Phase 1 Study of Utomilumab (PF-05082566) In Combination with Rituximab in Patients with CD20+ NHL (Study B1641001)

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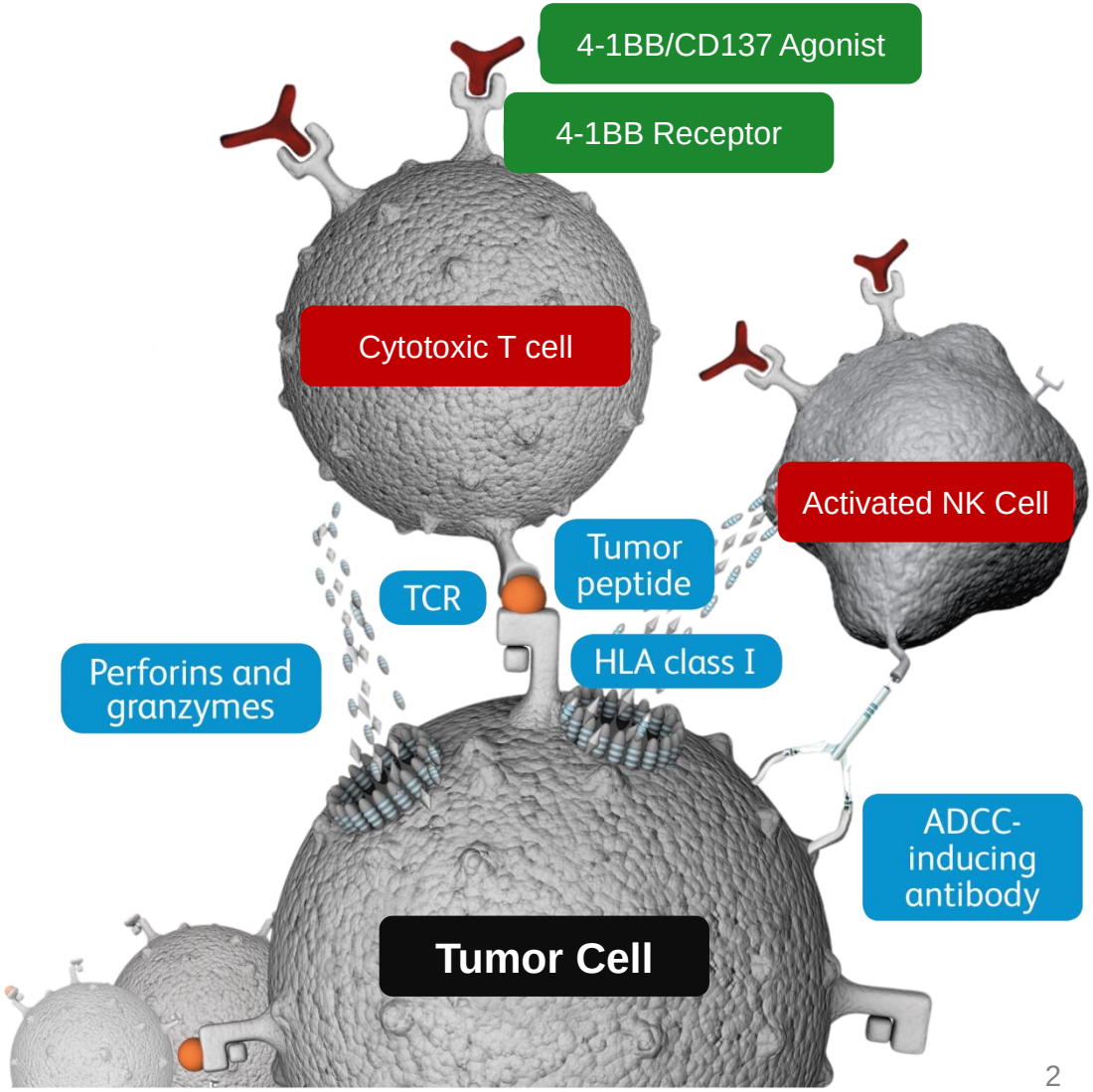
CD137/4-1BB Mechanism of Action

- A co-stimulatory molecule induced upon TCR activation that enhances cytotoxic T cell responses
- Increases NK cell mediated killing of tumor cells targeted with IgG1 mAbs
- Utomilumab (PF-05082566) is a fully human IgG2 CD137/4-1BB agonist



