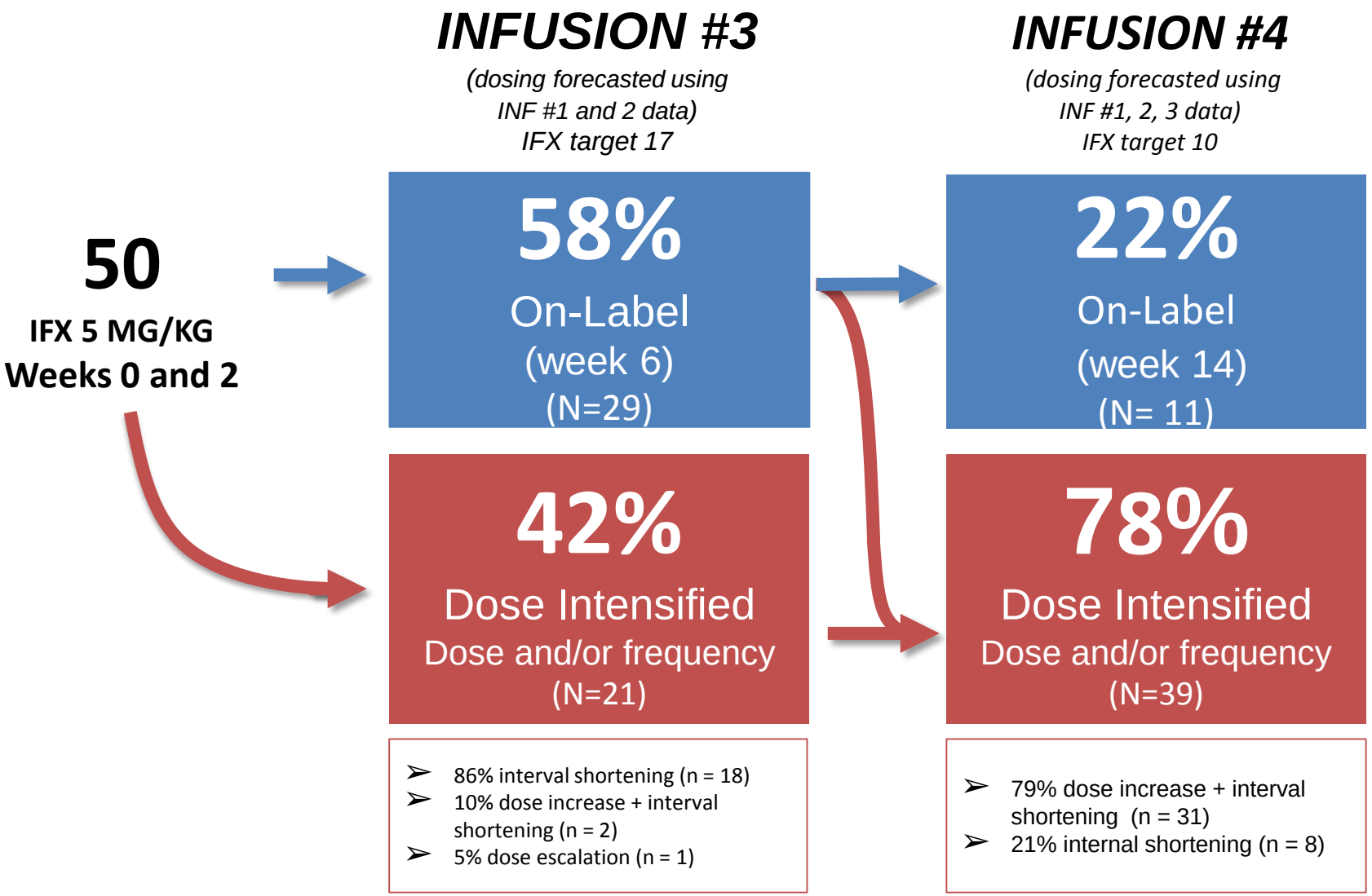
Exclusions:

