Dutch Childhood Oncology Group
Early Clinical Trial Consortium
DCOG - ECTC

Erasmus MC
University Medical Center Rotterdam

CRISP

A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies
Study ITCC 053

Crizotinib registration (IMP) adults

(EMA; Date of first authorisation: 23 October 2012)

- Crizotinib is indicated for
  - The first-line treatment of adults with **ALK-positive advanced non-small cell lung cancer** (NSCLC)
  - The treatment of adults with previously treated **anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)**
  - The treatment of adults with **ROS1-positive advanced non-small cell lung cancer (NSCLC)** adults with previously treated, anaplastic lymphoma

- The recommended dose schedule of XALKORI is 250 mg twice daily (500 mg daily) taken continuously. Treatment should be continued until disease progression or unacceptable toxicity

- If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken twice daily. If further dose reduction is necessary, then the dose should be modified to 250 mg taken once daily based on individual safety and tolerability

- Capsules 200 mg and 250 mg approved

Quoted from the Xalori SPC

ALK aberrations in pediatric patients

Translocations and Rearrangements

- **ALCL:** ~ 90% harbor *ALK* translocations with NPM1 as the fusion partner in ~75%
- **Inflammatory myofibroblastic tumor (IMT):** 45–65% carry *ALK* rearrangements

Mutations and Amplifications

- **Neuroblastoma:** 8–10% carry activating point mutations; ~2% carry ALK gene amplification; the frequency increases at relapse, where ALK mutations have been reported in ~17% of patients.

Expression

- **Rhabdomyosarcoma (RMS):** ALK protein is expressed in about 70% of alveolar RMS cases, typically without an *ALK* mutation. Other ALK abnormalities reported include ALK gene copy number gain, rare point mutations and whole exon deletions.

Clinical data: Crizotinib phase I pediatric trial

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study

Yael P Mossé, Megan S Lim, Stephan D Voss, Keith Wilner, Katherine Ruffner, Julie Laliberte, Delphine Rolland, Frank M Balis, John M Maris, Brenda J Weigel, Ashish M Ingle, Charlotte Ahern, Peter C Adamson, Susan M Blaney

79 patients from 2009 to 2012
with median age 10 years

3 strata:

- **A1:** Dose escalation → relapsed/refractory tumours and ALCL (N= 43)
- **A2:** Expansion→ ALK or MET fusion proteins, mutations or amplifications (N= 25)
- **A3:** Basket for neuroblastomas not feasible for A1 (N = 11)

Dose levels assessed: 100, 130, 165, 215, 280, 365 mg/m^2 per dose

Dose level 365mg/m2 showed 2 DLTs: therefore 280 mg/m^2 was the MTD

Overall well tolerated

Mossé Y et al. Lancet Oncol. 2013

Clinical data: Crizotinib phase I pediatric trial (FDA WR)

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ALK Translocated tumours

- ALCL (n=9): 7 CR, 1PR, 1SD → 6/9 CRs on 165 mg/m^2
- IMT (n=7): 3PR, 4SD → 5/7 on 280 mg/m^2

ALK mutated neuroblastoma (n=11):

- 1CR, 3 SD, 7PD

Non ALK or MET translocated tumours

- RMS (n=3): 0 responses (not informed about ALK or MET status)

Mossé Y et al. Lancet Oncol. 2013

Dose-limiting toxic effects observed at each dose level (mg/m^2 per dose twice daily) by cohort

	Number of patients entered	Number of patients evaluable	Number of patients with cycle 1 DLT	Cycle 1 DLT type (number)	Subsequent cycle DLT type (number)
Part A1 relapsed or refractory solid tumours, including CNS tumours or ALCL					
100	4	3	0	None	None
130	6	4	0	None	Neutrophil count decreased (1)
165	8	6	0	None	Diarrhoea (1)
Part A1 *					
215	8	7	2	Dizziness (1); intracranial haemorrhage (1)	None
Part A1 relapsed or refractory solid tumours, including ALCL; CNS tumours excluded					
280	6	5	0	None	Diarrhoea (1); skin infection (1)
365	11	6	2	Increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and GGT (1); neutrophil count decreased (1)	Alkaline phosphatase increased (1); neutrophil count decreased (1)
Part A2 recurrent or refractory malignancies with confirmed ALK fusion proteins or *ALK* mutations					
100	2	2	0	None	Increased alanine aminotransferase and aspartate aminotransferase (1)
165	12	12	1	Neutrophil count decrease (1)	Eye disorders—blue discoloration to vision (1)
215	1	1	0	None	None
280	10	9	0	None	Oedema limbs (1), neutrophil count decreased (1)
A3 relapsed or refractory neuroblastoma, with or without bone marrow involvement					
130	2	1	0	None	None
165	3	3	0	None	None
215	3	3	0	None	None
280	3	3	0	None	None