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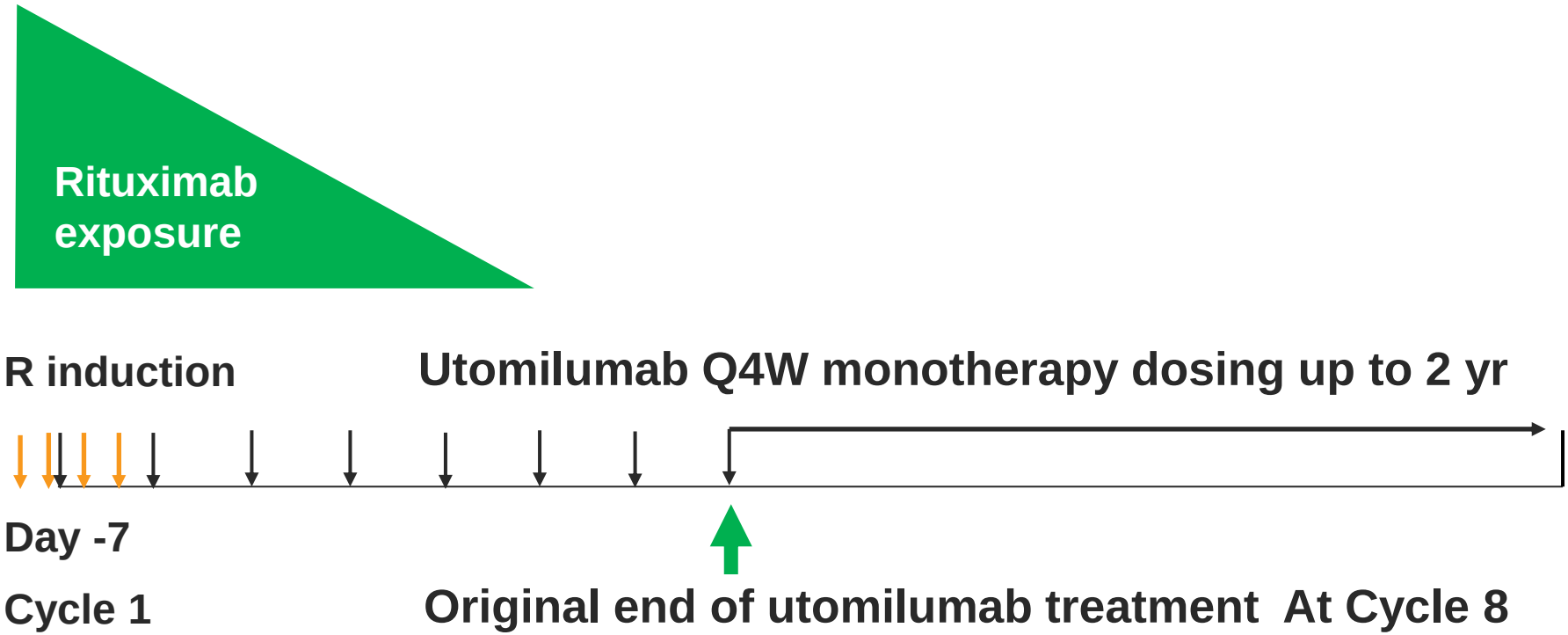
Study B1641001 Treatment Schema
Rituximab Induction Followed By Utomilumab

- Range of utomilumab Doses: 0.03 to 10 mg/kg
- Rituximab induction at 375 mg/m2



Study Objectives

Primary:

- Safety and tolerability of increasing doses of utomilumab with rituximab in CD20 + B cell lymphoma

Secondary:

- Evaluate overall safety profile
- PK/ADA of utomilumab and rituximab
- Anti-tumor effect
- Explore mechanism of anti-tumor effect

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Enrollment Criteria

Inclusion Criteria

- Relapsed/Refractory CD20+ Non-Hodgkin's lymphoma
  - Now focusing on R-refractory FL and on relapsed DLBCL
- Measurable disease (Cheson 2007 criteria)
- Age ≥ 18 years or older
- ECOG performance status of ≤1
- Adequate organ function

Exclusion Criteria

- CNS primary or CNS metastases
- Monoclonal antibody within 60 days of first dose
- Prior therapy with an agent of the same mechanism

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Patient Characteristics

Patients Treated (Total = 45), n (%)	Male 26 (58) Female 19 (42)
Number of Prior Therapies (%)	1-3 25 (55.6) > 3 20 (44.4)
Mean Age (range)	61.1 (38-84)
B Cell Lymphoma Subtype, n (%)	
Follicular Lymphoma*	30 (66.67)
Mantle Cell Lymphoma	5 (11.1)
DLBCL	3 (6.67)
Small Lymphocytic Lymphoma	2 (4.44)
Marginal Zone	4 (8.89)
Nodular LPHL	1 (2.2)

**includes pts with transformation*

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Linear PK and Low Incidence of ADA

- Linear PK in dose range of 0.03 to 10 mg/kg
- Mean $t_{1/2}$ is ~20 days based on preliminary POPPK analysis.
- The incidence of ADA for utomilumab was ~ 8%.

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The Combination Is Well Tolerated

Adverse Event	Rituximab (TE) Label Reference		Rituximab + Utomilumab (TE)		Rituximab + Utomilumab (Related)	
	All grades (%)	Grade III/IV (%)	All Grades n (%)	Grade III n (%)	All Grades n (%)	Grade III (%)
Fatigue	26	1	15 (33.3)	0(0)	11 (24.4)	0(0)
Infusion Related Reactions	77	3	9 (20.0)	2(4.4)	9 (20.0)	2(4.4)
Rash	15	1	9 (20.0)	0 (0)	5 (11.1)	0 (0)
Diarrhea	10	1	6 (13.3)	0 (0)	4 (8.9)	0 (0)
Nausea	23	1	4 (8.9)	0 (0)	3 (6.7)	0 (0)
URTI	--	--	7 (15.6)	0 (0)	2 (4.4)	0 (0)
Headache	19	1	6 (13.3)	0 (0)	4 (8.9)	0 (0)
Pyrexia	53	1	6 (13.3)	0 (0)	2 (4.4)	0 (0)

No AEs > Grade 3 and Grade 3 infusion reactions were related to rituximab only

No relationship between dose of utomilumab and frequency and severity of AE's

Out of 45 patients

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Summary of response data in NHL in B1641001

