

# Horizon Scan for Histology- Independent Therapies targeted at Cancer



June 2021

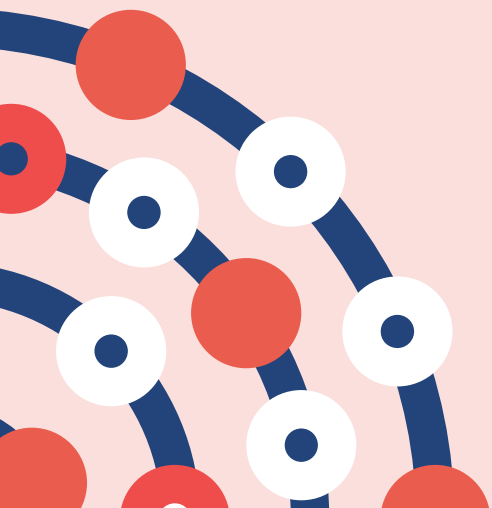


# Disclaimer:

This project is funded by the National Institute for Health Research (NIHR) [HSRIC-2016-10009/Innovation Observatory]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.



# Background & Objectives



# NIHR Innovation Observatory

- NIHR-funded, horizon scanning and research centre based at Newcastle University
- One of our key remits is to deliver horizon scanning intelligence and early awareness notification service to national healthcare bodies within the UK
- Working closely with the Accelerated Access Collaborative (AAC) and national bodies such as NHS E&I and NICE, to support accelerated access of new innovative health technologies and services to NHS patients



# Background

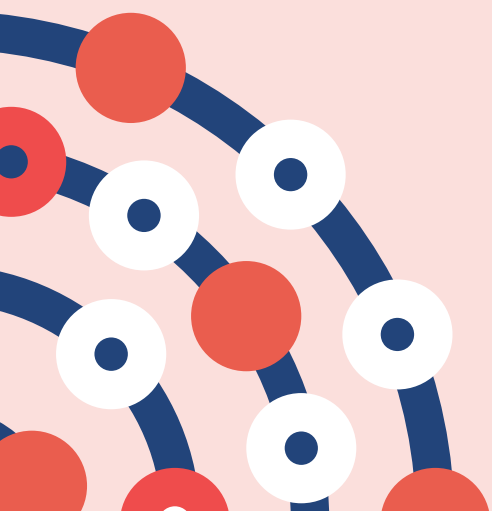
- Histology-Independent Therapies (HITs) for cancer, or Tumour-Agnostic Therapies (TATs), are recent innovations in oncology wherein treatment is based on the cancer's genetic and molecular alterations rather than cancer type and/or site of origin
- Three HITs currently have regulatory approval: Pembrolizumab (FDA), Larotrectinib (FDA, EMA) and Entrectinib (FDA, EMA)
- In June 2019, the NIHR Innovation Observatory undertook a rapid horizon scan for 'potential' HITs that were within a ~5 year timeframe to obtaining a product licence (Marketing Authorisation) in the EU/UK
- Following the rapid scan, it became clear that more detailed information was needed on these therapies in order to prepare for their entry into the NHS.
- Additionally, the COVID-19 pandemic may have affected the availability of genetic testing and therefore the progress of clinical trials for these therapies. Therefore, a refresh of the previous scan was required to understand the current pipeline of HITs.

# Objectives & Scope

- This scan was undertaken to refresh the June 2019 data in order to:
  - Provide an up-to-date product pipeline of HITs targeted at cancer currently under development
  - Provide additional data identified on these therapies as agreed by the working group
- The scan will be used to:
  - Inform the Early Stage Products work stream of the Accelerated Access Collaborative. Through understanding what products are becoming available and when, we will be able to focus efforts to ensure the smooth adoption of these technologies into the NHS.
  - Support the development of the National Genomic Testing Directory (NGTD) through information about genomic mutation targets of the HITs in the development pipeline. Information is needed on the increased genomic testing required to inform development of the genomic testing infrastructure and capability.



# Method



# 'Potential' HITs: Scanning Criteria

- The NIHR Innovation Observatory maintains a comprehensive database ('Medicines Innovation Database') of innovative medicines in clinical/regulatory development with a focus on those with potential UK/EU launch/availability within ~5 years
- The Medicines Innovation Database contains individual 'Technology Records', defined as innovative medicine(s) + indication(s). Key data fields are collated for each Technology Record during routine horizon scanning and monitoring processes
- 'Potential' HITs are identified and tagged for each Technology Record based on the following criteria:
  - All indications identified as 'Solid tumours' or 'Haematological cancers' on the clinical trial record
  - All cancer site-specific indications with a 'genomic/biomarker' in the population subgroup (clinical trials inclusion criteria)

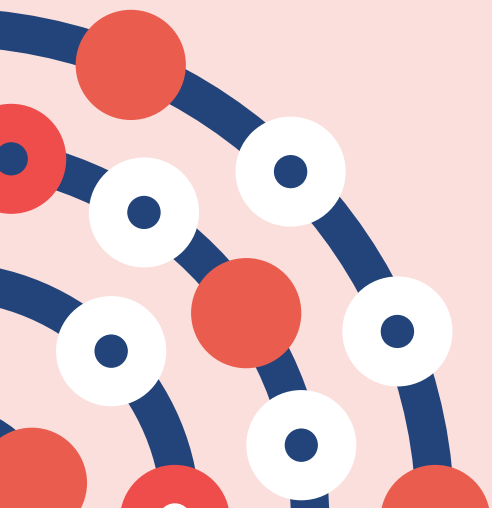


# 'True' HITs: Inclusion/Exclusion Criteria

- True HITs are not always simple to identify as such therapies may begin development as histology-independent or tumour-specific, open to subsequent change.
- For this scan, the following criteria were applied:
  - Inclusion
    - All technology records for solid tumours + genetic/biomarker subgroup
    - All technology records with multiple cancer indications + genetic/biomarker subgroup
    - Technology records with  $\geq$  phase I/II trials\*
  - Exclusion criteria
    - Technology records with solid tumour indications with no genetic/biomarker subgroup
    - Technology records with single cancer indications + genetic/biomarker subgroup
    - Technology records with no associated clinical trial
    - Technology records with already approved HITs being developed as line extensions in the same genetic mutation subgroup (i.e., pembrolizumab, larotrectinib, or entrectinib)