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study

Yael P. Mossé, Stephan D. Voss, Megan S. Lim, Delphine Rolland, Charles G. Minard, Elizabeth Fox, Peter Adamson, Keith Wilner, Susan M. Blaney, and Brenda J. Weigel

40 patients with ALCL or IMT ALK+ from 2009 to 2015

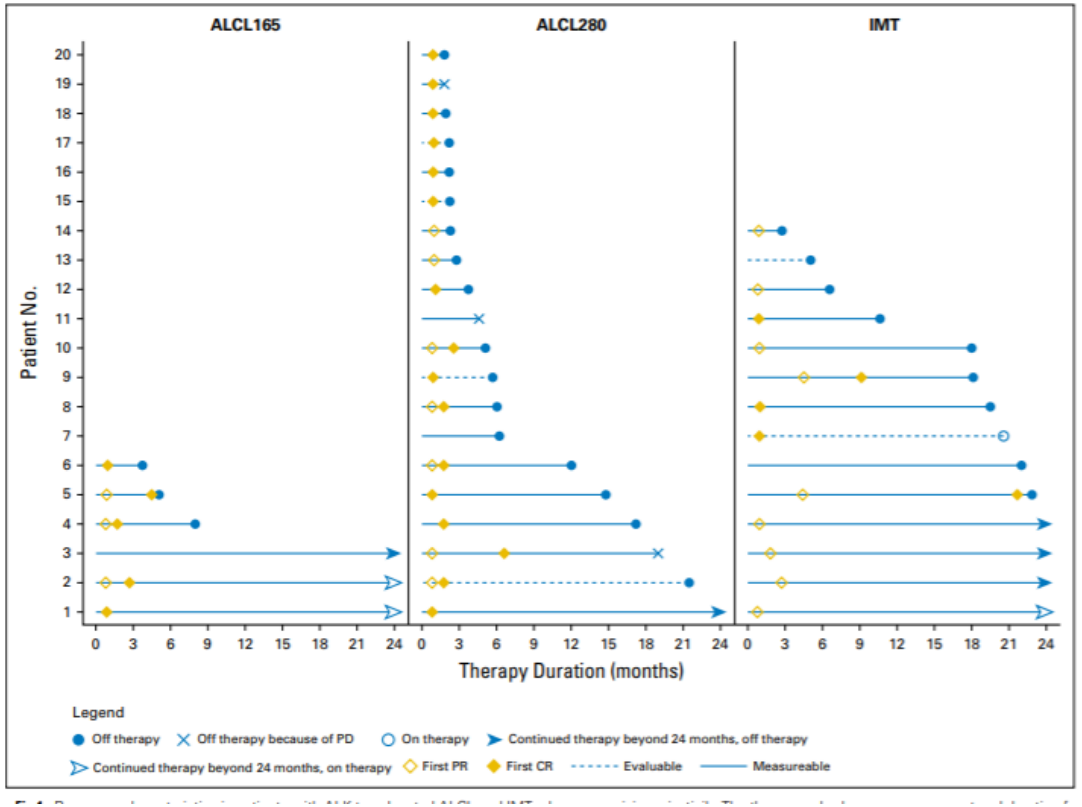


Table 2. Clinical Activity in Patients Treated With Crizotinib

Outcome	ALCL165 (n = 6)	ALCL280 (n = 20)	IMT (n = 14)
Best overall response			
Complete response	5 (83)	16 (80)	5 (36)
Partial response	0	2 (10)	7 (50)
Stable disease	1 (17)	2 (10)	2 (14)
Progressive disease	0	0	0
Therapy duration, years, median (95% CI)	2.79 (0.31 to n/a)	0.4 (0.18 to 1.0)	1.63 (0.55 to 2.30)
Time to first PR/CR, days, median (95% CI)	26.5 (24 to n/a)	27 (25 to 29)	28.5 (27 to 134)

NOTE. Data given as No. (%) unless otherwise indicated.
Abbreviations: ALCL, anaplastic large cell lymphoma; CR, complete response; IMT, inflammatory myofibroblastic tumor; n/a, not applicable; PR, partial response.

