Integrating our new therapeutics into (more) frontline protocols

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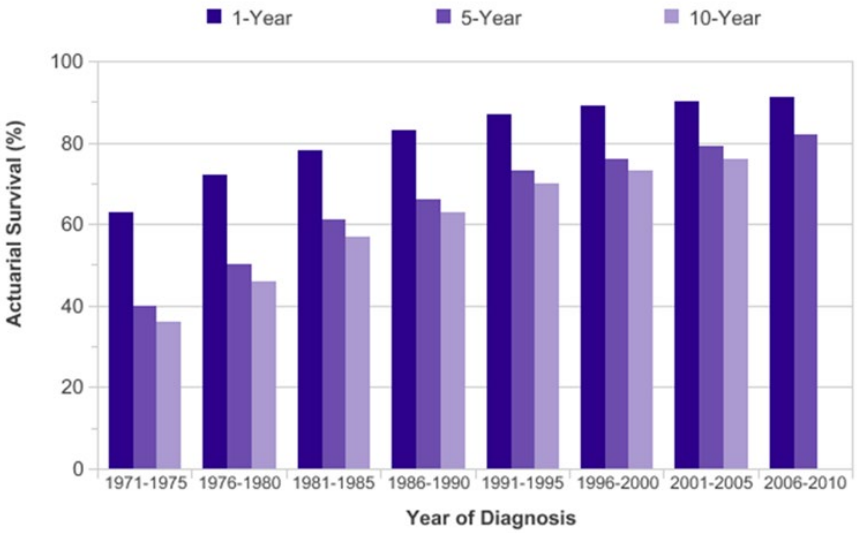
ITCC Introductory Course in Paediatric Drug Development
Utrecht, 15-16 October 2018

Childhood Cancer



Improvement in UK Survival Outcomes (1971-2010)

- **High risk groups remain poor prognosis despite toxic therapy:**
  - Neuroblastoma
  - Metastatic sarcoma
  - Certain brain tumours - pHGG, DIPG
  - High risk leukaemia
  - Relapsed lymphoma
- **Need for earlier introduction of agents targeting molecular drivers of cancer.**

Cancer in childhood is rare:

(<1% of all cancers < 15 years; 1% in teenagers/TYA)

BUT remains most common cause of death < 15 years (developed countries)

Unmet need: Faster, more efficient drug development

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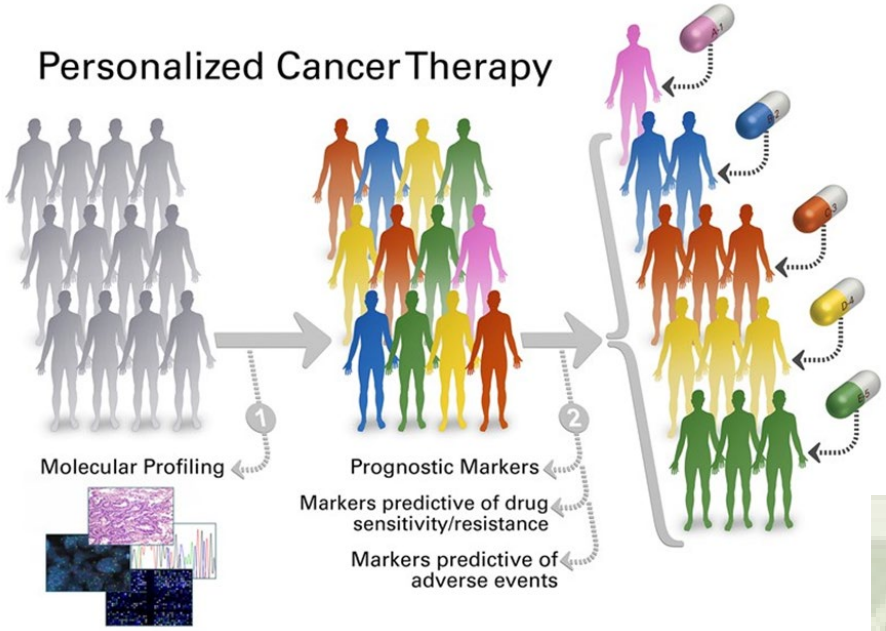
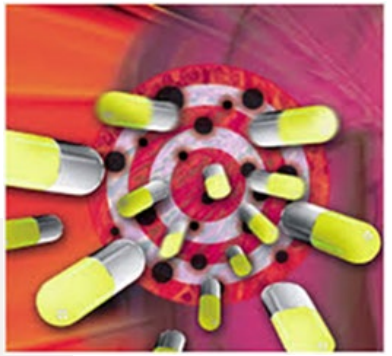
Overall Goals & Ethos of Paediatric Drug Development

- To **improve survival** for poor prognosis childhood cancers by accelerating the development of new drugs and advancing the best to more frontline therapy as quickly and safely as possible
- To **provide access** to hypothesis-driven, biomarker-rich early clinical trials of novel molecularly targeted agents within early phase trials – paradigm shift
- To **provide excellent, holistic, ethical multidisciplinary cancer care** for child/young person and family – some are palliative
- To **deliver high quality clinical trials data** to regulatory standards required & to facilitate licensing of best new drugs
- **To train a new generation** of paediatric oncology drug developers to drive forward progress in the field

Overall Goals:
Paediatric & Adolescent Programmes





Precision medicine and Personalised therapy

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The Long Process of Drug Development

10-15 years

Preclinical phase:
-Target identification
-Drug Discovery
-Preclinical testing *in vitro* & *in vivo*

Adults

Phase I

First-in-man;
Dose finding:
- DLT
- MTD/OBD
- RP2D

Safety/PK

Phase II

Small numbers; disease-specific; activity

Efficacy

Phase III

Large randomised controlled trials against standard treatment

MA/CLINIC

Long term follow-up data

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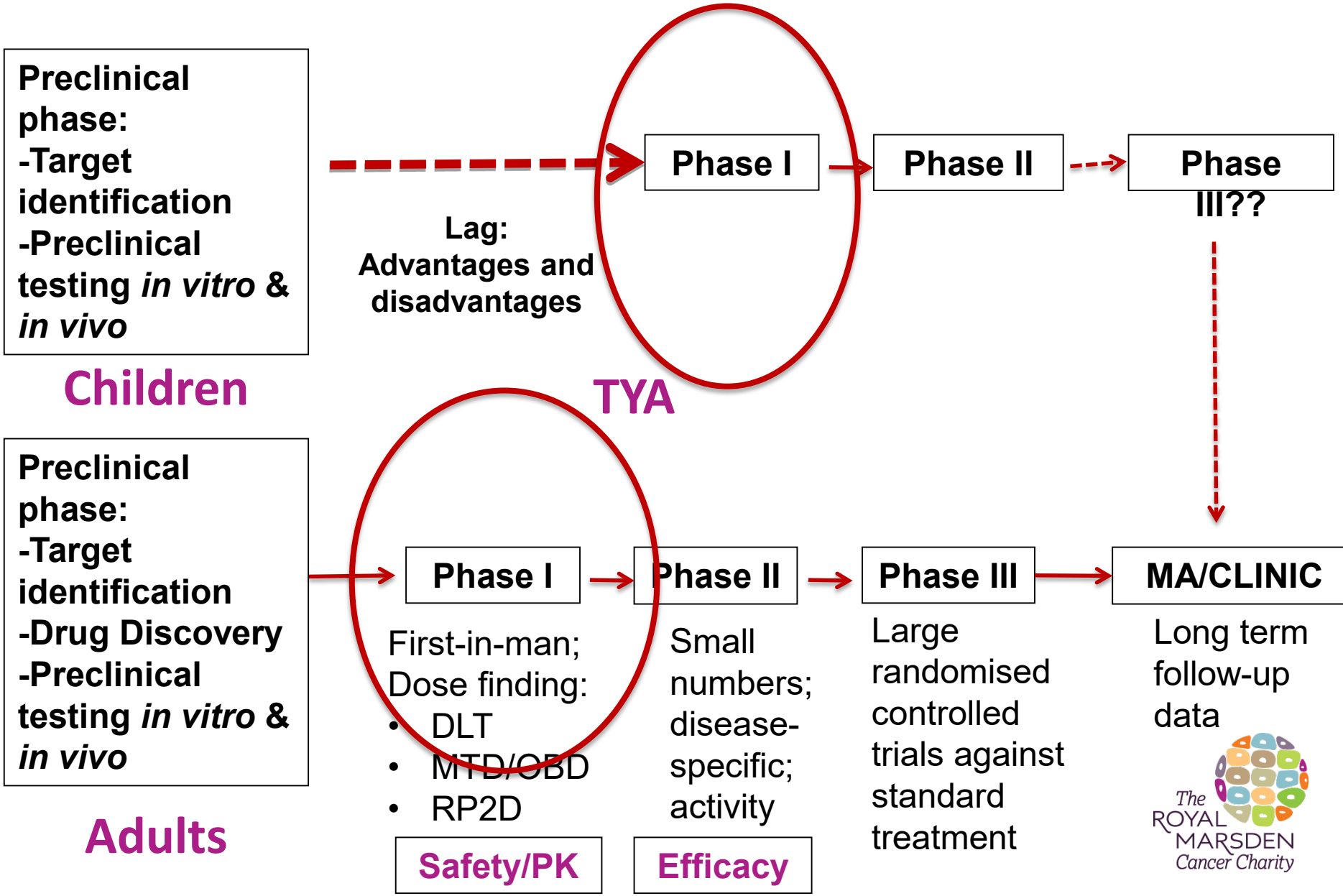
The Long Process of Drug Development



Bottlenecks to cancer drug development for paediatric patients

- **Drug supply**
  - For preclinical & clinical studies
  - Priorities – adult market; studies in patients <18yrs are perceived as high-risk by pharma
  - High drug attrition rates at all stages of development (<10% paediatric phase 1)

- **Funding**
  - **Industry-sponsored:** limited to PIP-driven trials; commercial income does not cover the cost of the academic studies
  - **Academic funding:** limited; relatively few clinical trial units sponsor paediatric phase 1 trials
  - **Charity**

- **Rarity of paediatric cancers & now molecular sub types**
  - Long recruitment / small studies / multi-centre / collaboration / expense
  - **Biology – less well understood; fewer recurrent mutations; drivers vs passengers; role of epigenetics**
  - Historical lack of biomarker development/ incorporation (Predictive; PD)

- **Regulatory Issues**
  - Regulatory obligations makes pharma fear entrusting academic investigators with trial delivery,

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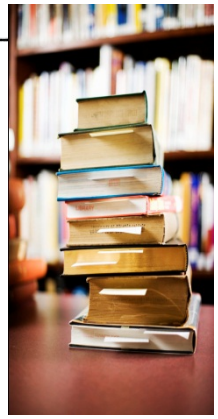

The European Paediatric Regulation (2006):

Aims:

- Improve the health of children & adolescents in Europe
- Increase high quality, ethical research into medicines for children
- Increase availability of **authorised** medicines for children (including age-appropriate formulations)
- Increase information on medicines (safety, toxicity, dosing, activity, efficacy; include in label/Summary of Product Characteristics)
- Without unnecessary studies in children or delaying authorisation for adults

Tools: Paediatric investigation Plans (PIPs), Waivers, Deferrals, Incentives & Rewards, Compliance Checks:

Companies agree plans with the European Medicine Agency's Paediatric Committee (PDCO)

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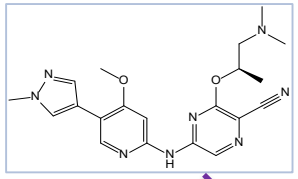
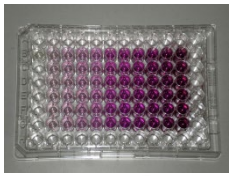
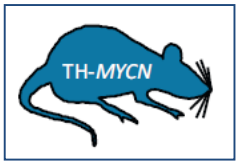
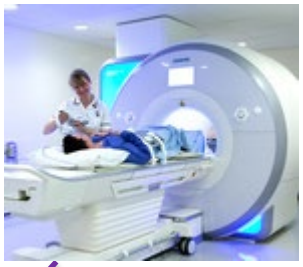
A whole package: infrastructure, investment, expertise





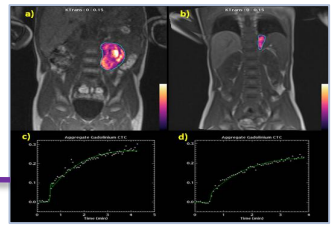


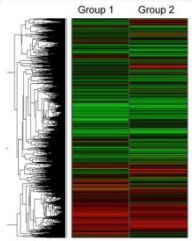


Centre for Molecular Pathology

Adult Drug Development Unit

Paediatric Drug Development Unit & Consortia





Biomarkers

- **The incorporation of scientific hypothesis with biomarkers into early clinical trials will accelerate and improve drug development for childhood cancers**
- **Uniquely placed to bring them into frontline treatment.**

Clinical/Academic/Pharma Partners

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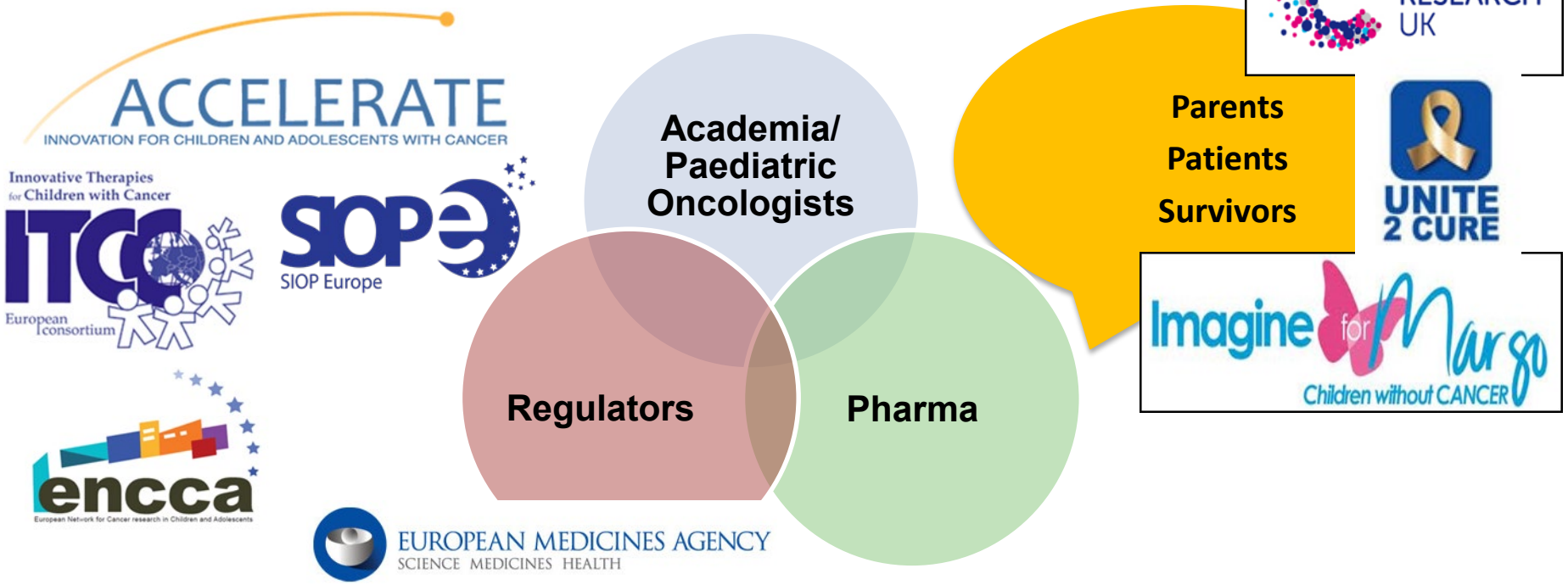
Multi-stake-holder interaction is crucial



