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Newcastle University

A Pipeline Analysis of Immuno-Oncology Medicines
Pembrolizumab, Nivolumab, and Atezolizumab

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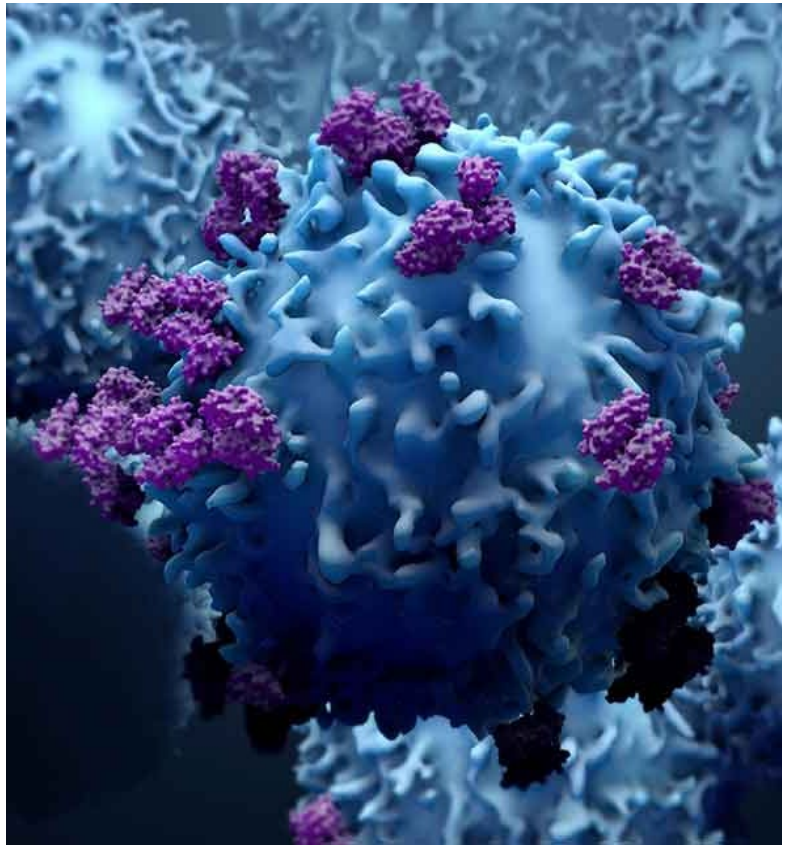
NIHR Innovation Observatory – who we are

- Horizon scanning centre based at Newcastle University, UK
- Funded by the National Institute for Health and Care Research (NIHR)
- Identify and track health innovations (e.g. medicines, devices, diagnostics and digital)
- The IO conducts horizon scanning for early awareness of medicinal products up to 5 years from Marketing Authorisation (MA)
- Notify the National Institute for Health and Care Excellence (NICE) to enable timely Technology Appraisals (TA)

Background

- Immuno-oncology, also known as cancer immunotherapy, is a form of cancer treatment that uses the body's own immune system to prevent, control, and eliminate cancer.
- Immuno-oncology is not a new concept, but it is considered a new treatment for clinical application amongst radiation therapy, surgery, chemotherapy, and genomic-targeted therapy.
- In the UK Life Sciences Vision, Cancer is described as one of 7 great healthcare challenges.
- Under this overarching mission, the Vision states that the government and sector will focus on immuno-oncology and cancer vaccines.
- Horizon scanning in this area is important because immuno-oncology offers highly promising therapeutic advancements that have the potential to revolutionise cancer care.
- In May 2022, the NIHR Innovation Observatory undertook a horizon scan for three major immuno-oncology products (Pembrolizumab, Nivolumab, Atezolizumab).



Objectives

- This horizon scan aimed to provide a comprehensive overview of future indications for selected immuno-oncology pipeline products:
  - Nivolumab
  - Pembrolizumab
  - Atezolizumab
- The outputs of this the scan will deliver the insight needed to support decisions about the reality and impact of adopting new immuno-oncology indications within the NHS.