	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	ORR 95% exact CI
All patients (n=43)	4 (9.3)	6 (14.0)	21 (48.8)	9 (20.9)	10 (23.3) (11.8, 38.6)
R-refractory* FL & MCL (n=19)	4 (21.1)	4 (21.1)	7 (36.8)	4 (21.1)	8 (42.1) (20.3, 66.5)
FL (n= 16)	4 (25.0)	3 (18.8)	5 (31.3)	4 (25.0)	7 (43.8*) (19.8, 70.1)
FL Expansion Cohort 1.2 mg/kg (n=3)	2 (67.7)	1 (33.3)	0	0	3 (100) (29.2, 100)
Mantle Cell (n = 3)	0	1 (33.3)	2 (66.7)	0	1 (33.3) (0.8, 90.6)

*(50%) 1 R-refractory FL patient with high level response but with new lesion, on biopsy comprised mainly T cells

As of Feb 2016

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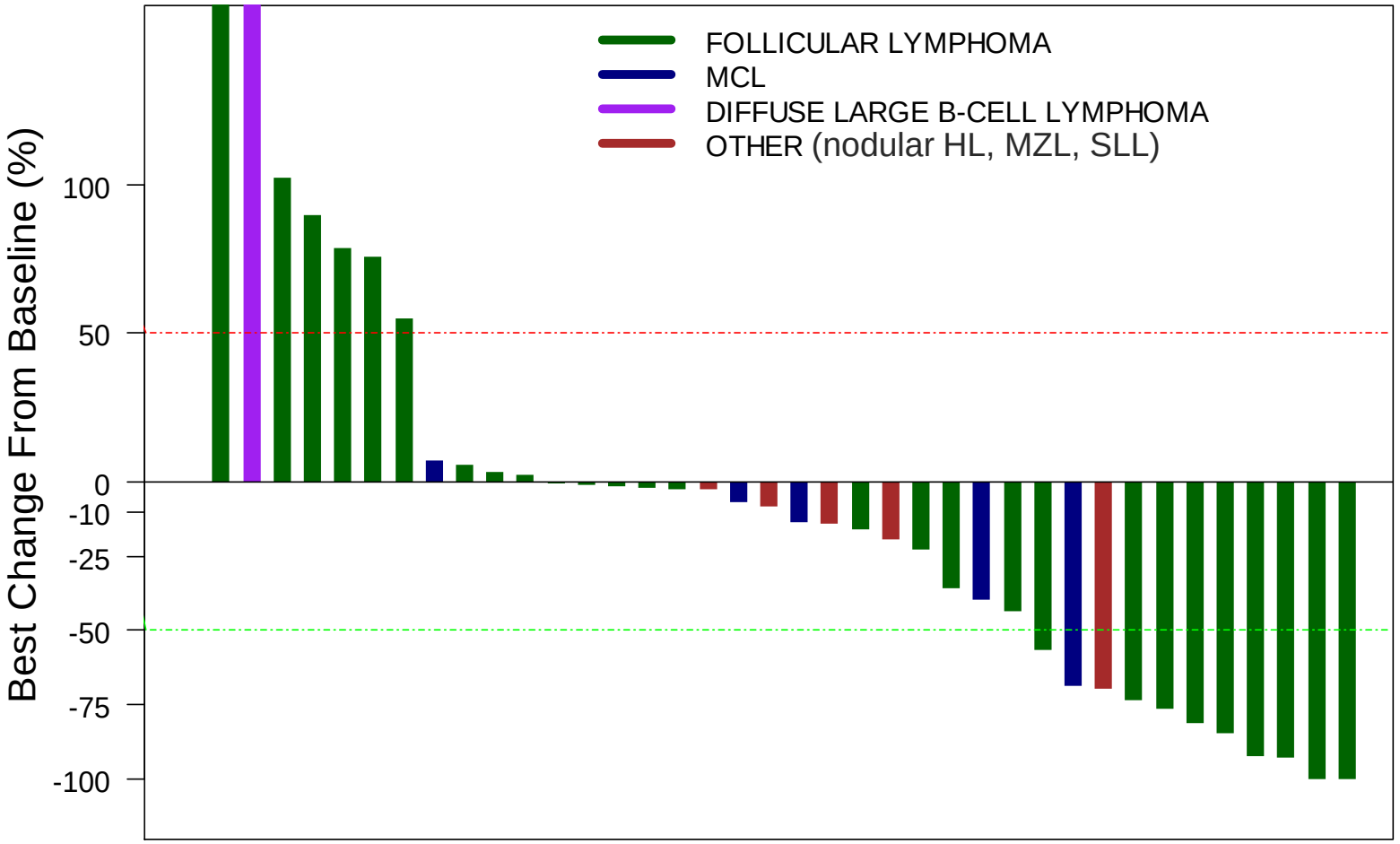
Anti-Tumor Activity: All NHL Patients



