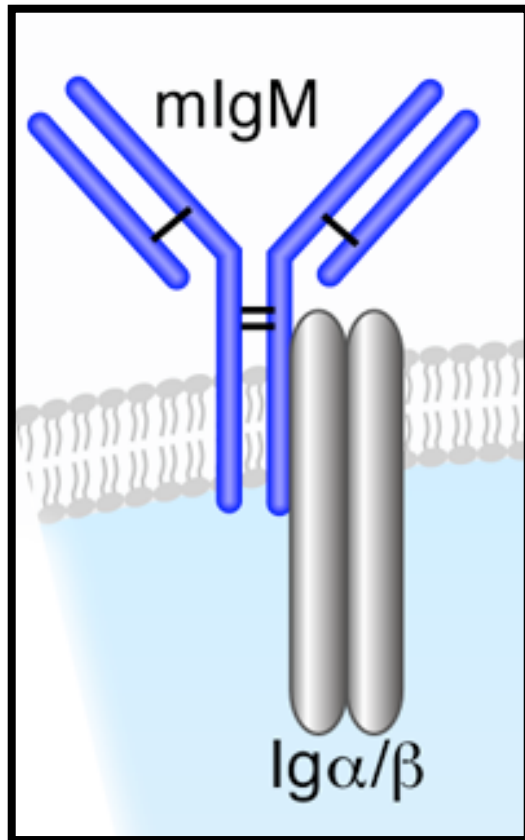


Fostamatinib Disodium, an Oral Inhibitor of Syk, is Well Tolerated and Has Significant Clinical Activity in Diffuse Large B-Cell Lymphoma and Chronic Lymphocytic Leukemia

Jonathan W. Friedberg, Jeff Sharman, Julia Schaefer-Cutillo, Patrick B. Johnston, Sven De Vos, Ann LaCasce, John P. Leonard, Larry D. Cripe, Rajni Sinha, Stephanie A. Gregory, John Sweetenham, Julie M. Vose, Ann M. Lowe, Ronald Levy and Margaret A. Shipp