- Dialogue about prioritisation of drugs / targets / studies eg Novel Drug Development Strategy (NDDS); ACCELERATE Paediatric Strategy Forums
- Mechanism of action-based drug development
- Novel trial designs; combinations; multi-company; adaptive
- Extrapolation from adult data; inclusion of adolescents > 12 years
- Personalised medicine & molecular profiling strategies
- Long term follow up data collection initiatives

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Phase I & II trials: *key strategies & priorities to help move forward more quickly*

- **Wide & balanced portfolio:**
  - Phase I and II; momentum essential; no gaps between studies (high attrition rate of drugs and studies)
  - Inclusive age range – infants, TYA patients
  - Broad eligibility and more targeted eligibility studies
  - Solid tumours, CNS tumours, Lymphomas, Leukaemias
  - Pharma-sponsored and investigator-led/academic studies
- **Make every patient count – efficient trial designs, maximise data use and biomarkers/biological information**
- **Extrapolate from adults where possible**
- **Increase access to trials and new drugs – lower age of inclusion in adult studies**
- **Tumour-specific & target-specific experts and groups driving drug development internationally**
- **Organised referral networks**

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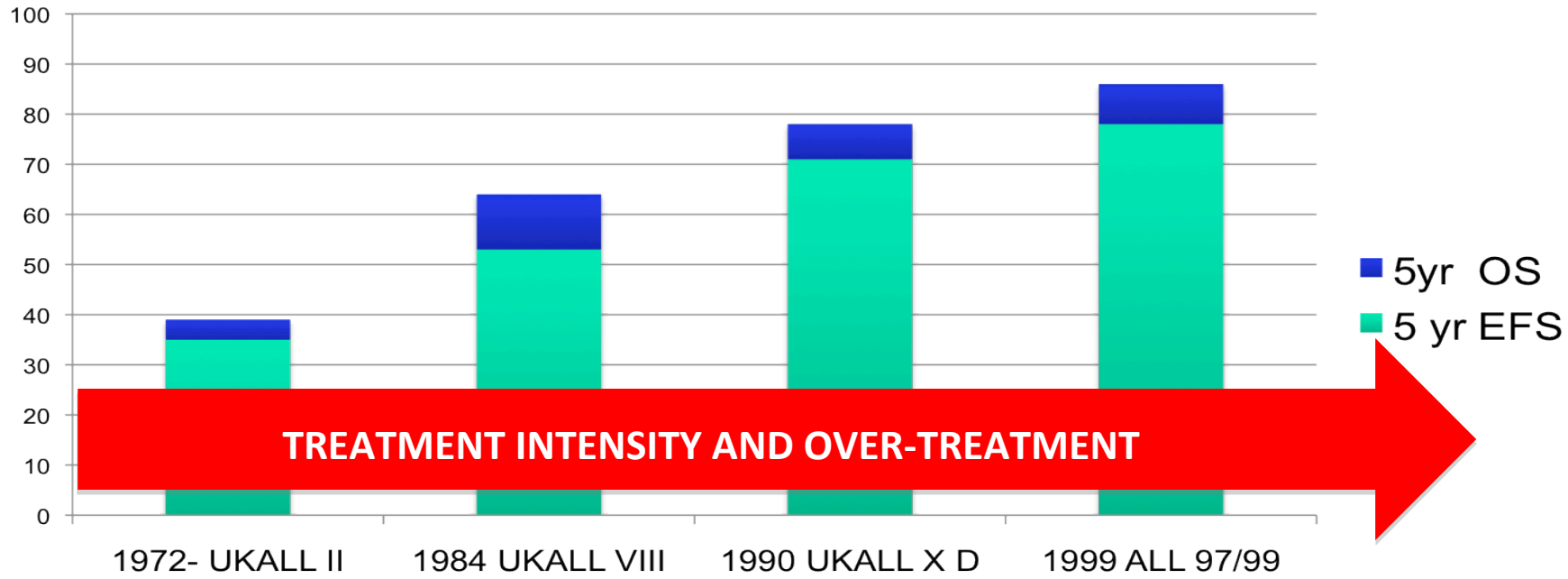
When/Why to move novel therapies forward to front line 'quickly'?

- Very poor prognosis diseases (eg DMG/DIPG) – upfront
- High risk/metastatic disease which respond but relapse (HGG, ARMS, HR MBL…) – consider window studies
- Strong oncogenic driver targets/effective drugs – to improve outcomes
- Very good prognosis diseases – reduce acute and long term toxicities

Improving outcomes: Childhood ALL led the way



Simple therapy Frequent breaks	Simple therapy Greater intensity	Intensified therapy for all patients	Risk directed therapy Based on age and WCC and early response

- UKALL 2003 – one vs 2 DI; MRD; further improvements
- UKALL 2011 – dexamethasone, pulses, HD MTX rand - ongoing
- 2019 - **ALL TOGETHER** – RISK GROUPBASED, TARGETED THERAPY, PATH TO CAR-T CELL FOR RELEVANT GROUPS

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Targeted therapy : Leukaemia led the way in adults…extrapolated to rare paediatric population

Imatinib (Glivec):

- Targeting BCR-ABL/the Philadelphia chromosome t(9;22) in chronic myeloid leukaemia in 2001
- Authorised on the basis of 5 CML studies 2133 adults & 54 children
- Generic biosimilar Imatinib authorised on the basis of showing bioequivalence once patent had expired

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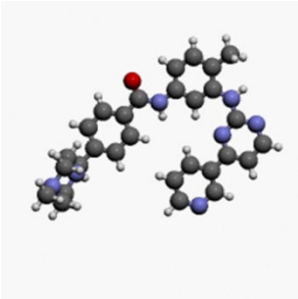
Progress

Imatinib

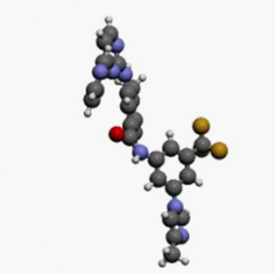
- 1st generation tyrosine kinase inhibitor
- Blocks the BCR-ABL enzyme
- Inhibits cell growth and induces apoptosis
- Initial use in CML (rare in children)
- Proven benefit in Ph+ ALL & incorporated into upfront treatment



Imatinib

Dasatinib…Nilotinib…Bosutinib.

- 2nd /3rd generation tyrosine kinase inhibitors
- Overcome resistance/intolerance to imatinib
- Delay/Avoid BMT



Nilotinib

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Targeted therapy success : Rituximab in high risk BNHL

(Rituximab approved in adults since 1997)

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy (CT) regimen.

Veronique Minard-Colin, Anne Auperin, Marta Pillon, Amos Burke, James Robert Anderson, Donald A. Barkauskas,

ASCO

- **Challenge:** rare population; high cure rate but high acute toxicity; few late toxicities; EFS ~90%
  - high risk group worse (80% or less)
  - Rituximab may have unexpected toxicity in children
- 1-year EFS 81.5% R- *vs* 94.2% R+

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Targets are important

- *Melanoma*
  - Adult disease; rare in children
  - BRAF V600E mutations in 50% –

BRAF inhibitors very successful

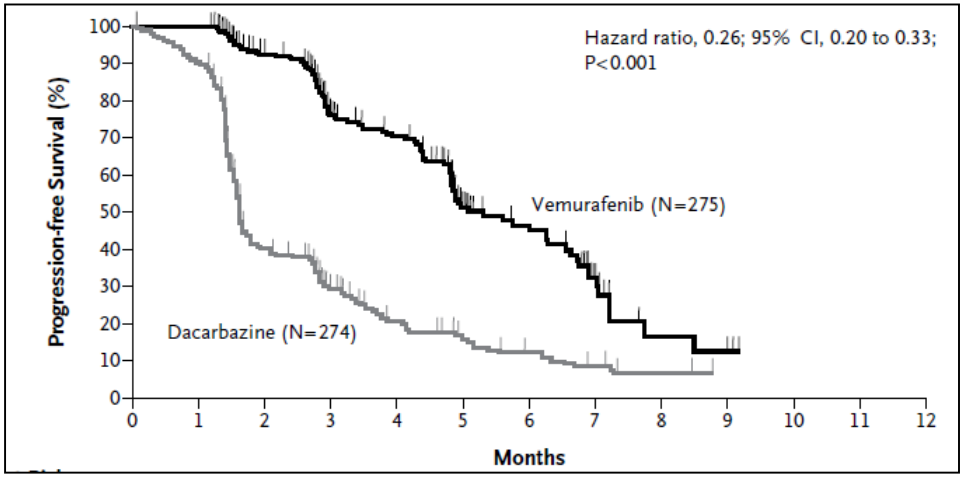
- Paediatric melanoma studies unfeasible & terminated early

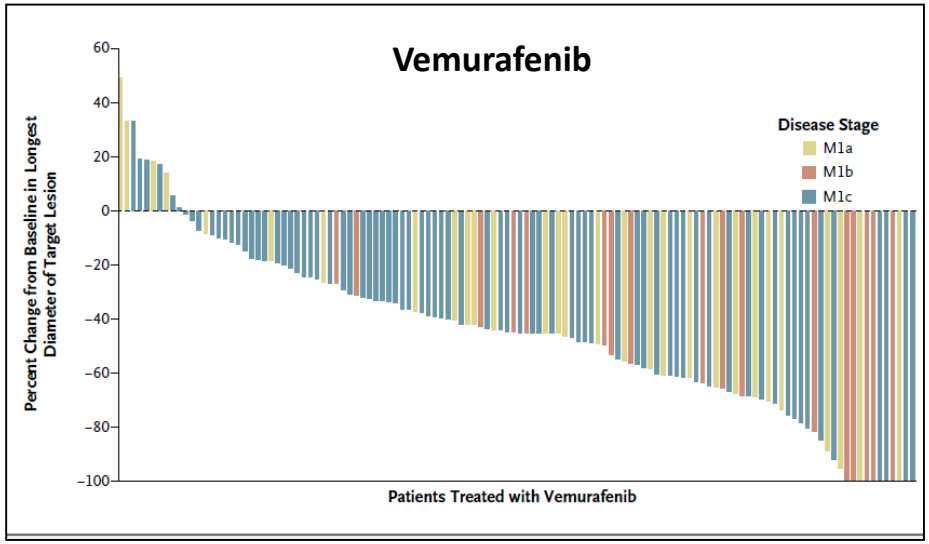
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

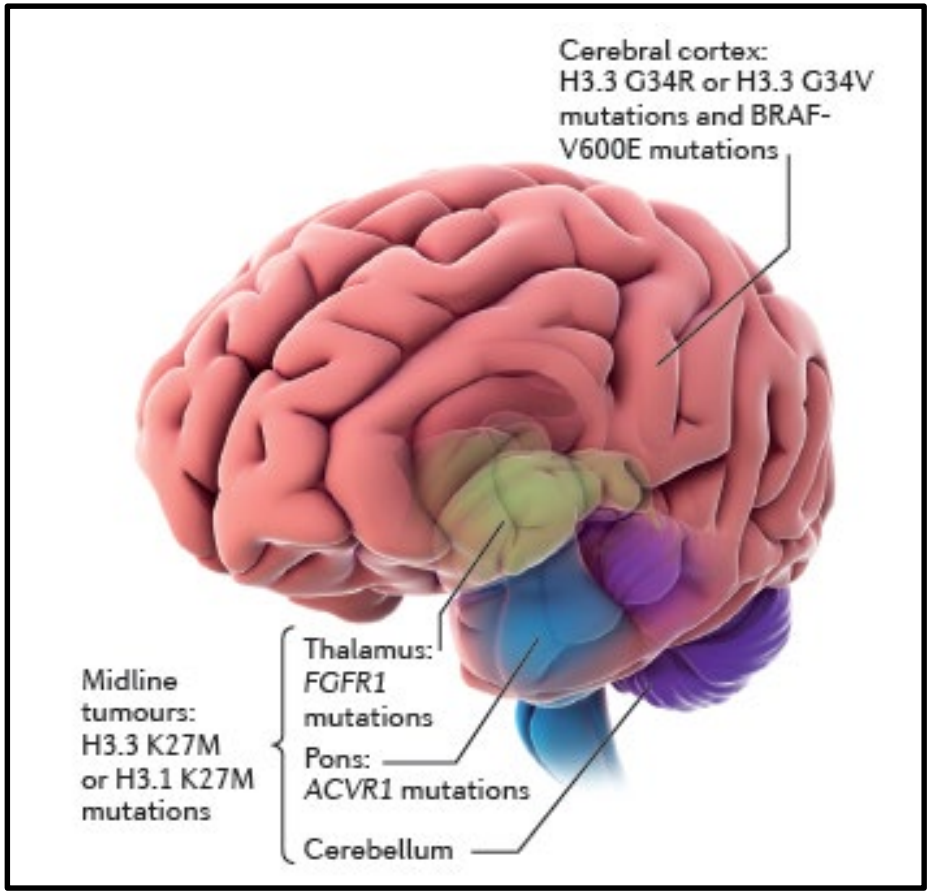
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,





Anatomical distribution and selective mutations distinguish subgroups of paediatric HGG



Jones et al, Nature Reviews Cancer, 2014

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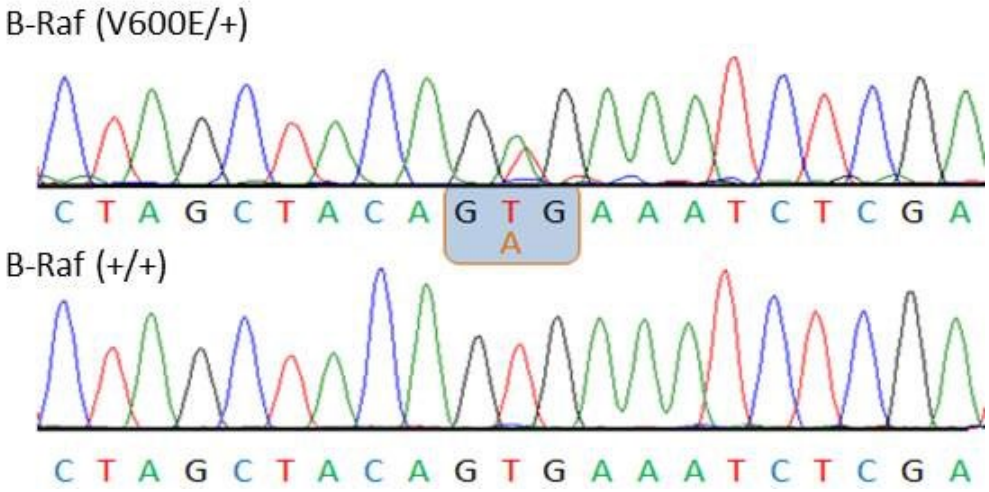
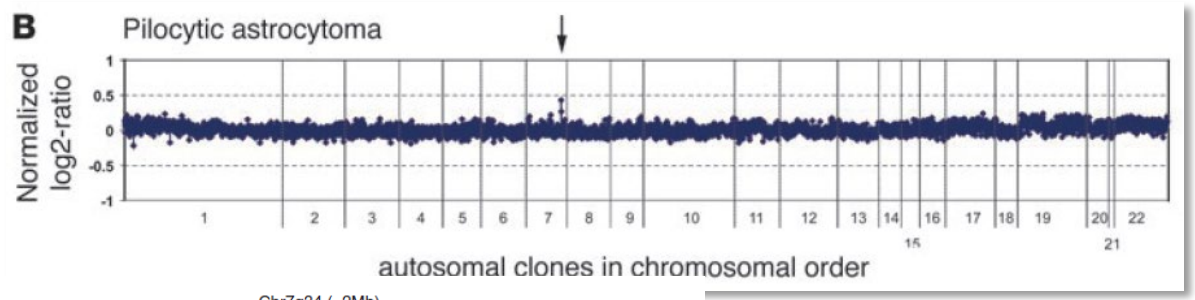
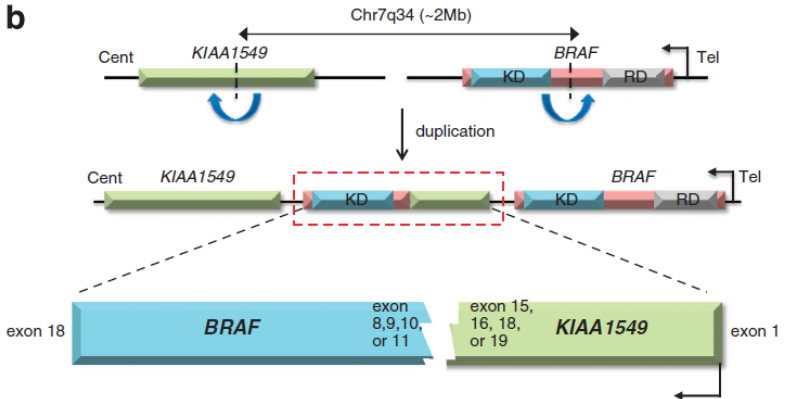
BRAF as an oncogenic driver in HGG & LGG:

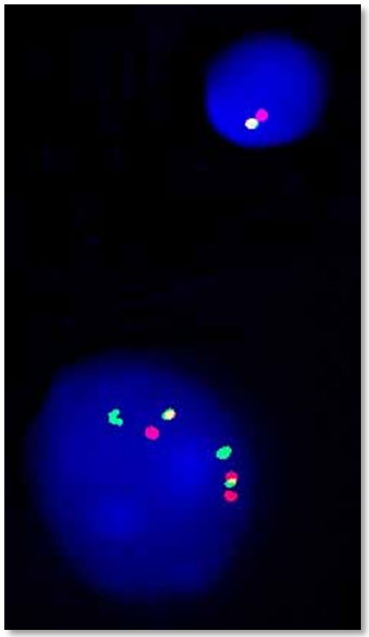
BRAFv600 point mutations in SOME HGG & SOME LGG



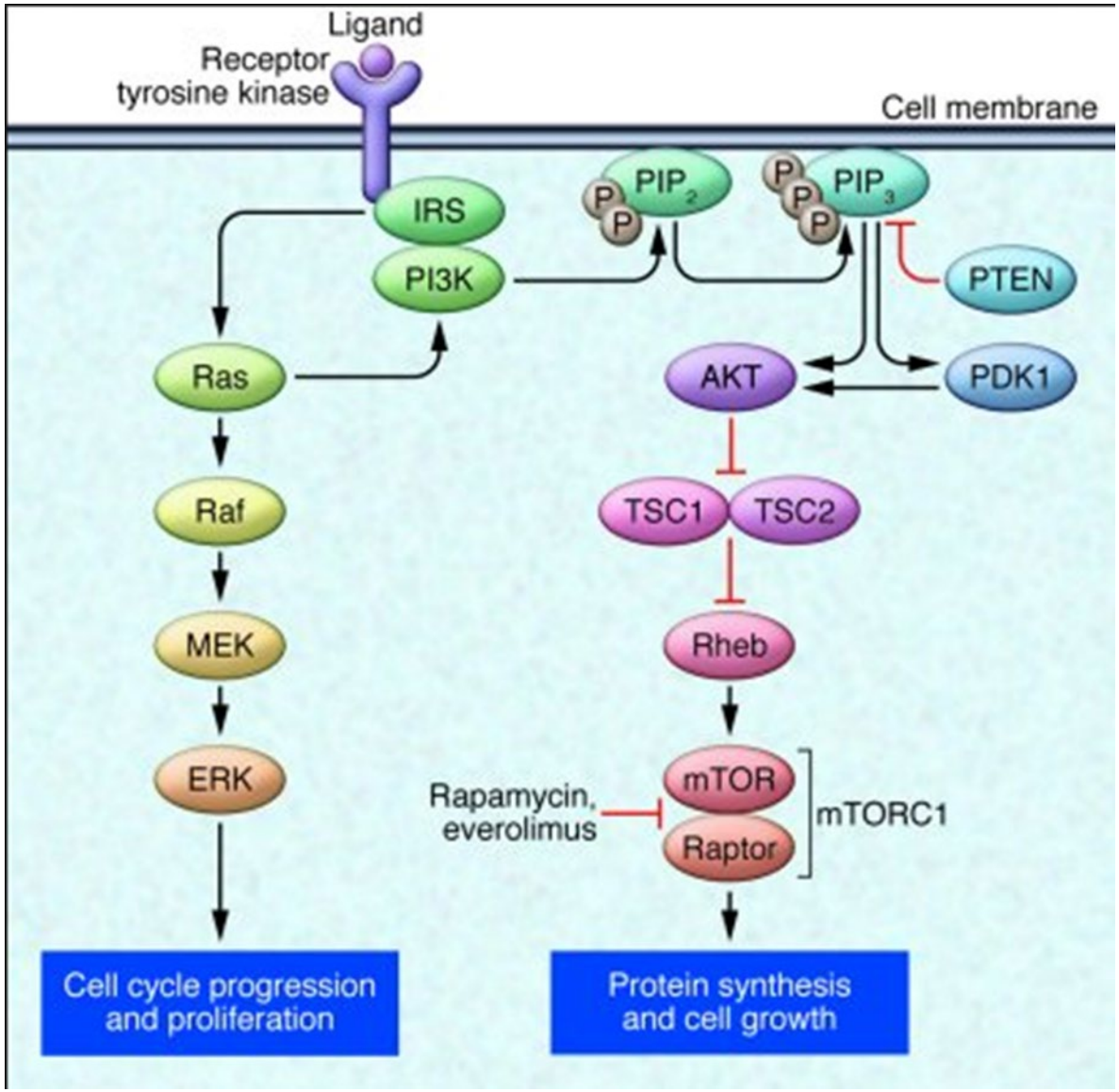




BRAF fusions in LGG



MAP Kinase (MEK) Cell Signaling Pathway



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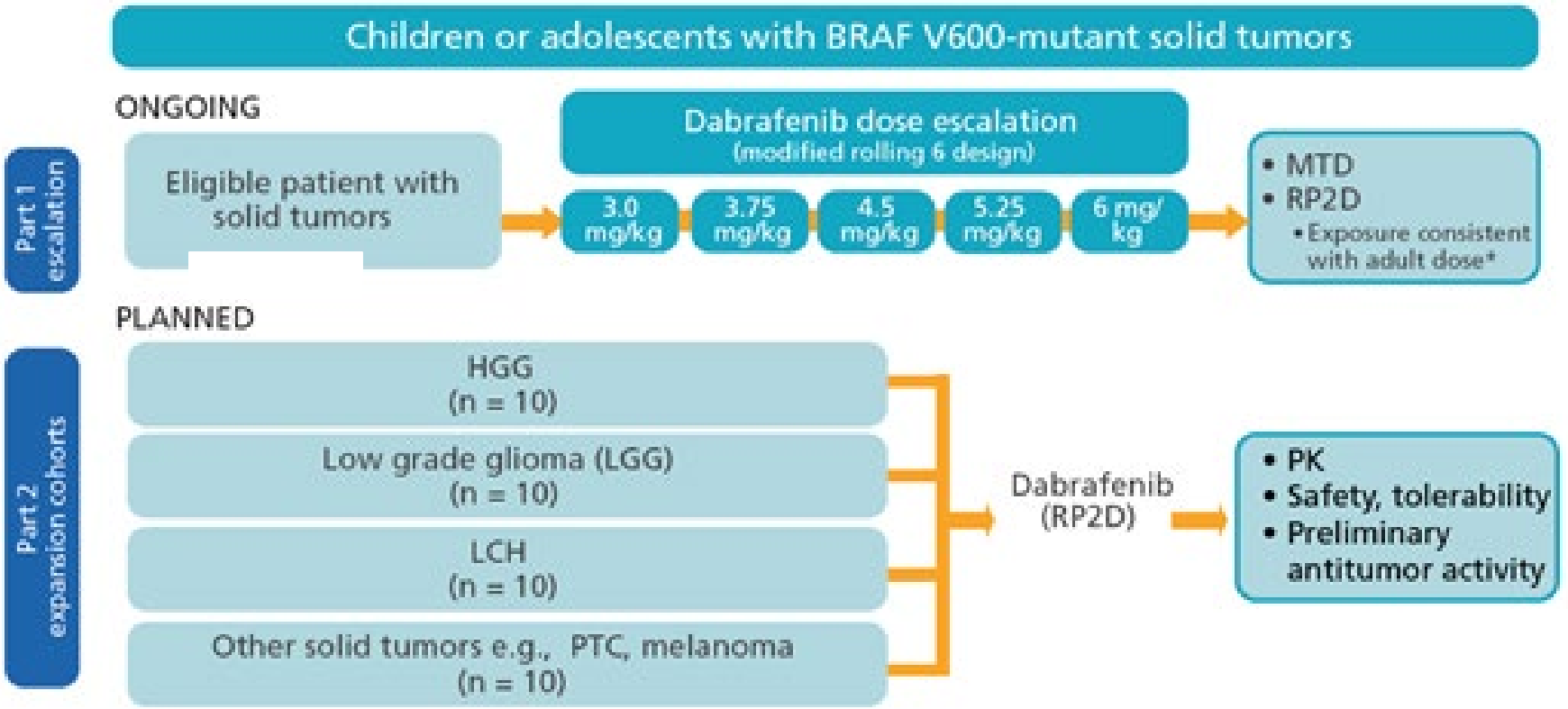
Complete Radiographic Responses in Pediatric Patients with BRAF V600–Positive Tumors Including High Grade Gliomas: Preliminary Results of an Ongoing Phase I/IIa Safety and Pharmacokinetics (PK) Study of Dabrafenib

Mark W. Kieran[1], Kenneth J. Cohen[2], Francois Doz[3], Ira J. Dunkel[4], Darren R. Hargrave[5], Trent Ryan Hummel[6], Irene Jimenez[7], Sarah Leary[7], Andrew D.J. Pearson[8], Christine A. Pratilas[9], James Whitlock[3], Michael Durante[10], Diana M. Gibson[11], Patricia Haney[10], Mark W. Russo[10], A. Benjamin Suttle[11], Birgit Geoerger[12]

ASCO 2016



Building on this:

Dabrafenib: *BRAFV600E inhibitor (BRAFV600)*

Trametinib: *MAP Kinase inhibitor (BRAF fusions)*

Combination *– improve efficacy; overcome resistance*

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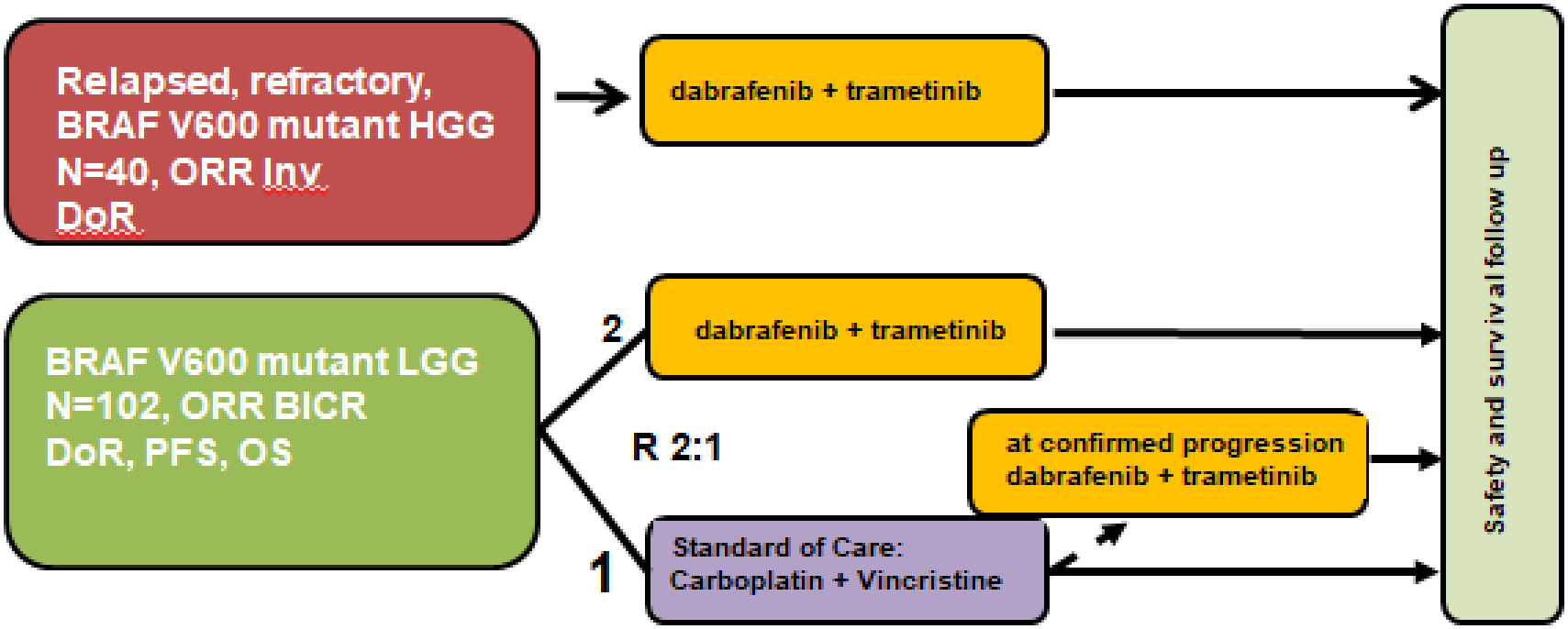
Moving forward BRAF & MEK inhibitors in BRAFv600mutant HGG & LGG: ***Study DRB436G2201***



