Hematological malignancy case presentation

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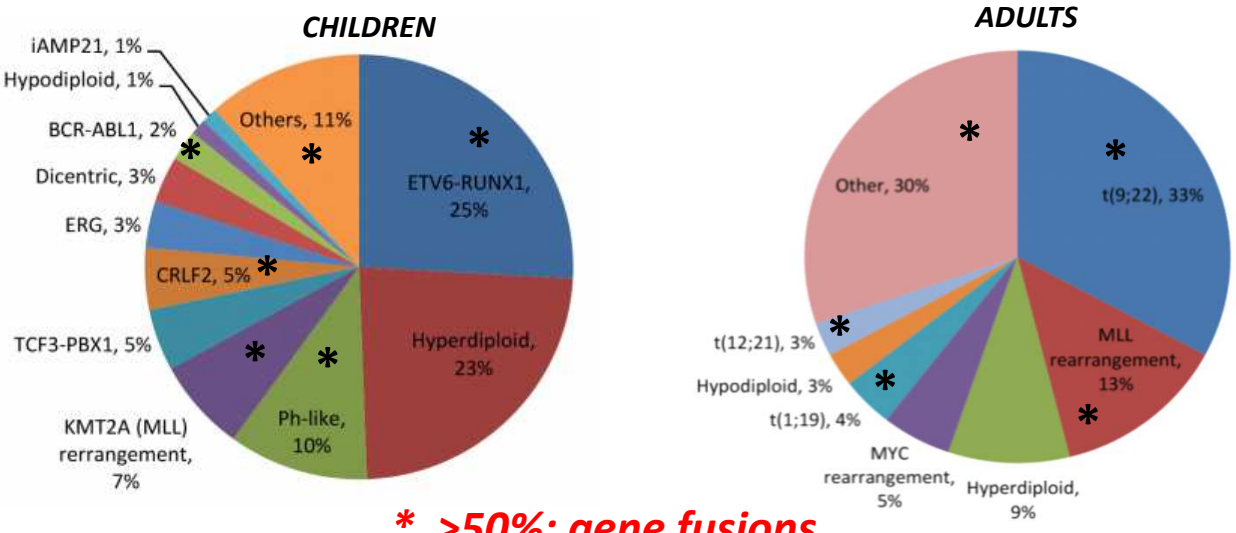
Nardi V, ….Hock H. Blood Adv. 2020

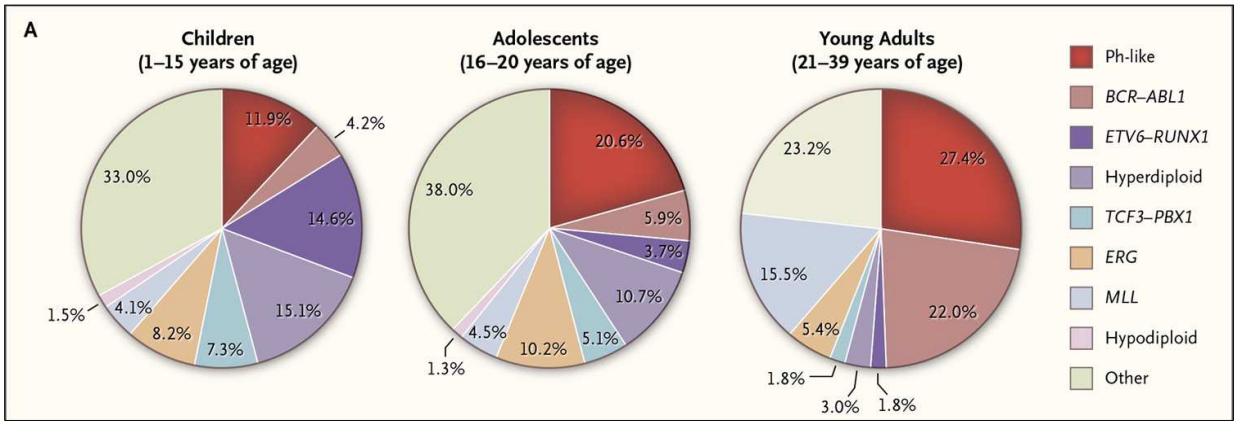
Frequency of genetic alterations in pediatric and adult ALL



