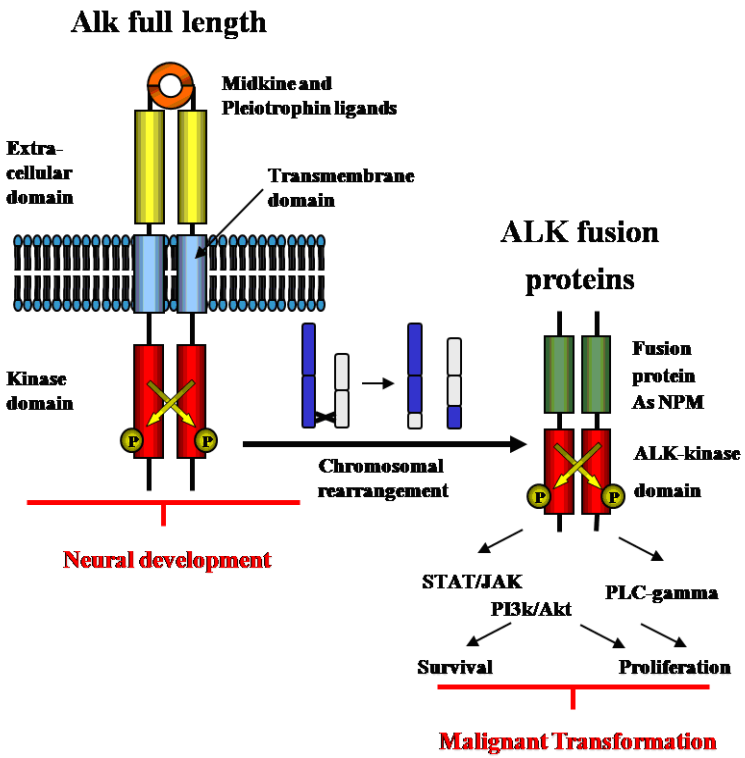
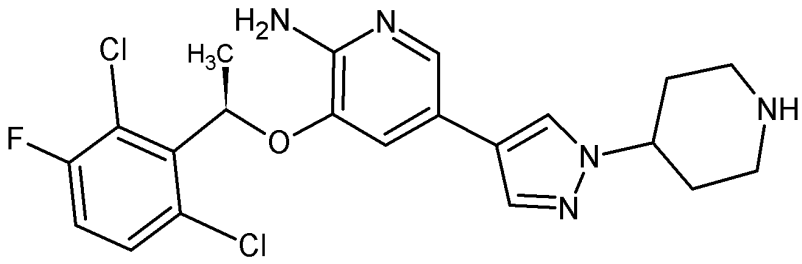
Crizotinib