Global effort in a rare population - 49 participating sites from 17 countries

Information courtesy of Darren Hargrave

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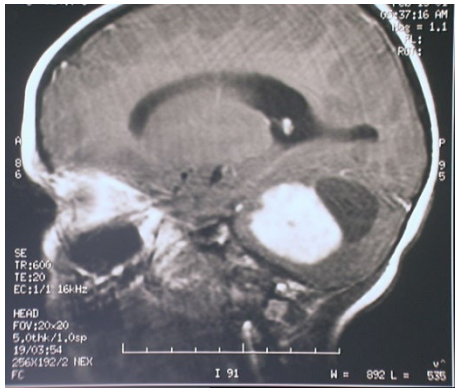
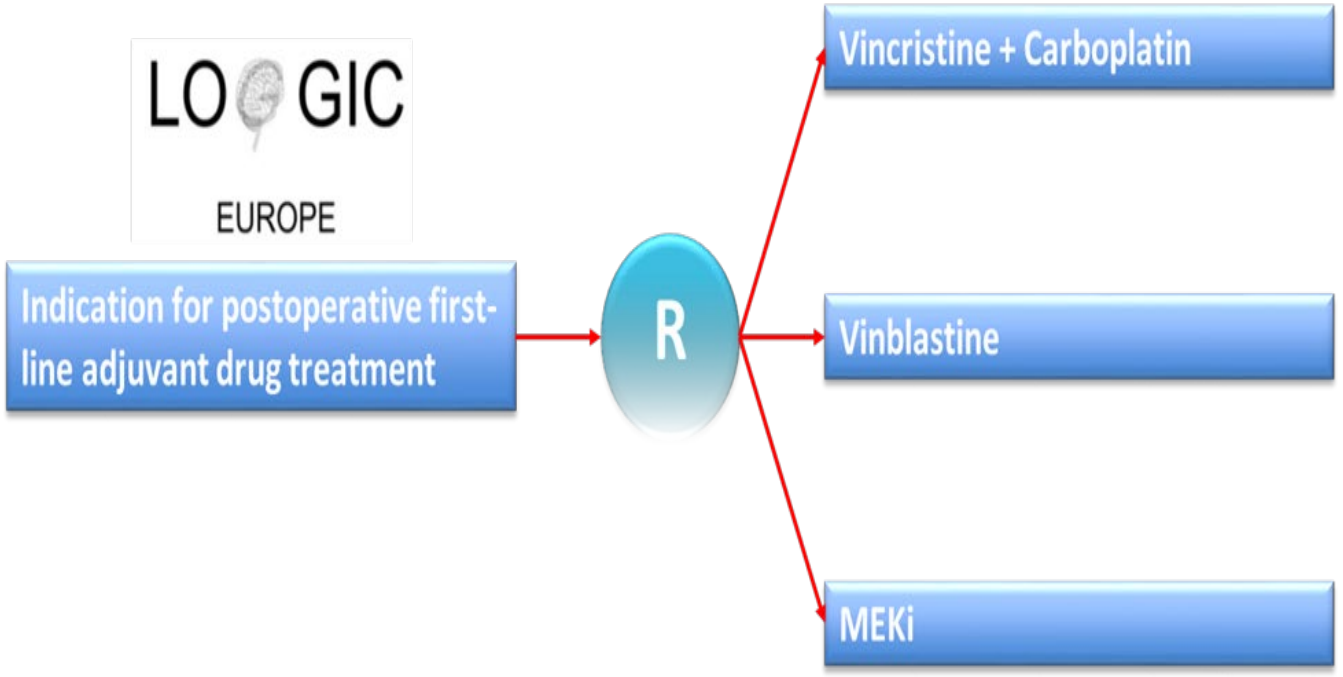
*Moving forward MEK inhibitors in LGG vs standard of care chemotherapy : upfront randomized **phase III***



LO GIC

EUROPE



To identify the **optimum treatment regimen for tumour growth control and improvement of neurological and visual function** comparing **Carbo+VCR** versus weekly **VBL** versus **MEKi** as first line treatment in (non) NF1-related LGG

Information courtesy of Darren Hargrave

The BRAIN TUMOUR CHARITY

Anti-angiogenics in pHGG: Stupp +/-Bevacizumab

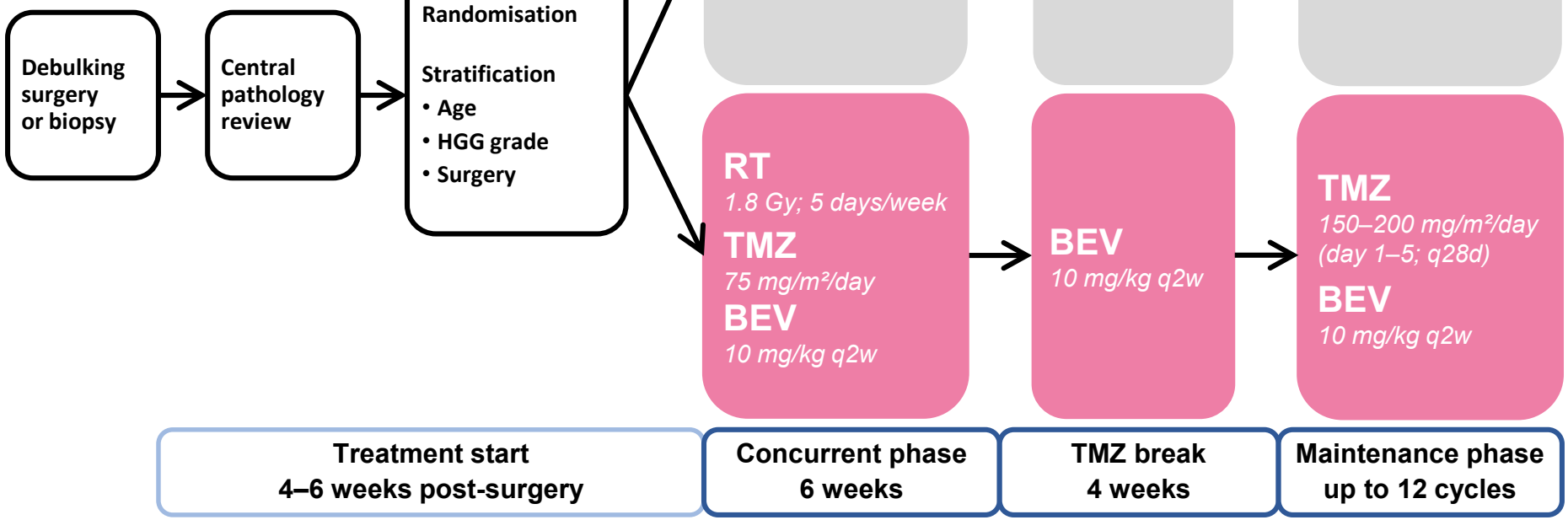
HERBY

Bevacizumab in Paediatric HGG Study

HERBY Study (BO25041)

Clinicaltrials.gov NCT01390948

A study of bevacizumab in paediatric patients with newly diagnosed supratentorial high grade glioma



- **Study population: patients aged ≥3 years to <18 years with newly diagnosed localised supratentorial or infratentorial cerebellar or peduncular HGG (WHO grade III/IV)**

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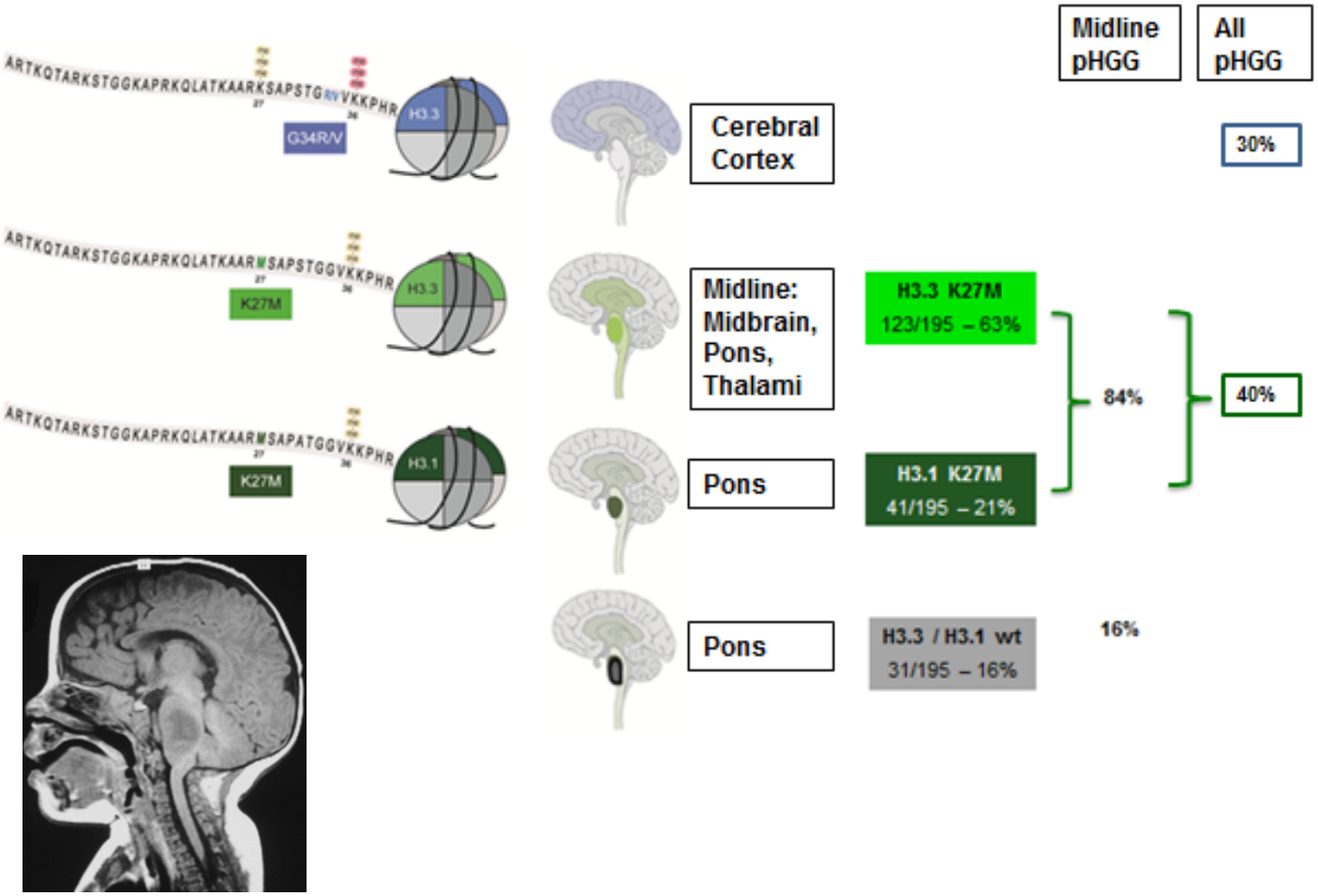
Anatomical distribution, incidence and clinical correlates of histone H3F3A and HIST1H3B mutations in pHGG

A



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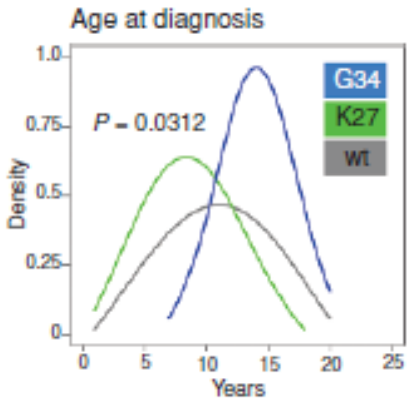

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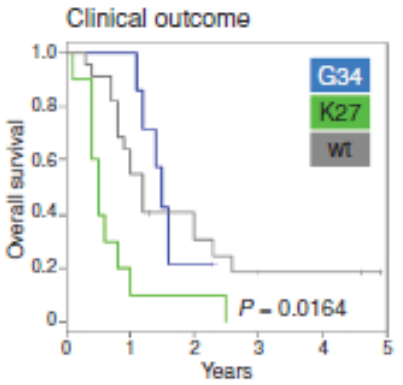

Bjerke, Cancer Discovery 2013

Modified from Jones, Nature Reviews Cancer 2014.
Incidence of H3.3/3.1 K27M and H3.3 G34R/V mutations from Buczkowicz 2014, Fontebasso 2014, Taylor 2014, Wu 2014, (Nature Genetics) and Gajjar, Clinical Cancer Research 2014.

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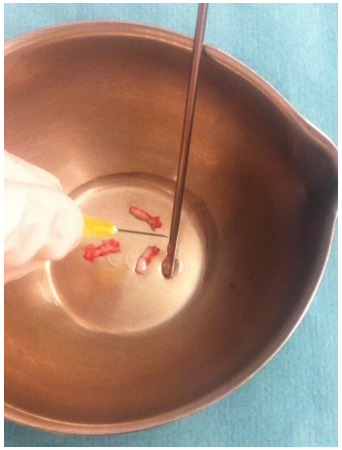
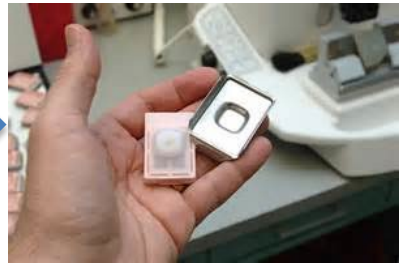
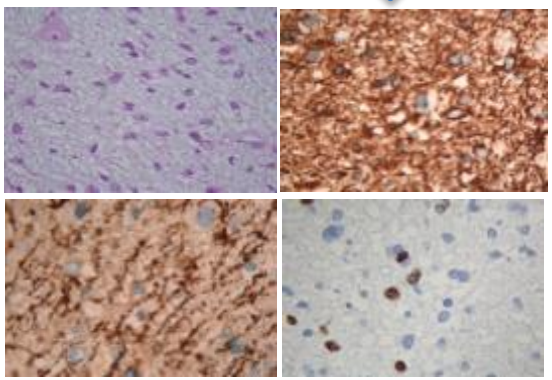
BIOMEDE Biology



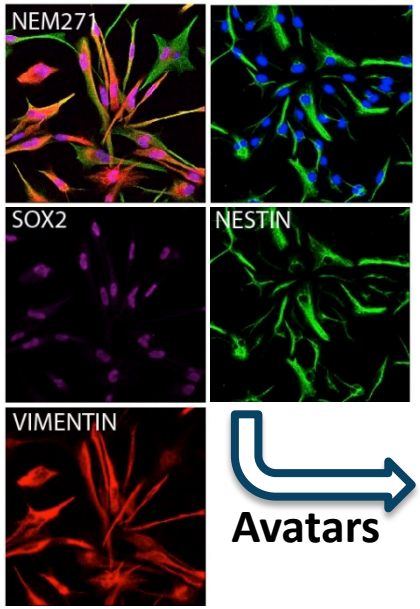




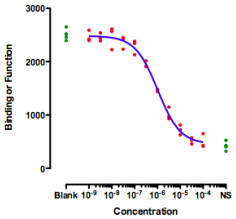
Diagnosis
- H3K27me3
- H3.3K27M

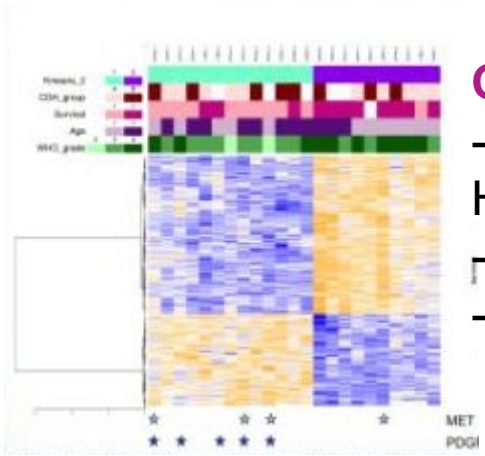
Biomarkers
- EGFR (IHC)
- PTEN (IHC)
- PDGFRA (FISH)

NEM271 (H3.1)