# Summary of Key Findings\*



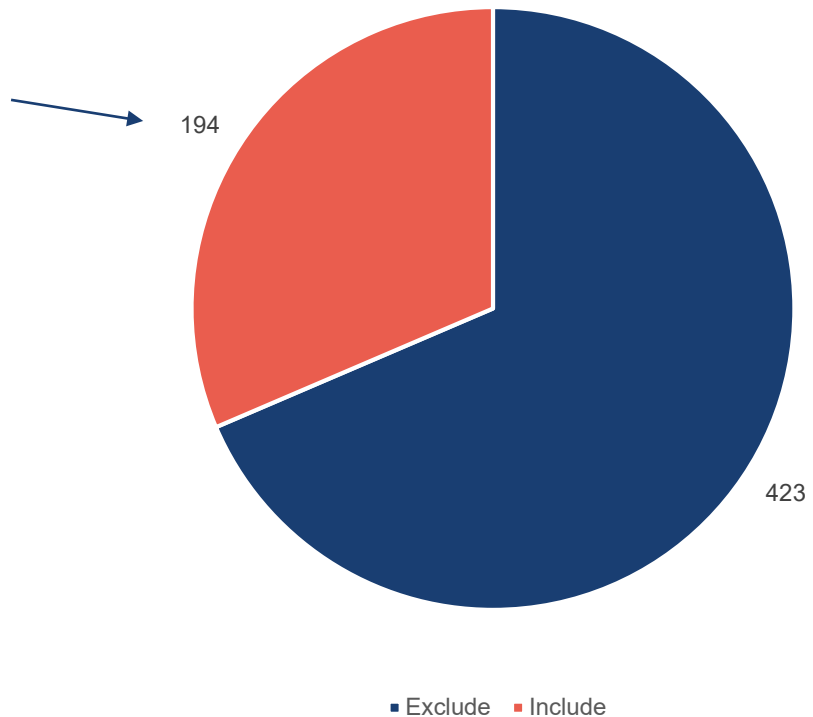
\*To be viewed/interpreted with the dataset provided

# HIT Horizon Scan Refresh 2021, Results

- After filtration, returned ~194 records that may reference potentially 'true' HITs

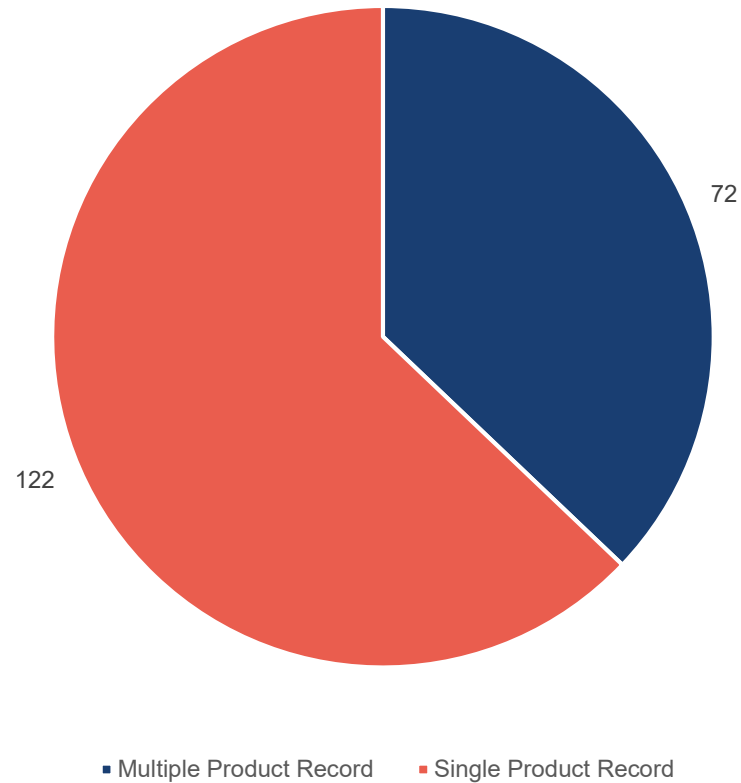
## Number of records included/excluded following criteria filtration

*Inclusion/exclusion criteria were applied to limit results to only those most likely to be potentially "true" HITs*