Carlo Gambacorti-Passerini

Bologna, April 28th, 2015

ALK: Anaplastic Lymphoma Kinase

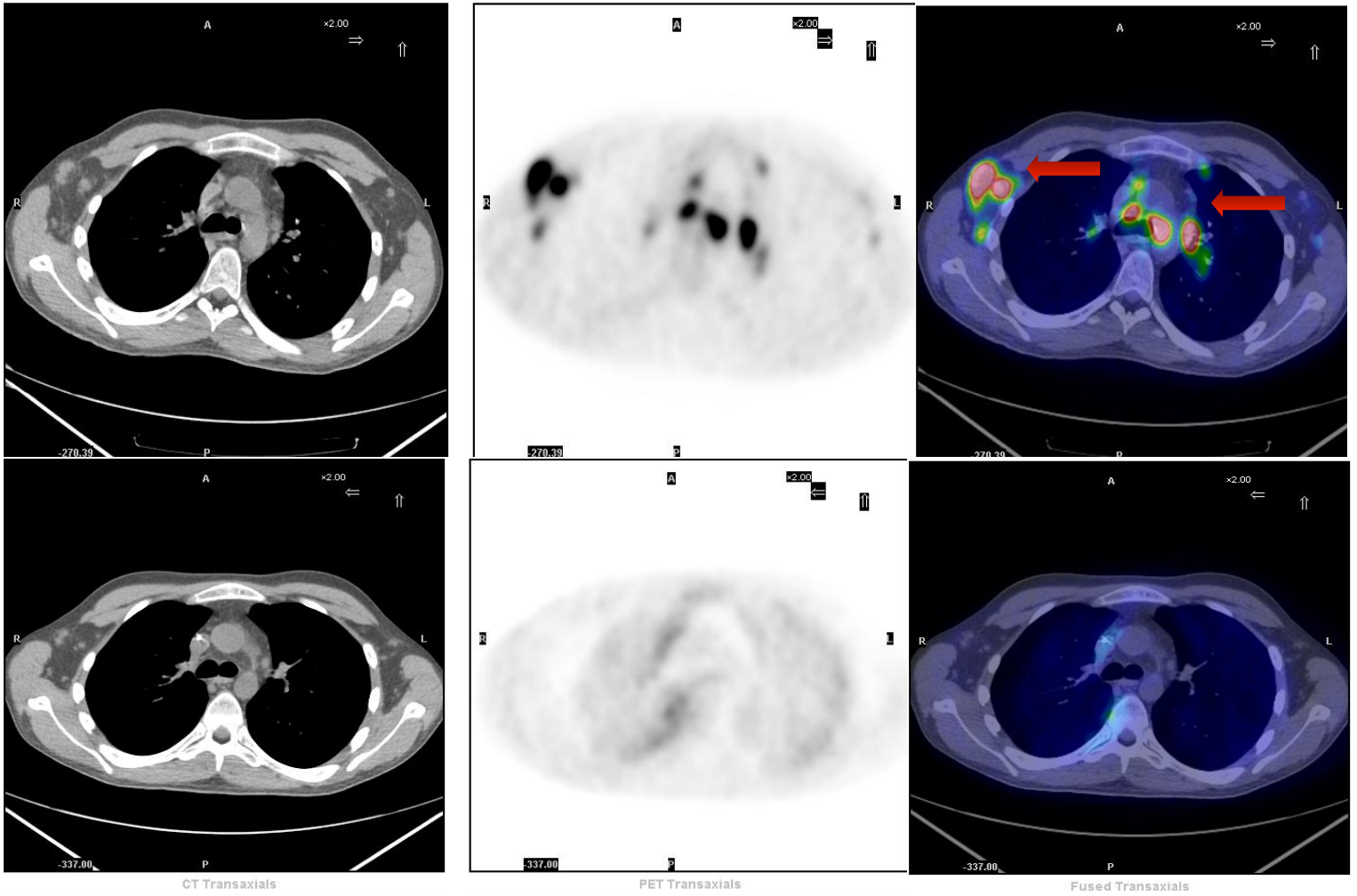




RESULTS¶

Day 0

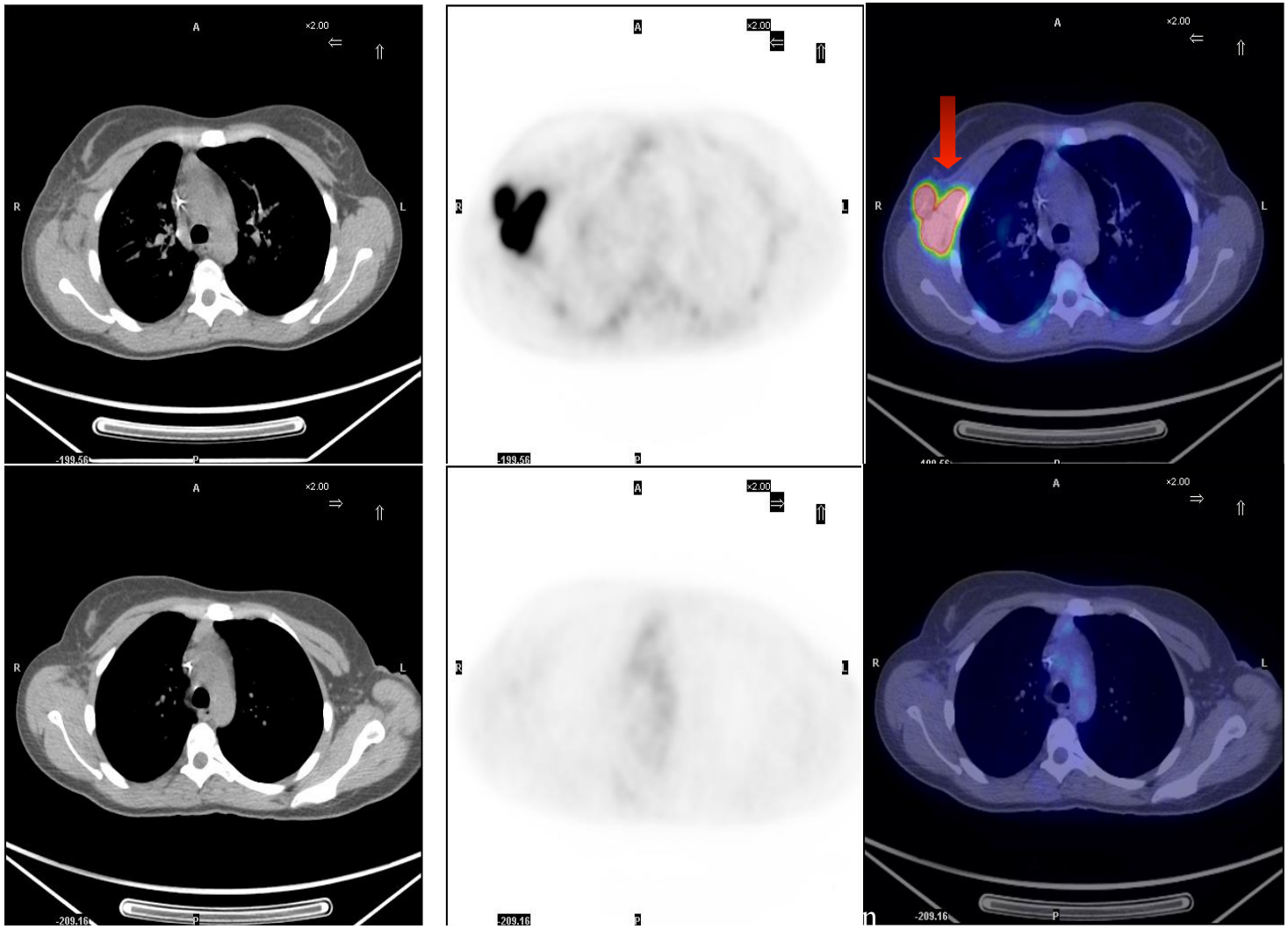
Day + 16



RESULTS¶

Day 0

Day + 28



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Crizotinib in Anaplastic Large-Cell Lymphoma