Avatars



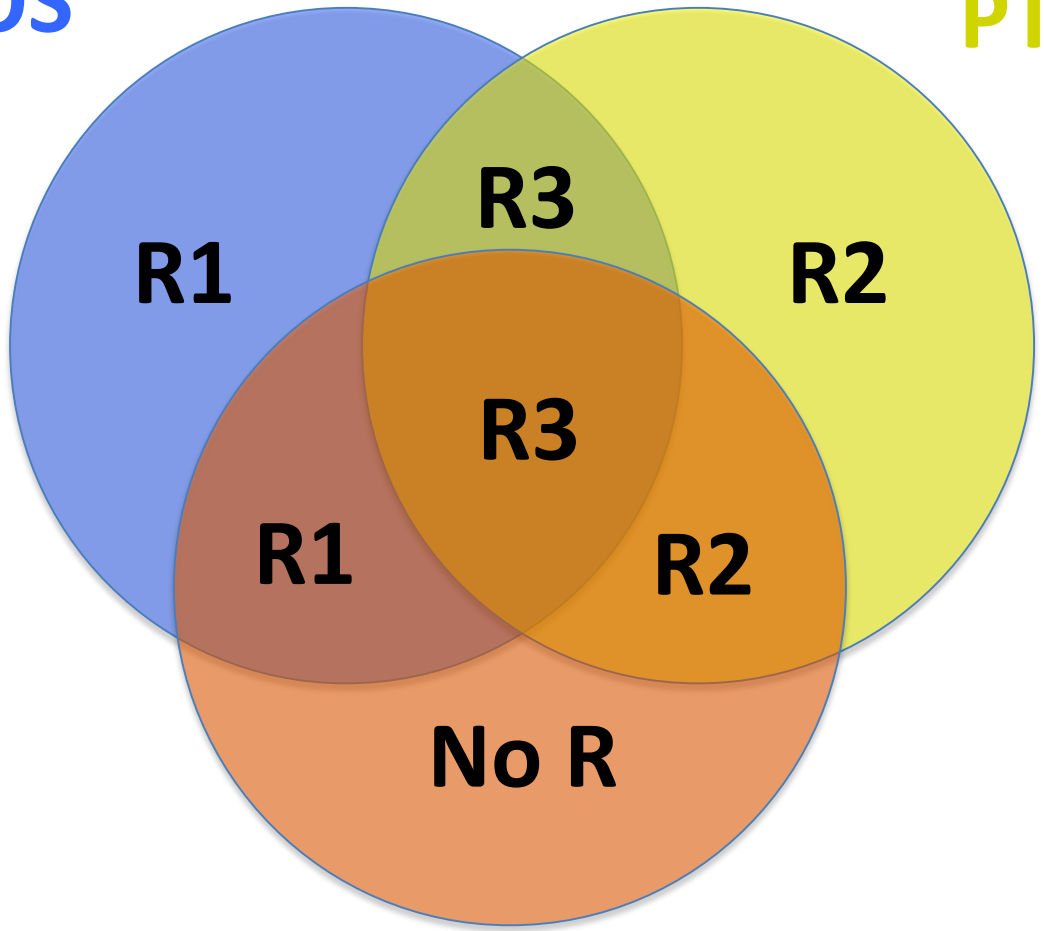


Genomics
- Sequencing H3.3 and H3.1
- WES (+ blood)
- RNAseq

CI Jacques Grill, IGR

EGFR POS

PTEN LOSS



BIOMEDE

PDGFRA AMP

R1=Erlotinib/Dasatinib; R2=Everolimus/Dasatinib;
R3=All 3

Concomitant with and adjuvant to radiotherapy

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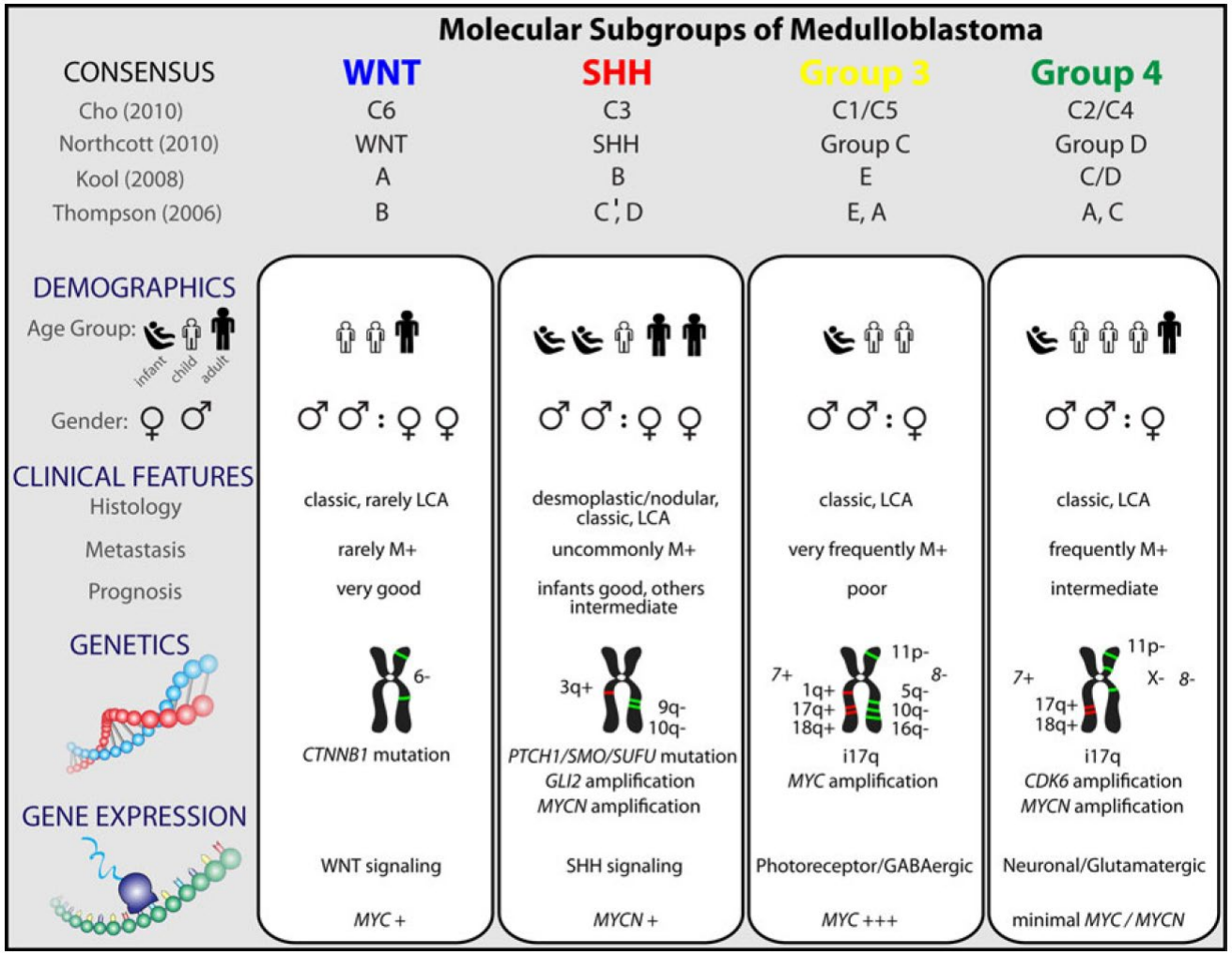
Medulloblastoma



Taylor et al. *ACTA Neuropathol.* (2011)

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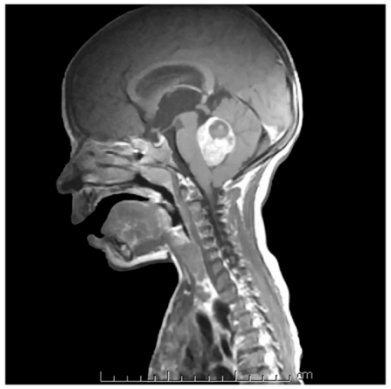
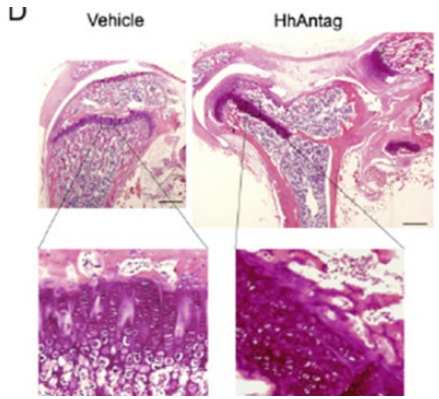
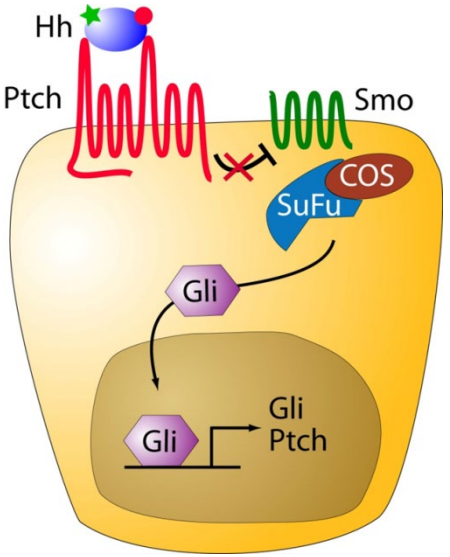
Medulloblastoma: Sonic Hedgehog Pathway

Novartis-sponsored; LDE225 in medulloblastoma and solid tumours potentially dependent on SHH signalling

- Phase I → Phase III
- Adults and children.
- Molecular pre-screening in tumour tissue for 5-gene SHH signature (more common in adults; children <10%).
- Oral drug; daily dose; 4 weekly
- Well-tolerated.
- Unusual side effects: elevated CK; effects on growing bones & teeth.
- Study abandoned by company due to feasibility of phase III/rarity of disease







ASCO

Cancer Cell
Article

Transient Inhibition of the Hedgehog Pathway in Young Mice Causes Permanent Defects in Bone Structure

Cell PRESS

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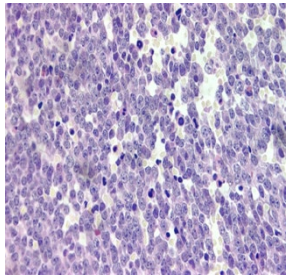
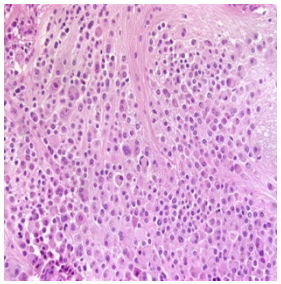
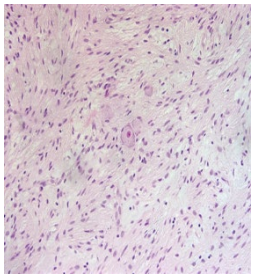
Neuroblastoma: a spectrum of diverse biology & clinical behaviour



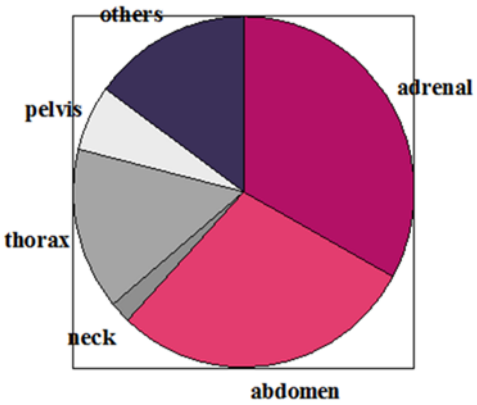
Undifferentiated neuroblastoma

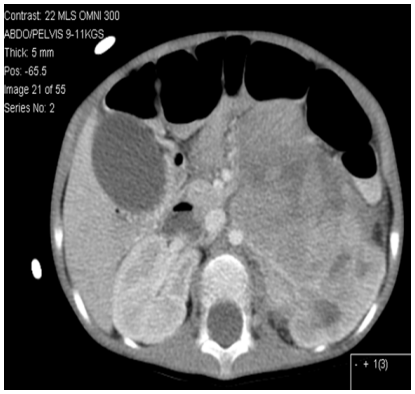


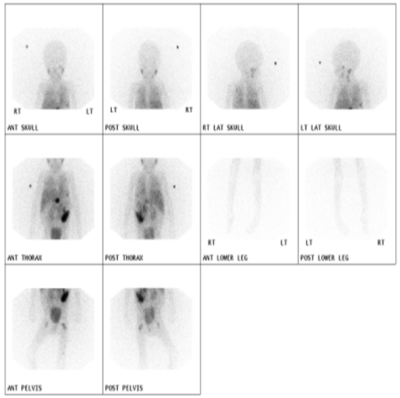
Differentiating neuroblastoma

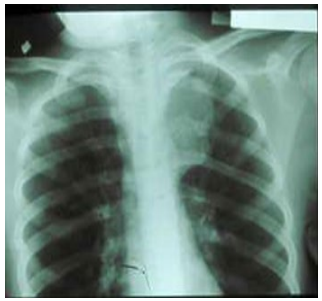


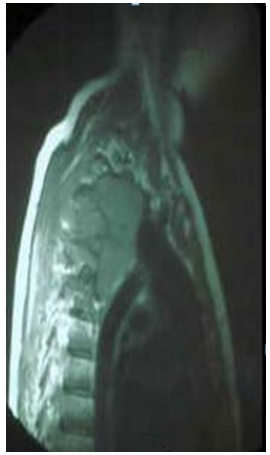
Ganglioneuroma

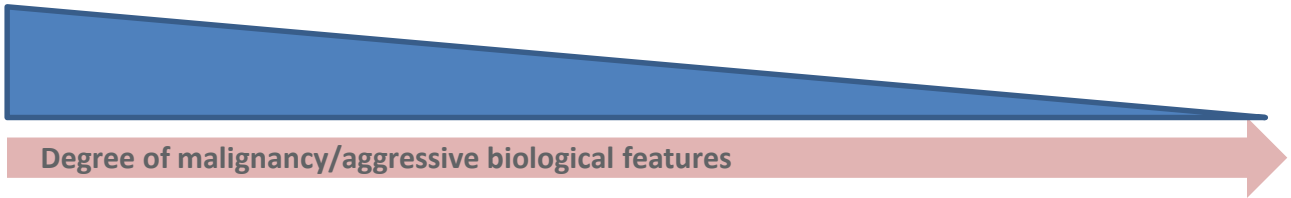












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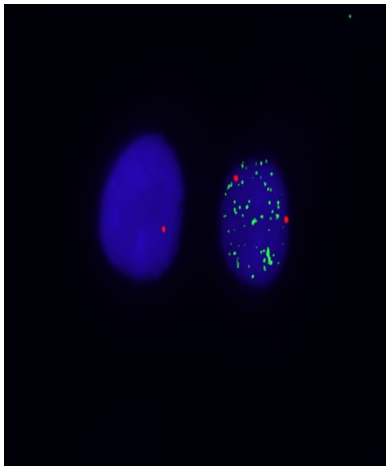
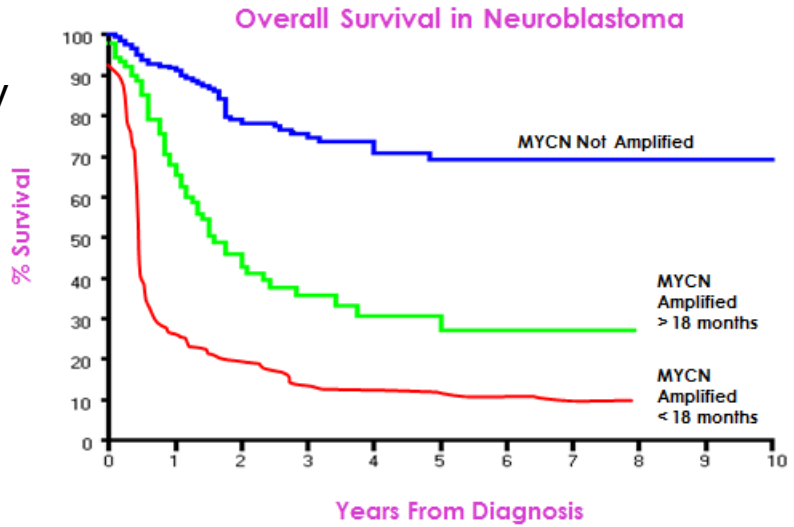
MYCN in neuroblastoma: A major determinant of outcome



Dual-coloured FISH

- Proto-oncogene on chromosome 2p24.3 identified in 1999
- 4-fold number of *MYCN* FISH signals compared to the reference probe
- *MYCN* amplification in 25% of all neuroblastoma, 50% of high risk patients
- *MYCN* amplification **in infants** – especially powerful as a prognostic factor: <u>10% versus 85% survival</u>



- **Almost 15 years after *MYCN* identification:**
  - utilised in clinical trials to guide standard upfront treatment
  - key target for novel therapies; is it 'druggable'?