ALCL (RR): 88% (23/26)

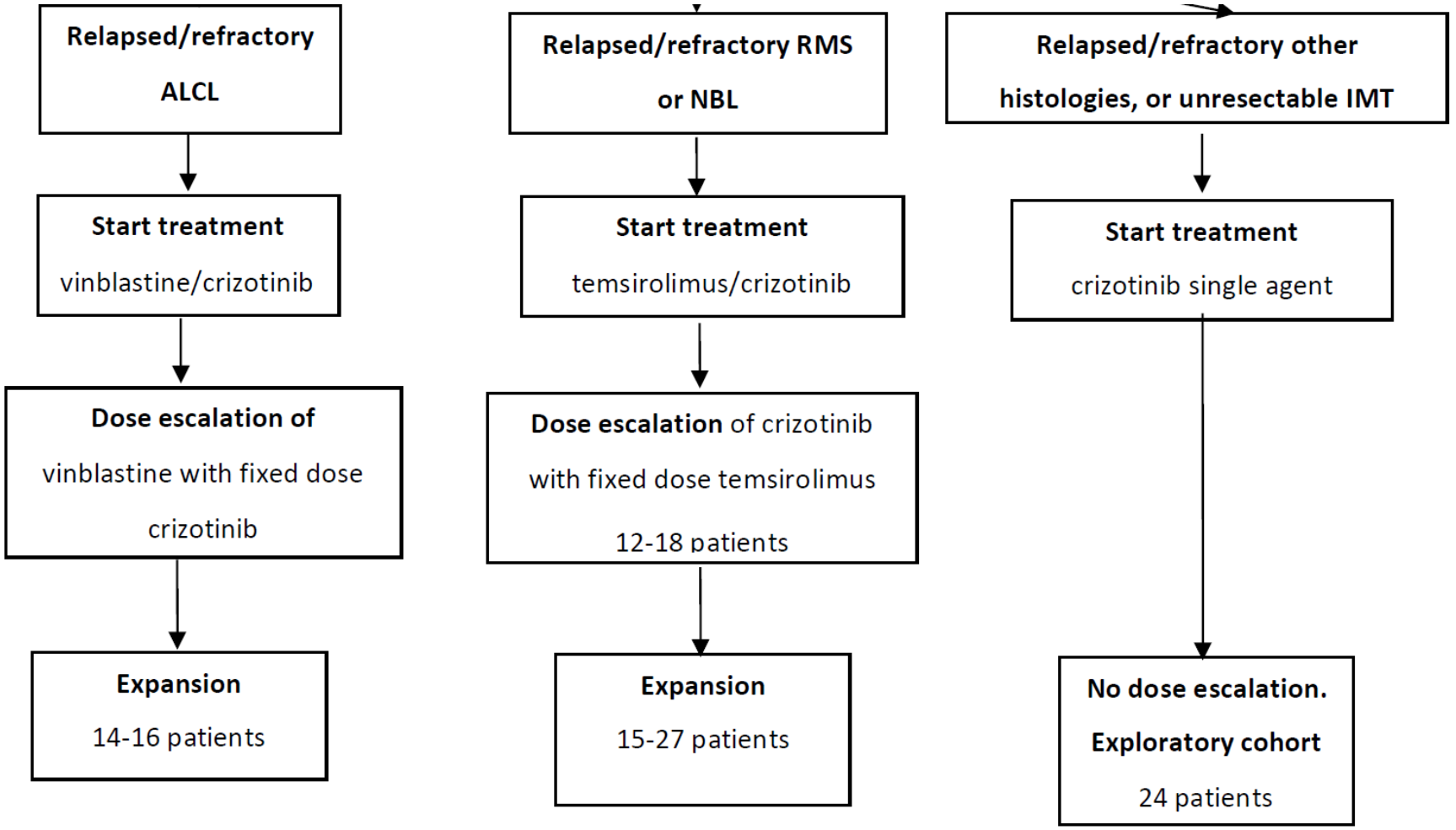
IMT (RR): 86% (12/14)

