

# Advances in Treatment for Neuroblastoma

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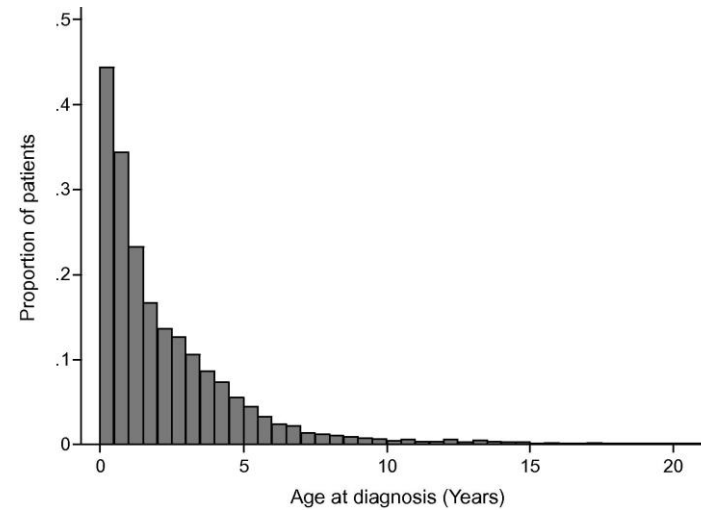
# Neuroblastoma

## Incidence



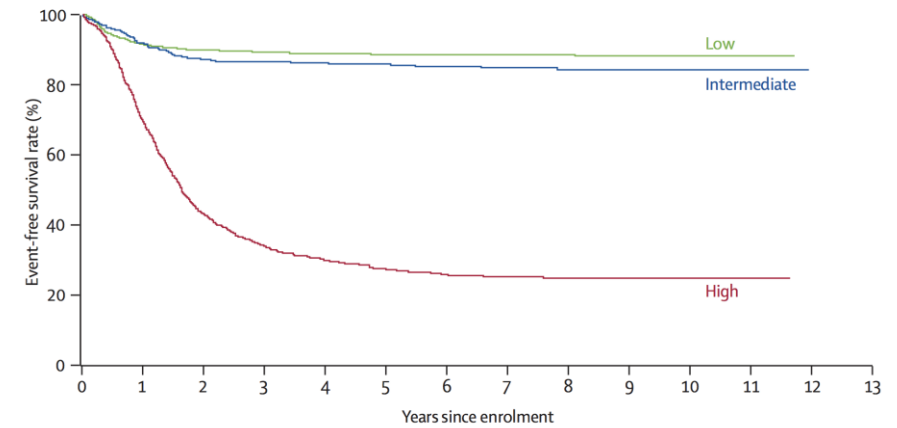
~80 cases per year total  
~40 high-risk neuroblastoma

## Age distribution



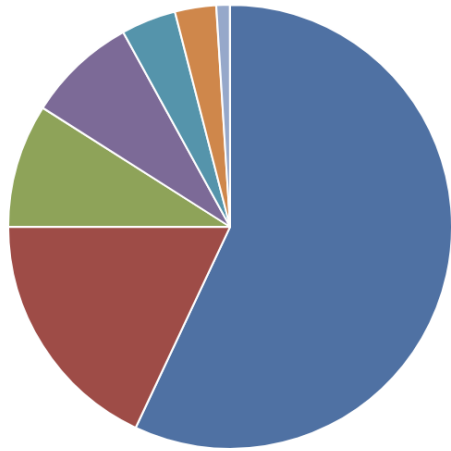
Moroz et al. EJC 2011

## Outcomes



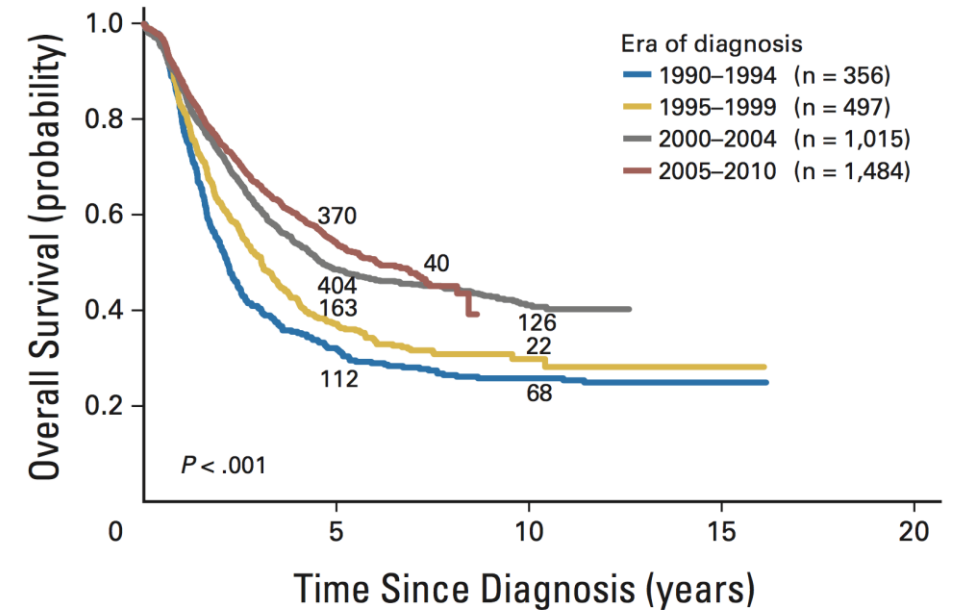
Maris et al. Lancet 2007

# High-risk neuroblastoma



Cancer  
57% of childhood deaths 1-19yr  
(Centers for Disease Control)

↓  
Neuroblastoma  
~10% of cancer deaths  
~200 annually in US  
(Smith et al. JCO 2010)



(Pinto et al. JCO 2015)

## Of patients with HR-NBL

10-15% primary refractory disease

50-60% relapse

Significant risk of death from disease ... and long-term late effects among survivors

# Neuroblastoma risk-stratification

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
					No		E Low
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS					No		C Very low
	< 18			NA	Yes		Q High
				Amp			R High