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Standard treatment of high risk neuroblastoma

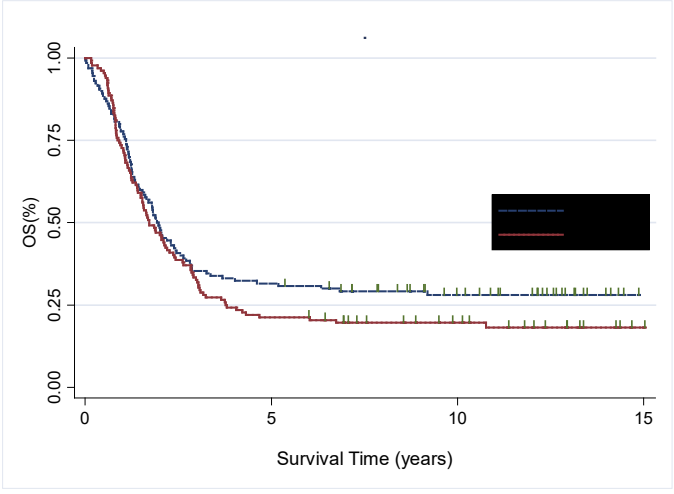
Induction Chemotherapy	**Surgical Resection**	**Myeloablation & Autologous Stem Cell Rescue**	**Radiotherapy**	**Minimal Residual Disease Therapy**

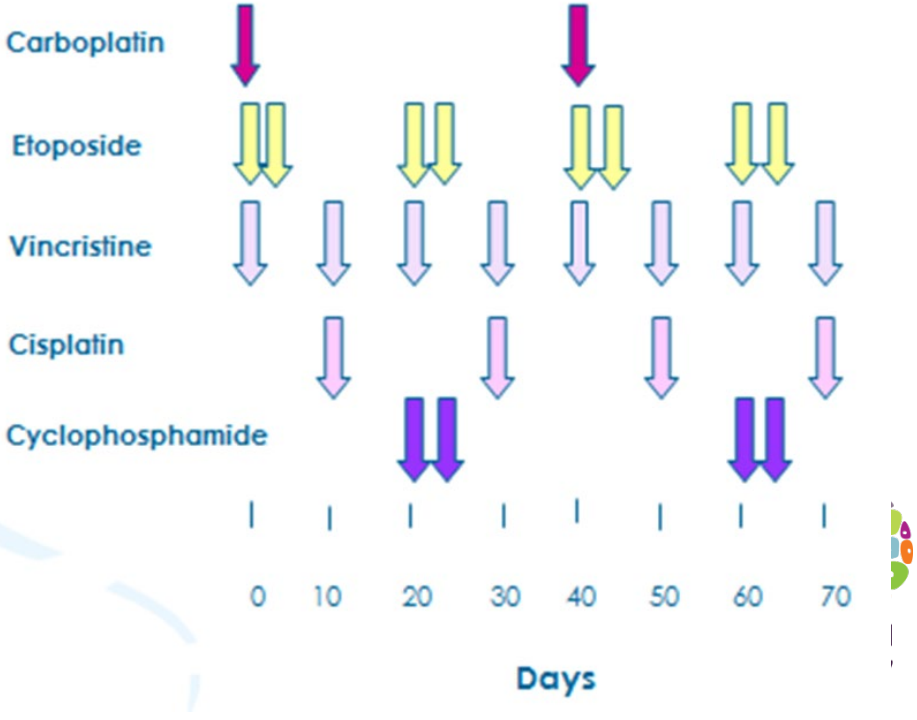
Improving outcomes through randomised studies: induction chemotherapy

Induction Chemotherapy	**Surgical Resection**	**Myeloablation & Autologous Stem Cell Rescue**	**Radiotherapy**	**Minimal Residual Disease Therapy**

Standard (OPEC/OJEC) vs Rapid Induction :

Previous Trial – ENSG5

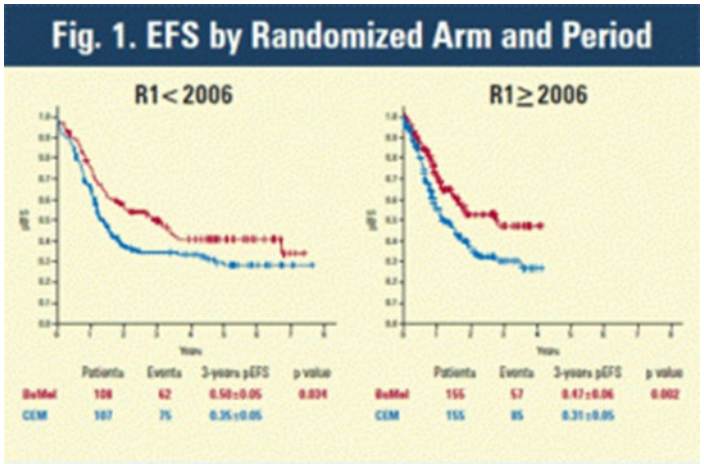


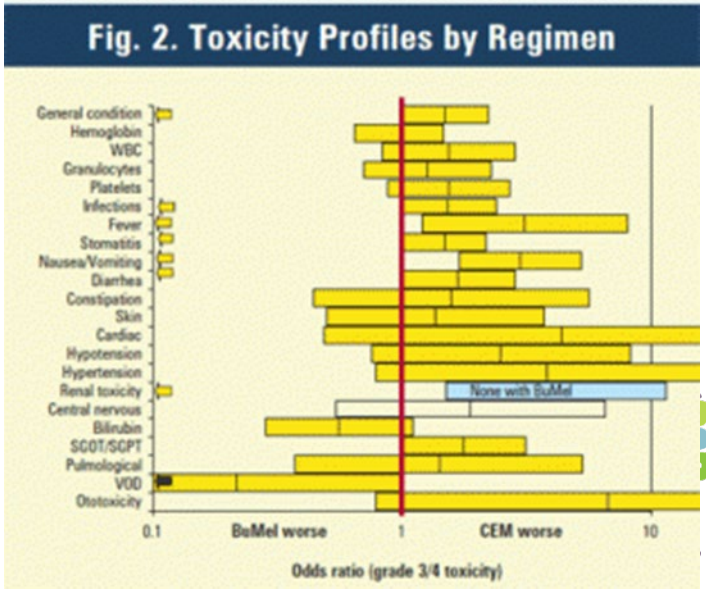


Improving outcomes through randomised studies: Myeloablative therapy & ASCT

- Consensus of previous studies show benefit of multiple agents rather than single agent melphalan
- US gold standard - carboplatin, etoposide, melphalan (CEM)
- EU gold standard - busulphan, melphalan (BuMel)
- **R1 Randomisation on SIOPEN study: BuMel vs CEM**

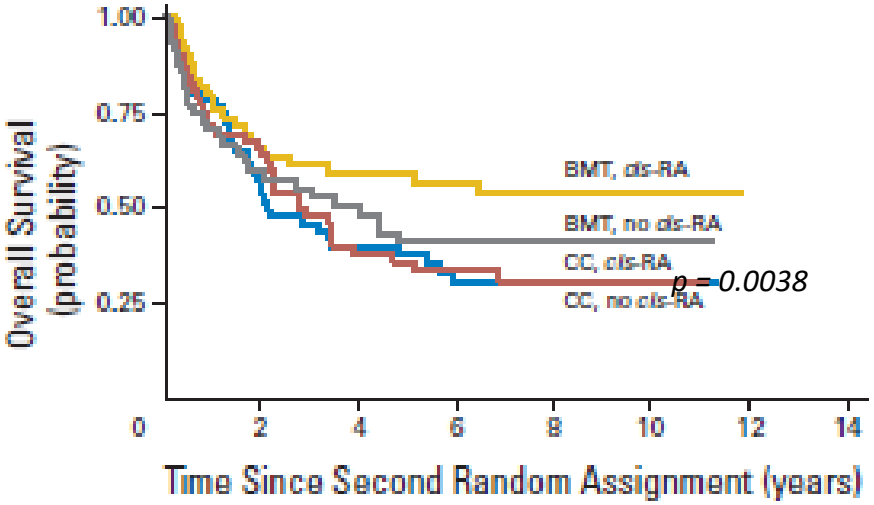
	BuMel	CEM
Number of patients	281	282
3 year EFS	49%	33%
3 year OS	60%	48%
3 year relapse/progression	47%	60%
Treatment-related death rate	3%	5%





Improving outcomes through randomised studies: Minimal residual disease strategies

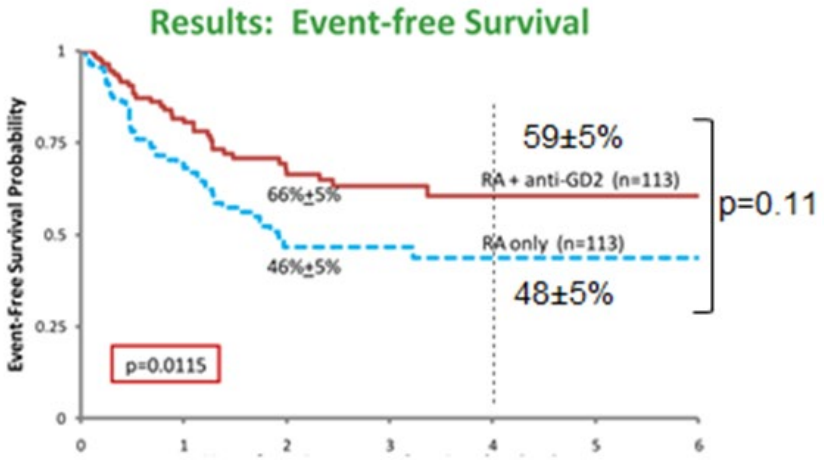
Differentiation therapy

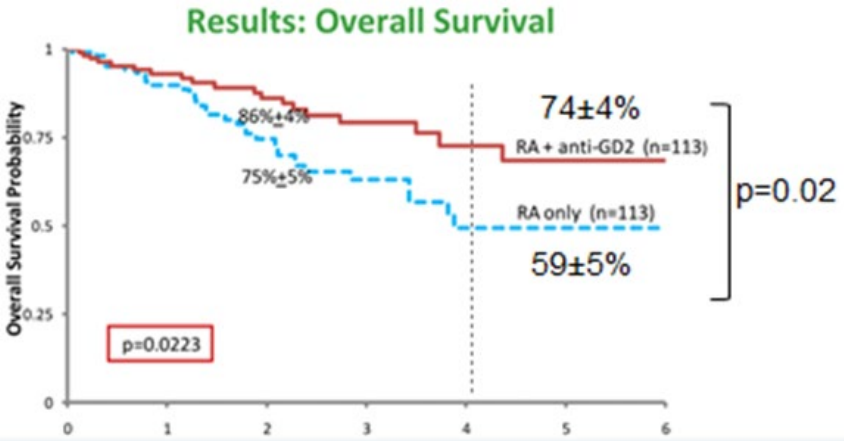


COG Study, Matthay K et al, JCO 2009

Immunotherapy

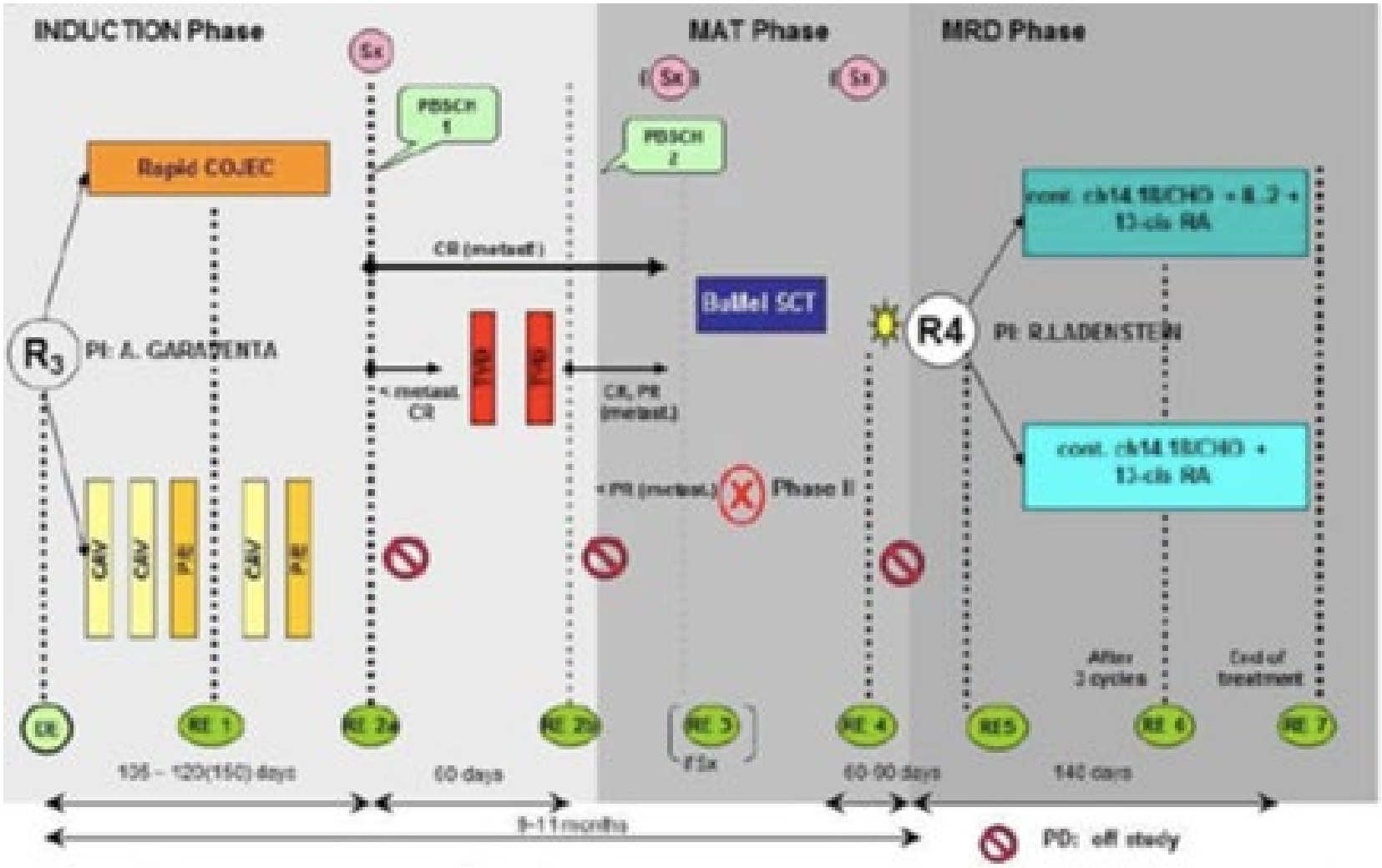
Anti-GD2 antibody + GM-CSF + IL-2 (+isotretinoin)





