ITCC Education meeting Amsterdam

Workshop 5 – Simulated Molecular Tumor Board

Example 4

Neuroblastoma

Oncologist: Clinical synopsis

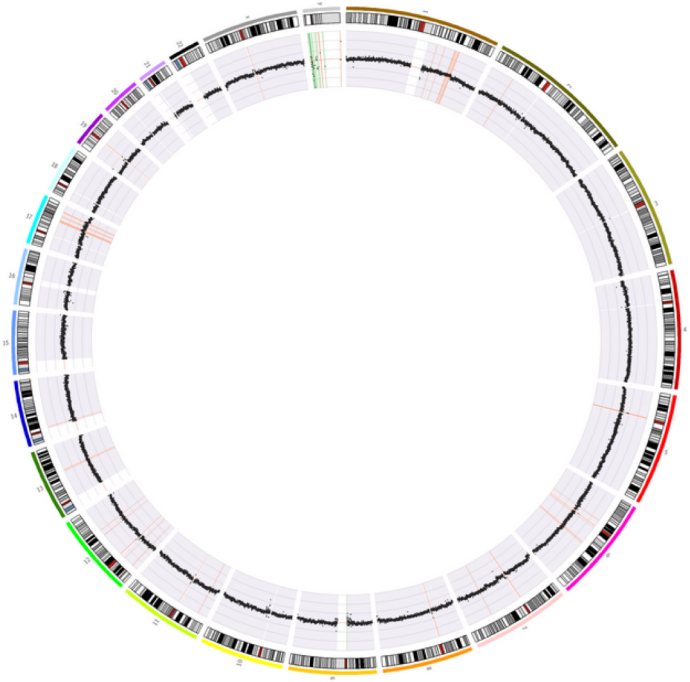
- Gender: Female
- Age: 4 years
- Primary Tumor:
  - Neuroblastoma
- History:
  - relapse of distal femur

Pathologist: Tumor biopsy

- Sample: relapse
- Type: tru cut distal femur
- Quality: good
- Tumor content: 40% (but after DNA analysis appears to be ± 25%)
- DNA isolation: good
- RNA isolation: not enough material

- Germline DNA: blood sample

Genomics: Copy number profile



circos plot with tracks for

- chromosome and band
- copy number log2 ratio for tumor vs. normal (0 = diploid)

▼ CopyNumber list

gains (red) | losses (green)

link	Gene	logfold	Info	link	Gene	logfold	Info
View	NF1	0.2767	chr17:29460000-29729999 (269999)	View	TNFSF11	-0.3818	chr13:43130000-43169999 (39999)
View	FASLG	0.2446	chr1:172350000-173309999 (959999)	View	HDAC3	-0.2198	chr5:141010000-141239999 (229999)
View	RAD51C	0.2306	chr17:56750000-57749999 (999999)	View	JAG2	-0.1953	chr14:105560000-106559999 (999999)
View	RPS6KB1	0.2306	chr17:57750000-58749999 (999999)	View	AKT1	-0.1953	chr14:104560000-105559999 (999999)
View	FOLH1	0.2278	chr11:49150000-49959999 (809999)	View	GLI2	-0.1546	chr2:120940000-121939999 (999999)
View	CCL2	0.2097	chr17:31890000-32699999 (809999)	View	PORCN	-0.1475	chrX:48280000-49179999 (899999)
View	CDK6	0.2067	chr7:92350000-93349999 (999999)	View	PIM2	-0.1475	chrX:48280000-49179999 (899999)
View	MET	0.2041	chr7:115400000-116399999 (999999)	View	HDAC6	-0.1475	chrX:48280000-49179999 (899999)

No relevant copy number changes
(possibly missed because of low percentage tumor cells)

Genomics: Somatic (=tumor) variants

Variant Allele Frequency

Variant reads in RNA-seq

Amino acid change in protein

link	chrom	chromstart	reference	alleleseq	VAF	VarRNA	GeneSymbol	AA change	info	Logos
view	chr2	29432663	C	T	0.12		ALK	p.R1275Q	Info	C A
view	chr4	170322845	G	T	0.05		NEK1	p.D1152E	Info	
view	chr8	124195328	C	A	0.04		FAM83A	p.P78H	Info	
view	chrX	43590993	C	A	0.12		MAOA	p.F283L	Info	

C: Cosmic Mutation
A : Actionable Gene (accoring to grp.ither.ither_genelist_v2018)
VAF 0.10: VAF <=0.1

▼ OncoKB (1 hits)