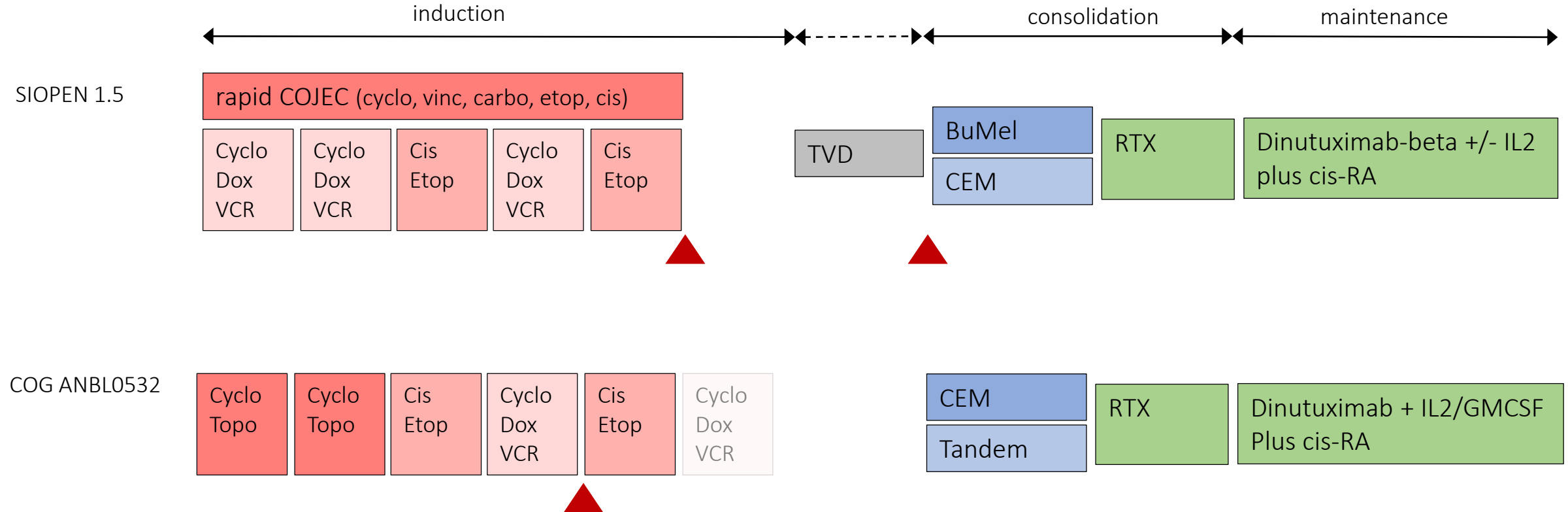
(Cohn et al. JCO 2009)

COMPLICATED!

High-risk neuroblastoma

- metastatic disease in patients >18 months
- MYCN-amplified disease (except stage 1)
- localized disease >18 months, unfavourable histology

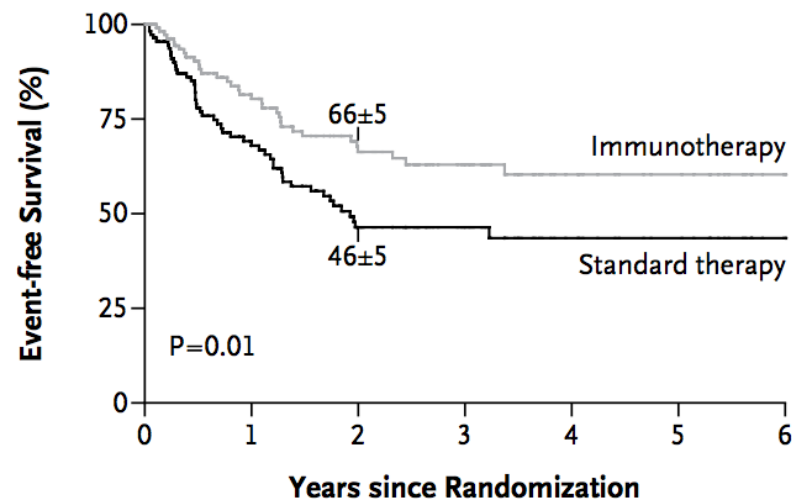
# Current treatment for high-risk neuroblastoma