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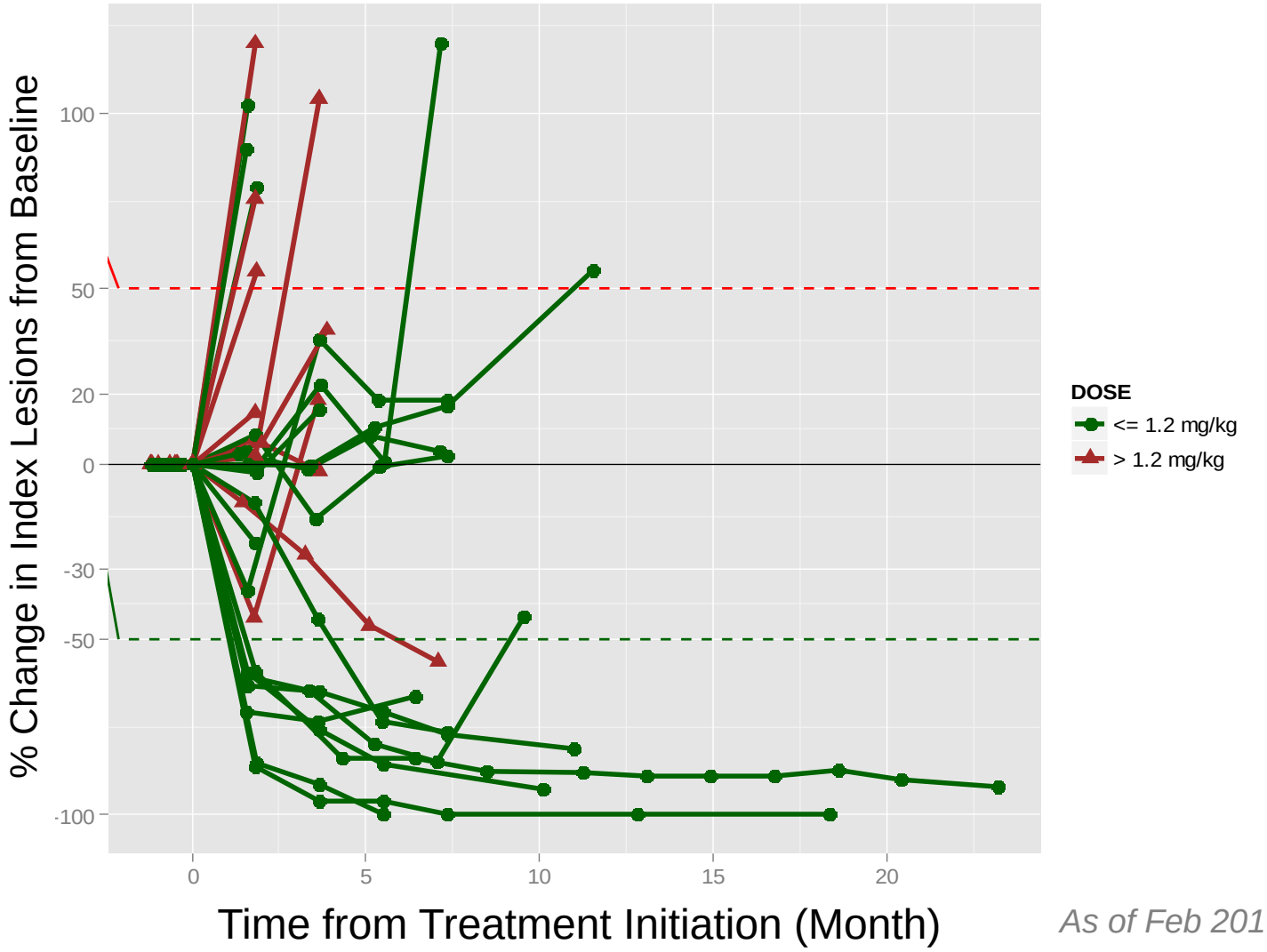
Change in Tumor Burden: All FL patients