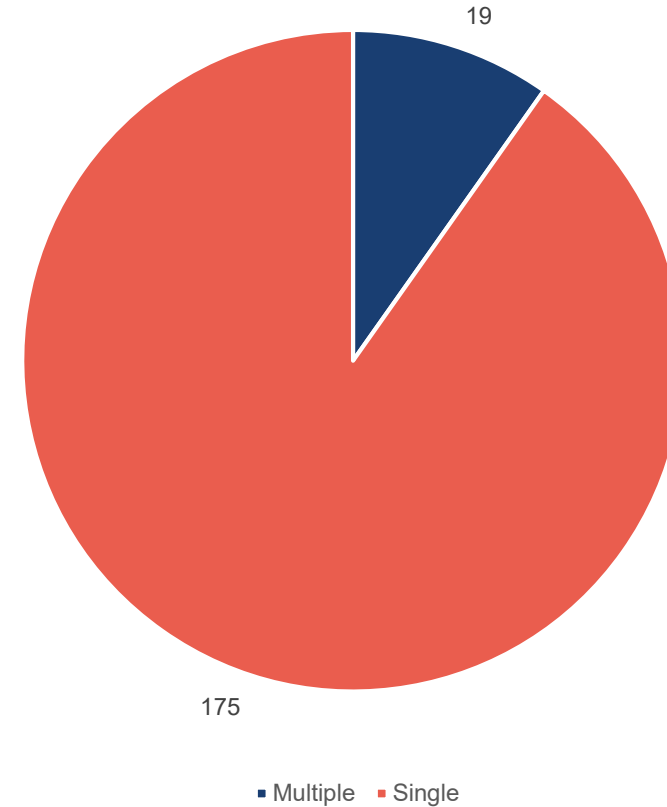


# HIT Horizon Scan Refresh 2021, Results

Potentially 'true' HITs by Single vs. Multi-Product Records



Potentially 'true' HITs by # of CTs associated with Record



# HIT Horizon Scan Refresh 2021, Results

- What interventions appear most often?\*

Intervention	ALL Records	Product Description
Pembrolizumab	13	humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Activation of T-cell-mediated immune responses against tumor cells
Nivolumab	11	fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1, PCD-1) with immune checkpoint inhibitory and antineoplastic activities. Activation of T cells and cell-mediated immune responses against tumor cells
Atezolizumab	9	humanized, Fc optimized, monoclonal antibody directed against the protein ligand PD-L1 (programmed cell death-1 ligand 1), with potential immune checkpoint inhibitory and antineoplastic activities
Olaparib	9	small molecule inhibitor of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) with potential chemosensitizing, radiosensitizing, and antineoplastic activities. Inhibits PARP-mediated repair of single strand DNA breaks; enhancing cytotoxicity of DNA-damaging agents and may reverse tumor cell resistance
Ipilimumab	4	recombinant human immunoglobulin (Ig) G1 monoclonal antibody directed against the human T-cell receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), with immune checkpoint inhibitory and antineoplastic activities. Inhibits the CTLA4-mediated downregulation of T-cell activation. Leads to a cytotoxic T-lymphocyte-mediated immune response against cancer cells
Durvalumab	4	optimized monoclonal antibody directed against programmed cell death-1 ligand 1 (PD-L1; B7 homolog 1; B7H1), with potential immune checkpoint inhibitory and antineoplastic activities
Trastuzumab Emtansine	4	HER2 antibody-drug conjugate comprising a conjugate of trastuzumab and maytansinoid DM1; microtubule inhibitor and directed to cells overexpressing HER2
Tremelimumab	3	human immunoglobulin (Ig) G2 monoclonal antibody directed against the human T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4), with potential immune checkpoint inhibitory and antineoplastic activities
Selpercatinib	3	orally bioavailable selective inhibitor of wild-type, mutant and fusion products involving the proto-oncogene receptor tyrosine kinase rearranged during transfection (RET), with potential antineoplastic activity. Inhibition of cell growth of tumors cells that exhibit increased RET activity
Rucaparib	3	a PARP inhibitor used as an anti-cancer agent; first-in-class drug targeting the DNA repair enzyme poly-ADP ribose polymerase-1

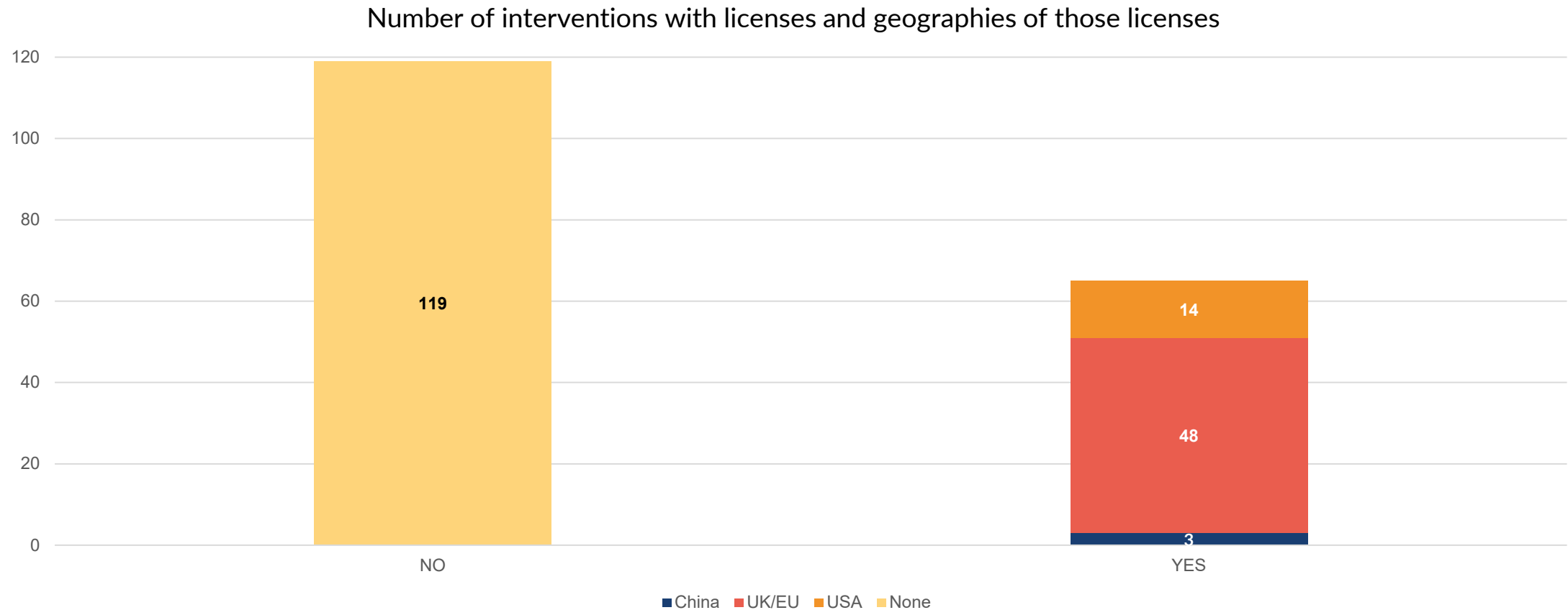
# HIT Horizon Scan Refresh 2021, Results

- What interventions appear most often as Single Product Records?