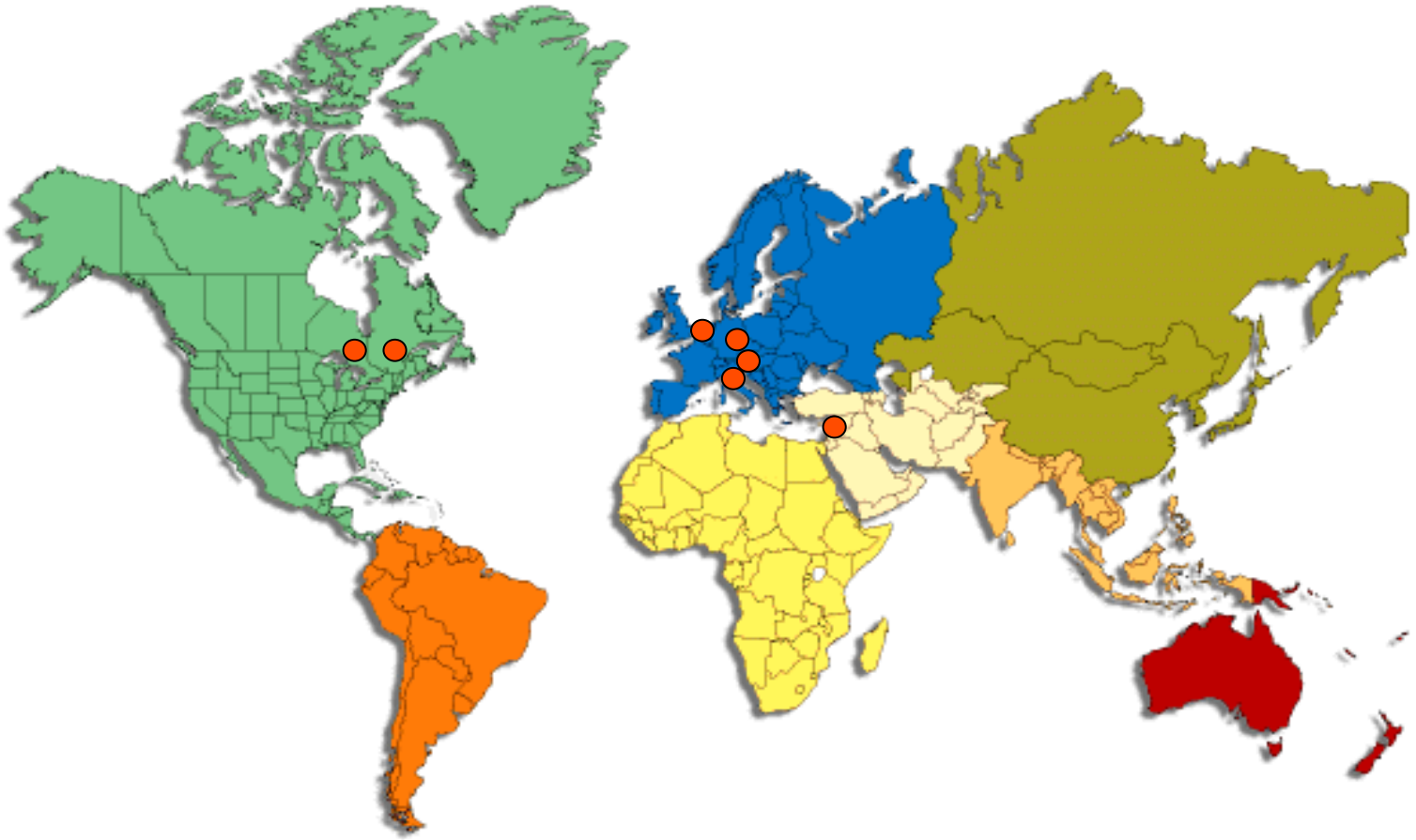
N ENGL J MED 364;8 NEJM.ORG FEBRUARY 24, 2011

Patients and methods

Patients	11 (7 males, 4 females)
Median age	28 years (range 19-55)
Disease	11 Non-Hodgkin Lymphoma (NHL) 9/11 Anaplastic Large Cell Lymphoma (ALCL) 2/11 DLBCL
Prior lines of treatments	1-4 (median 3) 3 autologous BMT 2 allogeneic BMT
Inclusion criteria	Adequate organ function, ECOG performance status 0-4 Measurable disease, expression of ALK by IHC and/or FISH