All Variants

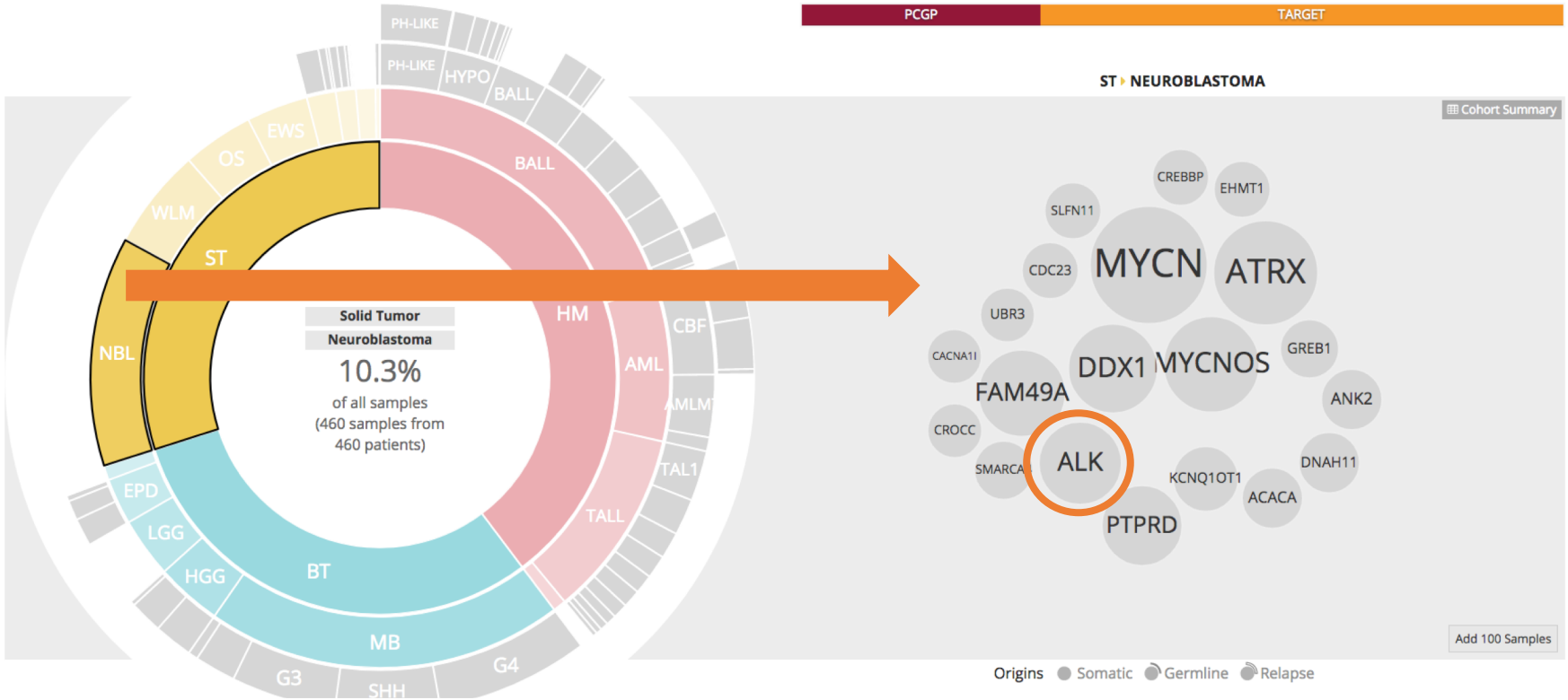
Gene	Alteration	Oncogenicity	Mutation Effect
ALK	R1275Q	Oncogenic	Gain-of-function

VAF: compare variant allele frequency with tumor % of biopsy:

more likely 24% than 40%!