# Recent advances in HR-NBL therapy

## Addition of immunotherapy to maintenance

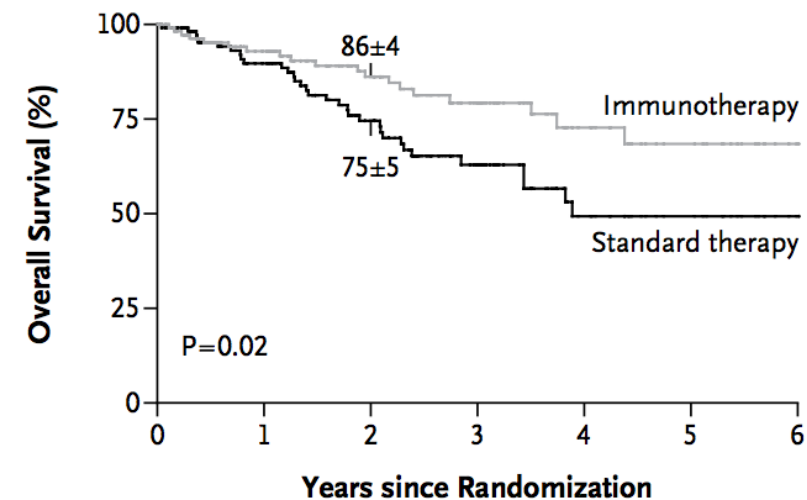
**A Event-free Survival**



**No. at Risk**

Immunotherapy	113	69	47	29	15	9	3
Standard therapy	113	59	32	20	10	8	1

**B Overall Survival**

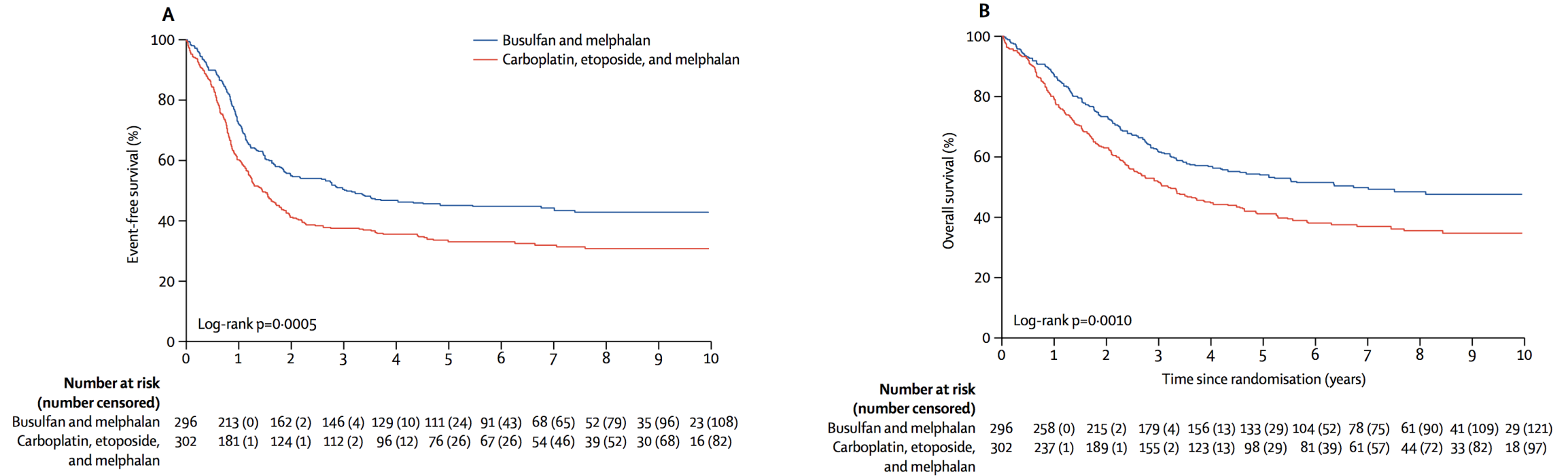


**No. at Risk**

Immunotherapy	113	77	59	37	20	10	3
Standard therapy	113	79	51	26	12	9	1

# Recent advances in HR-NBL therapy

## Benefit of BuMel over CEM (after rapid COJEC induction)



(Ladenstein et al. Lancet Oncol 2017)

# Recent advances in HR-NBL therapy

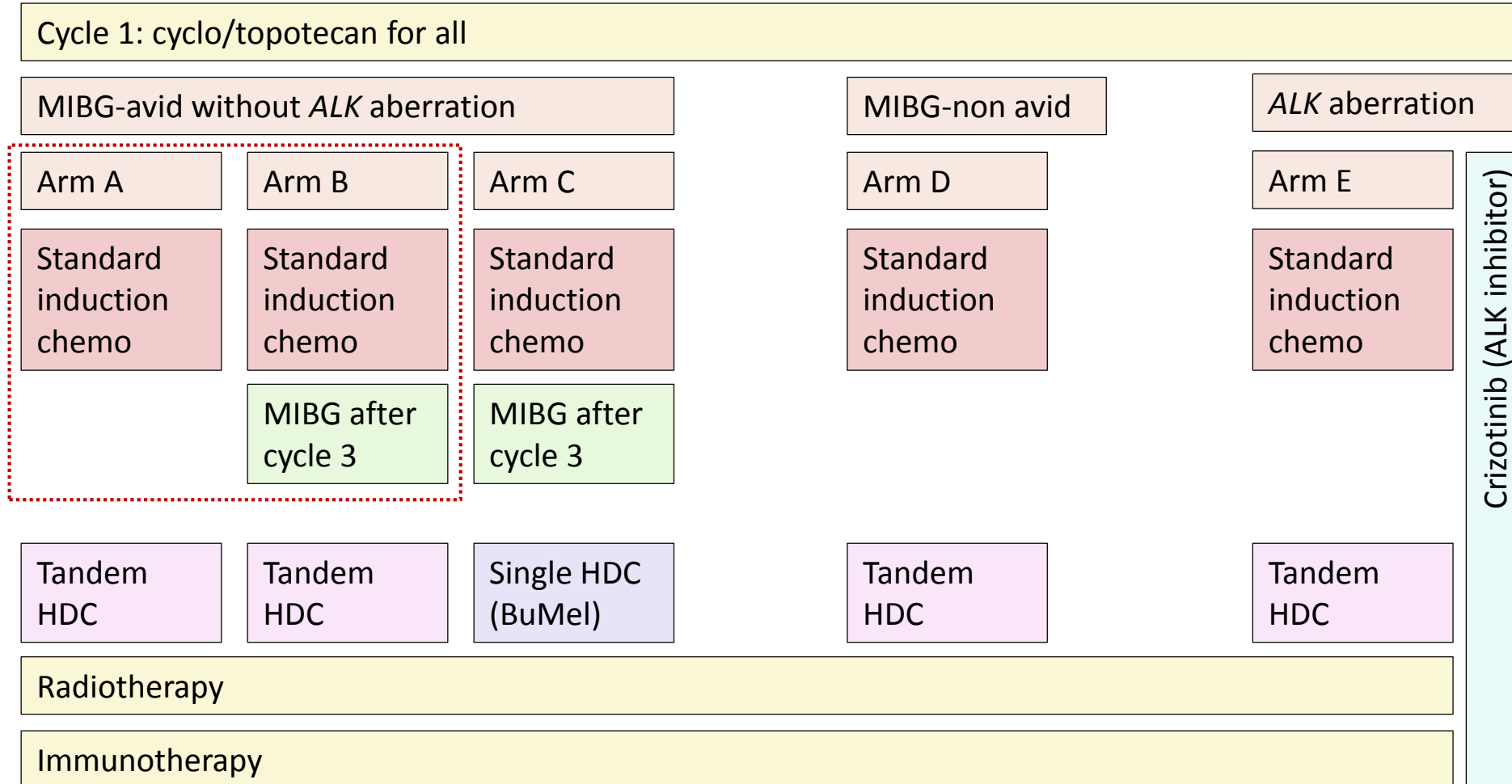
## Benefit of tandem HDC (thio/cyclo+CEM) over CEM (COG ANBL0532)

	Single	Tandem	
Number	179	176	
3-yr EFS	48.8 (41.1–56.5)	61.8 (53.8–69.8)	p=0.0082