**** >50%: gene fusions***

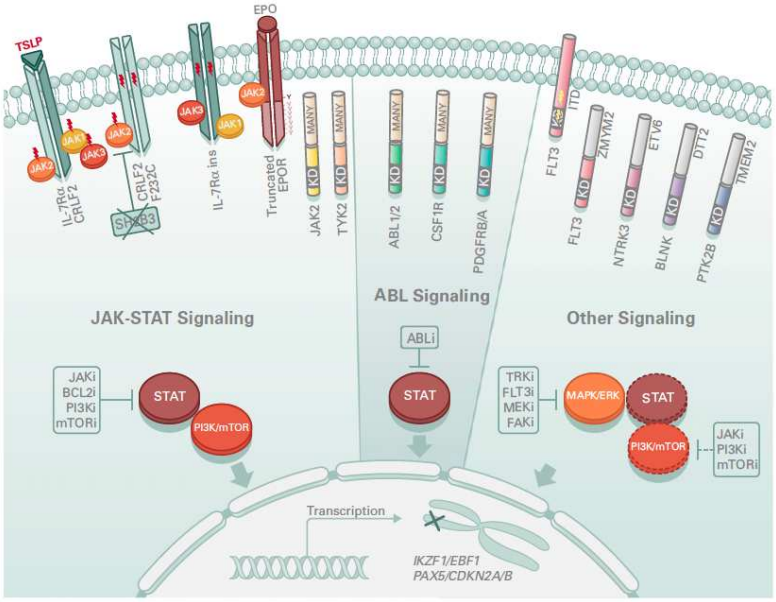
Zhang, X. et al. Oncotarget 2017

Ph-like B-ALL subgroup, a new entity in the WHO 2016 update with poor prognosis is common in the young adult and pediatric population



Graubert TA. N Engl J Med 2014;371:1064-1066.