Exclusion criteria	Uncontrolled cardiac or infectious diseases, Pregnancy Use of known potent CYP3A4 inhibitors/inducers or substrates
Therapy schedule	Crizotinib (250mg BID) as monotherapy until disease progression
Response evaluation	CAT/PET scan (day 28, months 2, 3, 6, 9, 12, 18, 24, 36) FISH by ALK break-apart probe on BM (Shin HJ et al. Diagn Cytopathol 2003;29:61-6) PCR for NPM/ALK on peripheral blood (Mussolin L et al. Leukemia

METHODS

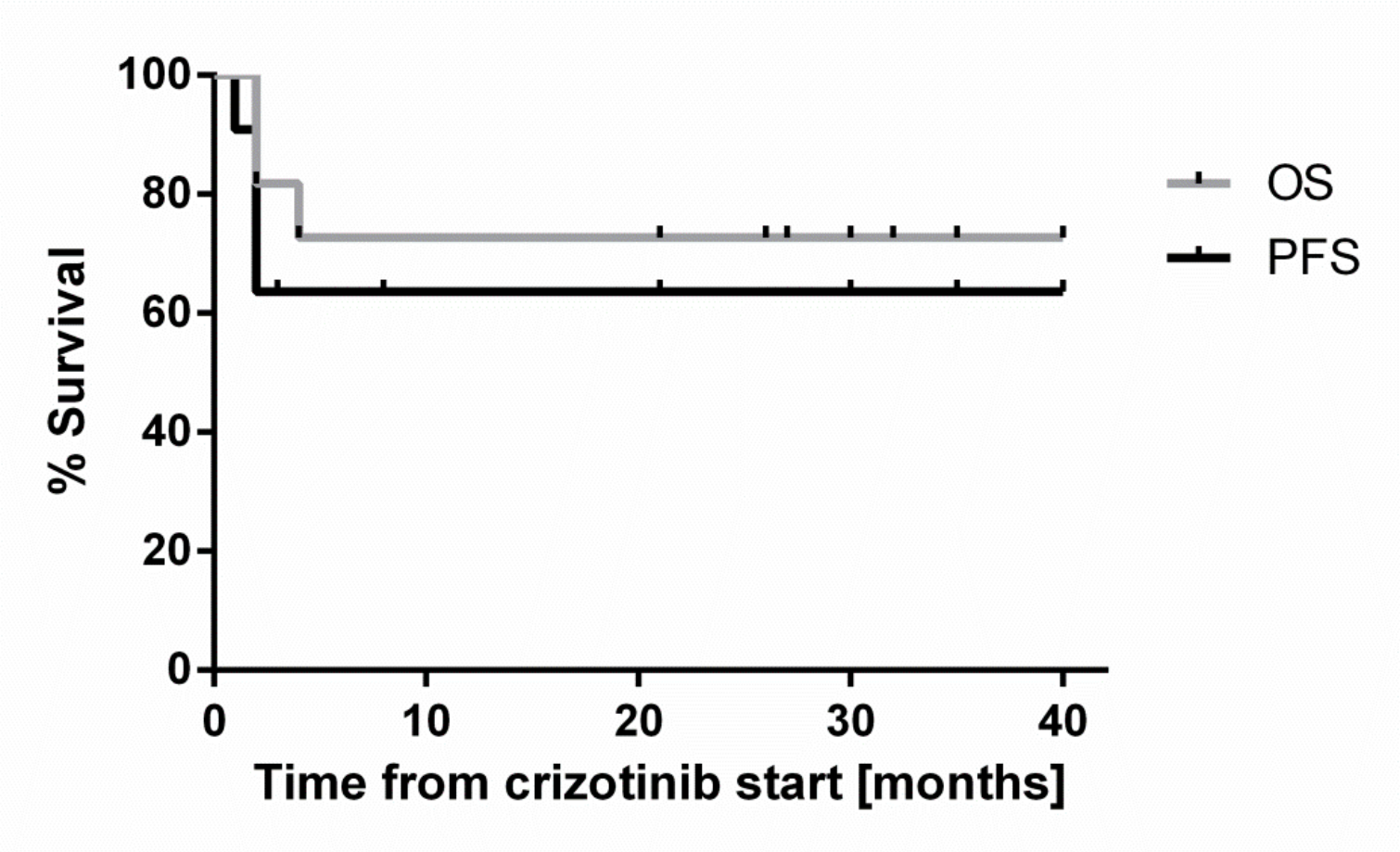
- Type of trial: investigator initiated, compassionate use, named patient protocol