Project Approach

Phase 1 Baseline Horizon Scanning May – Oct 2022*	Phase 2 Clinical Engagement Nov 2022 – May 2023	Phase 3 Reporting June 2023
• Project brief refined and scanning criteria agreed • Exporting data from MInD • Data cleaning • Analytics on scanning and engagement with NHSE • Finalise scan and provide overview report	• Schedule clinical engagement • Undertake clinical discussions • Record and transcribe outputs • Undertake thematic analysis • Develop draft report	• Finalise holistic horizon scanning report bringing together phases I & II • Approval from HSSG for wider dissemination

*Original timeline was to complete in summer 2022 – delay due to comprehensive analysis on complex dataset and clinical engagement

Data Source

- The NIHR Innovation Observatory undertakes routine horizon scanning as part of its core function, utilizing a robust methodology to identify and track innovative health technologies.
- It maintains a comprehensive database - MInD ('Medicines Innovation Database') - of these innovative medicines, focusing on those with potential UK/EU licence/launch within ~3 - 5 years.
- The NIHR Innovation Observatory's MInD contains individual 'Technology Records' (also referred to as 'Topics'), defined as innovative medicine(s) + indication(s) that triangulates intelligence from:
  - 'hard' data sources (clinical trials registries, research funders, regulatory authorities),
  - 'soft' intel (news/media, social media) and
  - 'pharma' intel (company websites, press releases, direct engagement with companies)

Inclusion Criteria

- Technology records ('Topics') on MInD associated with Pembrolizumab, Nivolumab and Atezolizumab
- Oncology indications
- Clinical trials information associated with each technology record were included*

Exclusion Criteria

- Technology records marked as 'No plans to launch in the UK', and 'No development reported'
- Non-oncology indications

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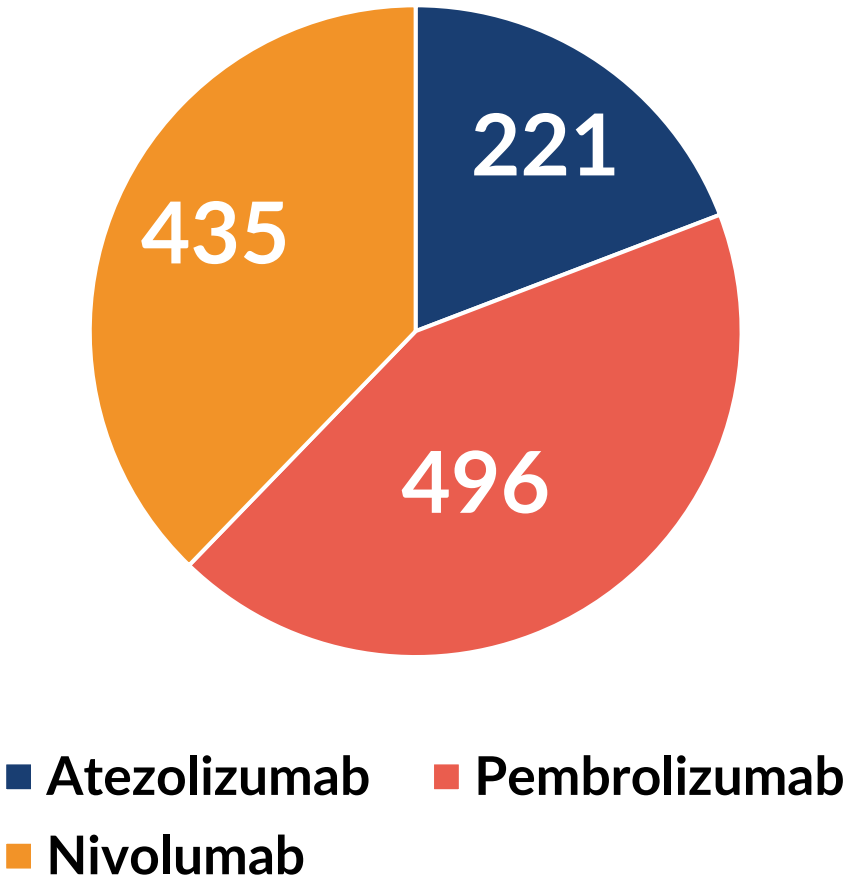
* A record consists of a specific intervention for a specific indication associated with one or more clinical trials. For instance, NIHR-IO ID 21728 is for Tivozanib in combination with Nivolumab for renal cell cancer and is associated with 2 trials NCT03136627, NCT04987203.