Ph-like ALL is largely driven by activated kinases, amenable to targeted therapy

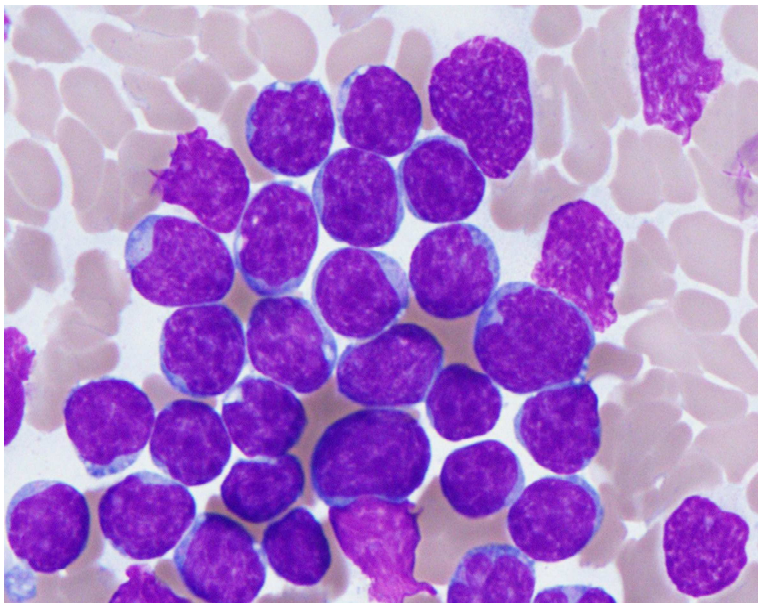


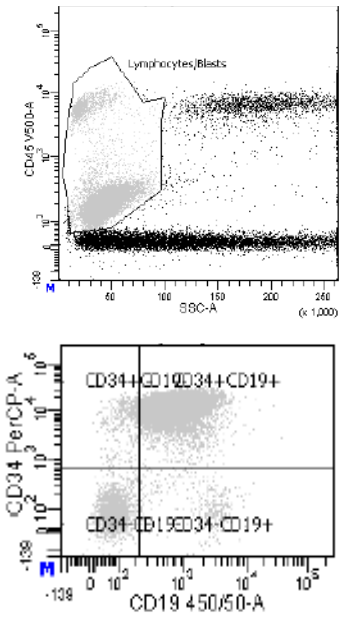
Iacobucci I., and Mullighan C.G., JCO 2017

Case

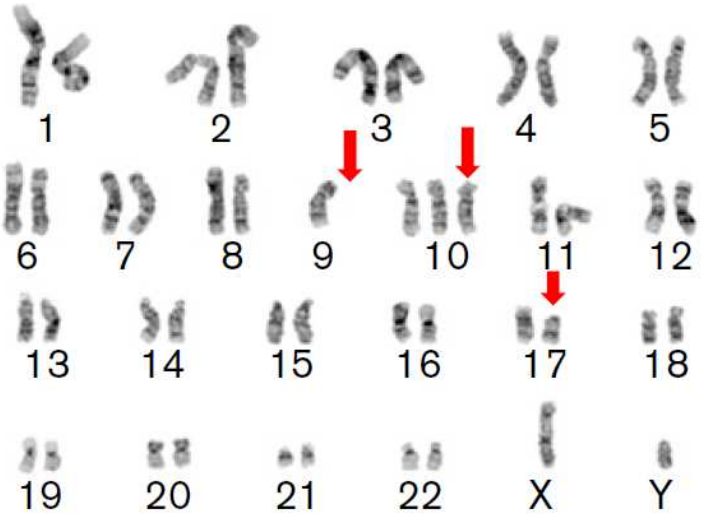
61 yo male with Legionella pneumonia and pancytopenia

Initial bone marrow findings





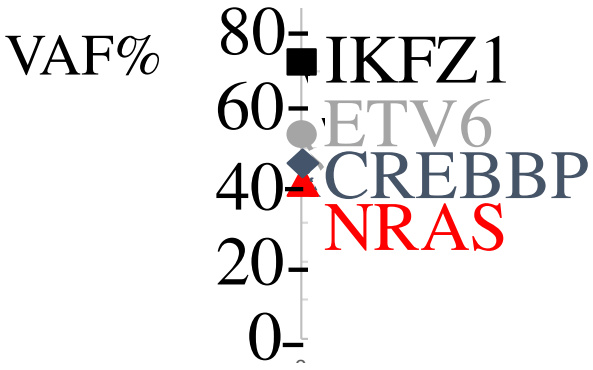
Cytogenetic analysis at diagnosis



Negative *BCR-ABL1* RT-PCR

46,XY,-9,+10,del(17)(p11.2)[cp4]/46,XY[5]

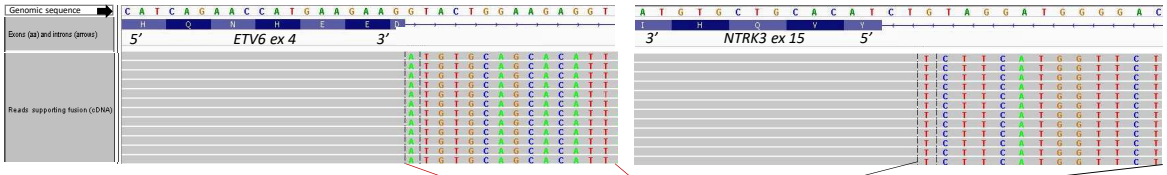
Routine targeted DNA sequencing revealed 4 mutations