RESULTS

B symptoms and LDH levels	Normalized within 30 days after crizotinib starts
ORR	10/11 (90.9%, 95%CI, 58.7-99.8%) 9/10 CR (81.8%, 95%CI 48.2-97.8%) 1/10 PR (10%, 95 CI, 0.2-44.5%)
	ALCL group : 9/9 (100%) achieved CR
Toxicities (all grade I / II)	ocular flashes (10 patients), peripheral edema (3), skin rash (1), erectile dysfunction (1)
Laboratory abnormalities (all grade I / II)	neutropenia (2), thrombocytosis (1) and LFTs elevation (1). No patient died from a cause related to treatment.
Follow-up (40 months - October 2013)	4/11 patients in CR under continuous crizotinib treatment and negative by NPM-ALK Q-PCR; 4/11 patients (2 DLBCL, 2 ALCL) progressed; 3 died. 3/11 patients received crizotinib before/after allogeneic BMT

Overall Survival (OS) and Progression Free Survival (PFS)



2-years PFS: 63.7% (95% CI 30.8-89.1 %)
2-years OS: 72.7% (95% CI 39.1-94.0 %)

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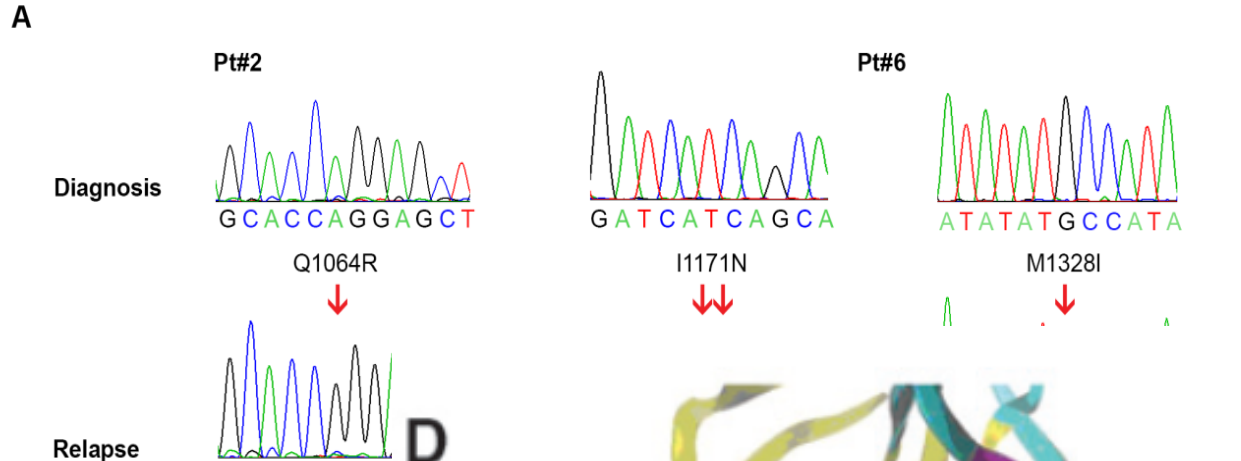
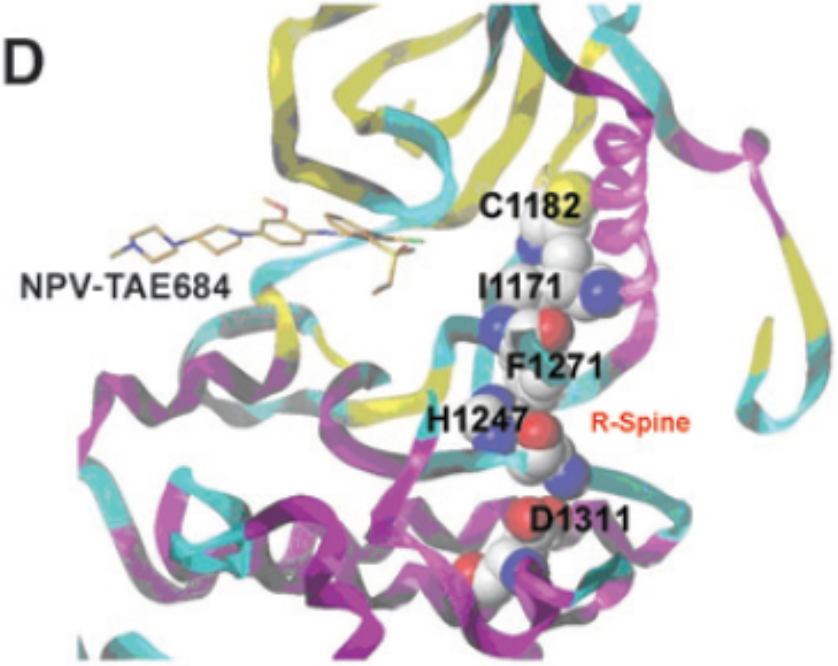
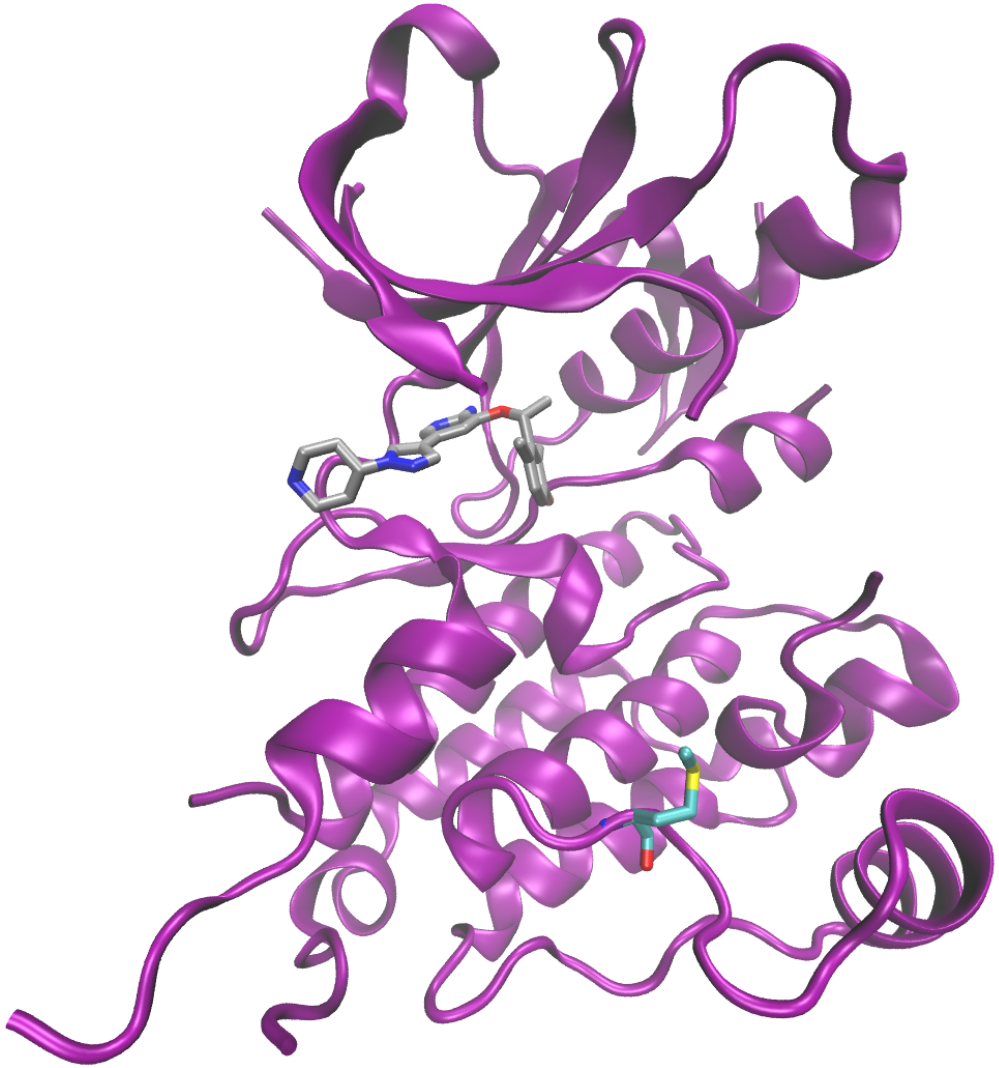
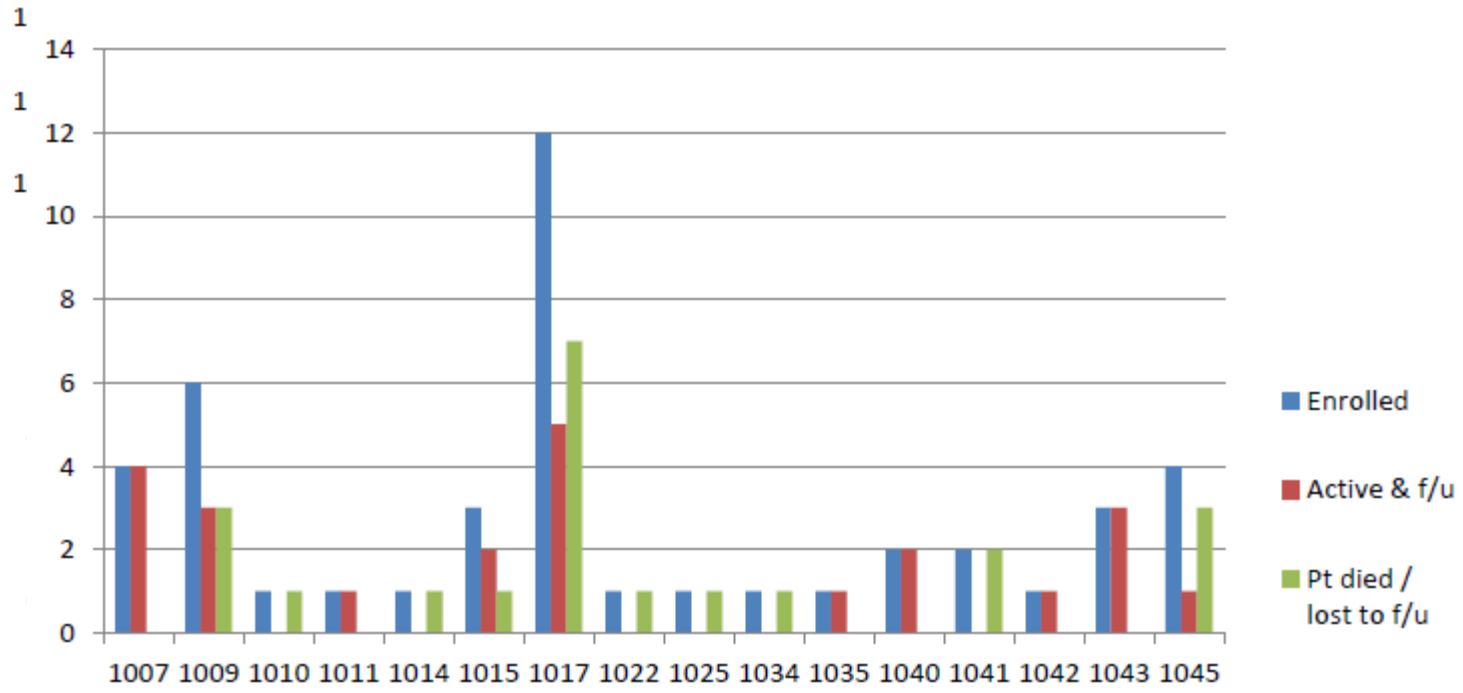
Patient #	Age	diagnosis	Stage (Ann Arbor)	ECOG	BM involvement (%)[&]	Previous therapy lines (n)	TTN LDH days	TTN Fever days	Previous BMT	Response, duration (months)
