Paediatric Bespoke Therapeutic Discovery Workshop on Osteosarcoma

Community Priorities

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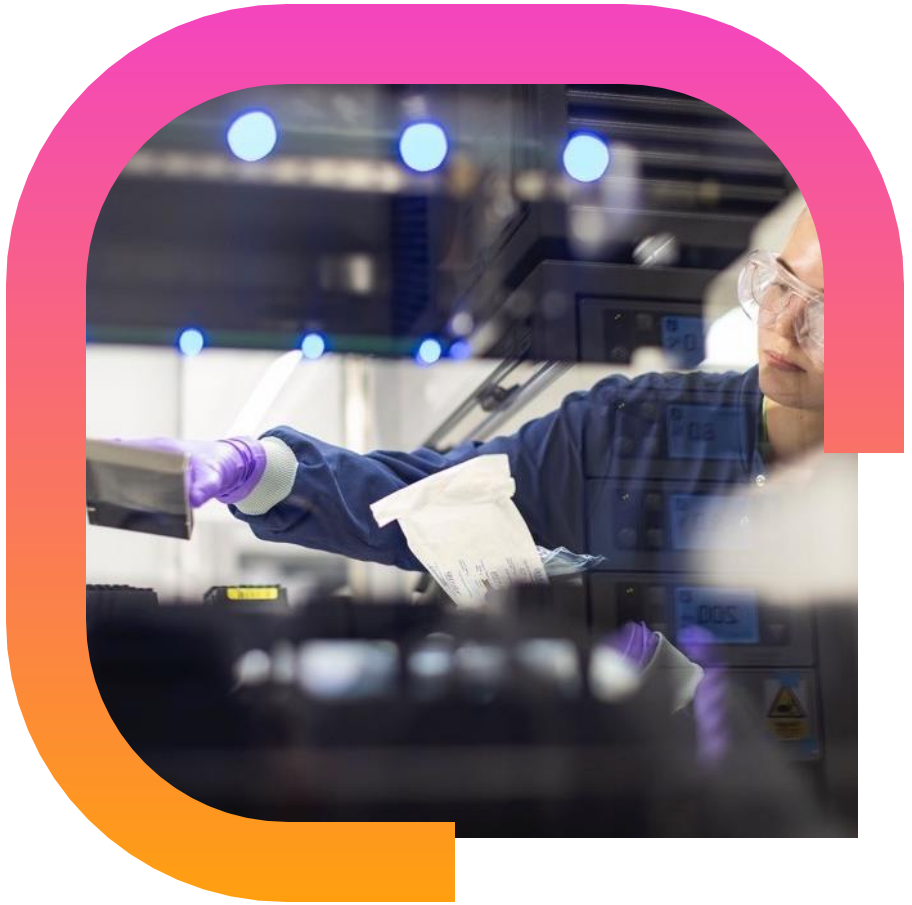
Introduction

Transforming scientific discoveries into impact for patients with rare diseases and in global health.