Overview of the Immuno-Oncology Dataset

- The initial scan on Innovation Observatory's MInD retrieved 1226 topics associated with Pembrolizumab, Nivolumab and Atezolizumab
- 1152 topics associated with 1225 clinical trials met the inclusion criteria

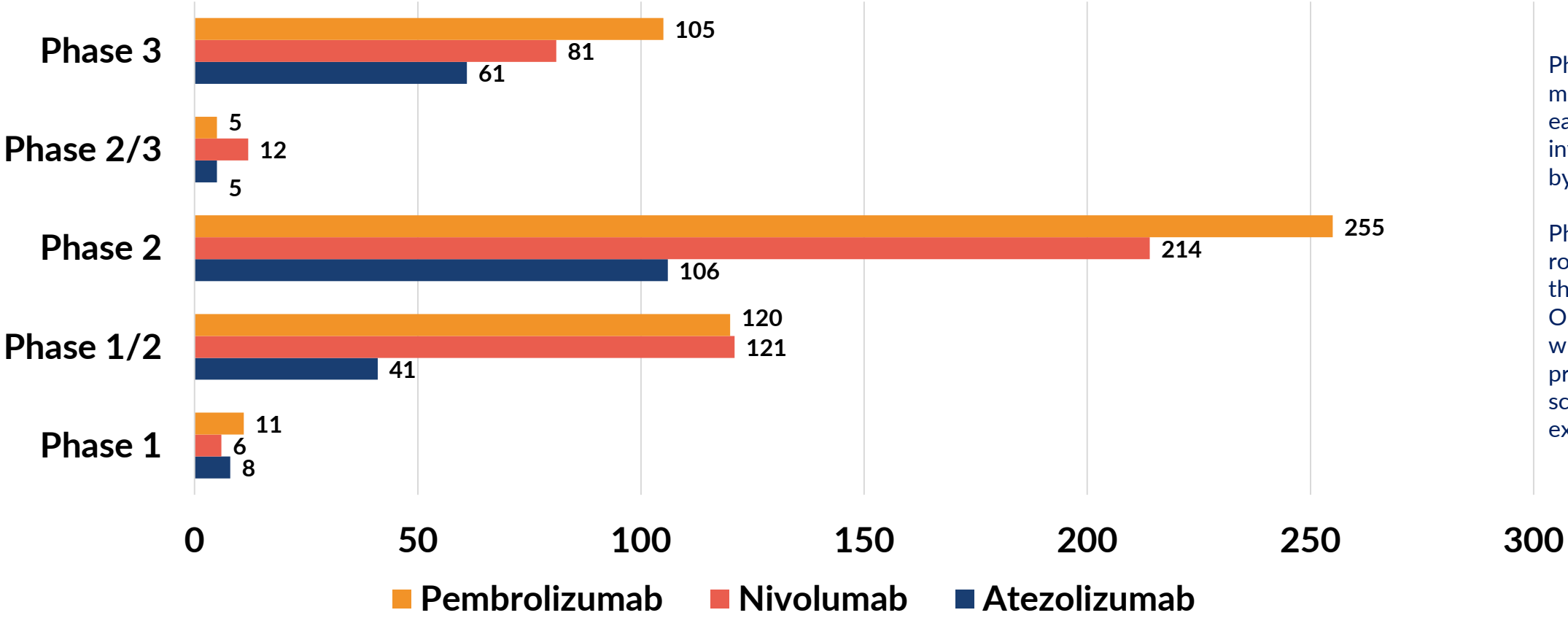
Drug	Number of Records	Number of Trials
Atezolizumab	221	234
Nivolumab	435	461
Pembrolizumab	496	530
Grand Total	**1,152**	**1,225**



Clinical trial activities of Immuno-Oncology Products: Trial Phase

What do we know about the associated clinical trials?

Trial phases of the clinical trials associated with each technology record for each immuno-oncology product



Phase II trials were most common across each of the products investigated, followed by phase III

Phase I trials are not routinely monitored by the Innovation Observatory, which is why very few presented in our initial scan and were later excluded