Intervention	Count	Product Description
Olaparib	5	small molecule inhibitor of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) with potential chemosensitizing, radiosensitizing, and antineoplastic activities. Inhibits PARP-mediated repair of single strand DNA breaks; enhancing cytotoxicity of DNA-damaging agents and may reverse tumor cell resistance
Selpercatinib	3	orally bioavailable selective inhibitor of wild-type, mutant and fusion products involving the proto-oncogene receptor tyrosine kinase rearranged during transfection (RET), with potential antineoplastic activity. Inhibition of cell growth of tumors cells that exhibit increased RET activity
Repotrectinib	2	orally available inhibitor of multiple kinases, including the receptor tyrosine kinase anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), the neurotrophic tyrosine receptor kinase (NTRK) types 1, 2 and 3, the proto-oncogene SRC, and focal adhesion kinase (FAK); inhibition of these kinases leads to the disruption of downstream signaling pathways and the inhibition of cell growth of tumors in which these kinases are overexpressed, rearranged or mutated
Palbociclib	2	orally available cyclin-dependent kinase (CDK) inhibitor with potential antineoplastic activity. Palbociclib selectively inhibits cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), leading to cell cycle arrest. This suppresses DNA replication and decreases tumor cell proliferation
Tazemetostat	2	orally available, small molecule selective and S-adenosyl methionine (SAM) competitive inhibitor of histone methyl transferase EZH2, with potential antineoplastic activity. Alters gene expression patterns associated with cancer pathways, resulting in decreased tumor cell proliferation
Bintrafusp alfa	2	investigational bifunctional fusion protein immunotherapy; designed to simultaneously target two immuno-suppressive pathways, transforming growth factor- $\beta$ (TGF- $\beta$ ) trap and an anti-programmed cell death ligand-1 (PD-L1)
Pembrolizumab	2	humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Activation of T-cell-mediated immune responses against tumor cells
Trastuzumab deruxtecan	2	HER2-targeted antibody-drug conjugate comprised of anti-epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab with a potent topoisomerase I inhibitor payload; delivers cytotoxic payload to HER expressing tumor cells
Avapritinib	2	small molecule kinase inhibitor targeting KIT D816V
Rucaparib	2	a PARP inhibitor used as an anti-cancer agent; first-in-class drug targeting the DNA repair enzyme poly-ADP ribose polymerase-1
Ulixertinib	2	orally available inhibitor of extracellular signal-regulated kinase (ERK) 1 and 2, with potential antineoplastic activity. Inhibition of ERK-dependent tumor cell proliferation and survival
Alectinib	2	orally active, small-molecule anaplastic lymphoma kinase (ALK) inhibitor
Tipifarnib	2	nonpeptidomimetic quinolinone; binds to and inhibits the enzyme farnesyl protein transferase, preventing the activation of Ras oncogenes, thereby inhibiting cell growth & induces apoptosis
Trastuzumab Emtansine	2	HER2 antibody-drug conjugate comprising a conjugate of trastuzumab and maytansinoid DM1; microtubule inhibitor and directed to cells overexpressing HER2

# HIT Horizon Scan Refresh 2021, Results

- How many interventions have regulatory approval (product licence) for use in other indication(s)?



# HIT Horizon Scan Refresh 2021, Results

- What indications are most often pursued?

Indications*	Count
Solid tumours	112
Non-Hodgkin lymphoma (NHL), Solid tumours, Histiocytic disorders	6
Haematological cancers	6
Haematological cancers, Solid tumours	4
Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer	4
Lymphoma, Solid tumours, Histiocytic disorders	3
Glioma, Solid tumours	3
Solid tumours, Primary central nervous system (CNS) tumours	2
Prostate cancer, Solid tumours	2
Non-small-cell lung cancer (NSCLC), Solid Tumours	2
Gastric cancer, Gastro-oesophageal junction cancer	2
Solid tumours, Melanoma	2
Gastro-oesophageal junction cancer, Gastric cancer	2
Non-small-cell lung cancer (NSCLC), Solid tumours	2
Head and neck cancer	2



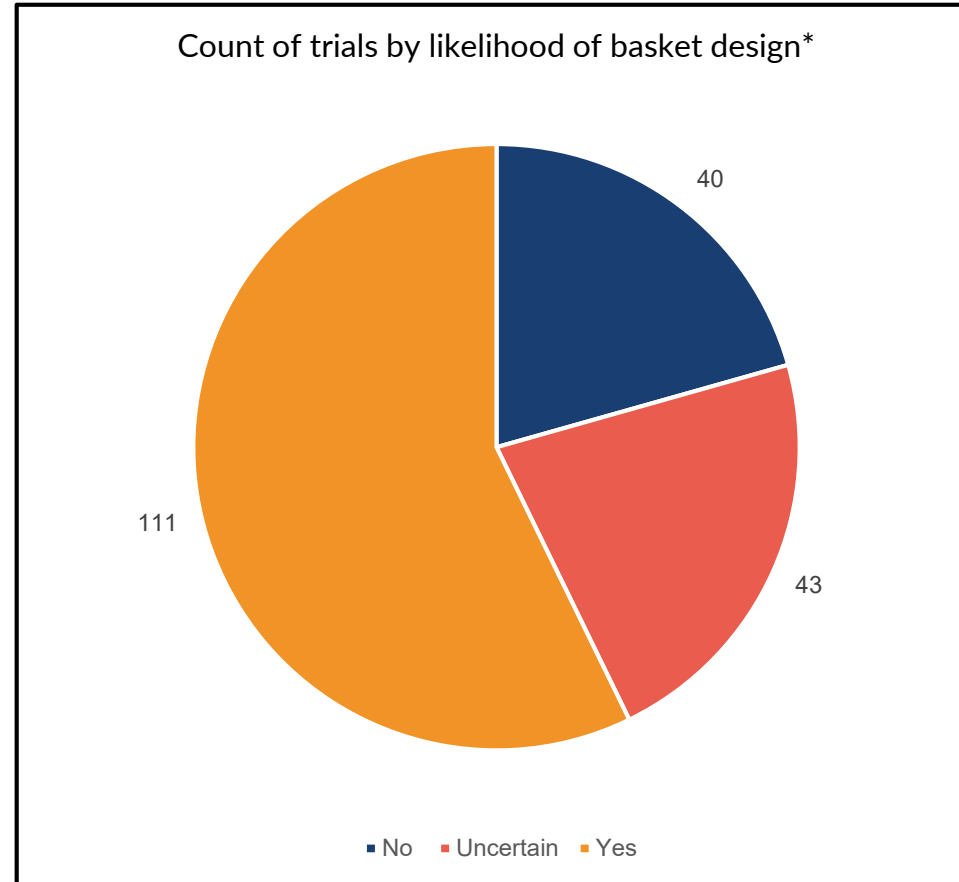
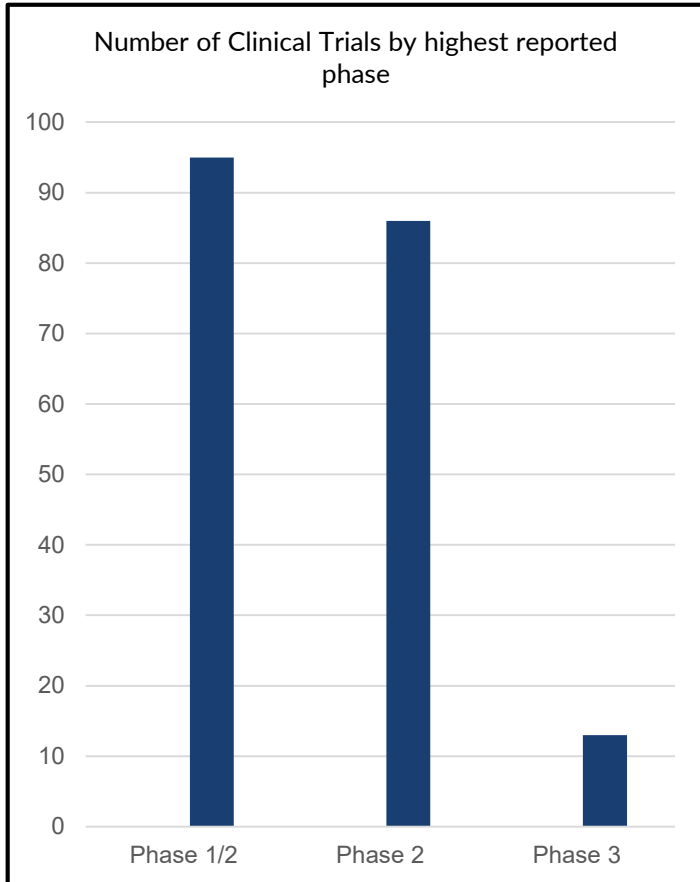
*When indications from records are separated, collected, and counted individually...*