Disease strata

Molecular pre-screening for ALK+, ROS1 or MET aberrancies

- **Stratum 1:** relapsed/refractory ALCL with ALK aberrations
- **Stratum 2:** relapsed/refractory Rhabdomyosarcoma (RMS) or Neuroblastoma (NBL) with *ALK* or *MET* aberrations
- **Stratum 3:** Inflammatory myofibroblastic tumors (IMT) and other ALK, ROS 1 or MET aberrant malignancies

Study design



Primary objectives

- **Stratum 1**: To determine the RP2D of vinblastine in combination with crizotinib
- **Stratum 2**: To determine the RP2D of crizotinib in combination with temsirolimus
- **Stratum 3**: To determine the safety and preliminary activity of single-agent crizotinib in *ALK*, *MET* or *ROS1* positive tumors

Study design dose escalation

Stratum 1

ALCL: Crizotinib 150 mg/m^2 BID is effective, no dose escalation - need to identify dose of VBL safe/PK/no interactions by dose escalation of Vinblastine

Vinblastine (mg/m2) once weekly	
-1	3.0
Start	**4.5**
2	6.0

Crizotinib (mg/m2 BID)	
-1	100
Start	**150**
2	200
3	**280**

Stratum 2

RMS/NBL: Active dose of crizotinib not known (no dose for single agent, start 150 mg/m^2 BID). Temsirolimus is quite toxic as single agent so will use 75% of normal dose (60 mg/m^2 once weekly)

Stratum 3

IMT/other ALK/ROS1/MET aberrancy: RP2D of crizotinib as per Mosse = 280 mg/m^2 for monotherapy

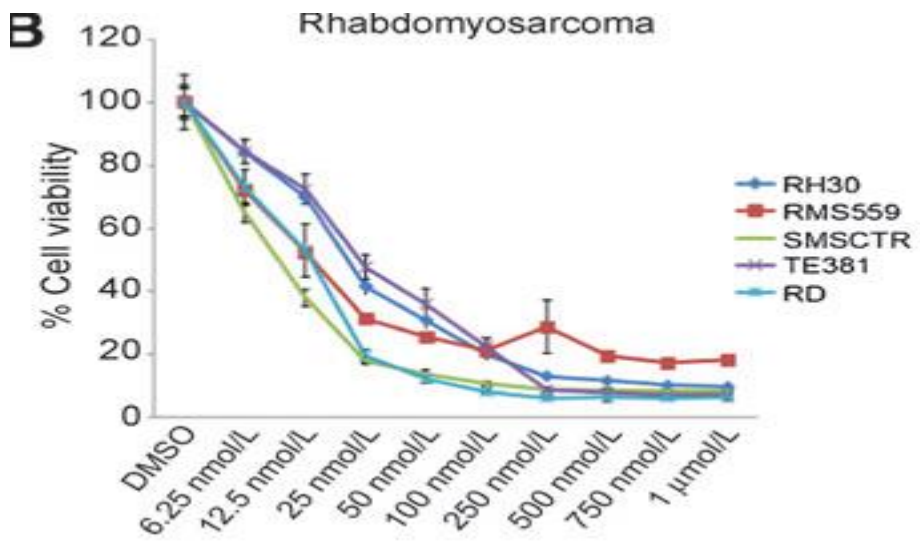
Rationale: Combination Crizotinib and Vinblastine

• Considering the **promising results for both crizotinib and vinblastine in patients with relapsed ALCL**, combing the 2 drugs seems a logical next step for optimizing treatment

• Vinblastine has been used frequently within the pediatric oncology:
It is used for gliomas, Langerhans cell histiocytosis, lymphomas and other malignancies