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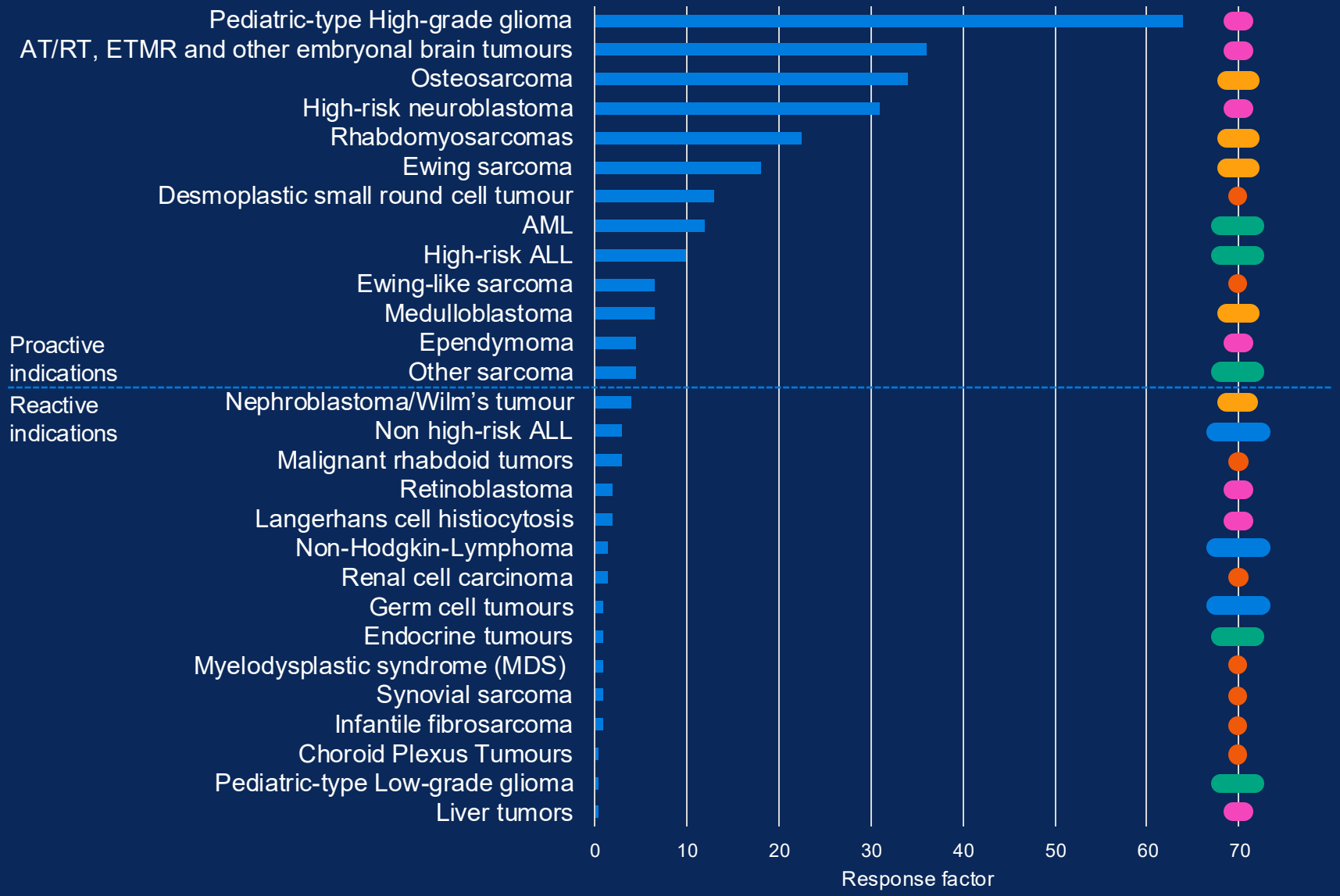
Clinically identified unmet needs



Incidence (Average no cases/year in UK):

- 0-25
- 26-50
- 51-100
- 100-200
- >200

Normalisation factor:

1: selected by respondent specialised in a cancer group different from that the indication belongs to, general paediatric oncologist or solid cancer oncologist

0.5: selected by respondent specialised in the cancer group that indication belongs to

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Paediatric Bespoke Therapeutic Discovery Workshops

- To understand the **epidemiology** of the cancer as well as the current **clinical standard** and the impact of this
- To discuss the **scientific evidence** for targets associated with selected indications
- To understand the **target tractability** and **developability**
- To **prioritise the targets**
- To discuss the **best drug modalities** for the priority targets
- To discuss **potential drug combinations** to progress into clinical trials