* Protocol Deviations n = 8

‡ Early Termination due to ATI n = 2,
INF #3 Not Yet Completed n = 1

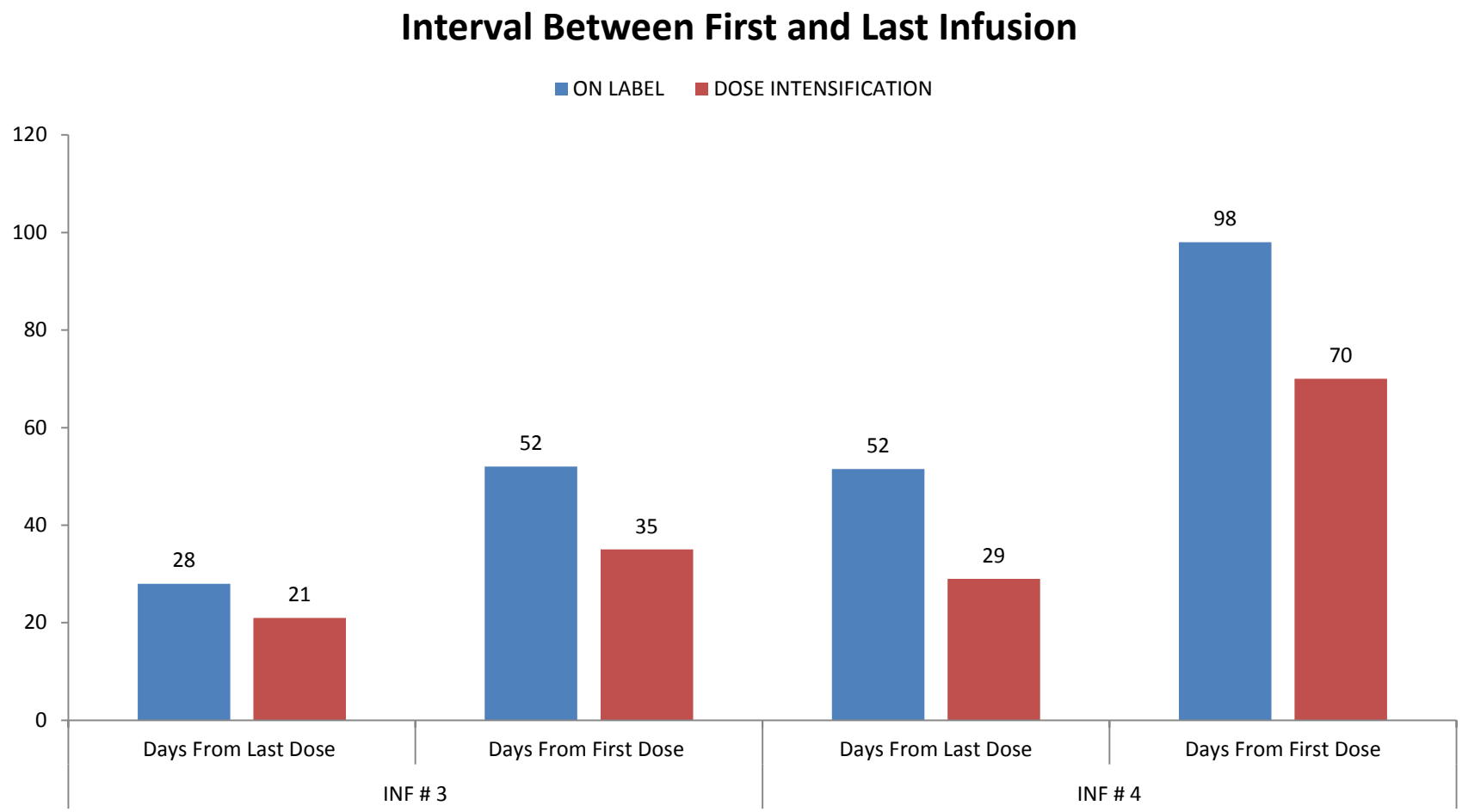
§ Early Termination due to Non-response n = 1,
Protocol Deviation n = 4,
INF#4 Not Yet Completed n = 3

Results: *i*Dose-Driven Dosing (N=50)