ALK mutation with additional information in OncoKB

Most frequent aberrations in neuroblastoma



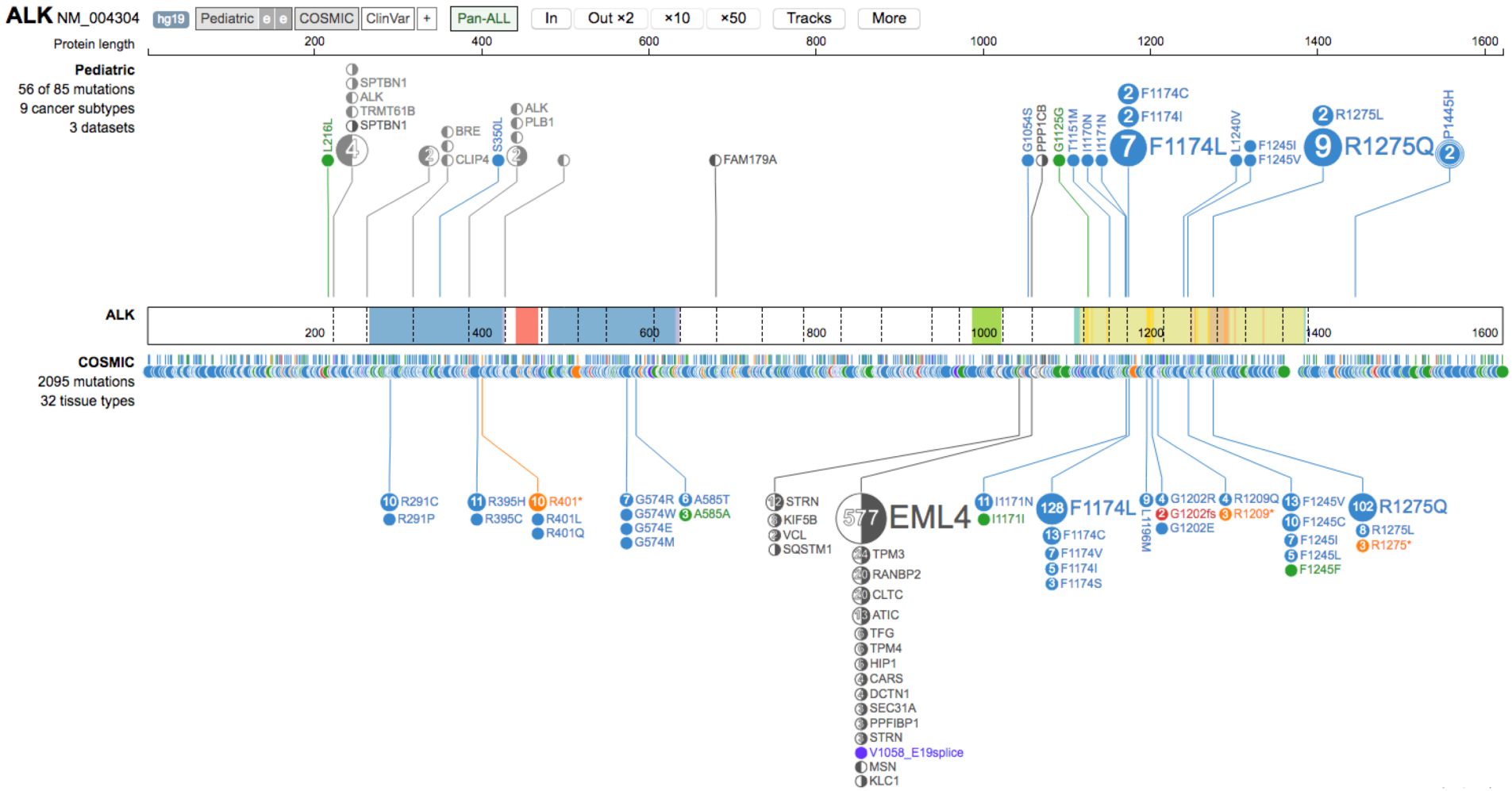
Source: Pediatric Cancer Database, St. Jude: pecan.stjude.org