TEAM PROTECT

CANCER RESEARCH UK

MIB AGENTS OSTEOSARCOMA ALLIANCE

The George Pantziarka TP53 Trust

Helping families with Li Fraumeni Syndrome and related conditions

C–FURTHER

Children's Cancer Therapeutics Consortium

ITCC

INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

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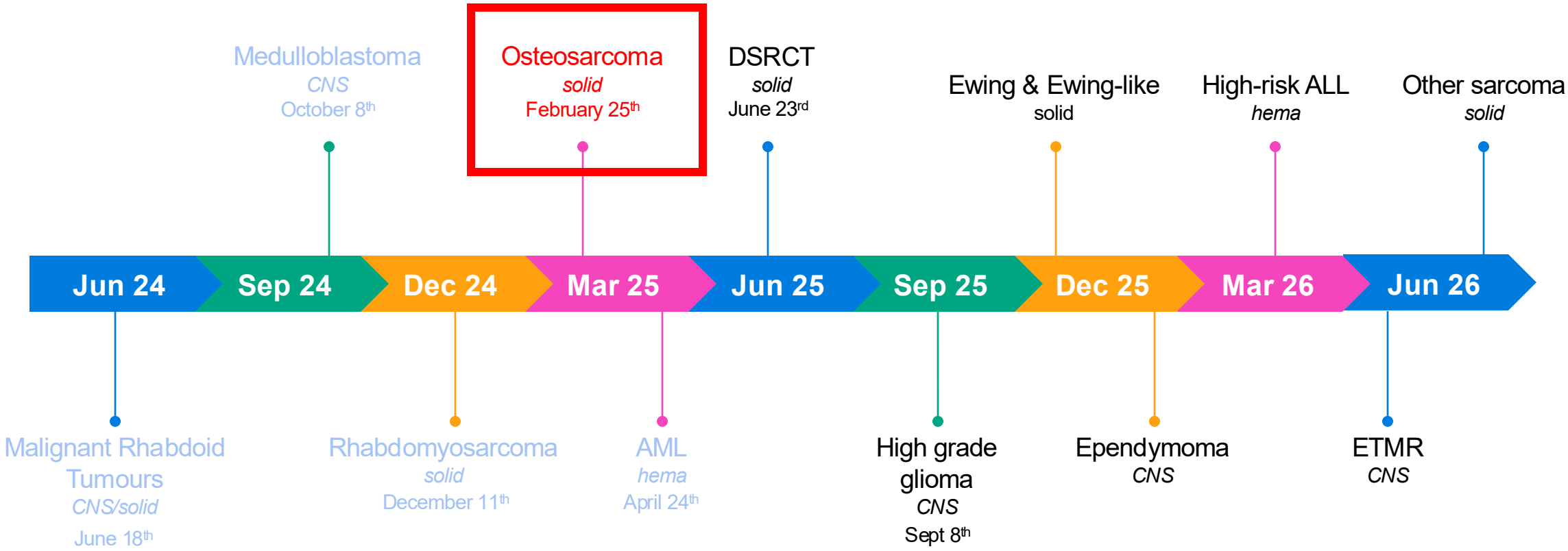
Planned workshop schedule



Potential pathways post workshop

- **Conclusions** about the drug development landscape
- **Identify and prioritise opportunities** to accelerate the development of paediatric bespoke therapeutics
  - Disease biology gaps: CRUK, other charities participating in the event
  - Targets for drug discovery: C-Further
  - Drug combinations ready to progress to clinical trials: ITCC, LifeArc, other charities participating in the event
- **CDAs can be (and have been) put in place** to enable further discussions with workshop partners to discuss progression options
- **Inform charity partners** of promising science and potentially inform new grant calls

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Workshop

OS Target Shortlisting

- Target longlist generated from:
  - Pipeline search (database searches)
  - Literature search (high level)
- 125 simple target genes/pathways identified
- Categorised by target location:
  - Intracellular (57 targets)
  - Cell-surface (30 targets)
  - *Already in clinic (38 targets)*
- Information on identification criteria was also included

- Longlist shared with invitees
  - 1 week for priority target responses
- We received:
  - 16 responses
  - 12 additional targets not in original longlist
- Six targets were selected for deep diligence covering a range of osteosarcoma biology