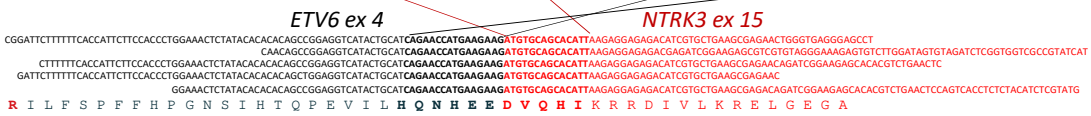
Routine targeted RNA sequencing revealed a gene fusion

Only few reads showed an *ETV6-NTRK3* fusion

A



B



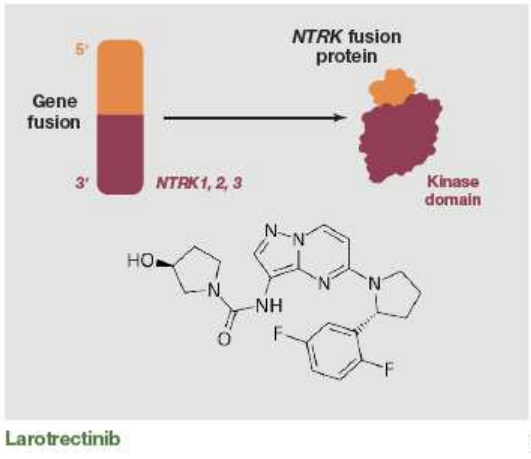
The fusion was in frame and predicted an activated kinase