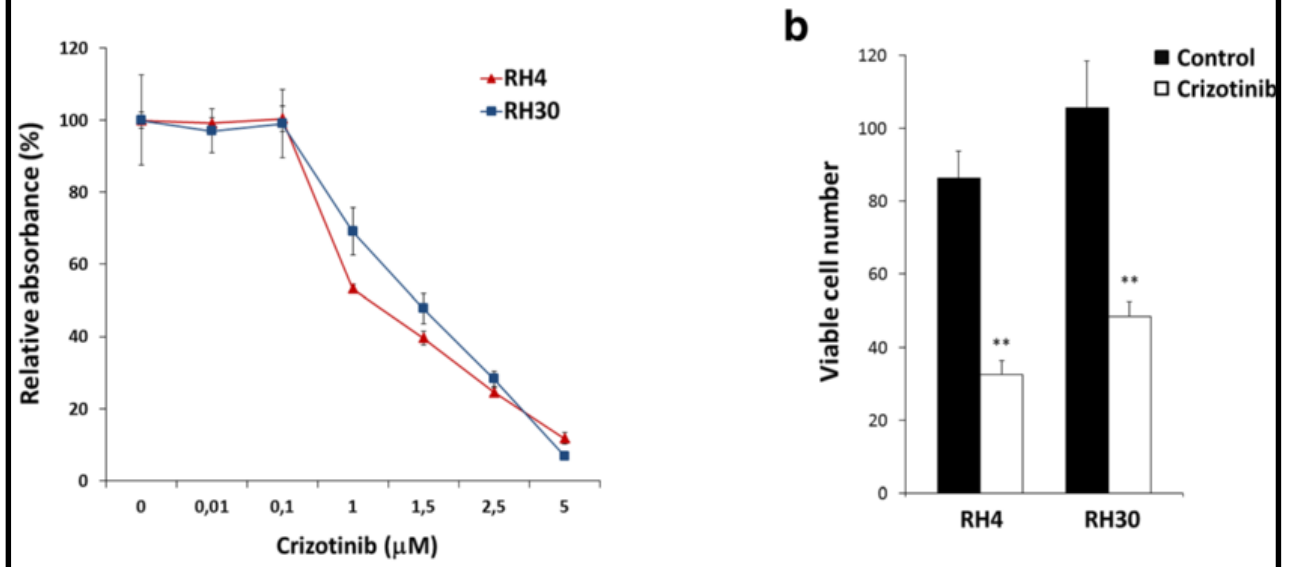
•Vinblastine was considered safe in most studies; the main toxicity being haematological

Rationale: Combination Crizotinib and Temsirolimus



In vitro mTOR inhibitie RMS (any)