COG Study, Yu et al, NEJM 2010

SIOPEN High Risk Neuroblastoma Strategy



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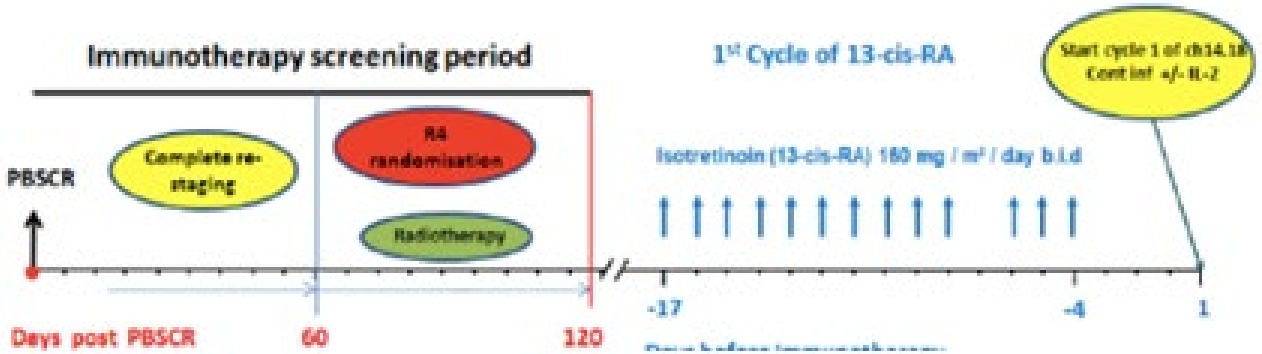
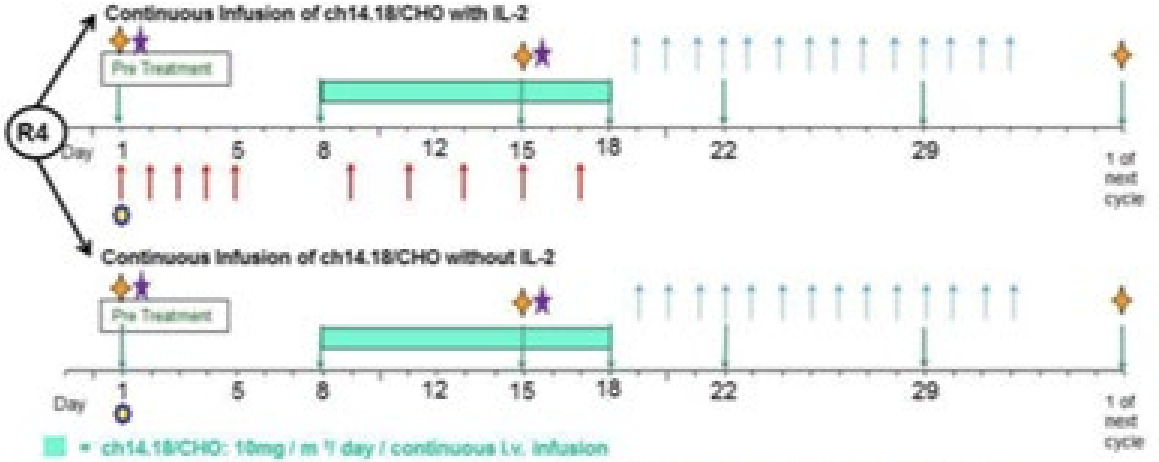
SIOPEN High-Risk Neuroblastoma Immunotherapy



R4 Randomisation: 35 day treatment cycle

ch14.18/CHO	100 mg/m²/cycle,	10 day: continous infusion
13-cis retinoid acid	2240 mg/m²/cycle,	14 days: 14 x 160 mg/m²/day
aldesleukin (IL-2)	30 x 10^6 IU/m²/cycle	10 days: 10 x 3 x 10^6 IU/m²/cycle



High-Risk Neuroblastoma Immunotherapy: Regulatory approval of anti-GD2 Ab (Dinutuximab-beta)

- Challenge of getting approval in a paediatric only target – most children very young – safety, toxicity, PK, efficacy
- Orphan drug designation EU 8/11/2012 – rare population
- Conditional approval EU 8/5/2018 on basis of high unmet medical need, positive benefit :risk ratio; more follow up & data to be provided.
- 3 studies:

➢ 2 studies in 88 relapsed/refractory pts in combination with IL2 & isotretinoin:

- Refractory pts: 70% & 78% 2yr OS
- Relapsed pts: 42% & 69% 2yr OS

➢ 1 study in 370 pts responding to upfront treatment, in combination with isotretinoin +/- IL2

- CR: 71% 3yr OS (irrespective of IL2 or not)
- PR: 63% 3yr OS + IL2; 54% 3yr OS – IL2

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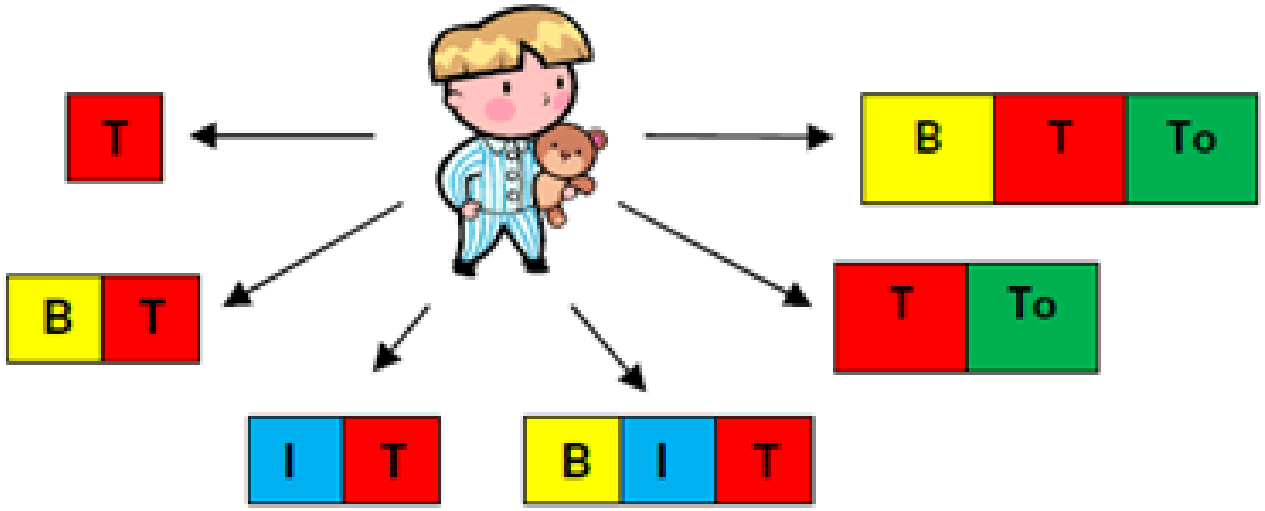
BEACON-Neuroblastoma: European Study

Phase II Randomised Trial for Relapsed/Refractory Neuroblastoma; Adaptive Multifactorial Design



T – Temozolomide
I – Irinotecan
To - Topotecan
B - Bevacizumab

- European target across 10 countries - enrolment of 160 patients
- Bevacizumab randomization was planned to closes after 120 – increased by DMC
- Molecular characterisation of tumours
- Functional imaging to elucidate the role of anti-angiogenic therapy
- Measurement of neuroblastoma mRNAs
- Due completion 2019
- BEACON2 multi-arm, multi-stage in development (new arms; newer targets)

Neuroblastoma – ALK as a target

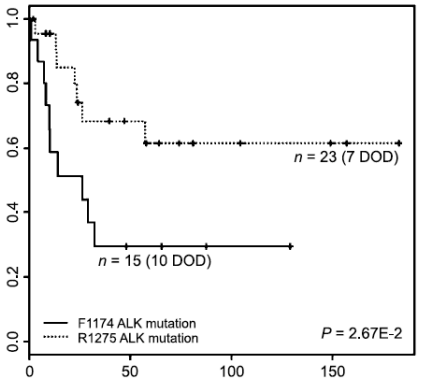
Vol 455|16 October 2008|doi:10.1038/nature07398 nature

LETTERS

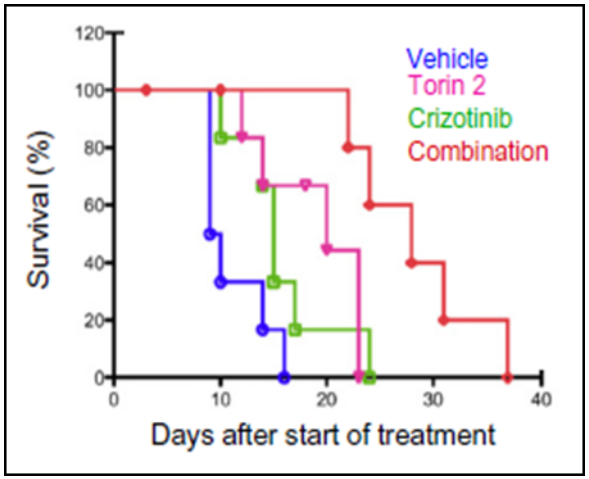
Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma

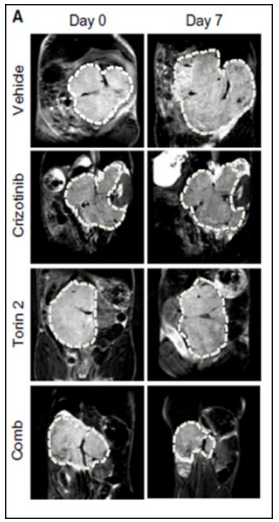
Isabelle Janoueix-Lerosey[1,2], Delphine Lequin[1,2], Laurence Brugières[3], Agnès Ribeiro[4], Loïc de Pontual[5], Valérie Combaret[6], Virginie Raynal[1,2], Alain Puisieux[6,7,8], Gudrun Schleiermacher[1,2,9], Gaëlle Pierron[4], Dominique Valteau-Couanet[3], Thierry Frebourg[10], Jean Michon[9], Stanislas Lyonnet[5], Jeanne Amiel[5] & Olivier Delattre[1,2,4]

- Mutations of ALK gene in 10% of neuroblastomas - F1174 & R1275
- F1174 mutation - 58.8% have MYCN amplification



Kaplan-Meier and long rank analysis of *ALK*-mutated and *ALK*-amplified tumours – F1174 mutated versus wild-type cases





Chesler lab, The ICR

Strategies

1. Direct inhibitors – crizotinib
2. Combination approach – CRISP (crizotinib + temsirolimus)
3. Novel compounds – ceritinib, lorlatinib

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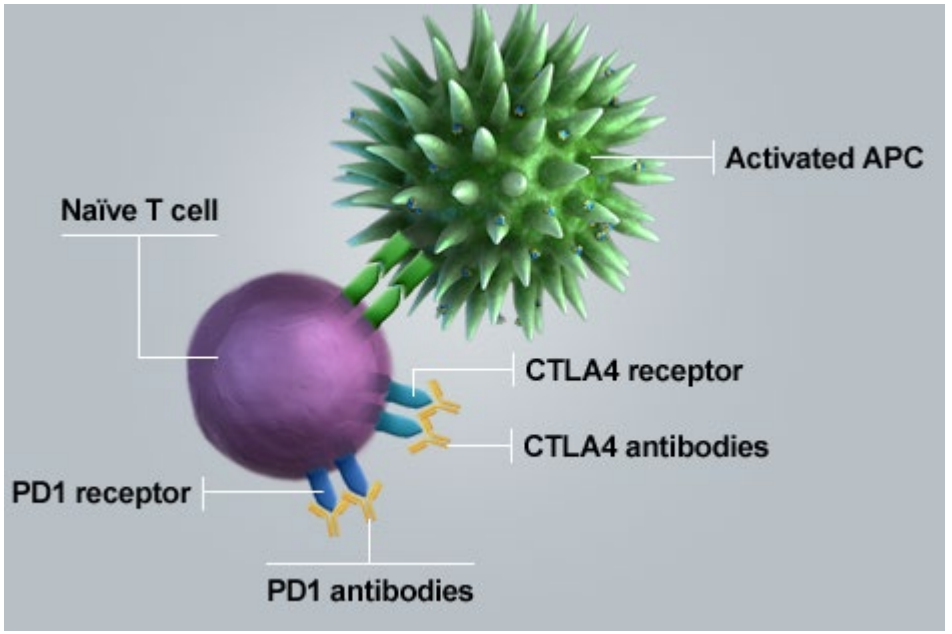
Targeting the immune checkpoints for cancer immunotherapy

- PD-1 and CTLA-4 are immune checkpoints which are upregulated and present on the surface of T cells in certain cancers, dampening T-cell activation & immune response to tumour; contributing to the tumour's ability to evade the immune system.

- Inhibiting a checkpoint ("releasing the brakes") on the immune system may enhance the anti-tumour T-cell immune response.



Modified from Sharma et al

PD-1/PD-L1 pathway thus plays a critical role in tumour evasion and is an attractive target for therapeutic intervention – 'recognising tumour as foreign'.

Challenges for Paediatrics: Immune checkpoint inhibitors

- Multiple PD-(L1) inhibitors in clinical development:
  - no overview of the whole class of drugs in advance
  - how do we identify the best in class overall/for a given disease?
- Paediatric cancers as a group are rare; relatively small (& finite) number of relapsed/refractory patients available for early phase trials
- How do we identify the best in class agents rapidly?
- How do we optimise design & efficiency of studies?
- Preclinical → Early phase → Front line combinations
- How do we achieve mechanism-of-action based drug development incorporating robust predictive &/or pharmacodynamic biomarkers (where possible)?
-

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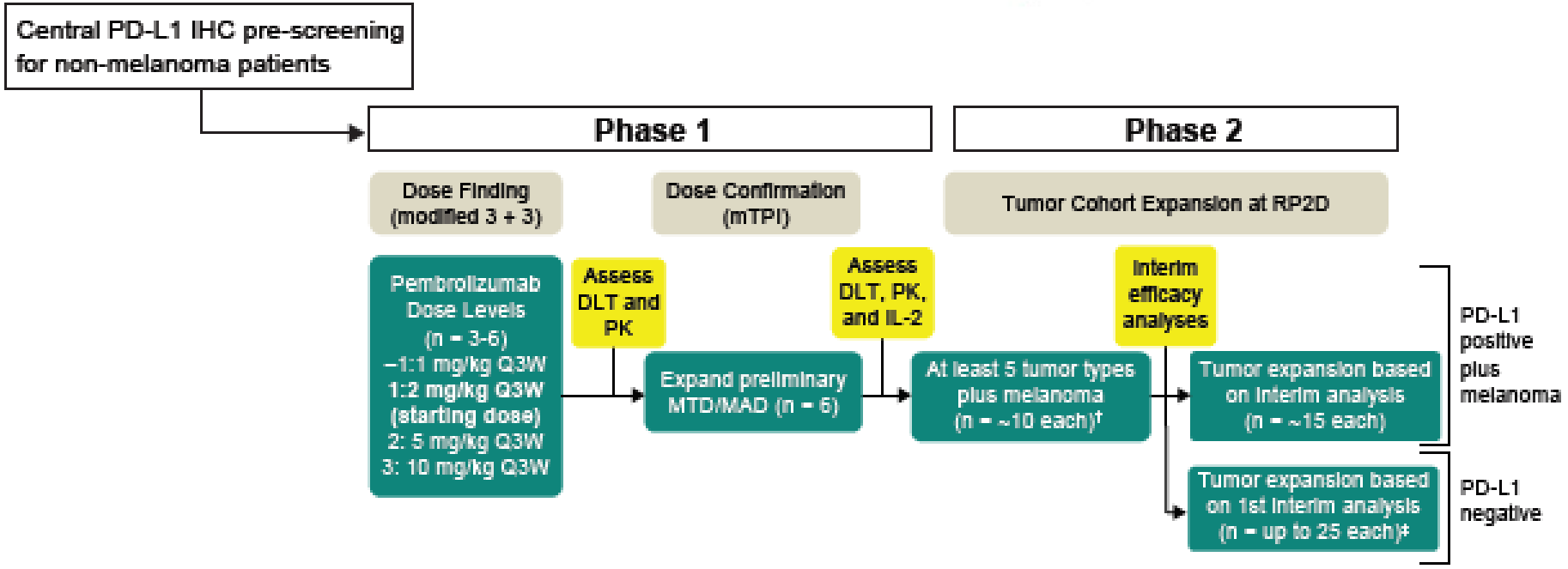
Pembrolizumab in Pediatric Patients With Advanced Melanoma or a PD-L1–Positive Advanced, Relapsed, or Refractory Solid Tumor or Lymphoma: Phase 1/2 KEYNOTE-051 Study