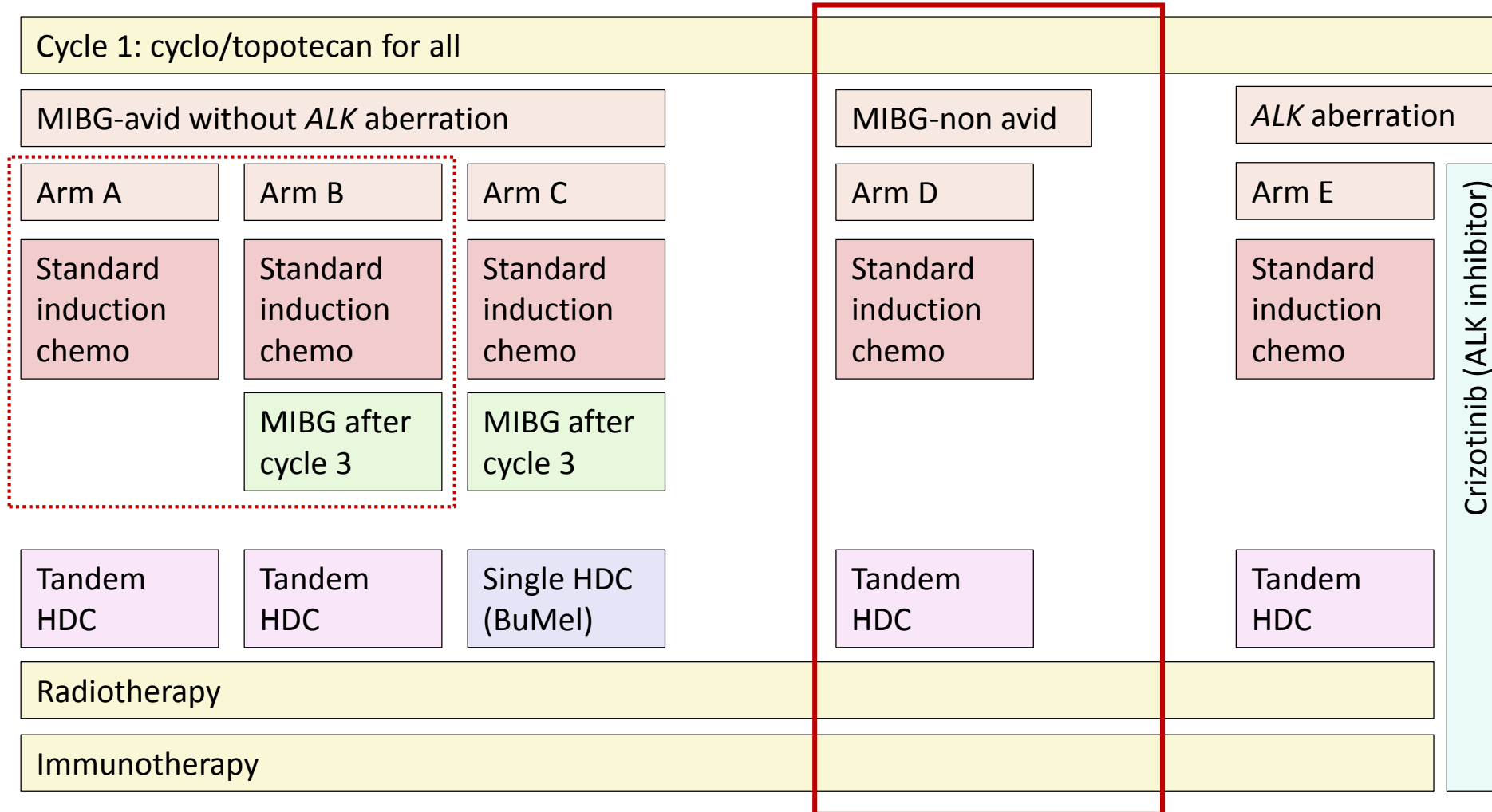
(clinicaltrials.gov)