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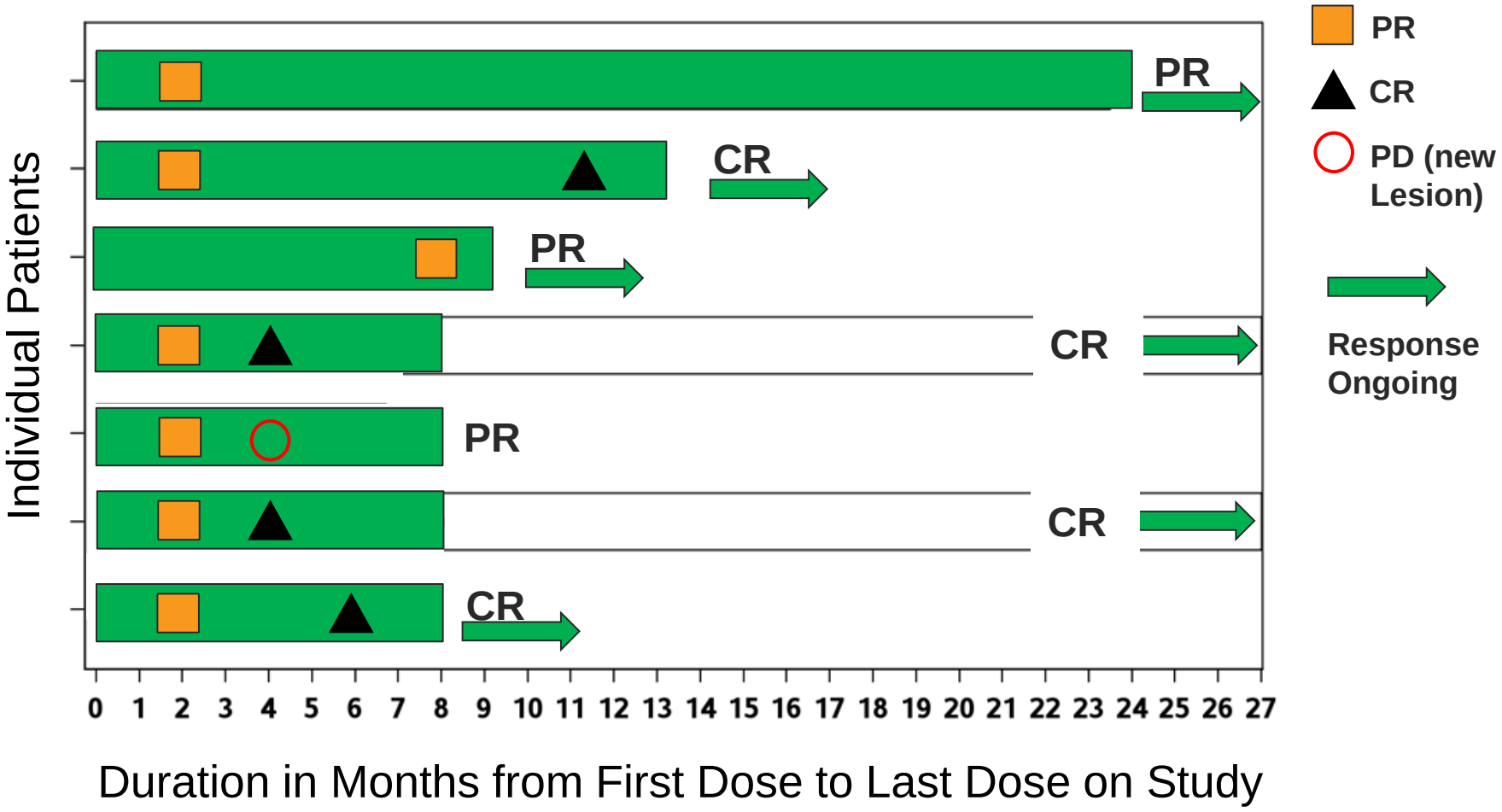
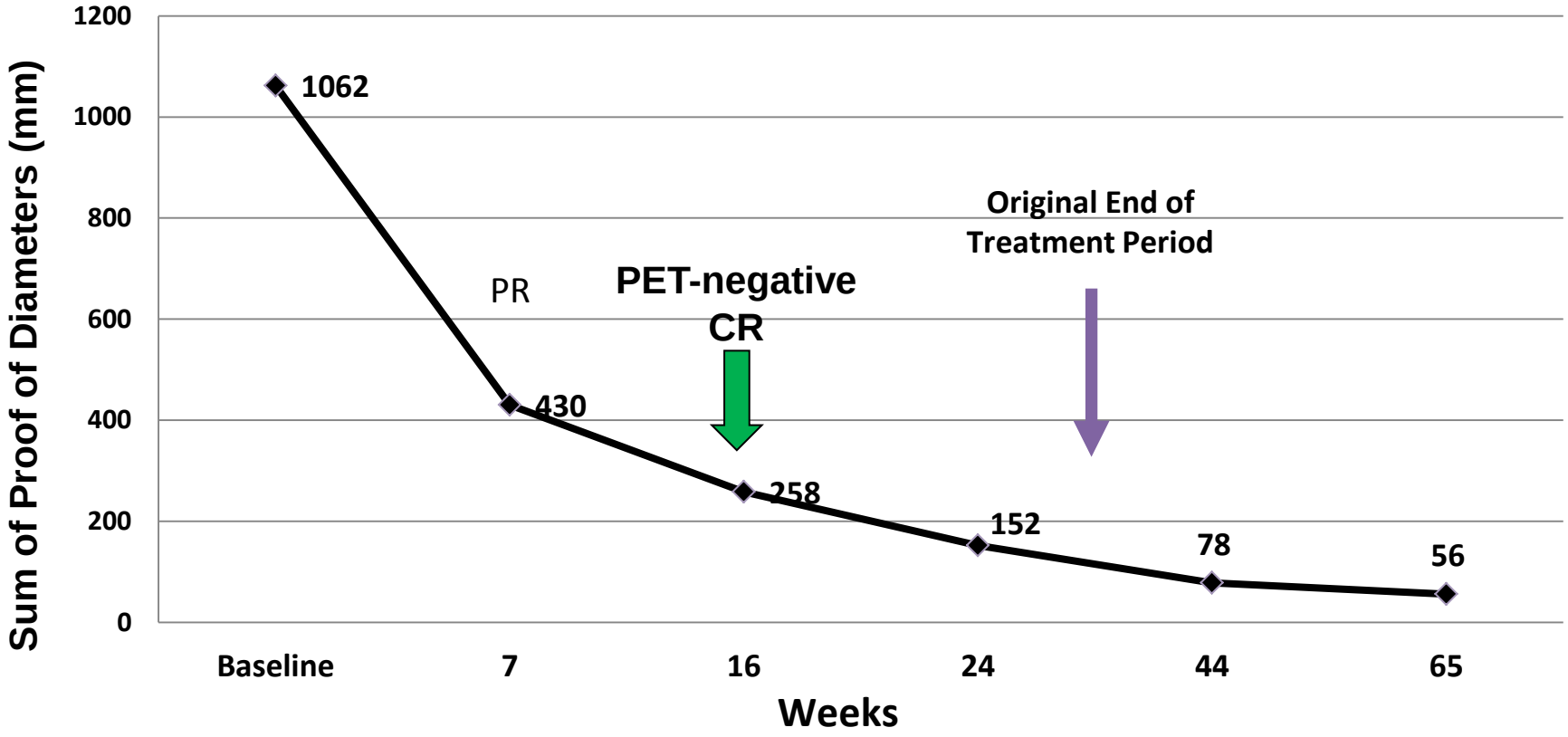
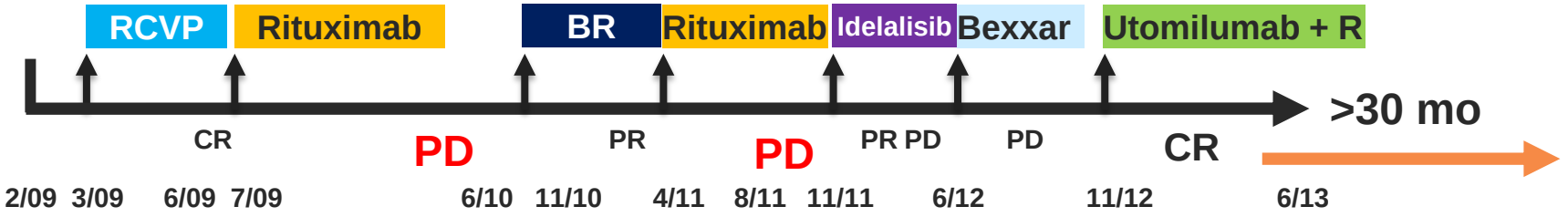
Response Is Generally Rapid and Durable In Patients With Rituximab-Refractory FL