Non-randomized, open-label, multicentre, phase 1/2 study

— Phase 1: dose-finding and dose-confirmation cohorts

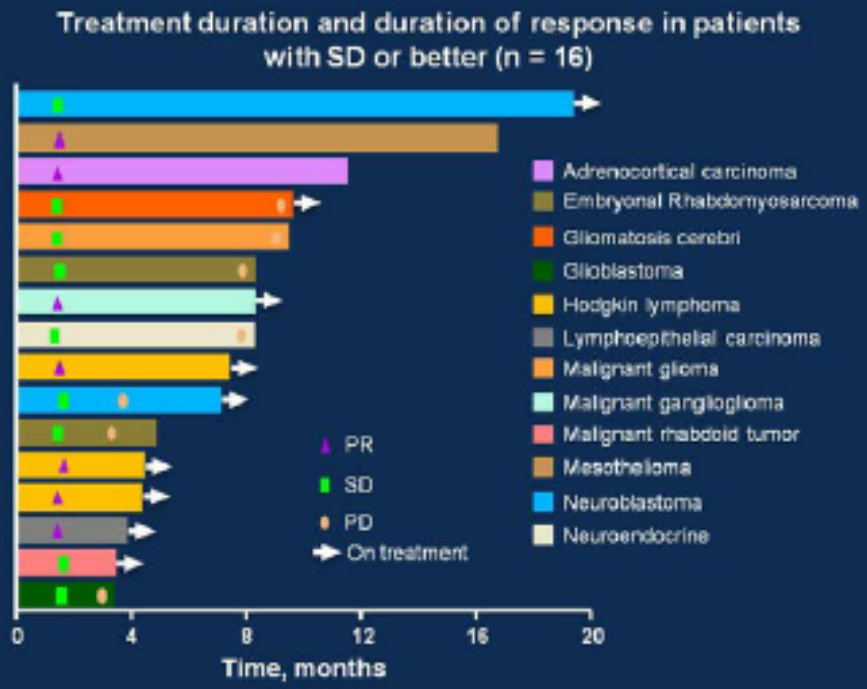
— Phase 2: tumor expansion cohort



Interim Results

Antitumor Efficacy (RECIST v1.1, Investigator)

	N = 87
ORR[a], % (95% CI)	8.0% (3%-16%)
Best overall response, n (%)	
Complete response (CR)	0
Partial response (PR)[b]	7 (8.0%)
Stable disease (SD)	9 (10.3%)
Progressive disease (PD)	43 (49.4%)



PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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[a]Confirmed responses only. [b]Patients with PR had Hodgkin lymphoma (n = 3) and mesothelioma, malignant ganglioglioma, adrenocortical carcinoma, and lymphoepithelial carcinoma (n = 1 each). Data cutoff date: Feb 17, 2017.

ORR 8% in PD-L1+ patient group

Geoerger, ASCO 2017

Interim Results

Patients

atezo iMATRIX

- As of February 1, 2017, a total of 85 patients have been enrolled, and 82 have been treated
- Median age at inclusion: 14 years (range, 2–29); 12% of patients were aged 2–<6 years, 19% were aged 6–<12 years, 48% were aged 12–<18 years, and 21% were aged 18–<30 years
- 46 patients (54%) were male
- Baseline Lansky/Karnofsky Performance scores: 60 (n=2); 70 (n=9); 80 (n=12); 90 (n=18); 100 (n=36); missing (n=8).

Tumor type	Number of patients (%)
Osteosarcoma	12 (14)
Ewing sarcoma	11 (13)
Neuroblastoma	11 (13)
Rhabdomyosarcoma	10 (12)
Soft tissue sarcoma	10 (12)
Wilms tumor	10 (12)
Hodgkin lymphoma	9 (11)
Non-Hodgkin lymphoma	3 (4)
Other	9 (11)

ORR 4.8% in unselected patient group

Geoerger, ASCO 2017

Better Predictive Biomarkers?

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 39

Mutational profiling of colorectal cancers with microsatellite instability

Elaine I. Lin[1], Li-Hui Tseng[2], Christopher D. Gocke[1,3], Stacy Reil[1], Dung T. Le[3], Nilofer S. Azad[3], James R. Eshleman[1,3]

ABSTRACT

Microsatellite instability (MSI) is caused by defective mismatch repair in 15–20% of colorectal cancers (CRCs). Higher mutation loads in tumors with mismatch repair deficiency can predict response to pembrolizumab, an anti-programmed death 1 (PD-1) immune checkpoint inhibitor. We analyzed the mutations in 113 CRCs without MSI (MSS) and 29 CRCs with MSI-High (MSI-H) using the 50-gene AmpliSeq cancer panel. Overall, MSI-H CRCs showed significantly higher mutations than MSS CRCs, including insertion/deletion mutations at repeat regions. MSI-H CRCs showed higher incidences of mutations in the *BRAF*, *PIK3CA*, and *PTEN* genes as well as mutations in the receptor tyrosine kinase families. While the increased mutations in *BRAF* and *PTEN* in MSI-H CRCs are well accepted, we also support findings of mutations in the mTOR pathway and receptor tyrosine kinase family genes. MSS CRCs showed higher incidences of mutations in the *APC*, *KRAS* and *TP53* genes, confirming previous findings. NGS assays may be designed to detect driver mutations for targeted therapeutics and to identify tumors with high mutation loads for potential treatment with immune checkpoint blockade therapies. Further studies may be warranted to elucidate potential targeted therapeutics against mutations in the mTOR pathway and the receptor tyrosine kinase family in MSI-H CRCs as well as the benefit of anti-PD-1 immunotherapy in hypermutated MSS CRCs or other cancers.

Better Predictive Biomarkers?

FDA News Release

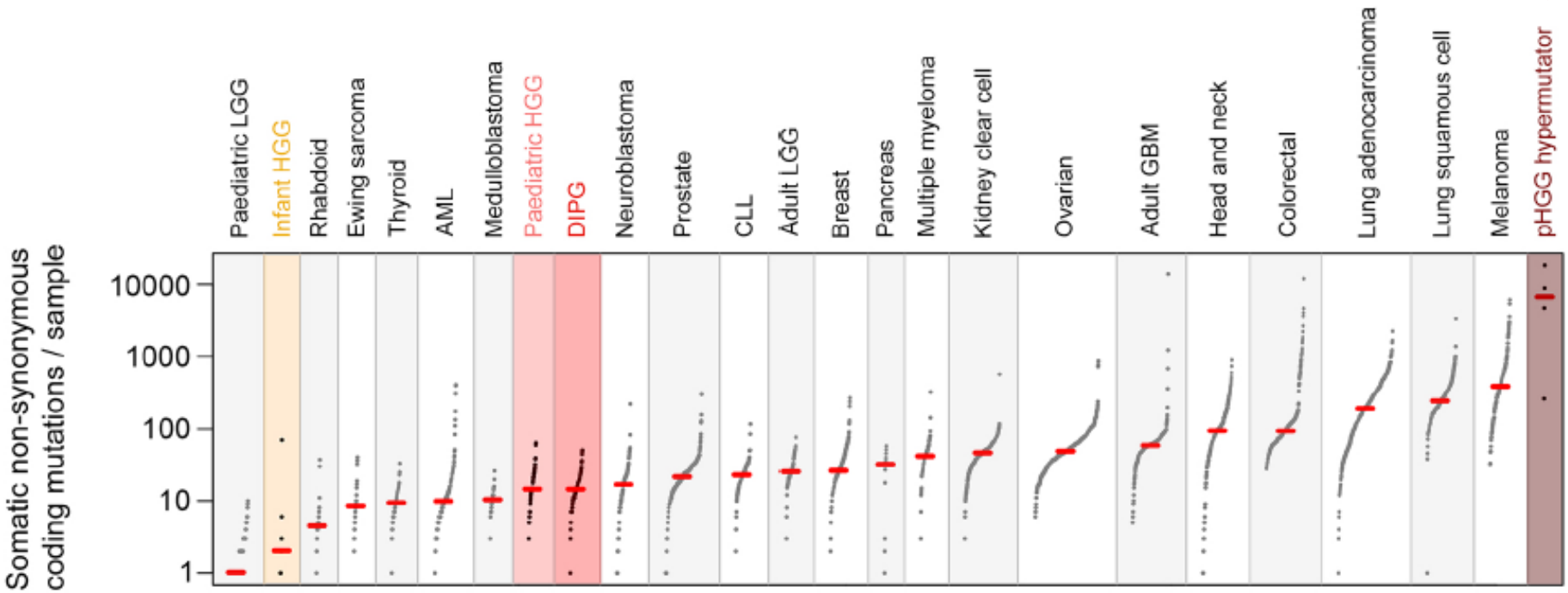
FDA approves first cancer treatment for any solid tumor with a specific genetic feature

FDA Approves Merck's KEYTRUDA® (Pembrolizumab) for Adult and Paediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

May 23, 2017

KEYTRUDA Now Approved for Patients with MSI-H or Mismatch Repair Deficient Solid Tumors That Have Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes MSI-H or Mismatch Repair Deficient Colorectal Cancer That Has Progressed Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

Mutational burden of paediatric tumours



Mutational burden of paediatric HGG compared to other cancer types.
Number of somatic non-synonymous coding mutations per sample are plotted on a log scale for a variety of paediatric and adult cancer types, and ordered by increasing median (red bar).

The ROYAL MARSDEN Cancer Charity

From data analysed in Jones et al, Nature Reviews Cancer, 2014

Immune checkpoint inhibitors in hypermutant GBM

VOLUME 34 · NUMBER 19 · JULY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

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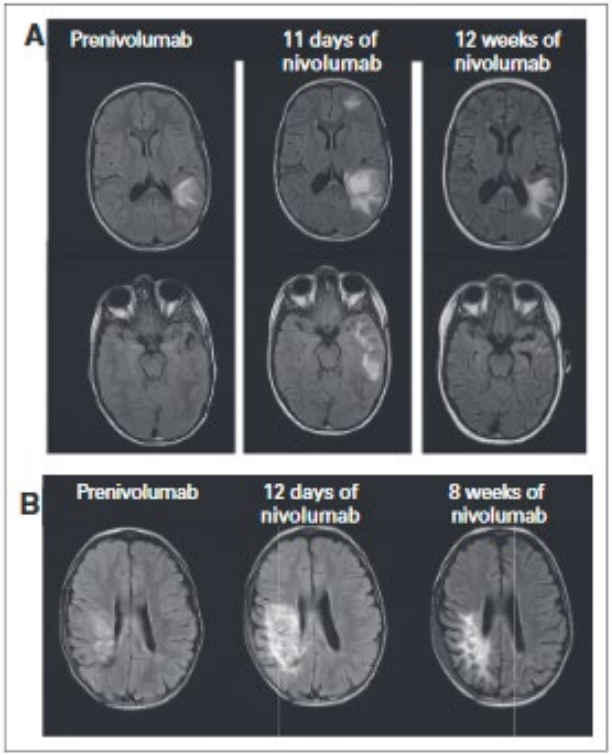

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Conclusions on immune checkpoint inhibitors:

- Multiple PD-(L)1 inhibitors in clinical development
- PIPs ongoing for several
- Safe & well-tolerated in children as single agents
- Activity in paediatrics disappointing in unselected patient groups, but optimal (biomarker-based) selection of patients is expected to change this.
- Excellent activity in Hodgkin's lymphoma & now approved for HL pts who have failed high dose chemotherapy & ASCT + Brentuximab verdotin
- We need to extrapolate from the adult experience: focus on MSI-high tumours and those with high mutational burden
- In paediatrics this is likely to include gliomas, osteosarcomas, soft tissue sarcomas, others….
- Combinations….

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When/Why to move novel therapies forward to front line 'quickly'?

- Very poor prognosis diseases (eg DMG/DIPG) – upfront
- High risk/metastatic disease which respond but relapse (HGG, ARMS, HR MBL…) – consider window studies
- Strong oncogenic driver targets/effective drugs – to improve outcomes
- Very good prognosis diseases – reduce acute and long term toxicities without reducing survival
- Still need sufficient evidence to move forward but much obtainable via efficiently novel designed phase I/II studies, extrapolation, ….eg Larotrectinib, Lenvatinib, Regorafenib.

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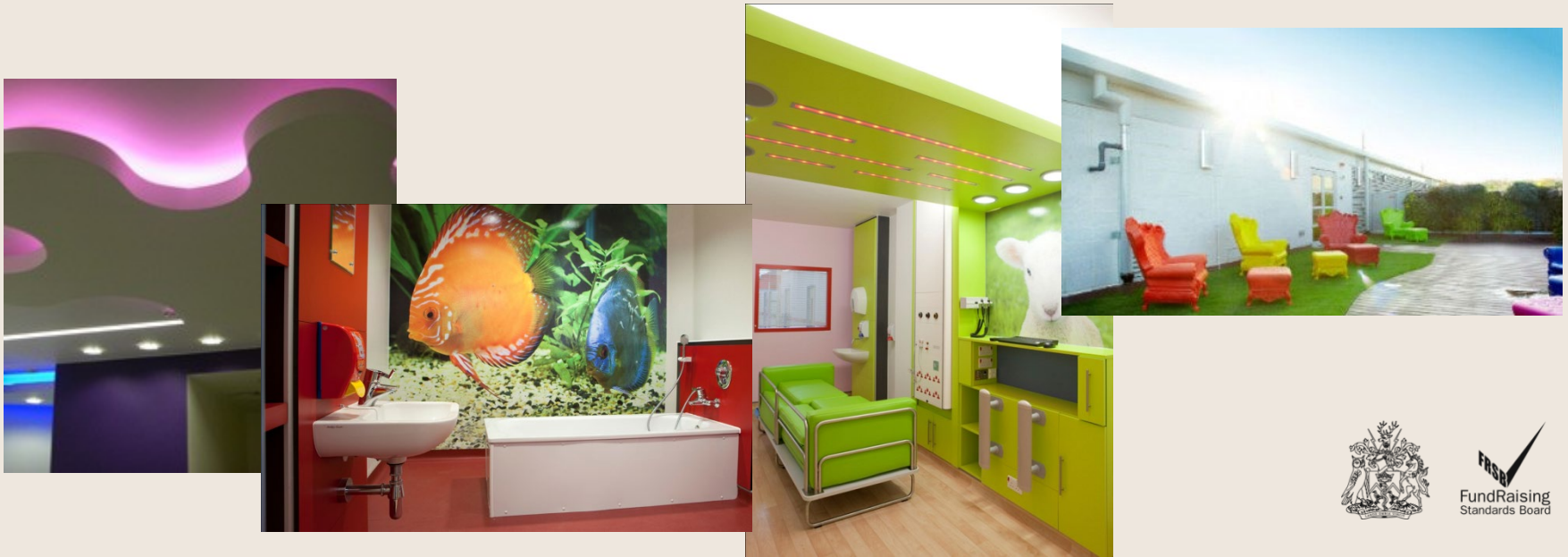
Thank You for your attention…

Questions & Comments?



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