# Next COG HR-NBL trial: ANBL1531

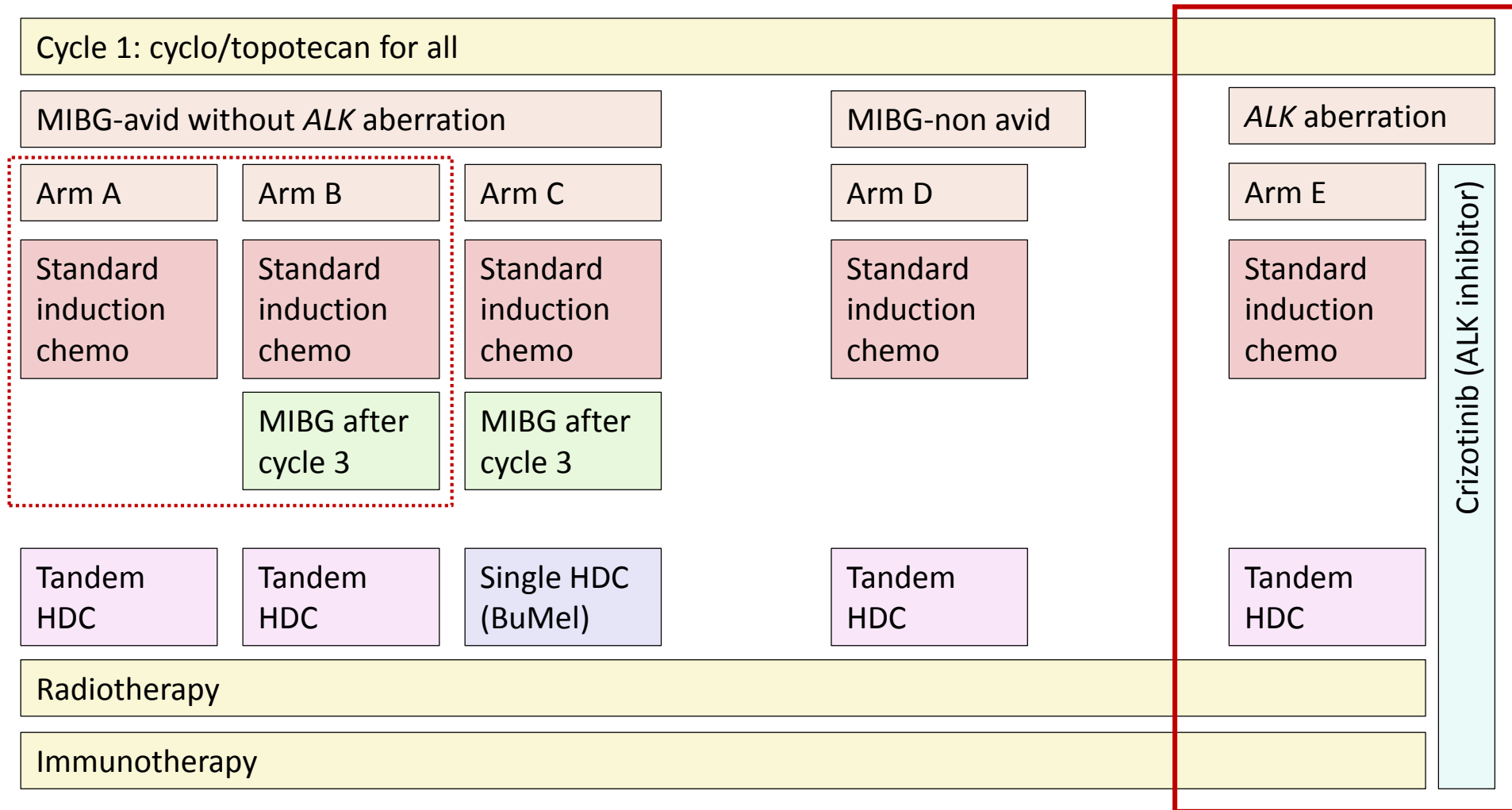


# ANBL1531



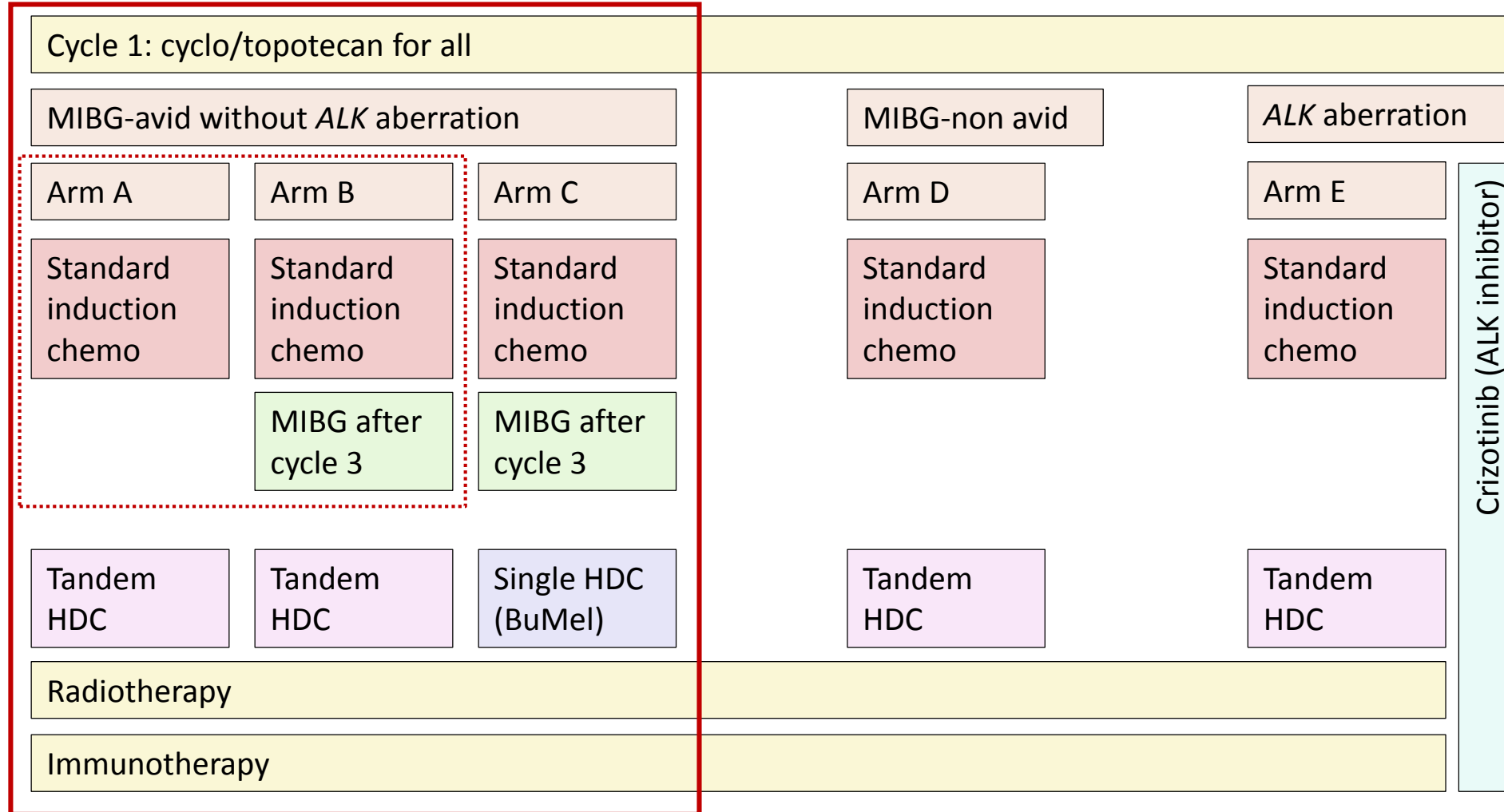
'standard' therapy with tandem HDC for MIBG non-avid disease

# ANBL1531



Addition of crizotinib for patients with *ALK* aberrations

# ANBL1531

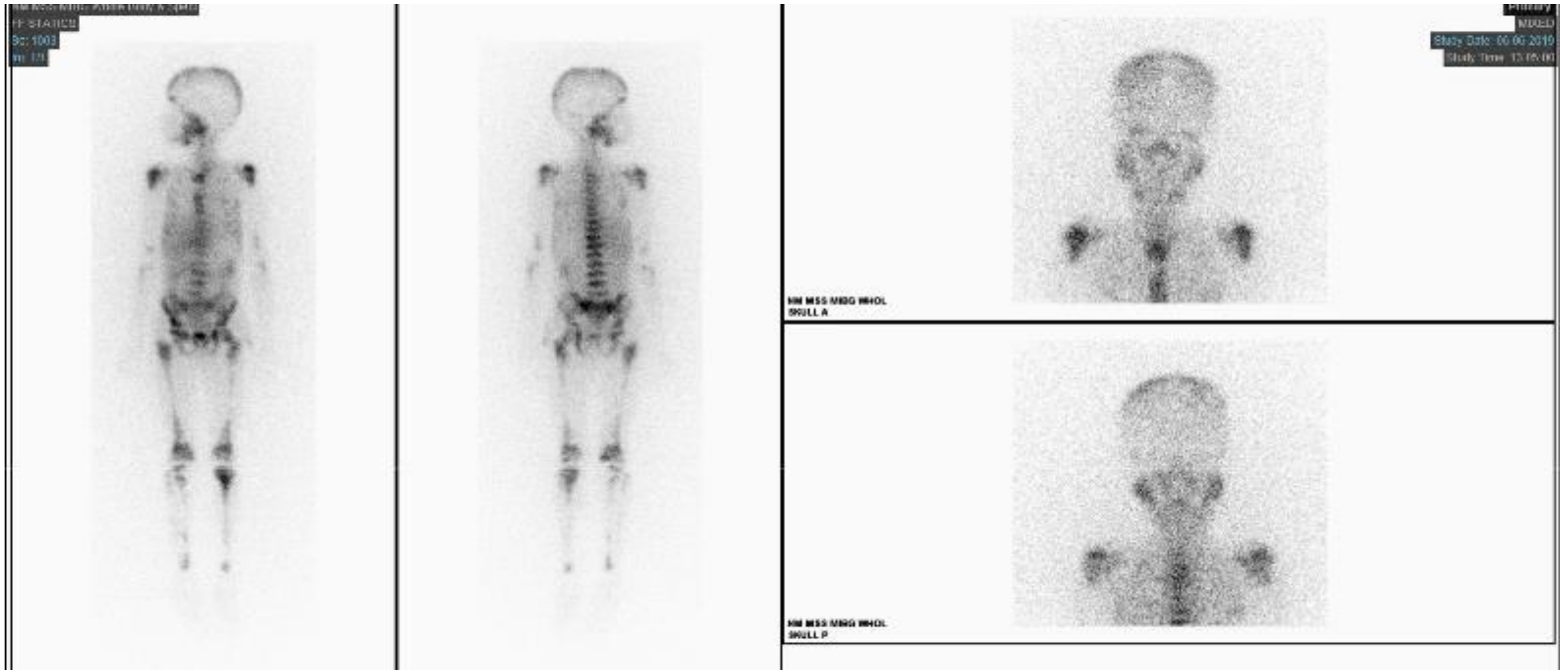


Patients with no *ALK* aberration and MIBG-avid disease...