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Scoring Matrix

Evidence level	Module	Quality	Scoring	Quantity	Scoring
Target	1. Target presence	Type of event / number of samples or patients / Type of analysis	Genomic/n>20/2 methods	Prevalence in cohort (separate	>10% in the cohort
			Overexpression/synthetic lethal>10<20, at least one reliable method		Between 2-10%
			n<10, one method		<2%
	2. Target validation *in vitro*	Methods (siRNA,CRISPR, iTAG)/ Type of models (cell lines, organoids)/number of models	Different methods/ Several types/ >3 models	Level of dependency and phenotypic recapitulation / frequency of dependency	Full dependency (>75% cell death OR transformation)/ >50 % of models
			Single methods / one type / 3 or < models		Partial dependency (<75% death OR growth arrest) / < 50% of models
			Single assay		No dependency
	3. Target validation *in vivo*	type of in vivo model / number of models / number of methods	>1 model type/ >1models or > 1 method	Level of dependency and phenotypic recapitulation	Full dependency (CR / complete tumor regression)
			1 model type		Partial dependency
			no validation of the developed tumors		No dependency
	4. Expected on target toxicity	GEM's to mimic interventions / RNA,protein expression	GEMs and expression	Level of expression in normal tissues and level of effect in GEMs	No tox expected
			Expression only		ambivalent
			none		Tox expected
	5 Tractability of the target protein	Available data on tractability	Tool Compound	Predicted trackability/ nr of compounds	High
			In silico analysis		Intermediate
			No data		Low

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Community Prioritised Focus

Targets

- eIF4A1
- KIF18A
- LRRC15
- ROR2
- RUNX2
- SMARCAL1

Clinical combinations

- DNA Damage Repair
- Indirect targeting MYC

Target Scoring

Target Scoring

LRRC15

Tumor: OS ,Target: LRRC15		
Module	Quality	Quantity
1. Target presence	Expression on RNA and Protein level, limited data in paediatric samples	Strong overexpression in OS samples, but unclear if this is only in OS cells
2. Target validation *in vitro*	shRNA in cell lines	Partial dependency (limited relevance for an ADC, important to assess antigen escape)
3. Target validation *in vivo*	Diverse ADCs on multiple models. Cell lines and PDX?	Mixed responses mainly related to expression levels of target
4. Expected on target toxicity	Expression analysis. No transgenics	Expression on normal supportive tissue cells, higher expression in OS samples
5. Tractability of the target protein	Multiple ADCs	Drugs tested in adult OS patients, but not tested in children yet

ROR2

Tumor: OS ,Target: ROR2		
Module	Quality	Quantity
1. Target presence	RNA and protein expression	Mild overexpression in osteosarcoma, correlated with poorer prognosis
2. Target validation *in vitro*	siRNA, CRISPR (DepMap)	Partial dependency
3. Target validation *in vivo*	CRISPR knock down in metastasis	Partial responses
4. Expected on target toxicity	Expression analysis and knock out mice	Some expression in other tissues including bones. Limb malformation in transgeneics, malformations in germ line affected pateints
5. Tractability of the target protein	Many compounds in development: ADCs, CARTs as well as small molecules	Some promising results in adult trials. Not tested in children, not tested in OS

eIF4A1

Tumor: OS ,Target: eIF4A1		
Module	Quality	Quantity
1. Target presence	RNA and Protein analysis	Increased expression, limited correlated to poor prognosis
2. Target validation *in vitro*	shRNA, siRNA, CRISPR and targeted compounds in cell lines and tumor slice models	CRISPR and siRNA dependency but not specific. Targeted compound causes partial cell death- not apoptosis markers
3. Target validation *in vivo*	Targeted compounds tested in orthotopic xenografts and canine xenografts	Partial reponses with "targeted" compounds
4. Expected on target toxicity	Expression data, Transgenics	Ubiquitously expressed. Transgenics not viable. Essential for B cell development
5. Tractability of the target protein	Small molecules have been developed against eIF4A proteins.	Compounds not specific for eIF4A1. Have not been tested in osteosarcoma patients