ETV6 | NTRK3

CCATGAAGAAG|ATGTGCAGCACATT

H E E D V Q H I

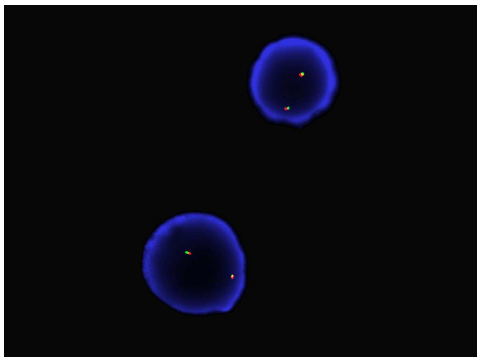
fusion sequence



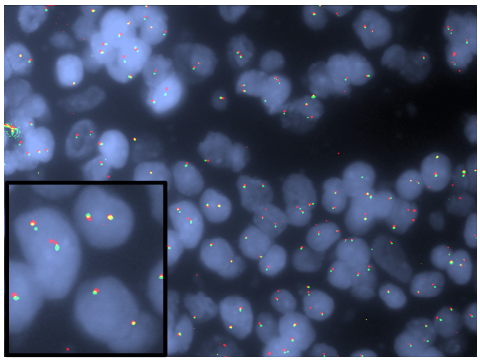
Larotrectinib

FISH did not support *ETV6-NTRK3* Rearrangement

ETV6 break-apart FISH on whole nuclei

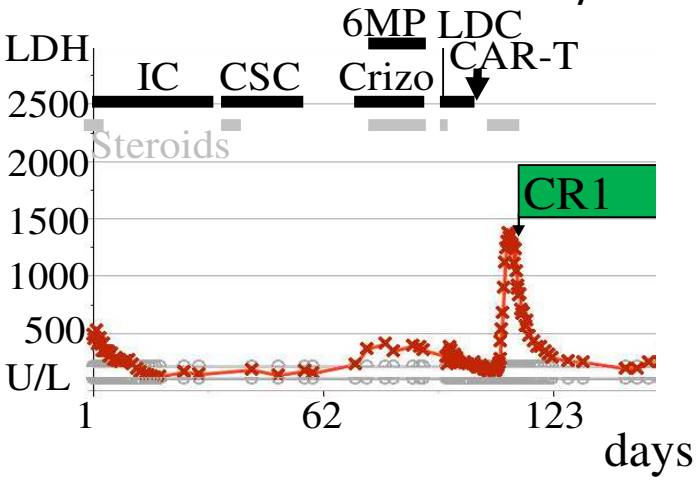


NTRK3 break-apart FISH on 4 um section



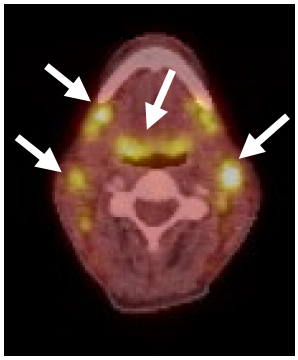
Conventional Chemo failed but allogeneic CART achieved a complete remission

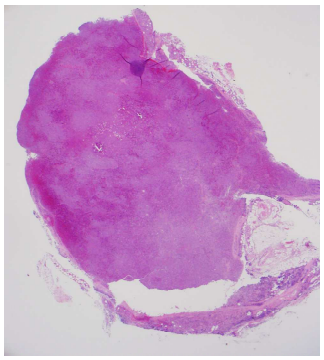
Clinical course reflected by LDH

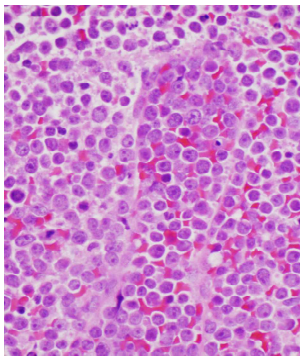


However, relapse occurred after 5 weeks:

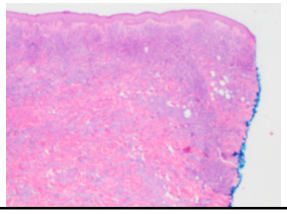
lymph nodes



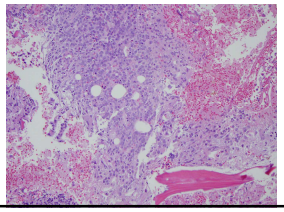




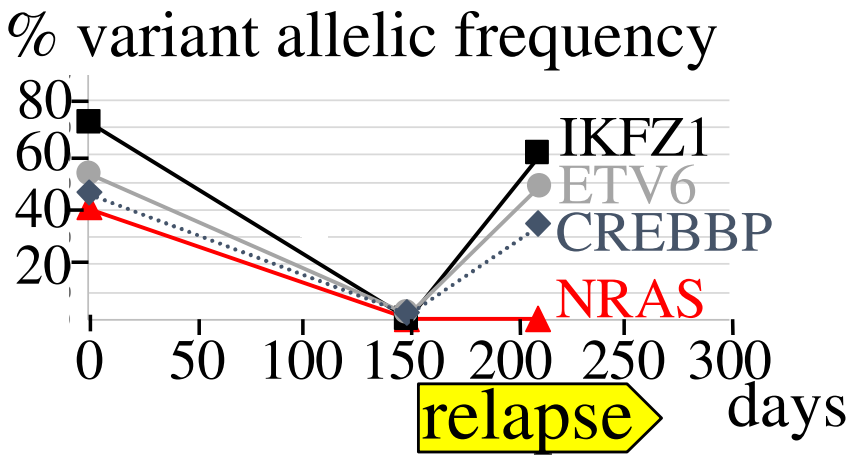
skin



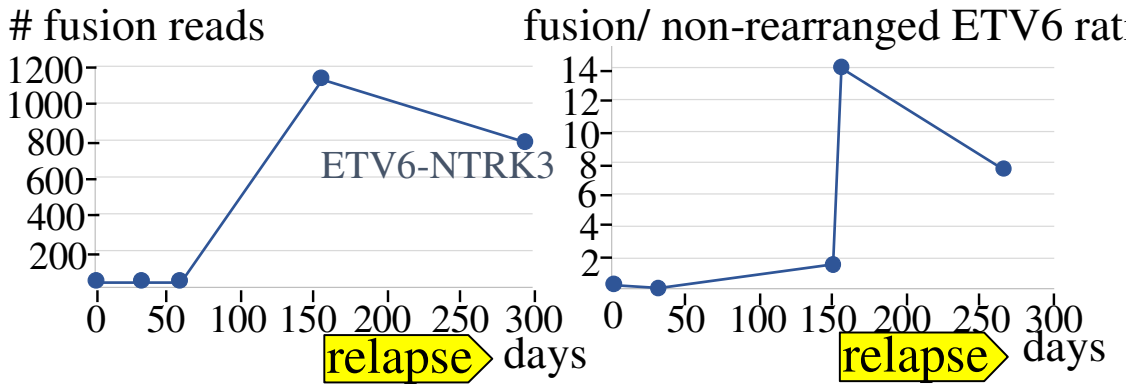
bone marrow



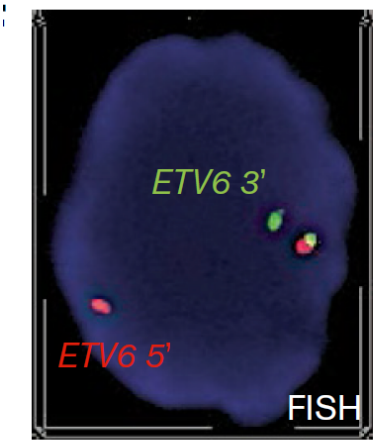
DNA sequencing results at relapse shows loss of the NRAS mutation



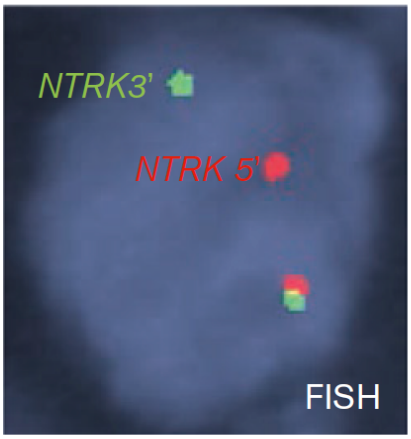
RNA sequencing at Relapse shows many reads supporting a fusion !