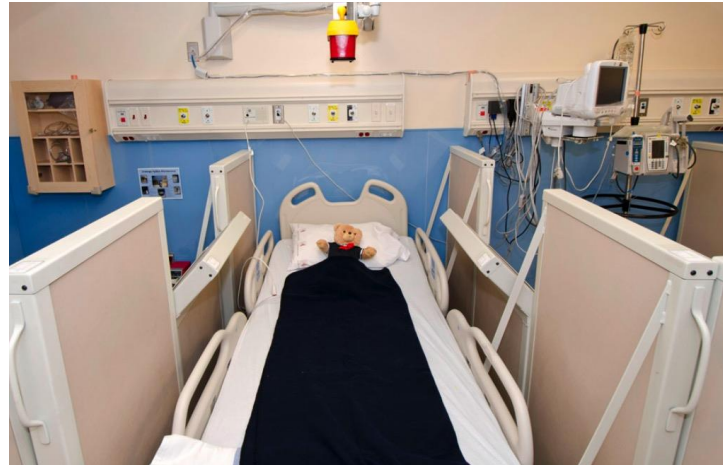
Main randomised questions

- 1) Addition of MIBG
- 2) Tandem vs BuMel

# MIBG therapy



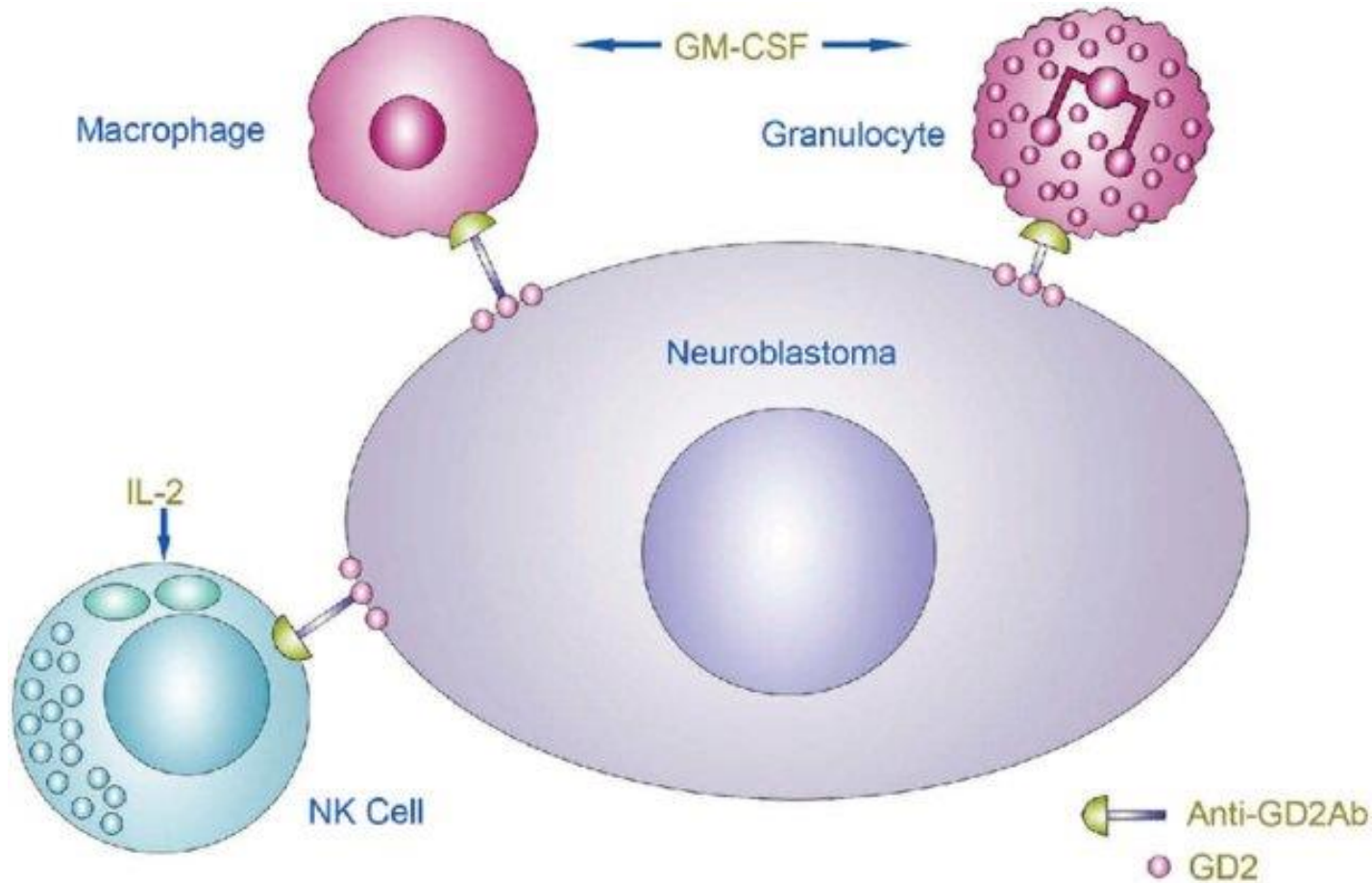
# MIBG therapy practicalities



- Protective isolation
- IV fluids
- Catheterization
- Thyroid protection
- Stem cell rescue



# Anti-GD2 immunotherapy



1	Anti-GD2	GM-CSF	Cis-RA
2	Anti-GD2	IL-2	Cis-RA
3	Anti-GD2	GM-CSF	Cis-RA
4	Anti-GD2	IL-2	Cis-RA
5	Anti-GD2	GM-CSF	Cis-RA
6			Cis-RA