1	26	ALCL	IIIB	2	3-->0	3: CHOP, DHAP, HD-VP16	29	2	no	CR, 40+
2	19	ALCL	IVB	3	8-->0	3: CHOP, DHAP, BEAM	22	10	ABMT	CR,2 †
3	22	DLBCL	IVB	3	65-->0	4: BFM, HD-CTX, HD-AraC, Bortezomib	21	Na	ABMT	PR,2 †
4	22	ALCL	IIB	1	0	3: CHOP, VAD, H-CyVAD	30	30	no	CR, 35+
5	39	DLBCL	IVB	3	n.a.	4: BEP, CHOP, ICE, H-CyVAD	19	Na	no	SD †
6	20	ALCL	IIB	2	15-->0	3: CHOP, DHAP, BEAM	30	10	ABMT	CR,2
7	47	ALCL	IIIBe	2	0	3: IEV, DHAP, CHOP	30	14	no	CR, 30+
8	28	ALCL	IIIB	2	0	3: CHOP, DHAP, mini-BEAM	Na	Na	no	CR 2
9	34	ALCL	IVBe	2	0	2: CHOP, ESHAP	Na	30	no *	CR,10
10	38	ALCL	IVB	4	0	3: CHOP, DHAP, VIM	28	15	allogeneic	CR,8
11	55	ALCL	IIIB	1	0	1: CHOP	30	30	no	CR, 21+