Slotkin et al, 2015

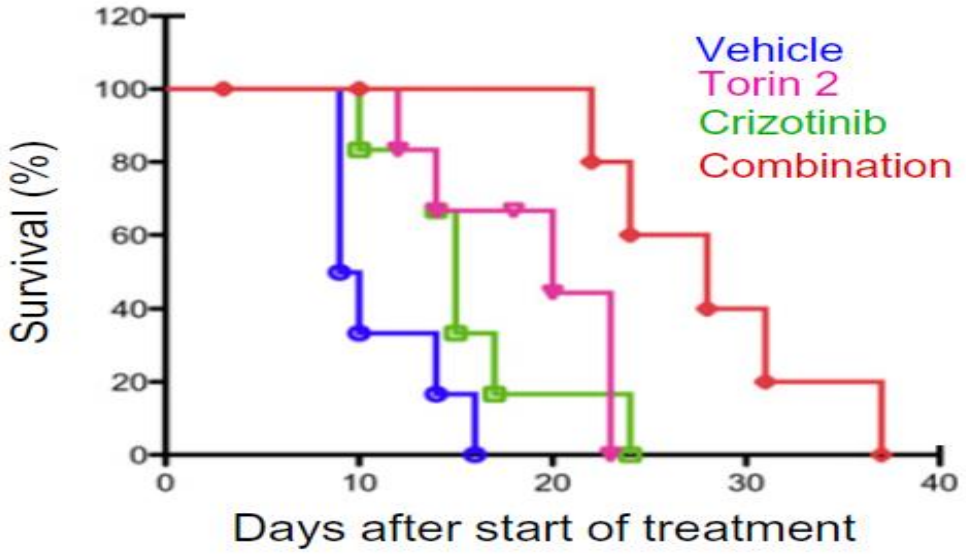


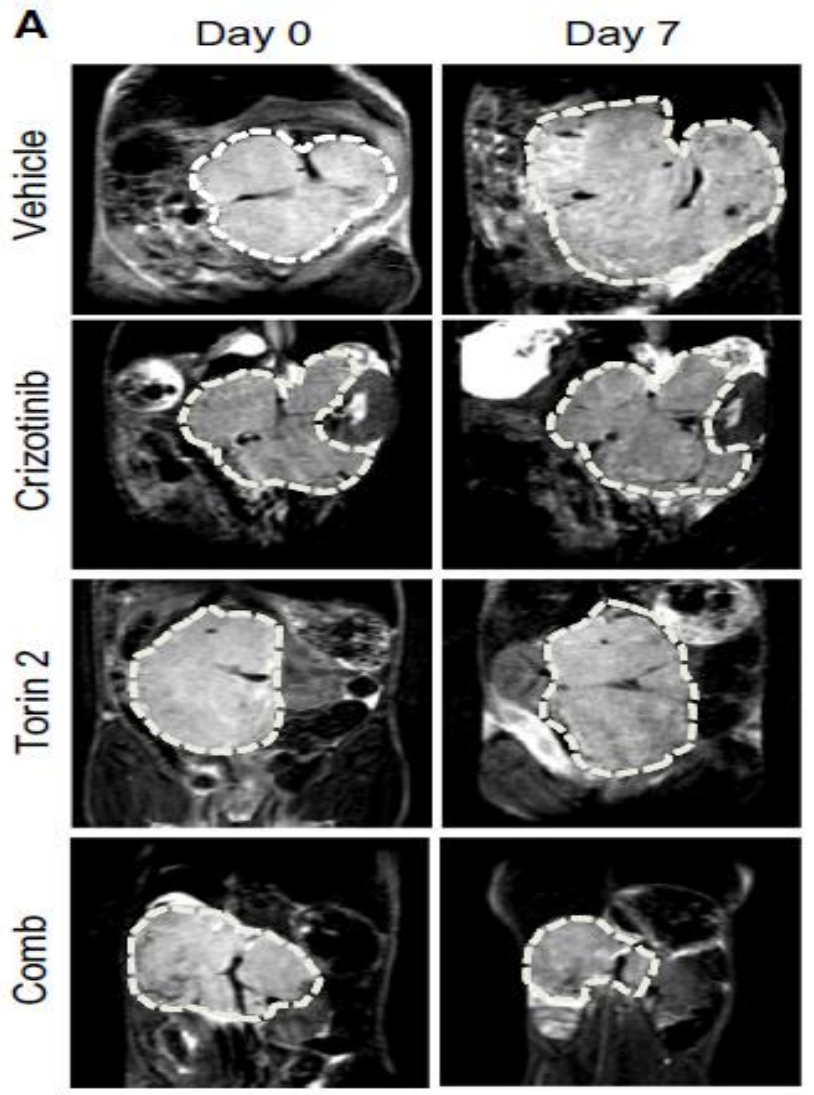
In vitro inhibition by crizotinib in ALK or MET + RMS

Megiorni et al, 2015

Combination of Crizotinib with mTOR inhibition is effective against ALK for NBL cells

ALK F1174L NMYC + mice 10 per group





- Chesler, *Cancer Cell*, 2012 –Confirmed by Moore *et al* Oncotarget 2014

Inclusion criteria – All strata

- Written informed consent from patients and/or from parents or legal guardians, according to local law and regulations
- **Age at diagnosis ≥1 year** of age and **≤ 21 years**
- Lansky play score > 60%; or Karnofsky performance status > 60%.
- Life expectancy ≥ 12 weeks
- Any previous systemic anticancer therapy must have been completed at least 2 weeks prior to initiation of study medication. At least 1 week for oral metronomic chemotherapies (e.g. cyclophosphamide or etoposide), and the patient has to be recovered from any toxicity from this therapy
- No treatment with any other investigational drug within the past 2 weeks prior to initiation of study medication
- Major surgery must have been completed at least 2 weeks prior to initiation of study medication (central venous access surgery or a needle biopsy are not considered major surgery)
- No persistence of adverse events, more than grade 2, from prior anti-cancer therapy deemed clinically relevant

Inclusion criteria – All strata

- Life expectancy ≥ 12 weeks

- Adequate hematological function, unsupported, last platelet transfusion > 72 hours and off colony stimulating factors: ANC ≥0.75x109/L and platelets ≥ 75x109/L for pts without bone marrow involvement.