Responses were confirmed

Patient 1: CR By Week 16 (0.12 mg/kg)





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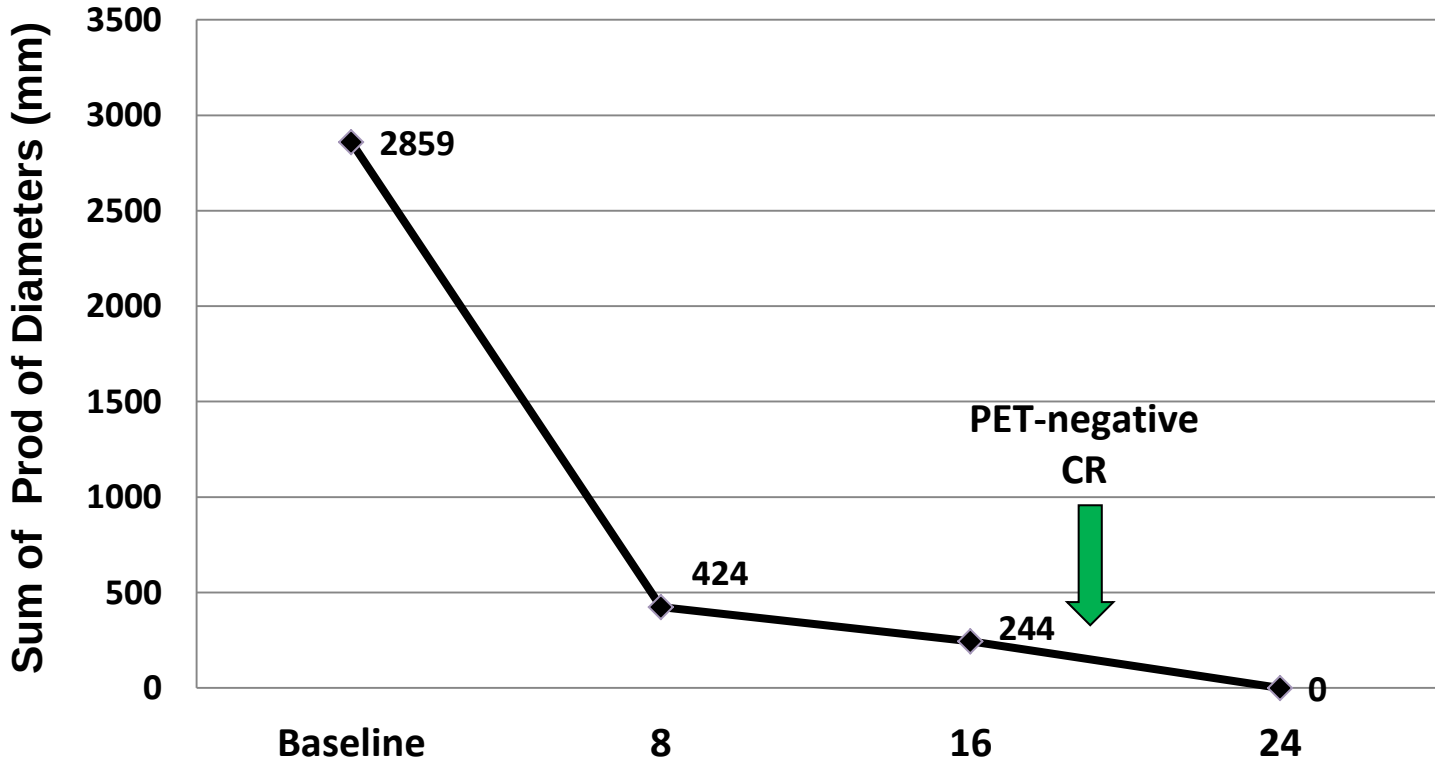
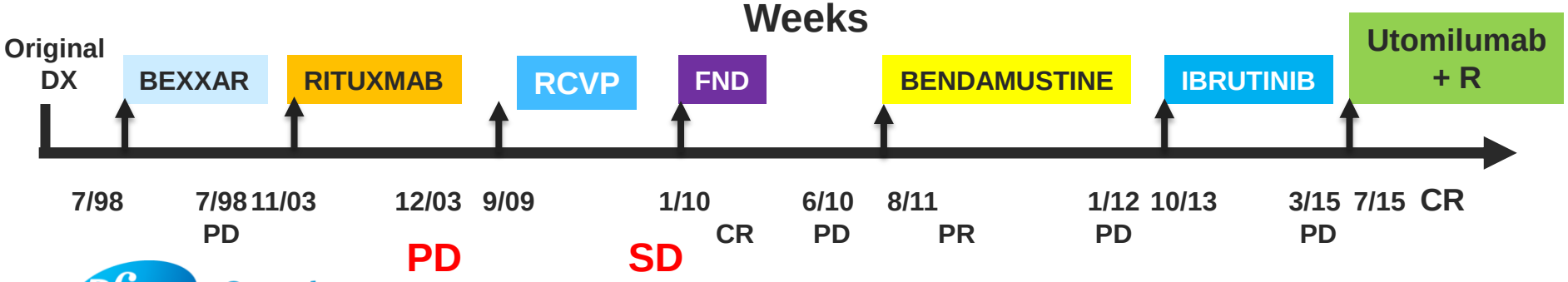
Patient 2: CR by Week 16 (1.2 mg/kg)