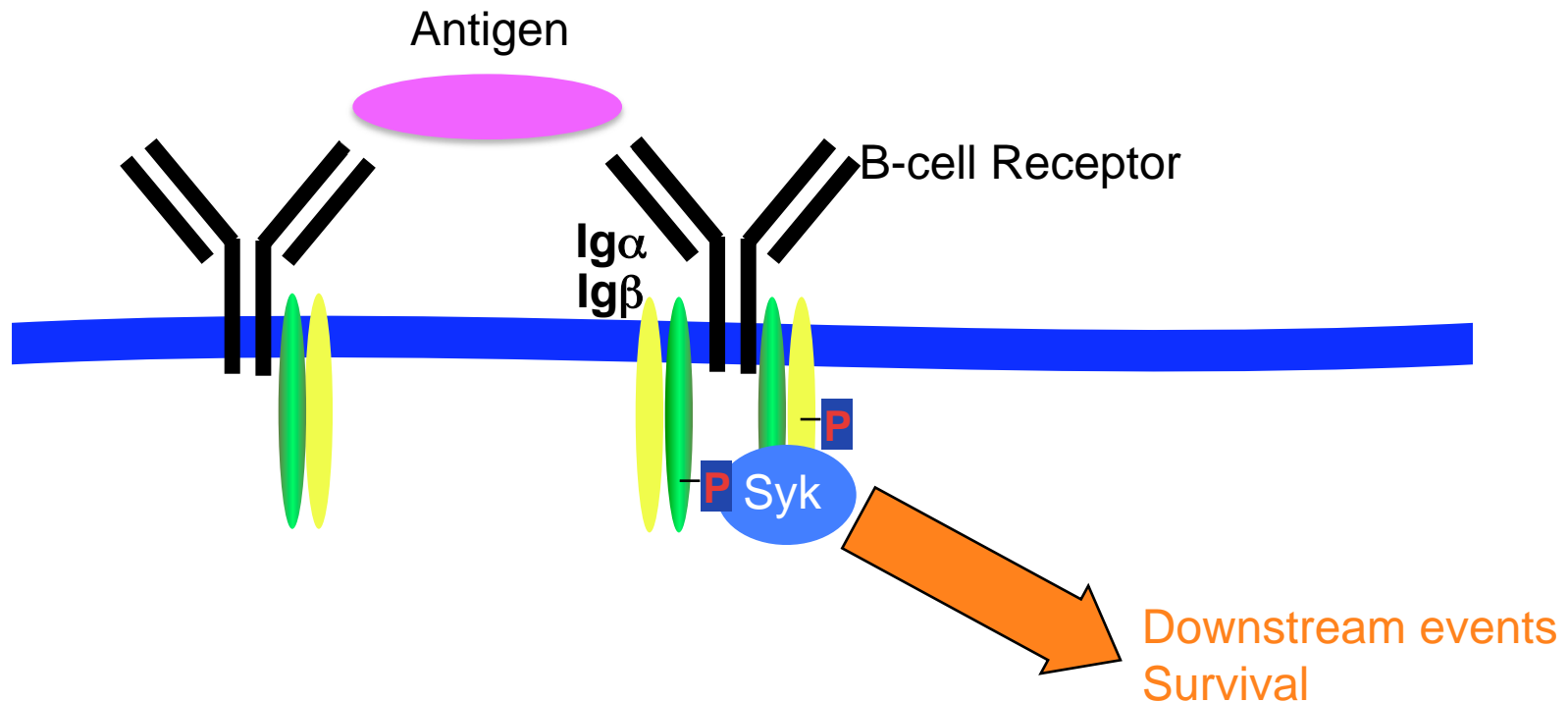
B-Cell Receptor (BCR) Signaling



- BCR is critical for normal B-cell maturation and survival:
 - transgenic mice with defective BCRs exhibit apoptosis of mature B-cells
- BCR is maintained on most B-cell lymphomas and tonic signaling through BCR maintains DLBCL survival *in vitro*