FISH at relapse (lymph node) confirmed cryptic *ETV6-NTRK3* rearrangement

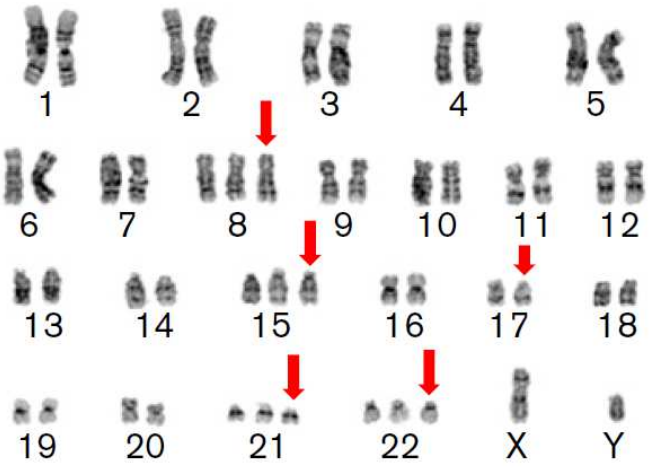


lymph node, day 156



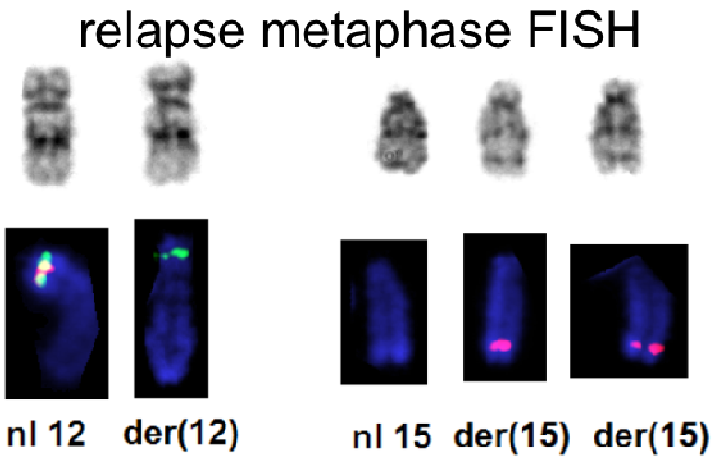
lymph node, day 156

Cytogenetic analysis at relapse: new related clone

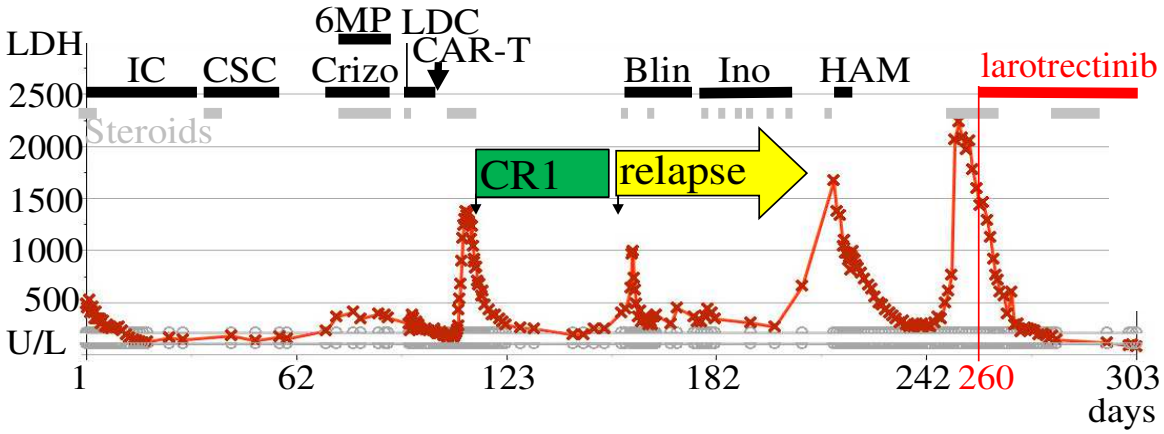


46,XY,-9,+10,del(17)(p11.2)[cp1]/ 49
51,XY,+5[5],+8[5],+15[2],del(17),+22,+22[5][cp6]/46,XY[cp13]

Cryptic Rearrangement Confirmed on metaphase FISH

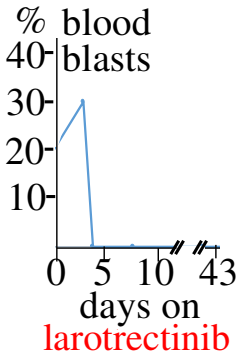


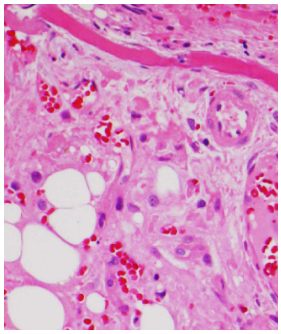
NTRK inhibitor showed clinical activity in relapse



NTRK inhibitor showed clinical activity in relapse

inhibitor treatment:





larotrectinib day 7

larotrectinib day 39

bone marrow

Key points:

- Ph-like ALL is aggressive and not rare, but amenable to targeted therapy
- Different subclones propagated by different driver mutations may predominate at different disease stages
- Repeated, sophisticated molecular testing can be beneficial (many fusions are cryptic)

Acknowledgment

We thank the patient and his family for participation in research studies.