- Patients with bone marrow involvement will be allowed to enter with ANC ≥0.5x109/L and platelets ≥50x109/L
- Normal renal function defined as ≤1.5 x ULN adjusted for age
- Normal liver function defined as ≤2.5 x ULN or serum creatinine for transaminases and ≤1.5 x ULN bilirubin, but ≤5 x ULN (and ≤2.5 x ULN for bilirubin) in case of liver involvement by metastases

- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up relevant

- A negative test for patients with childbearing potential within 7 days before the start of study medication and agreement to use effective contraceptive measures until 6 months after EOT

Additional inclusion criteria – Stratum 1 ALCL

Histologically or cytologically confirmed diagnosis of relapsed of refractory **ALCL**

- **Target gene aberration** as defined as:
  - ✓ The t(2;5) (p23;q35) translocation or translocation (1;2) (q21;p23) , t(2;3)(p23;q21), inv(2)(p23;q35), t(2;22).
  - ✓ This should be apparent in all tumor cells.
  - ✓ This can be proven by either ALK- immunohistochemistry, FISH or PCR

- Disease involvement :
  - ✓ For dose escalation measurable and non measurable disease is allowed
  - ✓ For dose expansion measurable disease is mandatory
  - ✓ Measurable disease is defined as at least one nodule with a longest diameter greater than 1.5 cm (pediatric)) NHL response criteria discussed later)

Additional inclusion criteria – Stratum 2 NBL/RMS

Histologically or cytologically confirmed diagnosis of relapsed or refractory **NBL** or **RMS**

Target gene aberration as defined as:

- ✓ A point mutation in the kinase domain of ALK that results in an amino-acid change, and is not a known polymorphism
- ✓ An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells), or in more than one-third of the tumor cells
- ✓ A translocation in >15% of the tumor cells (by break apart FISH-assay)

NOTE: so overexpression alone is not enough OR

- ✓ An amplification of the MET-gene, defined as of ≥5 MET signals per tumor cell (by break apart FISH)
- ✓ A MET mutation, defined as the presence of a somatic mutation (Direct, bi-directional sequencing of exon 16-19 of MET)
- ✓ A TFE3 rearrangement, defined as at least 15% of cells rearranged (FISH home-made break-apart TFE3 probe set: RP11-344N17 and RP11-552J9)

Additional inclusion criteria – Stratum 3 others

- Histologically or cytological confirmed diagnosis of other **solid tumor or lymphomas other than ALCL** (at initial diagnosis) that is relapsed or refractory to standard therapy.

- Or patients with newly diagnosed **IMT** in whom radical surgery is deemed infeasible or will result in significant morbidity/mutilation

- **Target gene aberration** as defined as:

  For **ALK**

  - ✓ A point mutation in the kinase domain of ALK that results in an amino-acid change, and is not a known polymorphism
  - ✓ An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells
  - ✓ A translocation in >15% of the tumor cells (by break apart FISH-assay)

  For **ROS1**

  - ✓ A ROS1 rearrangement in > 15% of the tumor cells (by break apart FISH-assay)

Additional inclusion criteria – Stratum 3 others

- For **MET**
  - ✓ An amplification of the MET-gene, defined as of ≥5 MET signals per tumor cell (by break apart FISH)
  - ✓ A MET mutation, defined as the presence of a somatic mutation (Direct, bi-directional sequencing of exon 16-19 of MET)
  - ✓ TFE3 rearrangement, define as at least 15% of cells rearranged (FISH home-made break-apart TFE3 probe set: RP11-344N17 and RP11-552J9)

- Disease involvement:
  - ✓ Measurable disease according to RECIST 1.1 , OR
  - ✓ Measurable disease as defined as at least one nodule with a longest diameter greater than 1.5 cm (pediatric NHL response criteria)