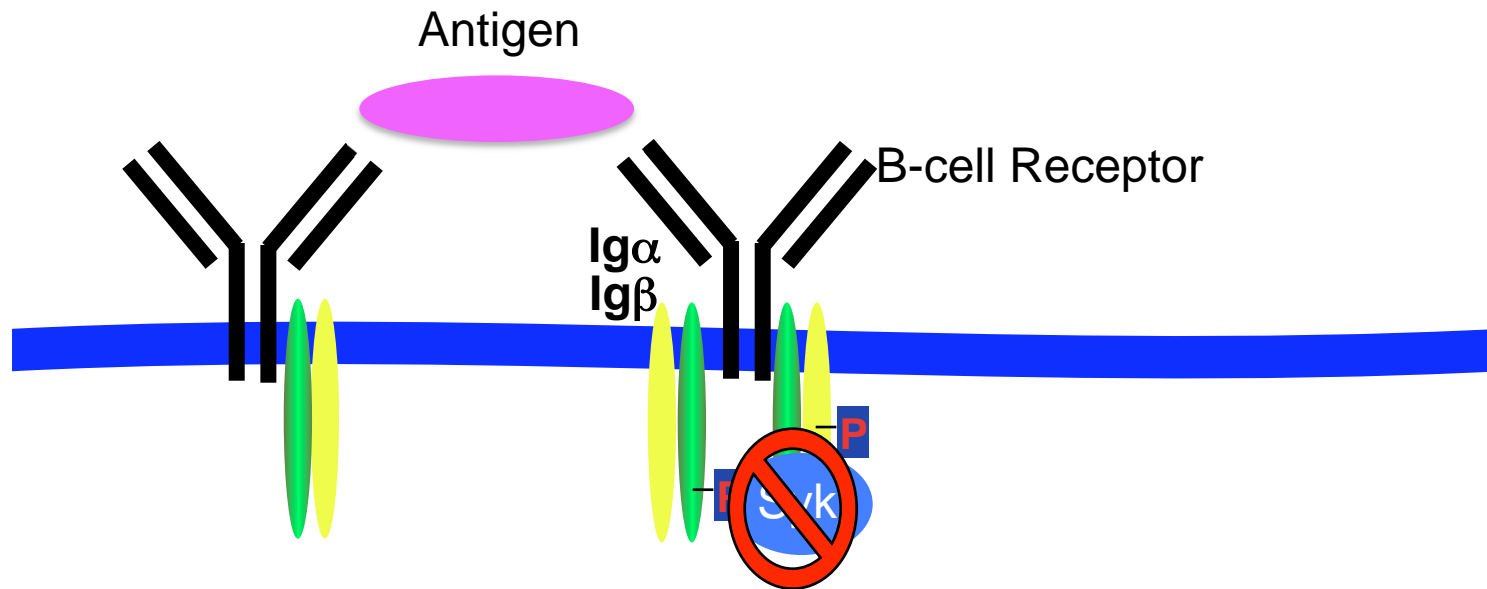
Cell 117:787, 2004
Blood 111:2230, 2008

Role of Syk and Modulation of BCR Signaling



Tonic BCR signaling requires Syk expression and activity (phosphorylation)

Role of Syk and Modulation of BCR Signaling



Fostamatinib Disodium: ATP-competitive Syk inhibitor

Tonic BCR signaling and lymphoma cell survival can be selectively targeted with this Syk inhibitor *in vitro*

Syk as a Therapeutic Target for NHL

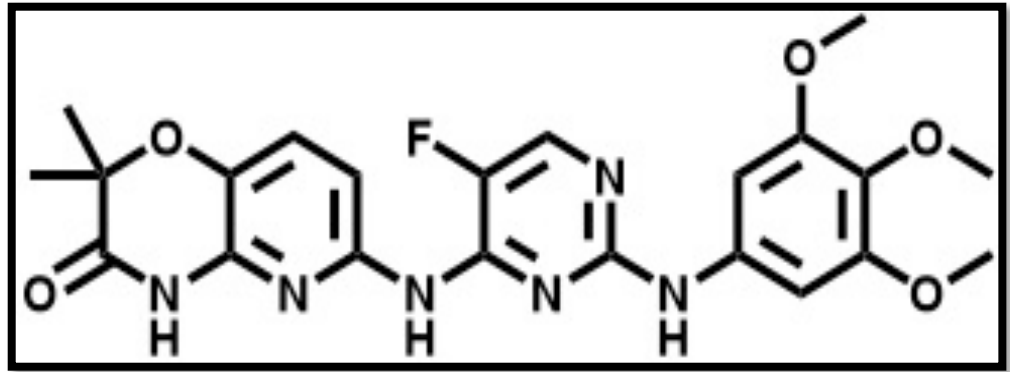
- Enhanced BCR-signaling through Syk occurs in follicular lymphoma cells compared with nonmalignant B-cells.
- A subset of DLBCL exhibits over-expression of BCR pathway components, including Syk.
- *Therefore, Syk represents a novel, rational therapeutic target for a subset of BCR-dependent NHL.*

Blood 108: 3135, 2006

Blood 108: 4156, 2006

Blood 105: 1851, 2005

Fostamatinib Disodium: Targeting Syk



- Oral Syk inhibitor
 - Specific and potent, pro-drug of R406 (shown)
- Human experience
 - Safety demonstrated in healthy human subjects
 - Activity demonstrated in Phase 2 trials (> 200 patients):
 - Rheumatoid arthritis
 - ITP

Phase 1: Fostamatinib Disodium

- Eligibility: Relapsed or refractory B-cell NHL
 - No limitations on prior therapies or age
 - Adequate organ function
 - Histologies:
 - DLBCL, FL, MCL, CLL/SLL, other indolent NHL