# Relapse HR neuroblastoma

ENSG, 1982-1992

5-yr post-relapse OS: **5.6%**

INRG

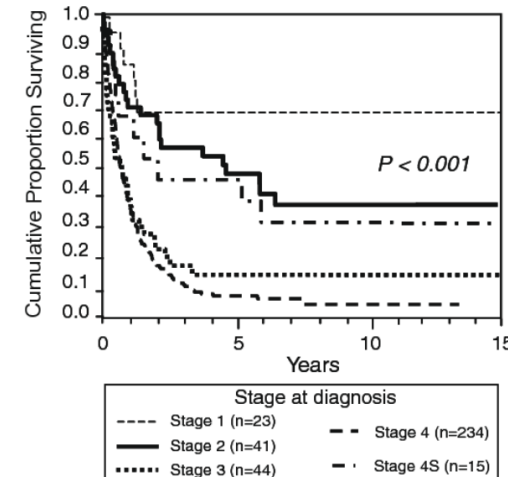
5-yr post-relapse OS: **8%** (stage M at diagnosis)

5-yr post-relapse OS: **4%** (stage M *MYCN*-A)

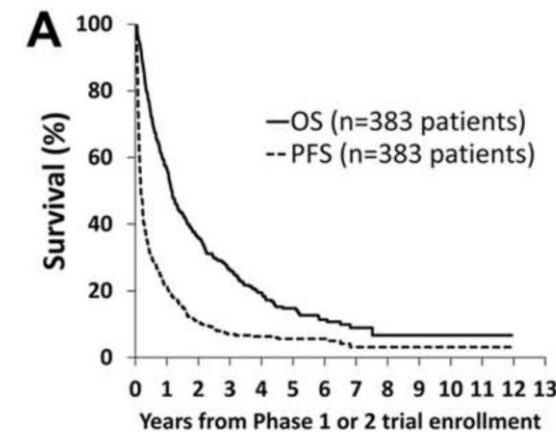
Treated on COG early-phase trials

4-yr post-relapse OS: **20%**

4-yr post-relapse PFS: **6%**



(Garaventa et al. EJC 2009)



(London et al. Cancer 2017)



# Treatment options for relapse HR neuroblastoma

Temozolomide + irinotecan

Cyclophosphamide + topotecan

$^{131}\text{I}$ -mIBG

ALK inhibitors

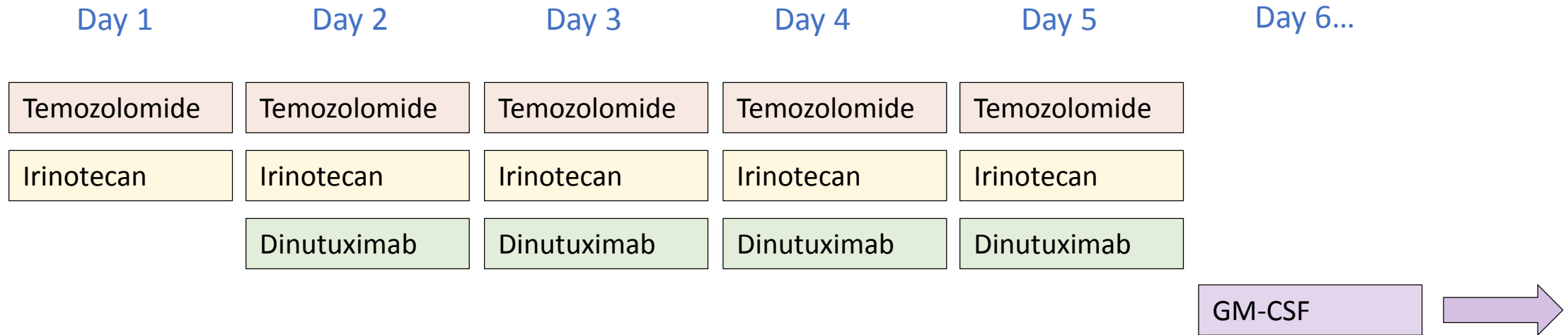
Other targeted therapy

Other early-phase trial options

Complex decisions:

- Prior therapy
- Previous toxicities
- Current symptoms
- Pattern of disease
- Patient/family preference

# ANBL1221: immunotherapy for relapse/refractory disease



# ANBL1221: results

	Irinotecan– temozolomide– temsirolimus (n=18)	Irinotecan– temozolomide– dinutuximab (n=17)
Complete response	0	5 (29%)
Partial response	1 (6%)	4 (24%)
Stable disease	10 (56%)	4 (24%)
Progressive disease	7 (39%)	3 (18%)
Not evaluated*	0	1 (6%)