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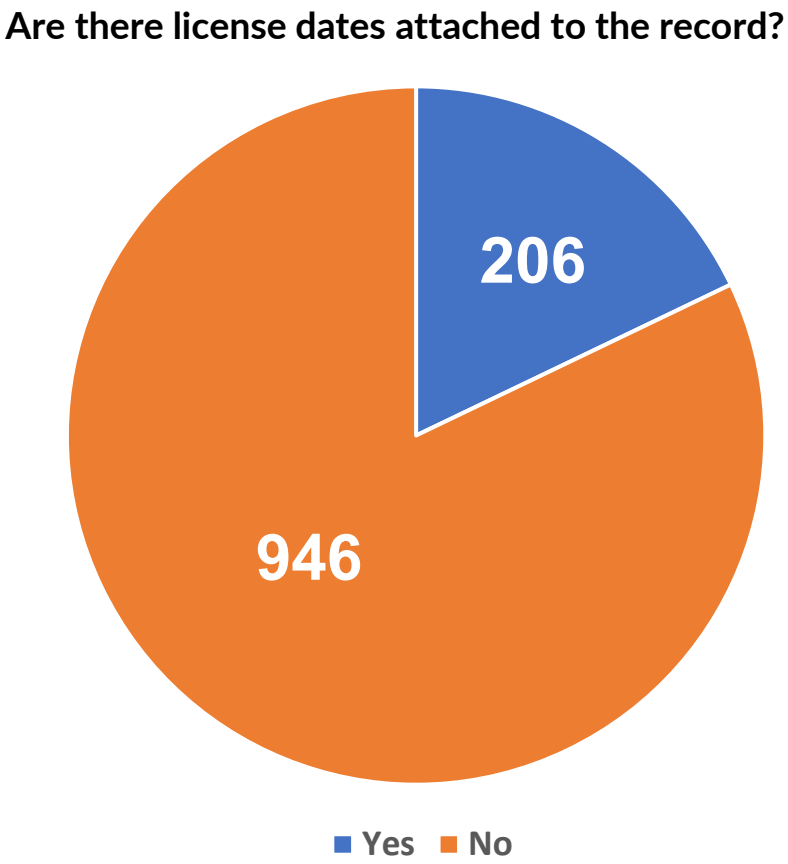
Regulatory status of Immuno-Oncology Products

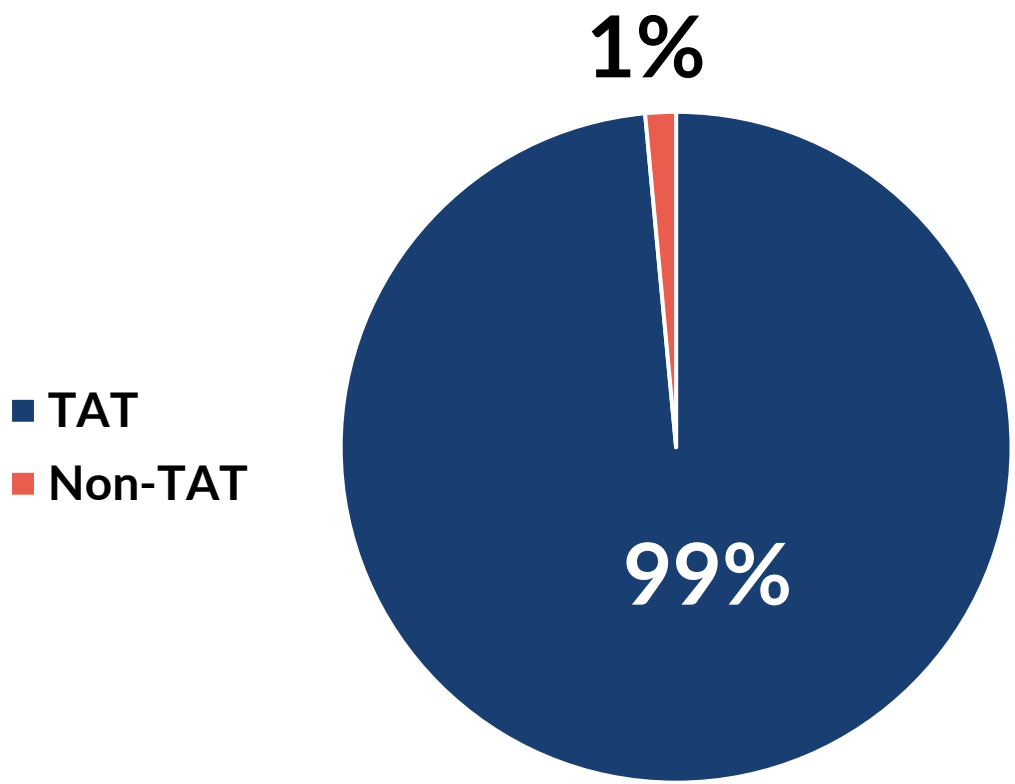
- 206 records have an estimated license (MA) date attached to them indicating they are coming through the pipeline or have already gained license
- License dates are gained through liaising with the company and platforms such as UK PharmaScan