RUNX2

Tumor: OS ,Target: RUNX2		
Module	Quality	Quantity
1. Target presence	DNA, RNA, Protein	Gain, amplification and strong overexpression
2. Target validation *in vitro*	CRISPR, siRNA, overexpression, shRNA and small molecules	Conflicting results. Less colonies, sensitization to chemo, but also tumor supressor role and reduced growth after overexpression
3. Target validation *in vivo*	Small molecules and shRNA	Slight reduction in growth
4. Expected on target toxicity	Expression, transgenic	Bone deformations reported in knock outs
5. Tractability of the target protein	Previously defined as undrugable. But CADD522 showed is a tractable target	CADD522 in development in adult cancer types

SMARCAL1

Tumor: OS ,Target: SMARCAL1		
Module	Quality	Quantity
1. Target presence	RNA and protein expression	No overexpression, potential synthetic lethal in ALT phenotype
2. Target validation *in vitro*	CRISPR screen in ALT positive OS, dTAG in ALT+OS	Dependency on SMARCAL1 in ALT phenotype OS cells *in vitro*
3. Target validation *in vivo*	No data	No data
4. Expected on target toxicity	Expression and germline events in humans	Broadly expressed in various tissues; germline gene defects correlated to lymphoma and hypersensitization to DDR drugs
5. Tractability of the target protein	Intracellular but druggable ATPase domain	Nothing in development

KIF18A

Tumor: OS ,Target: KIF18A		
Module	Quality	Quantity
1. Target presence	DNA aberrations	Frequent chromosomal instability
2. Target validation *in vitro*	No data	
3. Target validation *in vivo*	No data	
4. Expected on target toxicity	Expression data and GEM model	Expressed in all tissues but higher dependency in cells with CI. GEM mice are viable
5. Tractability of the target protein	Highly amenable to therapeutic targeting	Many compounds in development. But nothing in osteosarcoma

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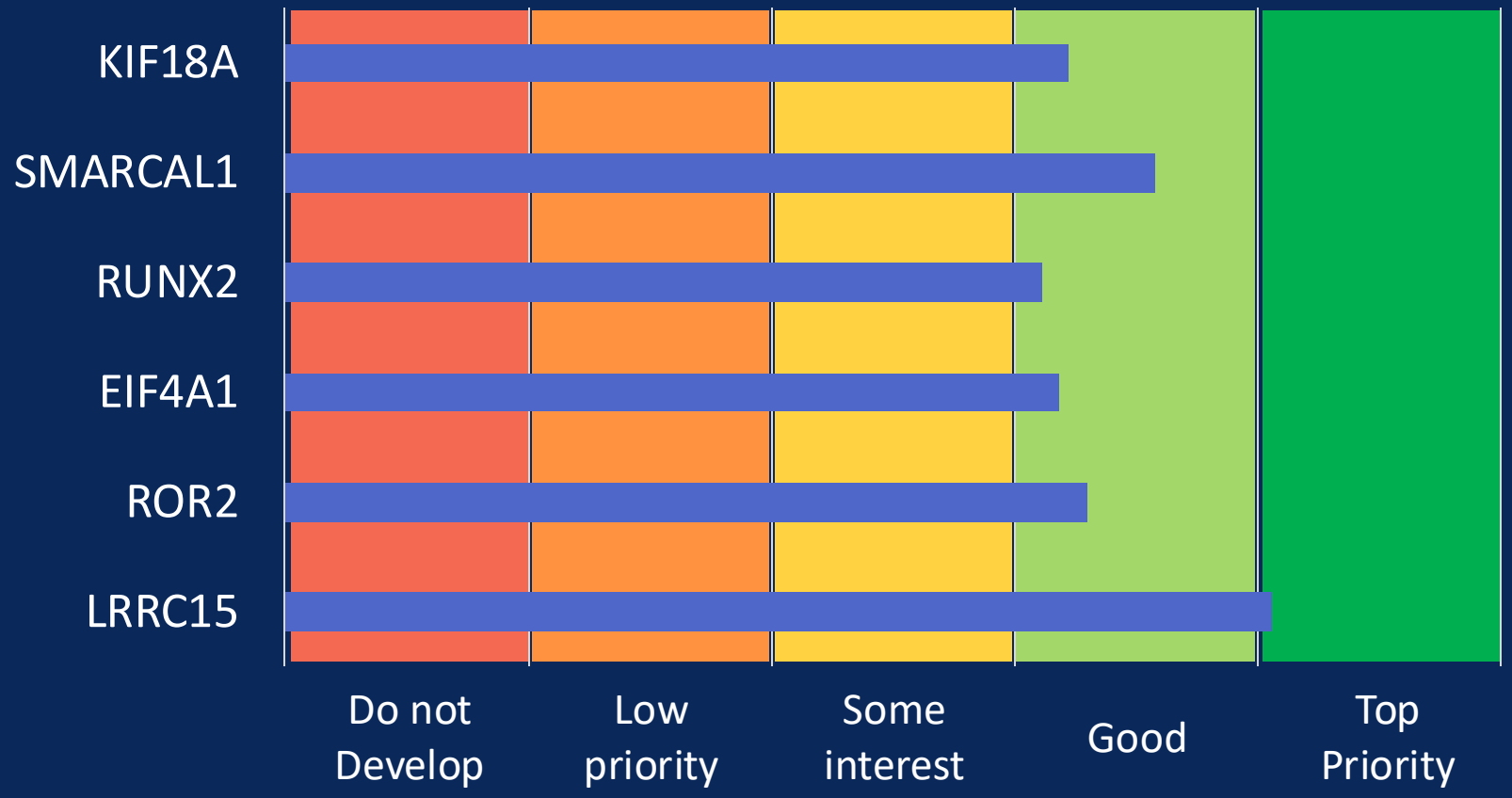
Target Prioritisation