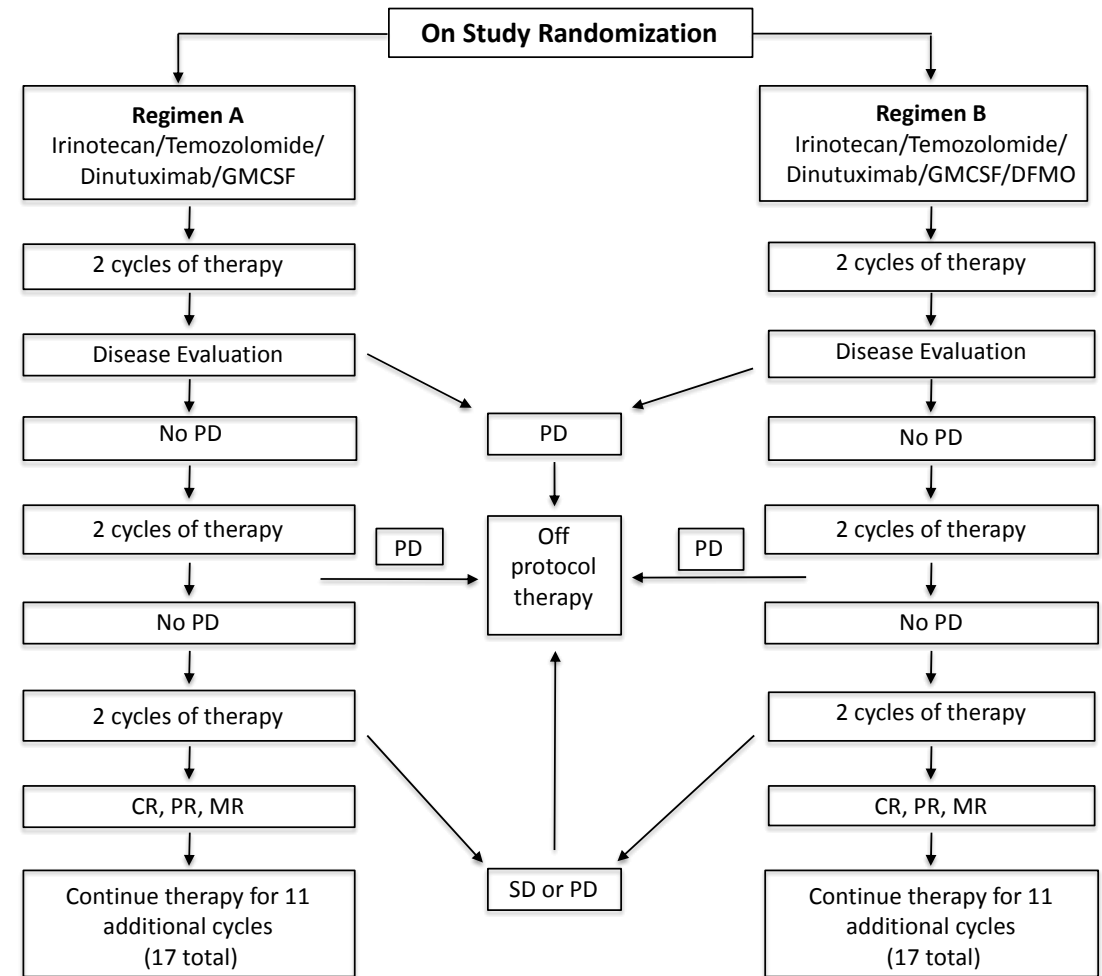
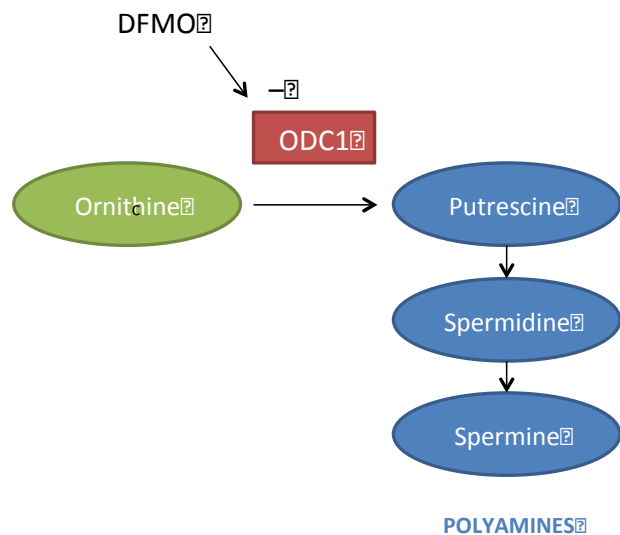
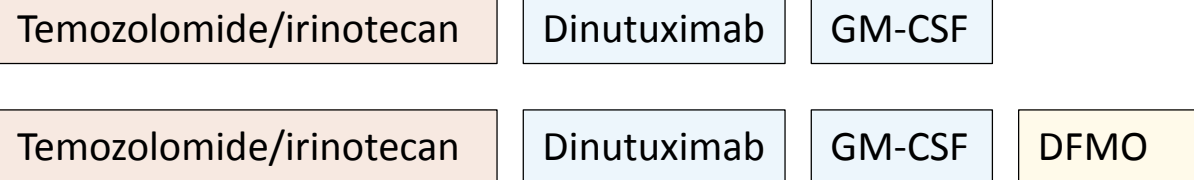
\*Patient not evaluated because of refusal to receive therapy after randomisation.

**Table 2: Best overall response by treatment regimen**

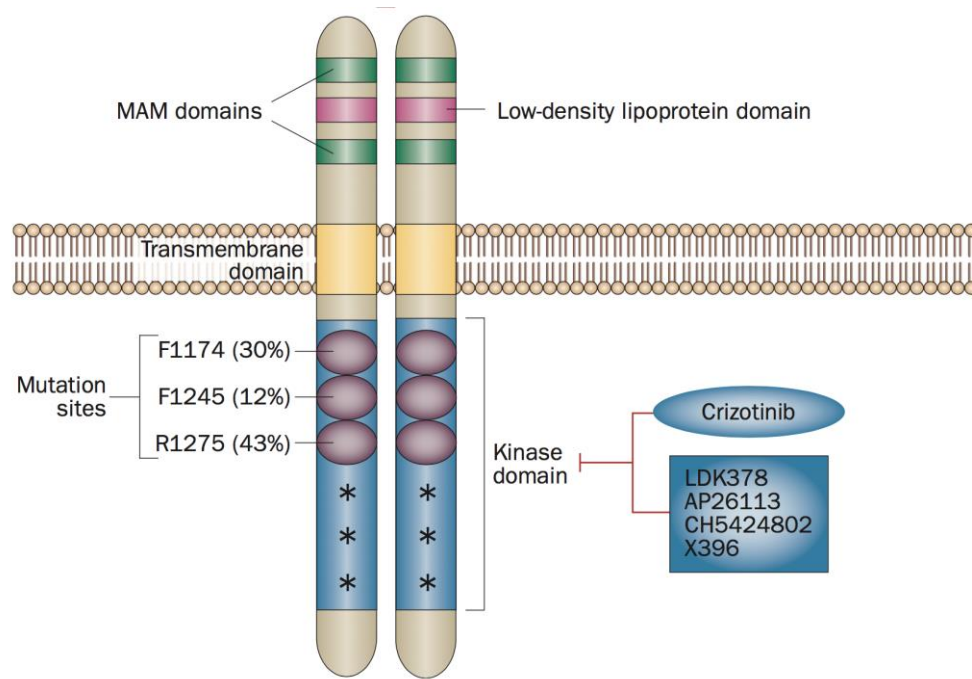
	Disease status at baseline	Measurable disease at baseline	MYCN amplified	Previous anti- GD2 antibody treatment	Total cycles of trial therapy received
Responder 1	Relapsed	Yes	No	Yes	6
Responder 2	Relapsed	Yes	No	Yes	17
Responder 3	Relapsed	Yes	Yes	Yes	17
Responder 4	Relapsed	No	Yes	Yes	10
Responder 5	Relapsed	No	No	No	14
Responder 6	Refractory	No	No	No	17
Responder 7	Refractory	No	Unknown	No	17
Responder 8	Refractory	No	No	No	3
Responder 9	Refractory	No	No	No	8

**Table 3: Characteristics of responders in the irinotecan–temozolomide–dinutuximab group**

# ANBL1821: next relapse study



# Targeted agents: ALK



Carpenter & Mossé Nature Reviews Clinical Oncology 2012

ALK mutations in ~8% diagnostic samples  
Increased rate at relapse

## Agents

- **Crizotinib** – to be tested frontline in COG ANBL1531
- **Certitinib** (LDK378) – paediatric phase I complete
- **Lorlatinib** – paediatric phase I ongoing via NANT; crosses BBB

# Summary

- **Tandem HDC** now standard for metastatic HR disease in COG
- Role of **MIBG therapy** (and **ALK inhibitor**) being tested in next COG trial
- **Temozolomide/irinotecan/dinutuximab/GM-CSF** has become standard for relapse/refractory disease in COG
- Next COG relapse trial will test addition of DFMO
- Multiple options for relapse HR disease
- **Not all neuroblastoma is high-risk**