Phase I trial

200 mg BID

250 mg BID

Primary endpoint

Determine safe,
tolerable dose for
Phase 2 study

Phase 1: Fostamatinib Disodium

Phase I trial

200 mg BID (N=6)

250 mg BID (N=7)

- Median age 74 (Range 52-91)
- Prior Rx: 2 ASCT; 4 RIT
- Histology:
 - DLBCL, n=3
 - MCL, n=3
 - FL, n=5
 - CLL/SLL, n=2

Phase 1 “DLT”:

Neutropenia, thrombocytopenia and diarrhea
DSMB decision: 200 mg BID is Phase 2 dose

Phase 2: Fostamatinib Disodium (200 mg BID)

- 68 patients enrolled: relapsed and heavily treated refractory lymphoma
 - **Group 1: DLBCL (N=23)**
 - ASCT, n=12
 - **Group 2: FL (N=21)**
 - RIT, n=8
 - ASCT, n=4
 - **Group 3: “Other” (N=24)**
 - CLL/SLL, n=11
 - Mantle cell NHL, n=9
 - Lymphoplasmacytic, n=1
 - MZL, n=3

Phase 2 (200 mg BID): All Related Serious Adverse Events

Serious Adverse Event	Group 1 (DLBCL)	Group 2 (FL)	Group 3 (Other NHL)	Total (n)
Febrile neutropenia	1	1	3	5
Pancytopenia	1	0	0	1
Upper abdominal pain	0	0	1	1
Diarrhea	0	0	1	1
Renal Failure	0	0	1	1
Superior vena cava occlusion	1	0	0	1

n=number of events

Phase 2 (200 mg BID): Incidence and Severity of Related AEs**

Adverse Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Diarrhea	34	7	0	0	41
Fatigue	25	16	0	0	41
Neutropenia*	6	7	10	7	31
Anemia	7	12	7	0	27
Thrombocytopenia	10	10	0	3	24
Hypertension	6	10	6	0	22
Nausea	18	3	0	0	21
AST increased	13	0	4	0	18
Headache	10	6	0	0	16

* Febrile neutropenia 7.5%

** Grade per CTCAE v.3. There were no related grade 5 events.

Phase 2: Efficacy

- Group 1: Diffuse large B-cell NHL
 - **ORR: 22%**
 - 1CR and 4PR (5/23); also 4SD
- Group 2: Follicular NHL
 - **ORR: 10%**
 - 2PR (2/21); also 11SD
- Group 3: “Other” NHL
 - **CLL/SLL ORR: 55%** (6/11 PR); 2SD
 - **MCL ORR: 11%** (1/9 PR); 4SD