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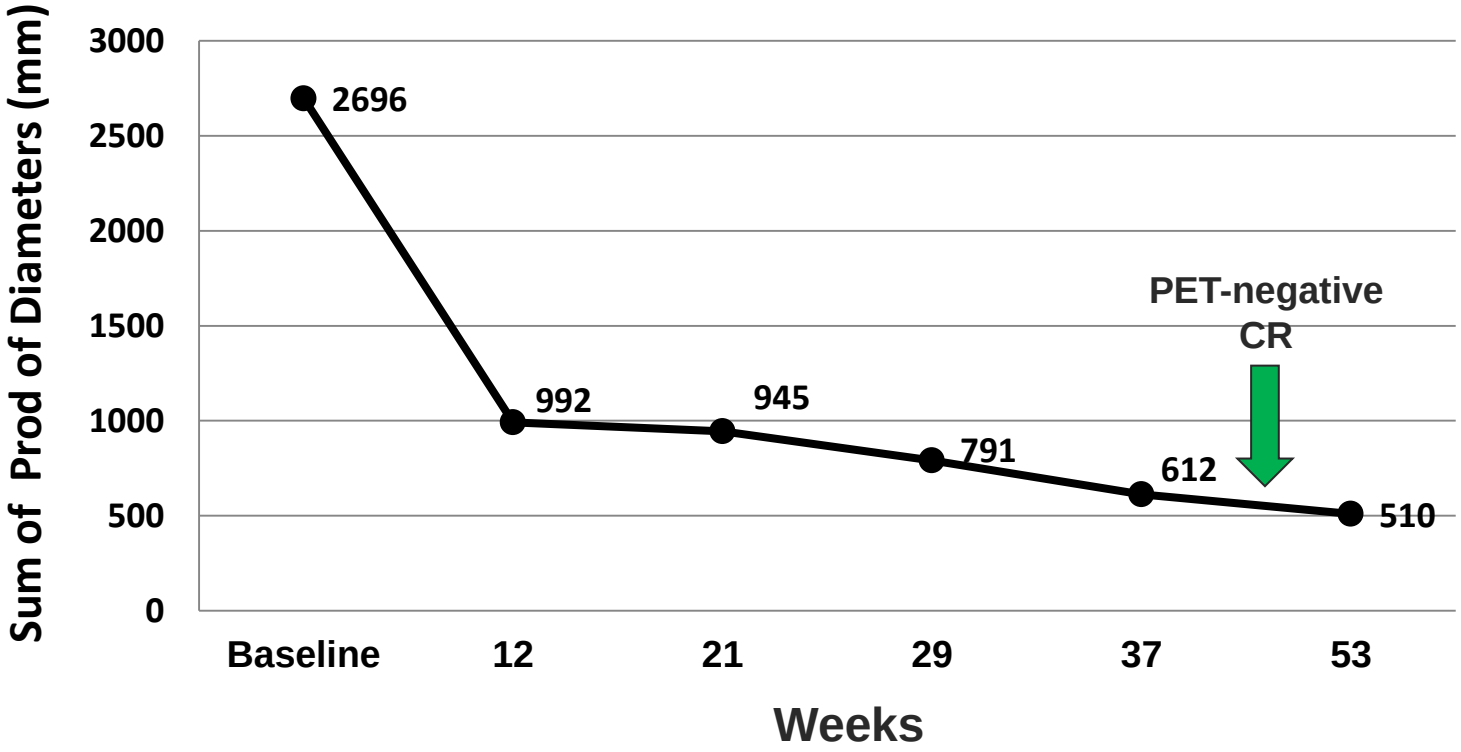
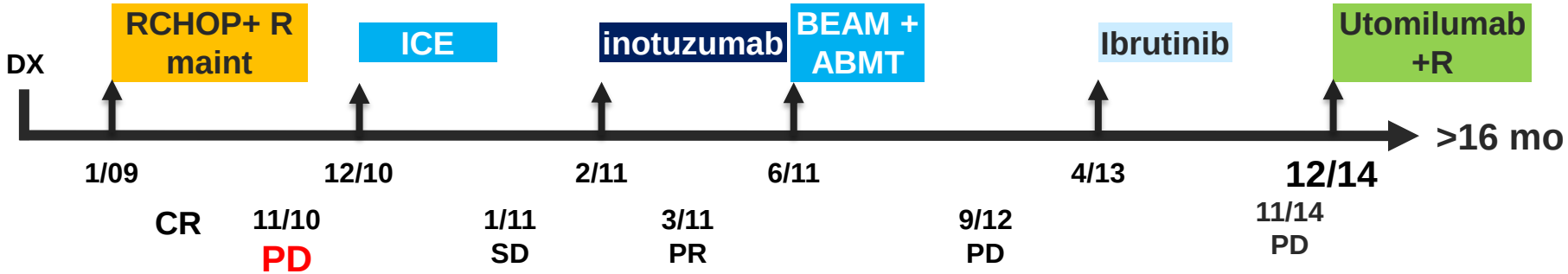
Patient 3: CR At Month 11 (1.2 mg/kg)