Outcomes

General Conclusions

- Substantial **unmet needs** in osteosarcoma: including the requirements to **increase survival**, **reduce toxicity**, improve **local control**, increase **accessibility to clinical trials**, **improve supportive care** and accelerate **development of patient communities**. There is lack of new therapeutics and tyrosine kinase inhibitors (TKIs) are being currently evaluated. The evaluation of new therapeutics is being challenged by **variable backbone therapies**
- A better understanding of **targeting developmental pathways** is a recurring theme in drug development for paediatric cancer, but the limitation is the need for better models

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Target Conclusions

- An **ADC targeting LRRC15** with an osteosarcoma-relevant payload is a very high priority
- **SMARCAL1** is a very high priority target, applicable to several high unmet need malignancies; **small molecule inhibitors and degraders** should be evaluated
- An **ADC targeting ROR2** with an osteosarcoma-relevant payload should be explored. ROR2 is also a relevant target for rhabdomyosarcoma
- There is a need for **pre-clinical evaluation of a KIF18A** target in osteosarcoma models, if positive an early phase trial should be undertaken.
- An early phase **clinical study of an EIF4A1 inhibitor** would be warranted. Inhibition of EIF4A1 is an indirect strategy to target MYC.
- **RUNX2** is potentially a good target for osteosarcoma, using PROTACs or an ADC (with unspecified target) with a RUNX2 inhibitor payload. Further **preclinical validation** is required, specifically around its role in osteosarcoma and the potential toxicity of its modulation in healthy tissues.

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Clinical Conclusions

- **MYC**: MYC is a critical driver in poor prognosis osteosarcoma. To date there are no developed direct or indirect strategies to target MYC. The results of the ongoing trial with the **direct inhibitor, OMO-103**, are awaited. **G quadruplex stabilisers** may be of interest. There is a need to develop a **consensus on** the levels of MYC expression required for **stratification**.
- **DNA damage repair** (DDR): It is a very high priority to exploit DDR mechanisms leading to synthetic lethality in osteosarcoma. **Biomarkers have not been identified**, and the proposed strategy is to embed **biological studies in early phase trials**. There are concerns about identifying a therapeutic index due to toxicity. The results of an ongoing trial a **PARP and an ATR inhibitor** in osteosarcoma are awaited. Combinations of PARP and DNA-PK inhibitors, PARP and ATM inhibitors and PARP and VEGF inhibitors should be considered in a **platform trial**.

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