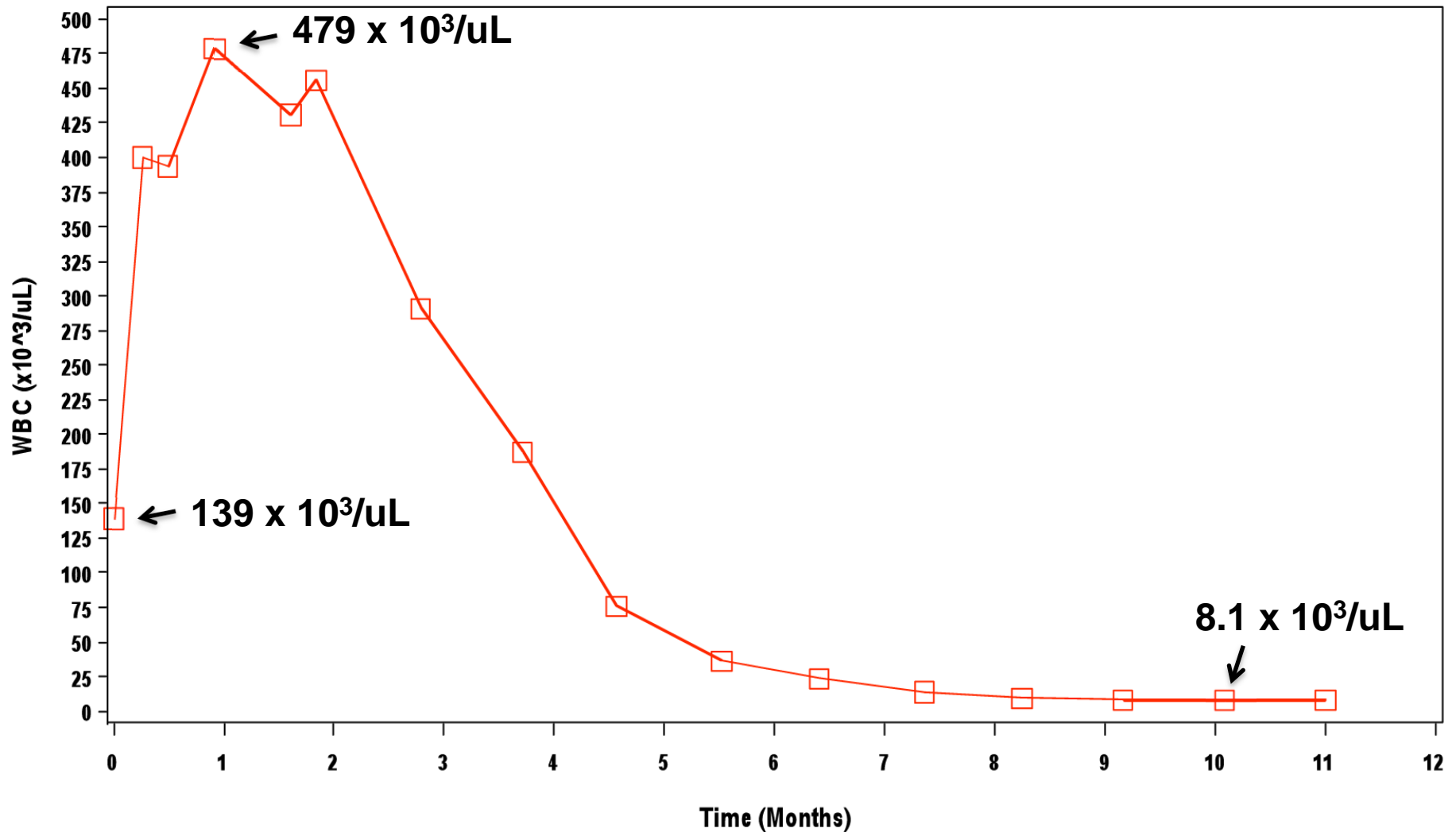
Diffuse Large B-cell Lymphoma: Nodal Response