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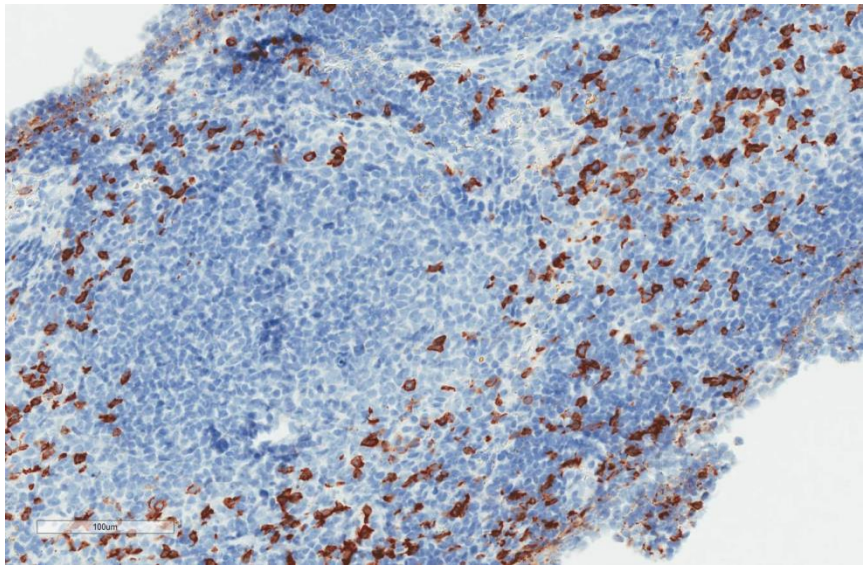
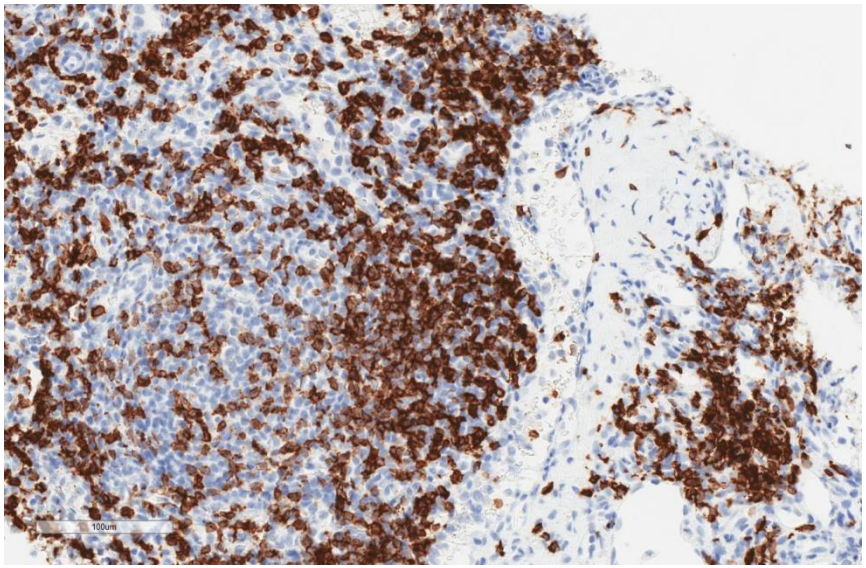
On-treatment Increase in Tumor Infiltrating CD8 T cells

Patient 3

Baseline



On treatment



Discussion

- R + utomilumab (PF-05082566) is well tolerated in patients with relapsed or refractory B cell NHL up to 10 mg/kg
- Preliminary ORR of 50% in R-refractory follicular lymphoma
  - Median Duration of Response at ≤1.2 mg/kg greater than 10 mo
- Tumor biomarker data are supportive of the induced expansion of anti-tumor CD8 T cells
- Expansion cohort of R-refractory FL ongoing at a dose of 1.2 mg/kg,
- DLBCL enrollment continuing in this study and in a new study with a triplet containing avelumab (anti-PD-L1)

Acknowledgments

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