NBL: Actionable event 1

ALK mutation G3824A: R1275Q

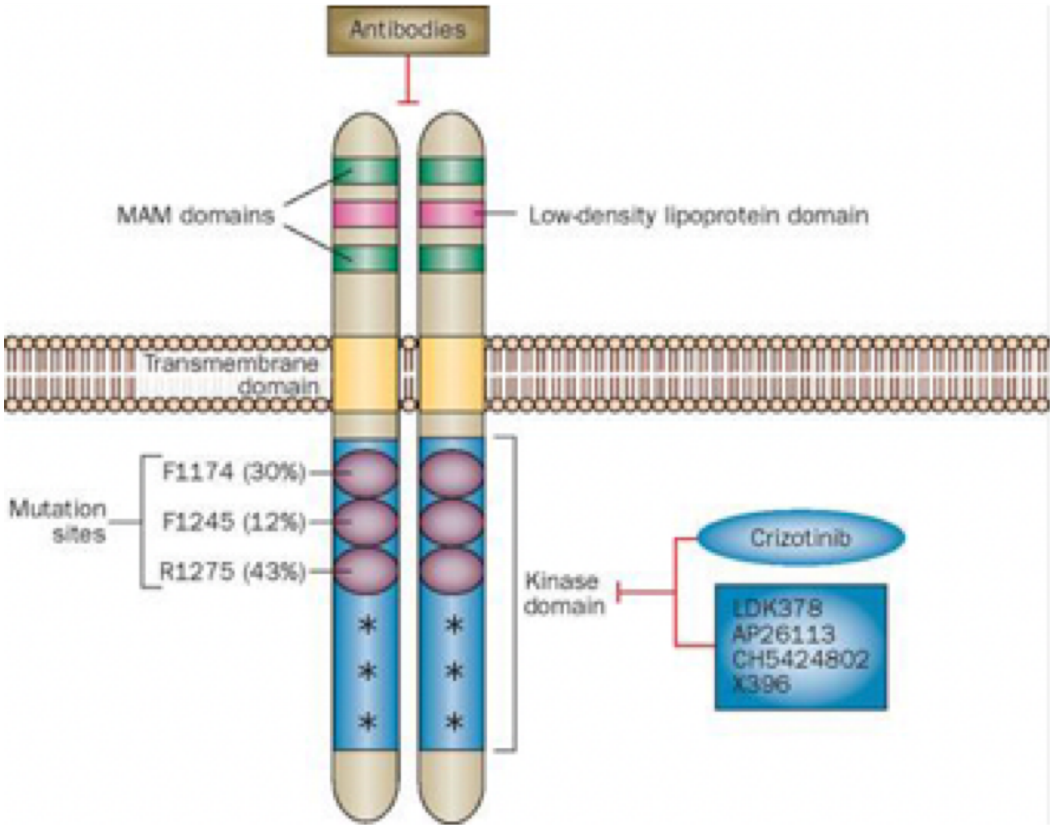
- chr2:29,432,663
- known activating mutation in kinase domain
- most frequent ALK mutation in neuroblastoma
- ALK is a driving oncogene in neuroblastoma
- ALK mutations more frequent in relapsed tumors
- direct target of ALK kinase inhibitors

ALK: oncogene often mutated/fused/amplified/overexpressed in solid tumors



Source: Pediatric Cancer Database, St. Jude: pecan.stjude.org

Receptor tyrosine kinase ALK: activated signaling



Compound availability

ALK inhibitor

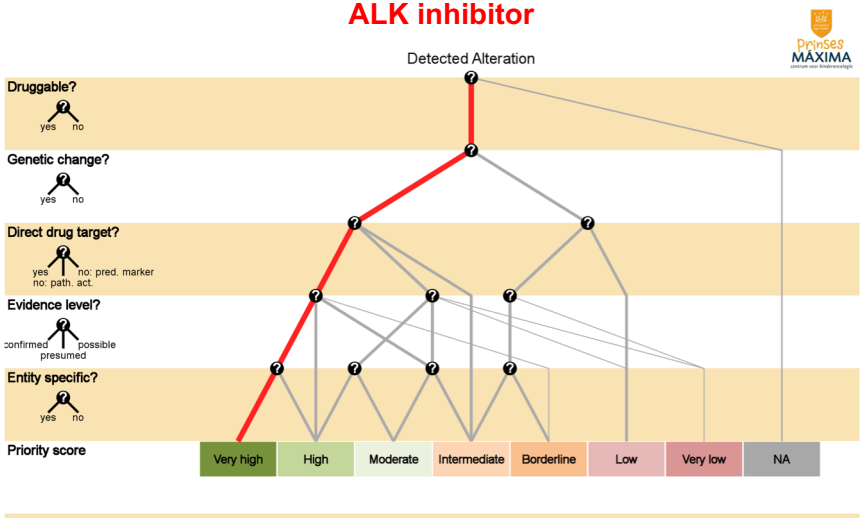
- Crizotinib: CRISP open in NL
- Ceritinib (LDK378): trial closed; trials open in US
- Lorlatinib: phase 1/2 US, (FR and UK not yet open)
- Alectinib: not in children yet

R1275Q mutation

- probably resistant to Ceritinib
- Possibly sensitive to Crizotinib and Alectinib

Solution example 4: Neuroblastoma

Actionable event 1: **ALK mutation**
ALK inhibitor



Alteration Type	Action of Drug	Target Type	Entity	Priority
Genetic	Direct	Confirmed	Specific	1. Very high

Activating mutation in a confirmed driver that is specific for neuroblastoma.
Actionable events with Very high priority are likely to be introduced in first line therapy.