RELAPSED PATIENTS:
ALK kinase domain obtained by PCR of PB PBMC and subjected to deep sequencing








1
14
1
12
1
10
8
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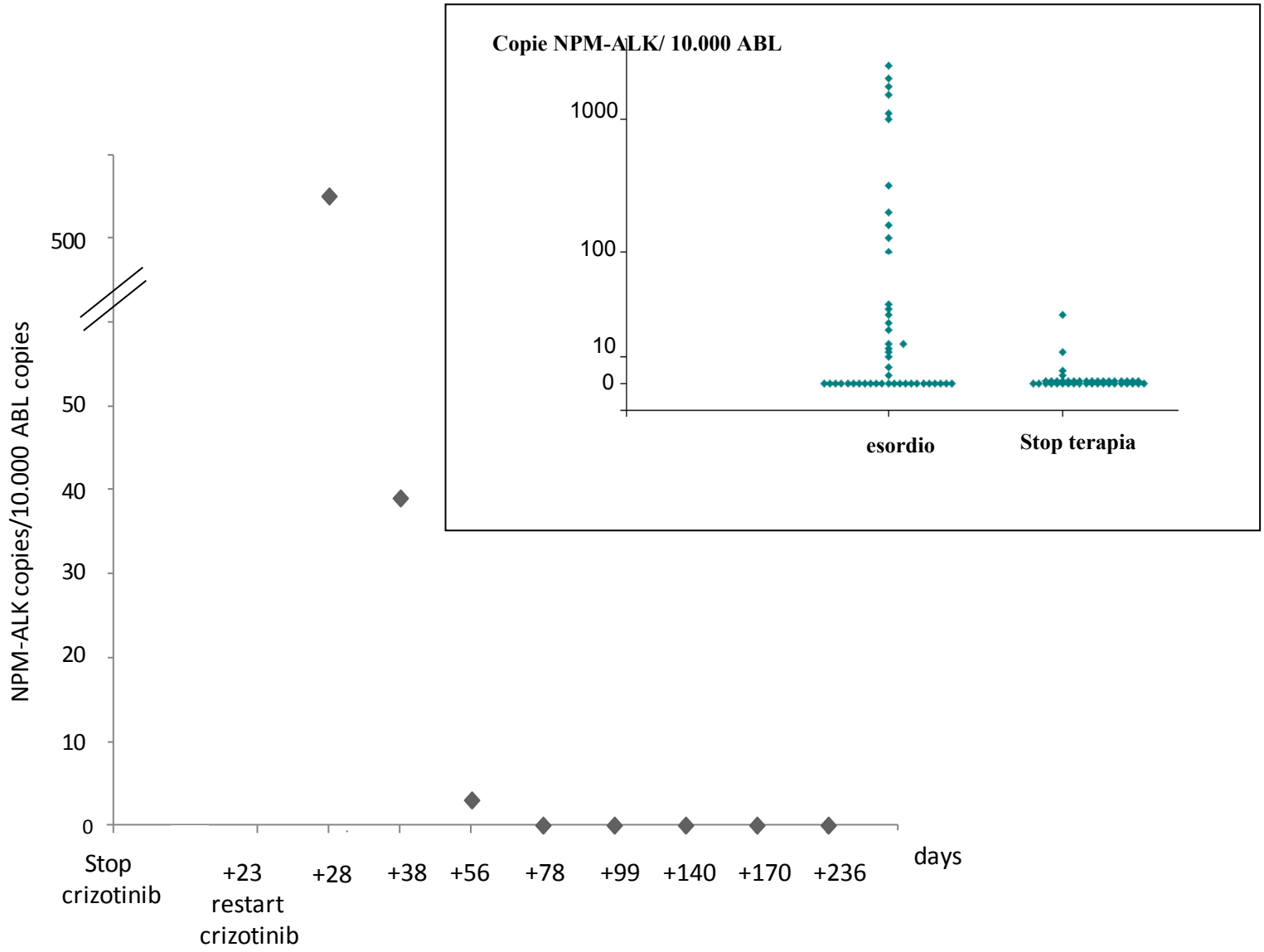
4
2
0
1007 1009 1010 1011 1014 1015 1017 1022 1025 1034 1035 1040 1041 1042 1043 1045
Enrolled
Active & f/u
Pt died / lost to f/u


Copie NPM-ALK/ 10.000 ABL
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NPM-ALK copies/10.000 ABL copies
500
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20
10
0
Stop crizotinib
+23 restart crizotinib
+28
+38
+56
+78
+99
+140
+170
+236
days

CONCLUSIONS

CRIZOTINIB IN ADVANCED, PRETREATED ALK+ LYMPHOMAS

- **Was well tolerated over a long period of time (up to >3 years).**
- **Exerted a potent antitumor activity:**

  -91% ORR

  - durable (> 6 months) responses in 5 patients

  - 2 year PSF 63.7 %

- **In relapsed patients mutations in the ALK kinase domain were identified.**

PLANS

- **Crizotinib should be made available to relapsed ALK+ ALCL patients.**

- **Crizotinib in combination with other agents for first line treatment is under discussion.**

- **Second generation ALK inhibitors should be tested in patients failing crizotinib.**