Before Treatment

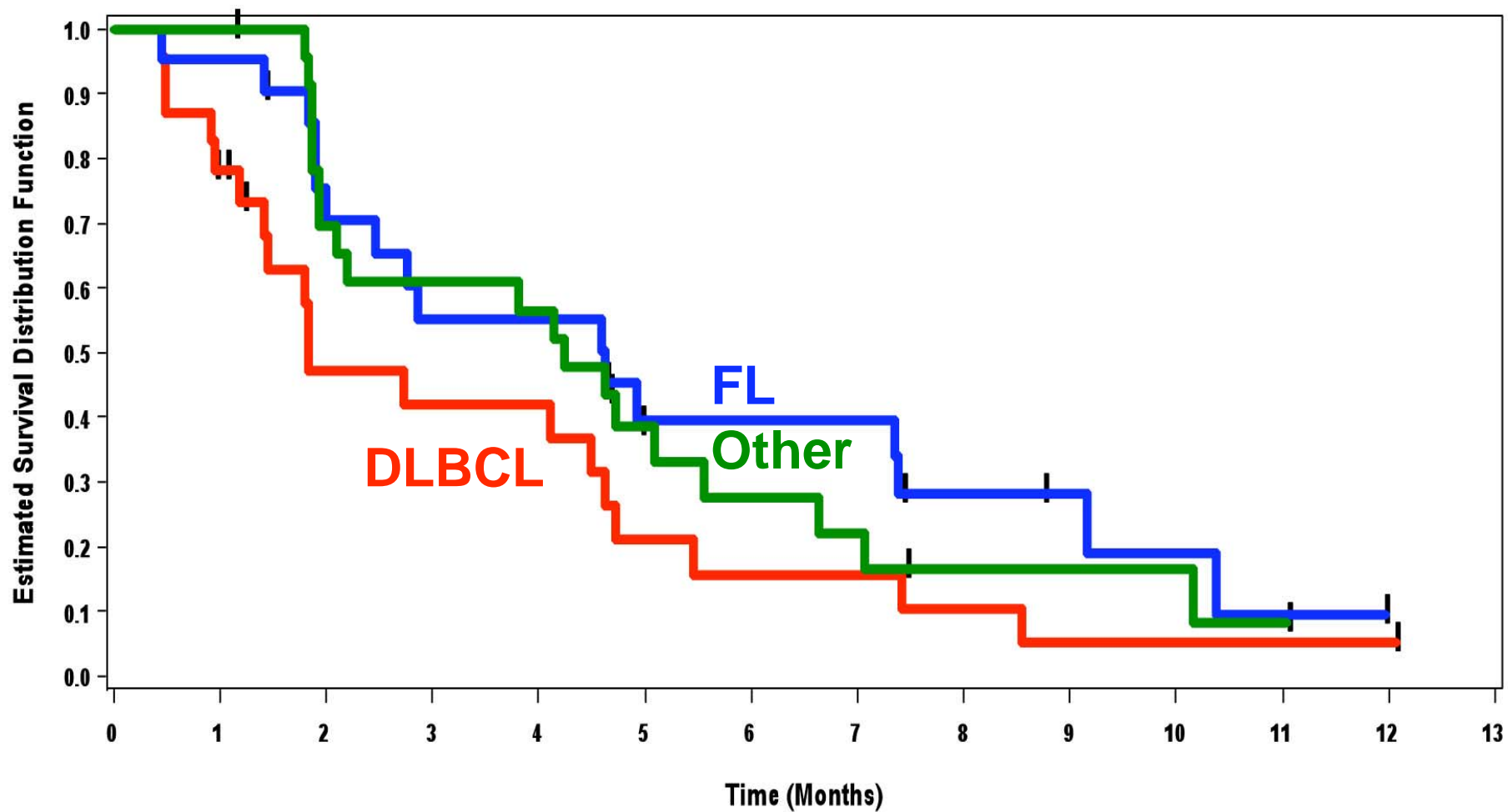
After Treatment



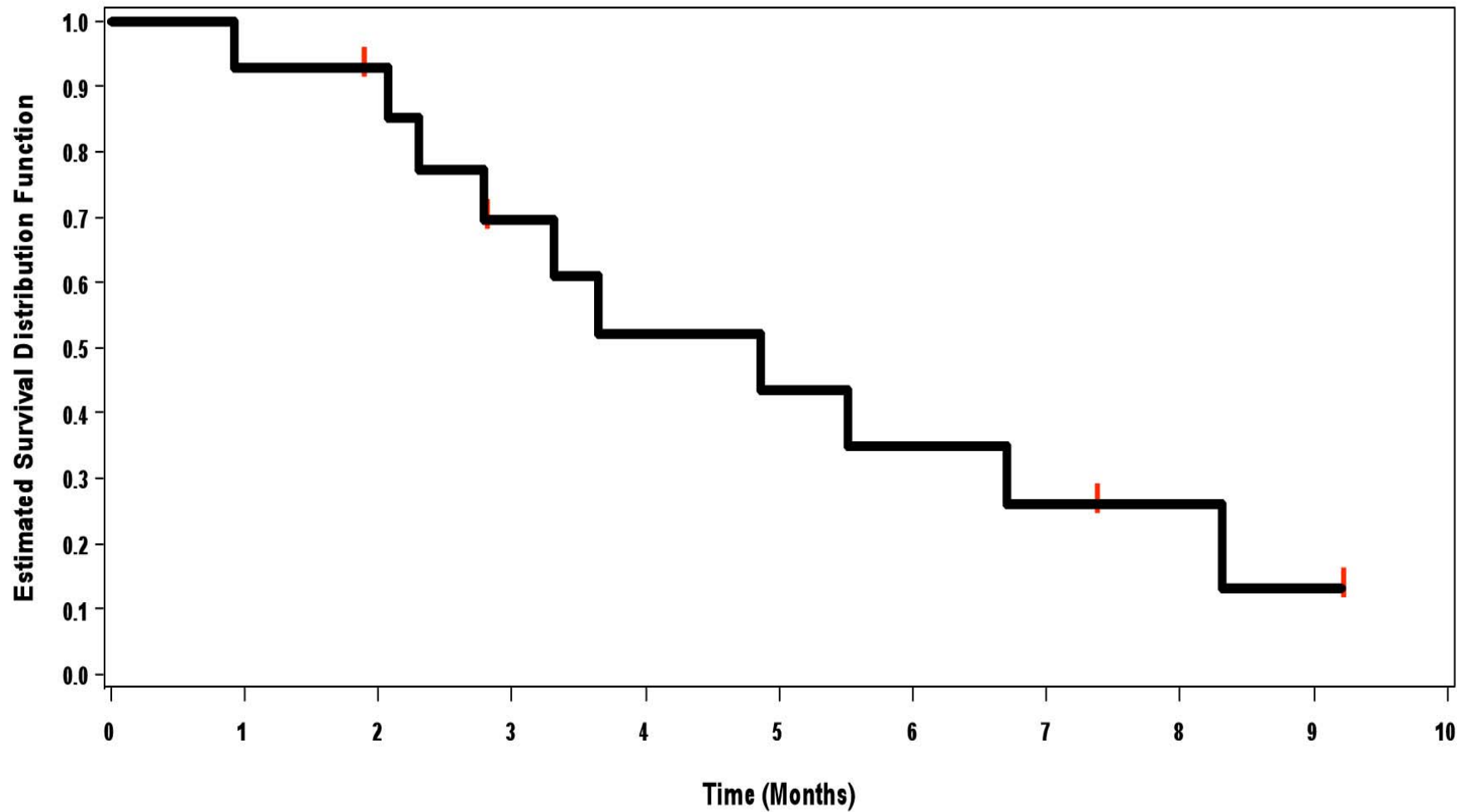
CLL- Response in Circulating Disease Over Time



Phase 2: Progression-Free Survival



Phase 2: Duration of Response



Summary: Fostamatinib Disodium in NHL

- **Inhibition of a critical survival pathway in B-cell lymphoma mediated by BCR results in tumor cell death and response in a proportion of heavily pretreated patients with CLL/SLL and DLBCL.**
- The most common toxicities are hematologic and reversible. No B-cell specific toxicities were observed.
- Rapid nodal responses were observed in patients with bulky disease
 - Transient increases in circulating CLL cells noted
- Additional clinical trials planned to confirm these results

Future Directions: Fostamatinib Disodium

- Approaches to identify tumors dependent upon tonic BCR signaling under development
 - Surface immunoglobulin receptor expression an indicator in DLBCL
 - Intracellular phospho-flowcytometry, IHC and RNA profiling under examination
- ABSTRACT 377 - “BCR-Signaling Diversity in Human Lymphoma B-Cells Correlates with Follicular Lymphoma Patient Clinical Outcomes”
- ABSTRACT 802 - “BCL-6 Regulates Tonic BCR Signaling in Diffuse Large B-Cell Lymphomas”