- **No prior therapy directly targeting ALK or ROS1 or MET**

CRISP ITCC-053_Steering Committee meeting
Study status update

Current recruitment status

Study ID	stratum	dose escalation Y/N	site	M/V	age at enrollment (yrs)	type of gen alteration 1=ALK, 2=ROS, 3=MET	date inf.cons.	start treatment	EOT	days in study	remarks
01-02	1	DL 1	#02 PMC	v	14	1	15-mei-18	22-mei-18	1-6-2018	10	studymed stopped 1-6-2018 DLT, died 08-06-2018
02-02	2	DL 1	#02 PMC	m	12	1	19-jun-18	19-jun-18	16-7-2018	27	did not qualify for cycle 2 + growth of tumor, died 10-10-2018
03-02	3	na	#02 PMC	v	20 months	1	13-feb-19	20-feb-19	24-4-2019	63	resection IMT on 24-4-2019
04-04	3	na	#04 Nino Jesus	v	13	3	20-sep-19	20-sep-19	24-9-2019	4	pt died (respiratory failure due to underlying disease)
05-02	2	Yes, DL2	#02 PMC	m	4	1	22-apr-20	23-apr-20	25-5-2020	32	SAE and disease progression, died 16-06-2020
06-12	1	Yes, DL -1	#12 Trousseau	v	9	1	5-jun-20	9-jun-20	7-jul-20	28	stopped DLT
07-05	2	No, DL2	#05 Le Fe	m	4	1	4-jan-21	n.a.	n.a.	0	revoked consent between screening and start treatment
08-02	2	No, DL2	#02 PMC	m	1	1	15-feb-21	15-feb-21	9-3-2021	22	C2D1 no PK done (no treatment received); stopped DLT; died 11-05 2021
09-02	3	na	#02 PMC	v	9	1	18-aug-21	3-sep-21			dose lowered, cumulative tox grade1-2
10-10	2	No, DL2, tems 40	#10 Curie	v	10	1	18-aug-21	1-sep-21	17-sep-21	16	DLT starting 7-9-21
11-32	2	yes, DL1, tems 40	#32 Barcelona	m	2	1	5-nov-21	18-nov-21	10-jan-22	53	no DLT

Inclusion for stratum 1 on hold since July 2020, because of DLT in both included patients.

Conclusion: combination of crizotinib and vinblastine is too toxic.

CRISP ITCC-053_Steering Committee meeting
Status participating sites

Country/ sites	NCC SIV/Activation
DENMARK (1 site)	open (27-oct-20)
FRANCE - Paris Curie (NCC)	open (6-aug-20)
FRANCE - Paris Trousseau	open (4-jun-20)
FRANCE - Paris IGR	open (14-apr-21)
FRANCE - Marseille	Decision not to participate 13oct2021
FRANCE - Nancy	No
FRANCE - Lille	open (21-dec-20)
FRANCE - Bordeaux	open (08-feb-21)
FRANCE - Toulouse	No
GERMANY- (4 sites) REJECTED	Rejection by CA in 2018; resubmission stratum 3 only
IRELAND (1 site)	SIV done 10-mar-21, last items to be finished before activation
Italy - Milano (NCC)	in submission process
Genova	decision by Italian NCC not to open this site autumn 2021
Monza	decision by Italian NCC not to open this site autumn 2022
Padova	decision by Italian NCC not to open this site autumn 2023
Roma	
Torino	

Country/ sites	NCC SIV/Activation
Netherlands (1 site)	open: 18-Apr-2018 temporarily on hold:18feb19 until 27aug19 re-opened (27aug2019)
SPAIN - Madrid (NCC)	open (13-09-2019)
SPAIN -Valencia	open (19-nov-20)
SPAIN - Barcelona	open (26-Nov-20)
UK - CRCTU Birmingham (NCC)	not applicable NCC only
UK - Birmingham	
UK - Leeds	
UK - London/Surrey RMH	open (08-sep-2021)
UK - London	
UK- Manchester	
UK - Newcastle	
UK -Cambridge	

Ghent, Belgium was asked to participate, still under discussion