Indications*	Count
Solid tumours	151
Haematological cancers	10
Histiocytic disorders	10
Non-Hodgkin lymphoma (NHL)	9
Gastric cancer	8
Acute myeloid leukaemia (AML)	6
Non-small-cell lung cancer (NSCLC)	6
Gastro-oesophageal junction cancer	6
Myelodysplastic syndrome (MDS)	5



# HIT Horizon Scan Refresh 2021, Results

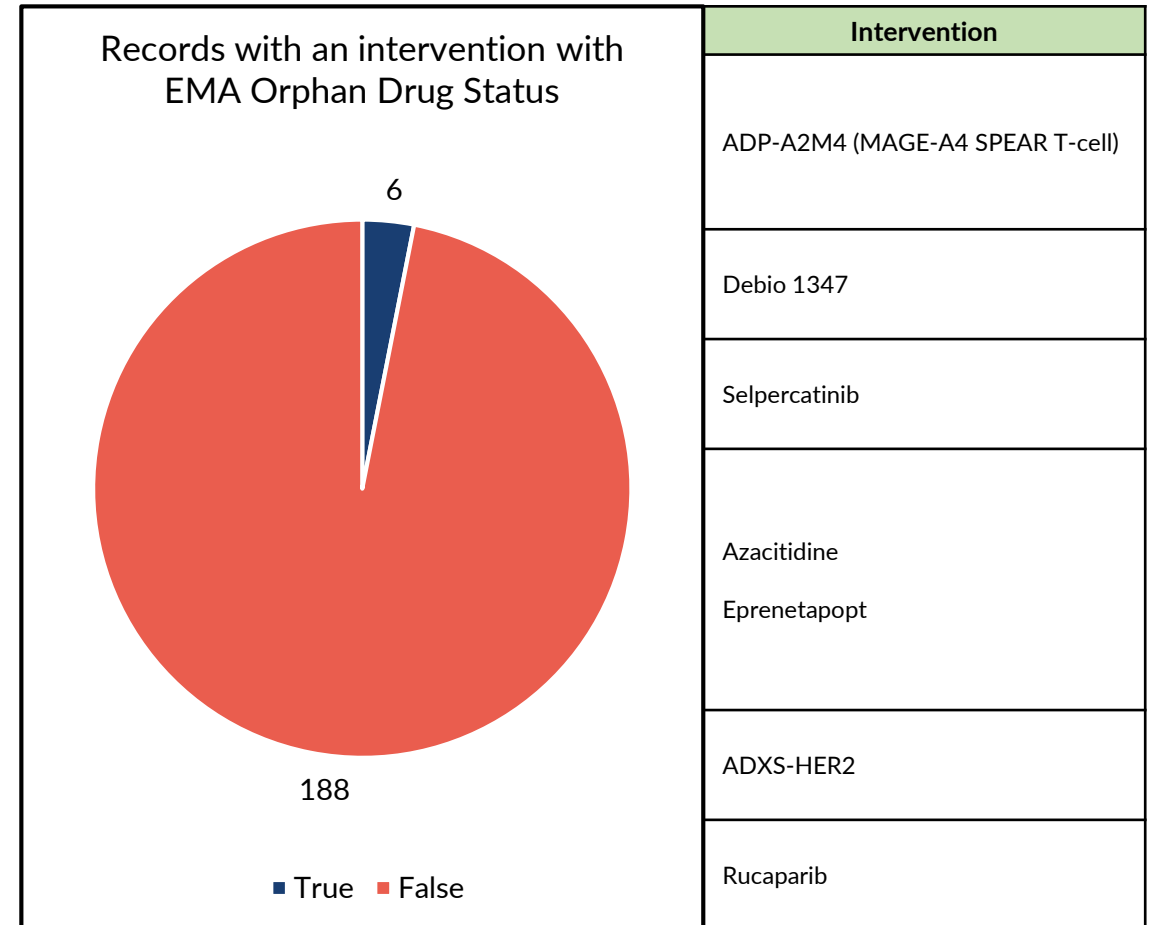
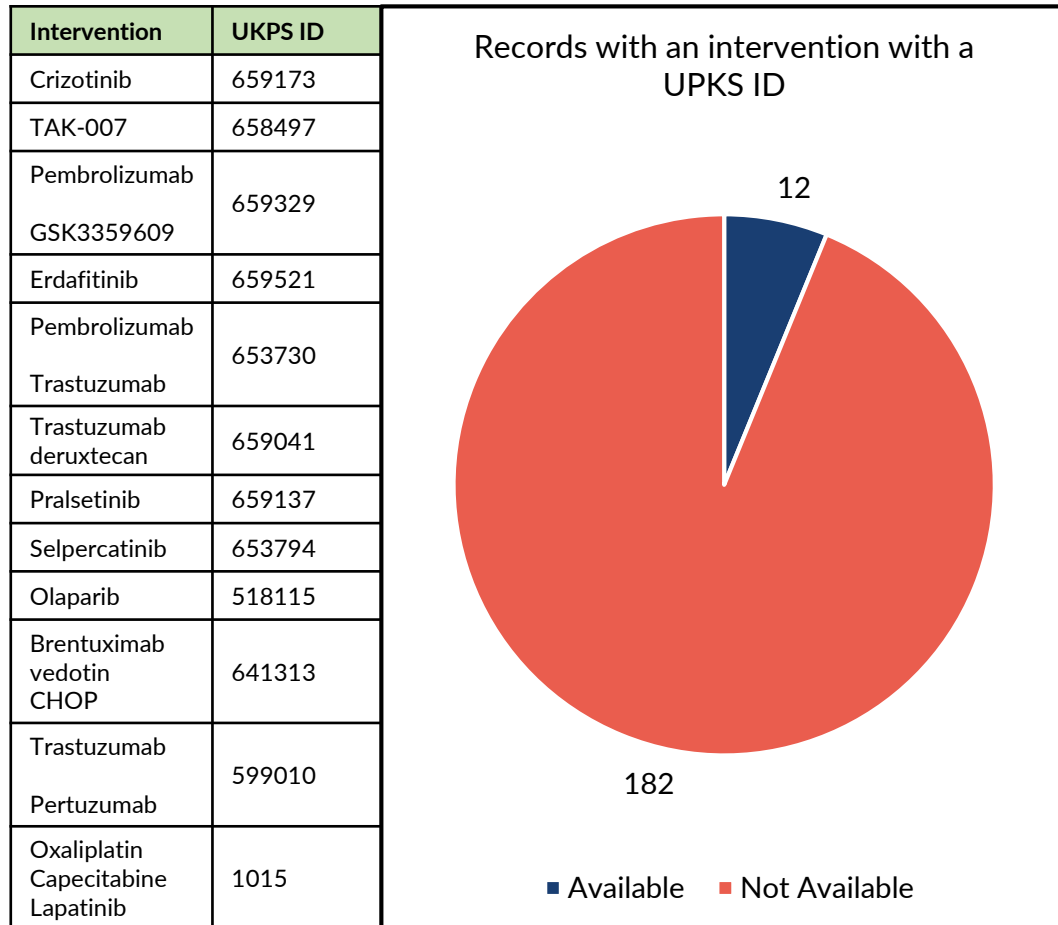
- What do we know about the associated clinical trials?