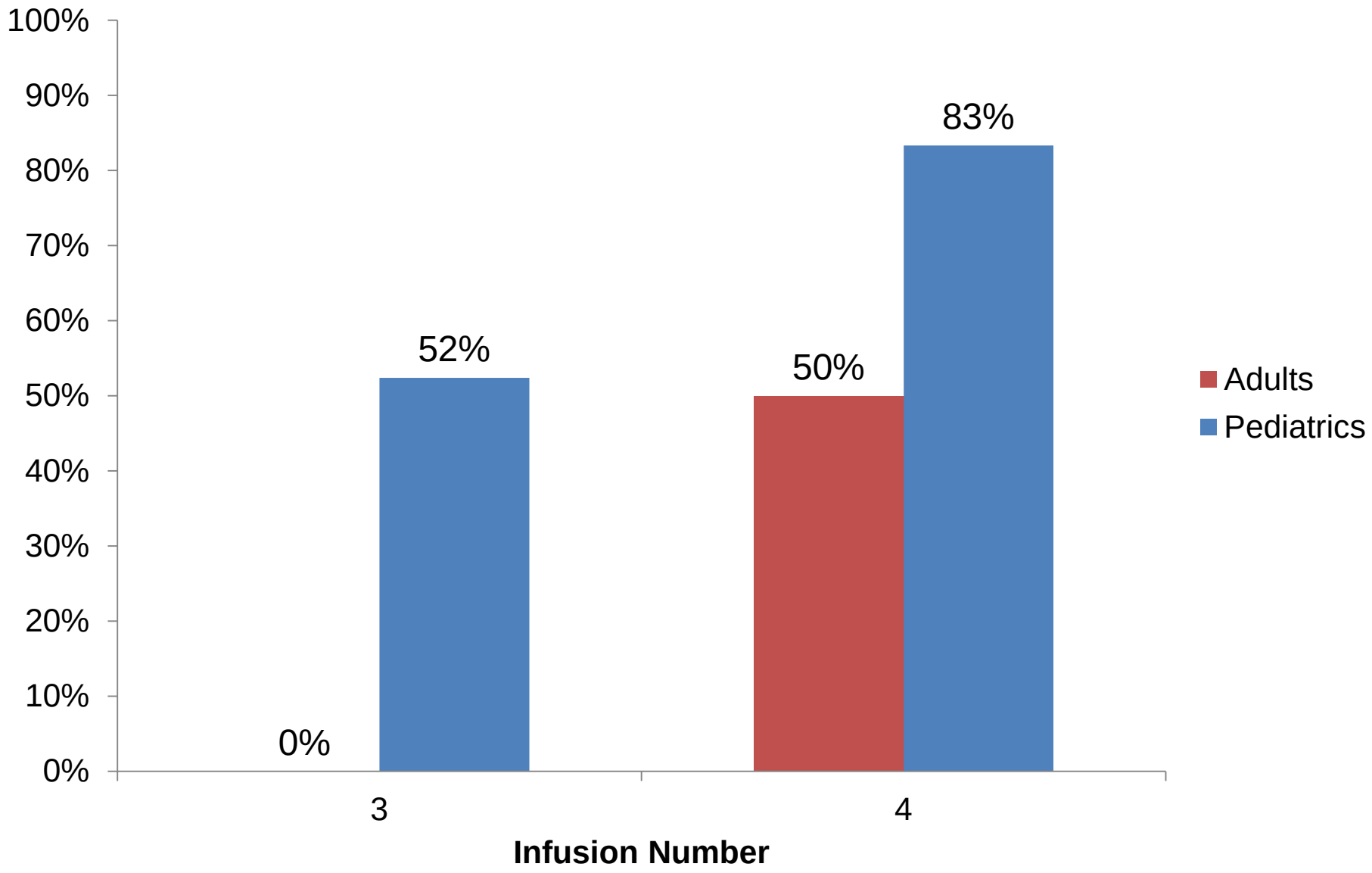


Results: Median Intervals

Dosing Intervals for Infusions #3 and #4, N=50



Pediatric vs Adult IBD IFX Dosing



Infusion 2 Characteristics

Grouped by SOC vs DI at Infusion #3

	INFUSION #2 Characteristics			
	On-Label at Inf#3 (n=29)		Dose Intensified at Inf#3 (n=21)	
	Median	IQR	Median	IQR
Albumin (n=48)	3.90	0.58	3.70	0.50
C-Reactive protein (n=47)	0.11	0.33	0.08	0.30
Weight	53.55	33.68	37.25	16.20
Dose (mg/kg)	5.00	0.11	5.00	0.11
IFX Concentration (n=49)	50.50	18.30	23.80	9.55

Infusion 3 Characteristics

Grouped by SOC vs DI at Infusion #4

	INFUSION #3 Characteristics			
	On-Label at Inf#3 (n=11)		Dose Intensified at Inf#3 (n=39)	
	Median	IQR	Median	IQR
Albumin	4.20	0.50	3.80	0.35
C-Reactive protein	0.06	0.06	0.21	0.46
Weight	57.60	32.35	43.50	22.65
Dose (mg/kg)	5.03	0.06	5.03	0.13
IFX Concentration (n=49)	31.10	22.25	18.95	15.63
# of Subjects w/ ATI (n=3)	0		3	

Exposure Response: A Clinician's Perspective

- Therapeutic Drug Monitoring not a foreign concept to pediatricians
- Early post induction drug concentrations improve durability
- Proactive Induction optimization is superior to post induction
- Children need optimization earlier than Adults
- **Exposure not dose is the target**
- **Age of 18 means you can vote but arbitrary for drug approval as more about pk similarity**
- PK dashboards provide a more robust dosing strategy for infliximab