Geographies of Clinical Trials	Count
Australia	1
EU (excl. UK)	12
EU (excl. UK), other countries	1
EU (excl. UK), United States	8
EU (excl. UK), United States, and other countries	10
EU (incl. UK)	2
EU (incl. UK), other countries	1
EU (incl. UK), United States	2
EU (incl. UK), United States, and other countries	32
France	1
Germany	1
Japan	1
None listed	11
United Kingdom	3
United Kingdom; United States	2
United States	95
United States, other countries	10
United States; Canada	1

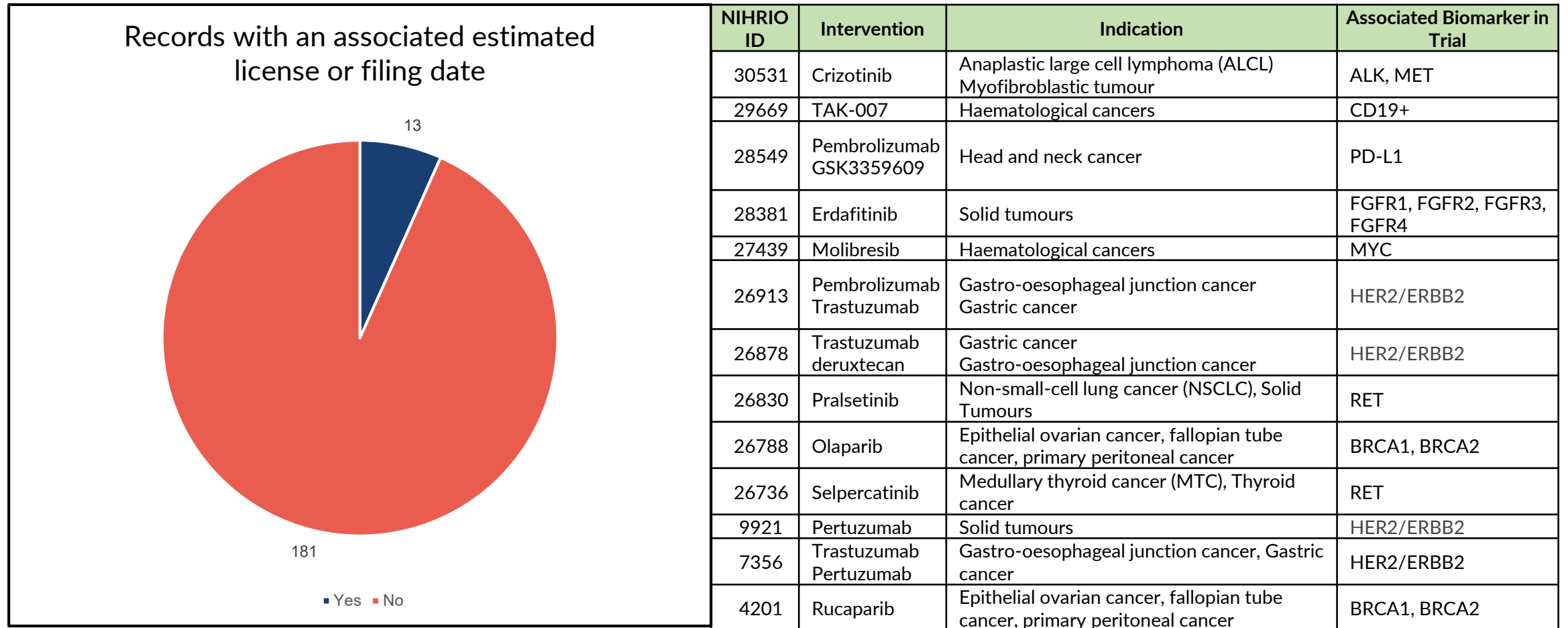
# HIT Horizon Scan Refresh 2021, Results

- What regulatory information do we have for these records?



# HIT Horizon Scan Refresh 2021, Results

- What regulatory information do we have for these records?



# HIT Horizon Scan Refresh 2021, Results

- What biomarkers appear most often in the records?

Biomarker	Count	Associated Tumors*
HER2/ERBB2	27	breast invasive ductal carcinoma, lung adenocarcinoma, colon adenocarcinoma, bladder urothelial carcinoma, and invasive breast carcinoma
KRAS	12	lung adenocarcinoma, pancreatic adenocarcinoma, colon adenocarcinoma, colorectal adenocarcinoma, and rectal adenocarcinoma
BRCA1	12	lung adenocarcinoma, breast invasive ductal carcinoma, colon adenocarcinoma, high grade ovarian serous adenocarcinoma, and bladder urothelial carcinoma
BRCA2	12	colon adenocarcinoma, lung adenocarcinoma, breast invasive ductal carcinoma, prostate adenocarcinoma, and endometrial endometrioid adenocarcinoma
PALB2	9	lung adenocarcinoma, colon adenocarcinoma, breast invasive ductal carcinoma, endometrial endometrioid adenocarcinoma, and bladder urothelial carcinoma
ATM	9	lung adenocarcinoma, colon adenocarcinoma, endometrial endometrioid adenocarcinoma, prostate adenocarcinoma, and breast invasive ductal carcinoma
RAD51	9	lung adenocarcinoma, glioblastoma, conventional glioblastoma multiforme, colon adenocarcinoma, and breast invasive ductal carcinoma
PD-L1	9	non-small cell lung carcinoma, breast carcinoma, cervical carcinoma, gastric carcinoma, head and neck squamous cell carcinoma, adenocarcinoma of the gastroesophageal junction
MSI-H	7	colorectal carcinoma and malignant solid tumor, endometrial carcinoma, and adenocarcinoma of the gastroesophageal junction
CHEK2	7	lung adenocarcinoma, breast invasive ductal carcinoma, colon adenocarcinoma, endometrial endometrioid adenocarcinoma, and bladder urothelial carcinoma
RET	7	lung adenocarcinoma, colon adenocarcinoma, thyroid gland medullary carcinoma, cutaneous melanoma, and melanoma
EGFR	7	lung adenocarcinoma, conventional glioblastoma multiforme, glioblastoma, breast invasive ductal carcinoma, and colon adenocarcinoma
TMB-H	7	malignant solid tumor, non-small cell lung carcinoma, breast carcinoma, colorectal carcinoma, endometrial carcinoma

# HIT Horizon Scan Refresh 2021, Results

- What biomarkers appeared absent from the National Genomic Test Directory for cancer?

Associated biomarkers in CTs		
AKR1C3	EphA2	Mesothelin expression
AKT2	FANCA	MRE11A
ATR	FANCC	MSS
AXL	FANCE	MTOR
BARD1	FANCF	MYC/N
BRIP1	FANCL	NBN
CCNE1	FANCM	Nectin-4 (PVRL4)
CCR5+	GNAQ/11	NTSR1
CD123+	GRPR	NY-ESO-1
CD19+	HER2/ERBB2	PALB2
CD22+	HLA-A	PD-L1
CD20+	HLA-A2	PD-L2
CD30+	HPV	PPP2R2A
CDK4	HRD+	PRAME
CDK6	IFNG	PSCA
CEACAM5	INT1	RAD51
CHEK1	KEAP1	SETD2
CLDN18.2	LAG-3	SSTR2
CLDN6	LAGE-1A	STK11
CLEVER-1	MAGE-A4	TMB-H
CYP2D6	MAP2K2	TROP2
dMMR	MAPK1	VEGFR
	MAPK3	Virus-associated*

# HIT Horizon Scan Refresh 2021, Results

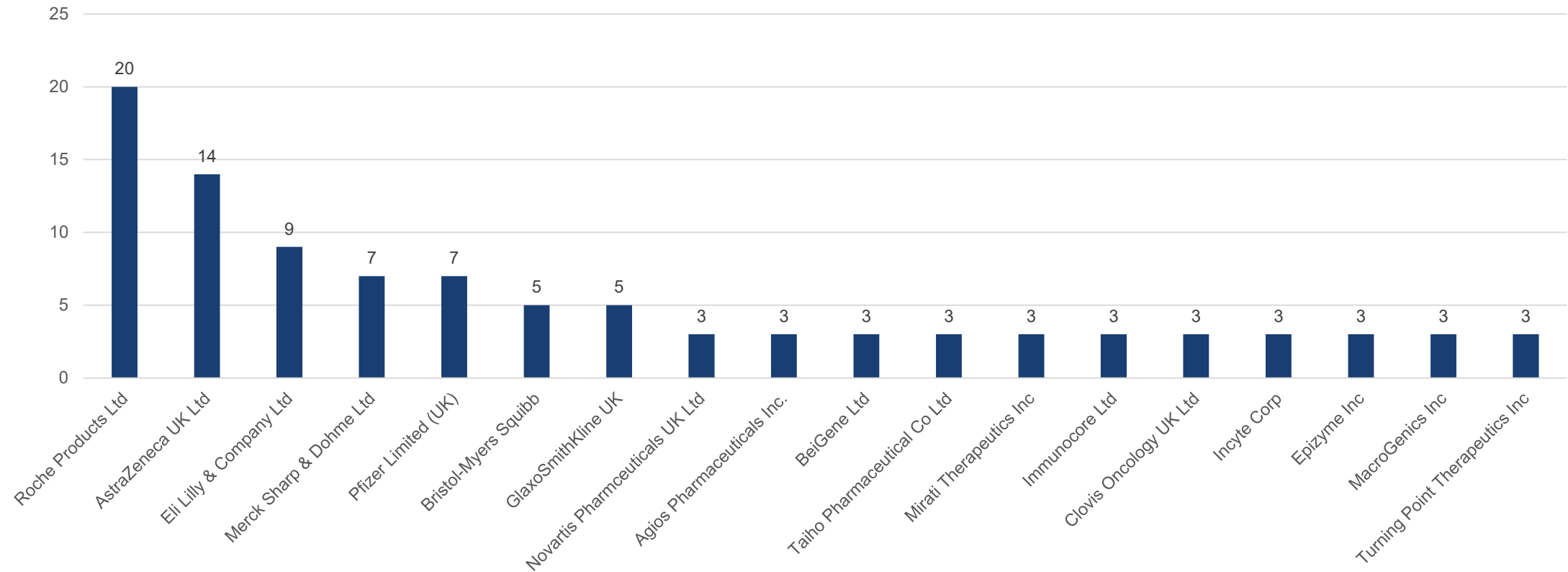
- What named tests were mentioned in clinical trials and with which biomarkers were they associated?

Test Name for Biomarker, if provided	Associated Biomarker in Trial	NGTD (Y/N)
DFCCI/BWH OncoPanel	MYC, CCNE1, RB, FBXW7, BRCA1, BRCA2, PALB2, RAD51, ATR, ATRX, CHEK2	Yes (MYC, RB1, FBXW7, BRCA1, BRCA2, ATRX, CHEK2) No (CCNE1, PALB2, RAD51, ATR)
FCVI/BWH OncoPanel	CCND1, CCND2, CCND3, CDK4, CDK6	Yes (CCND1, CCND2, CCND3) No (CDK4, CDK6)
Lynparza HRR-HRD assay	HRR genes (BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51), HRD deficiency (HRD+)	Yes (BRCA1, BRCA2, ATM, CDK12, CHEK2) No (BRIP1, BARD1, CHEK1, FANCL, PALB2, PPP2R2A, RAD51), No (HRD deficiency [HRD+])
DFCI/BWH OncoPanel, MGH SnapShot	BRCA, BARD1, BRIP1, CDK12, CHEK2, FANCA, FANCC, FANCE, FANCF, FANCM, NBN, PALB2, RAD51, MYC, FBXW7, CCNE1, ARID1A	Yes (ARID1A, BRCA1/2, CDK12, CHEK2, MYC, FBXW7) No (BARD1, BRIP1, FANCA, FANCC, FANCE, FANCF, FANCM, NBN, PALB2, RAD51, CCNE1)
mPACT protocol a MOIs panel	DDR genes: ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, MSH2, NBN, PALB2, RAD51, SMARCB1, VHL	Yes (ARID1A, ATM, ATRX, BRCA 1/2, CDK12, CHEK2, MSH2, SMARCB1, VHL) No (ATR, BAP1, BARD1, BRIP1, FANCA, FANCC, FANCD2, FANCE, FANCM, MRE11A, NBN, PALB2, RAD51)
Oncomine comprehensive assay or Foundation One CDx (for NGS), Guardant360 (for plasma cfDNA)	KIT, PDGFRA	Yes
Foundation Medicine F1CDx or F1LCx	ALK	Yes
DFCI/BWH OncoPanel	MET, NTRK1, NTRK2, NTRK3	Yes
INFORM molecular diagnostic platform.	TMB-H, PD-L1, MYC/N	No
Cervista assay	HPV	No
UCSF500, FoundationOne	SETD2	No
Indium SPECT, Gallium PET	SSTR2	No
Foundation Medicine	HER2/ERBB2	No

# HIT Horizon Scan Refresh 2021, Results

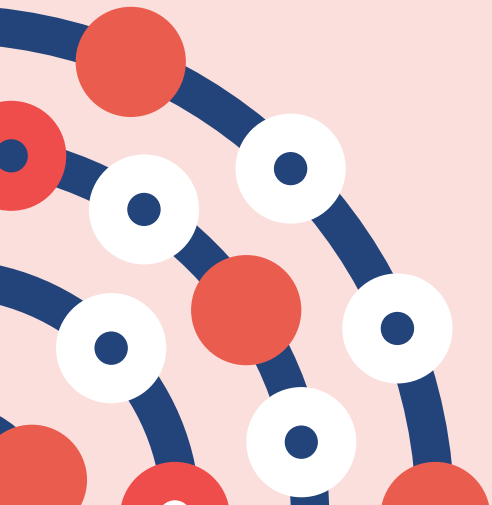
- What companies appear most active in this space?

Lead company counts from potentially 'true' HIT records\*





# Conclusion





# Summary of Key Findings

- Histology Independent Therapies (HITs) in the pipeline predominantly target solid tumours; there is a growing number targeting haematological cancers
- Of the 194 HITs identified in the scan, ~6% (n=12) have shown positive signals of an estimated <3 years time to UK launch/availability
- About 35% of the HITs currently have regulatory approval for at least one indication; several are being tested in site-specific indications, alongside the site-agnostic indications identified in this scan
- Majority of HITs are in phase I/II and II trials and utilise 'basket' trial designs; identification of the basket trial design is not always readily apparent from the clinical trial records
- There is a growing pipeline of HITs targeting novel genomic biomarkers not routinely tested in the NHS (i.e., not on the NGTD)

# Limitations

- Clinical and regulatory pathways for HITs are not always straightforward and the data provided comes with some degree of uncertainty around the progression of the HITs identified
- Publicly available information on genetic testing for HITs is often extremely vague, making it challenging to map with available tests on the NGTD
- The scan was performed by NIHR Innovation Observatory staff who are not oncology/genomics subject experts. Some of the specific genomic/biomarker targets listed will require further verification for 'true' HITs indications (e.g., virus-associated and Claudin protein targets)
- Data sharing - estimated product licence (Marketing Authorisation) dates are commercial-in-confidence data and have not been included in the scan dataset

# Recommendations/future work

- This scan provides an initial 'spine' of data of HITs in the pipeline; further data enrichment (e.g., prevalence, potential eligible patient populations, likely comparators/competitors, etc) and/or deep-dive (e.g. focus on specific genetic mutations) may be required to support workstreams of users
- Additional clinical/genomic expertise may be required to assess and further refine the 'true' HITs and genomic targets; feedback on this to the team will be of value for future scan/data refresh
- This scan focussed on 'basket' trial designs although other Master Protocol designs (umbrella and platform trial design) are included but not categorised as such; steer from stakeholders/users will be required if this is needed for any future work
- The NIHR Innovation Observatory provides ongoing scanning and monitoring of the clinical/regulatory pathway of HITs as part of its core remit – future work can be undertaken to provide a HITs 'dashboard' with real-time data

# Reflections on the scanning process

- What worked well?
  - Clear project brief and required data fields developed and agreed with AAC secretariat prior to project start
  - Communication and engagement with Working Group to support the scanning process at the start, and at interim time points
- What could be improved?
  - Involvement of subject matter experts/KOL (oncology, genomic) early in the scanning process – e.g. clarity on definitions and refinement of the inclusion/exclusion criteria to further reduce the noise in the data

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