Histology Status of Immuno-Oncology Products

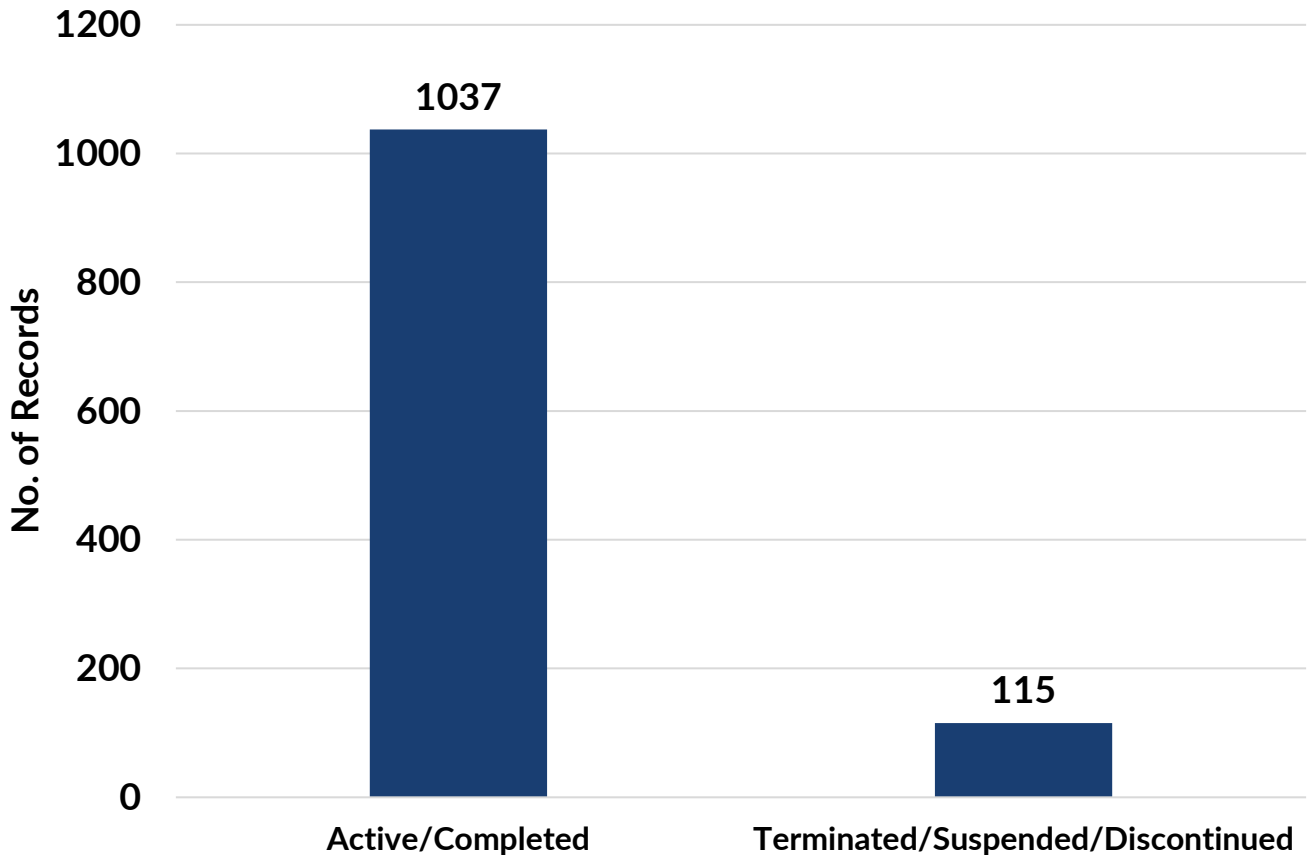
- 17 records were associated with clinical trials investigating Nivolumab, Pembrolizumab and Atezolizumab as Tumour Agnostic Therapy (TAT)
- Most of these were in combination with other interventions
- Atezolizumab had the highest proportion of TATs of all the drugs examined

Drug	Non-TAT	TAT
Atezolizumab	213	8
Nivolumab	431	4
Pembrolizumab	491	5
Grand Total	**1135**	**17**

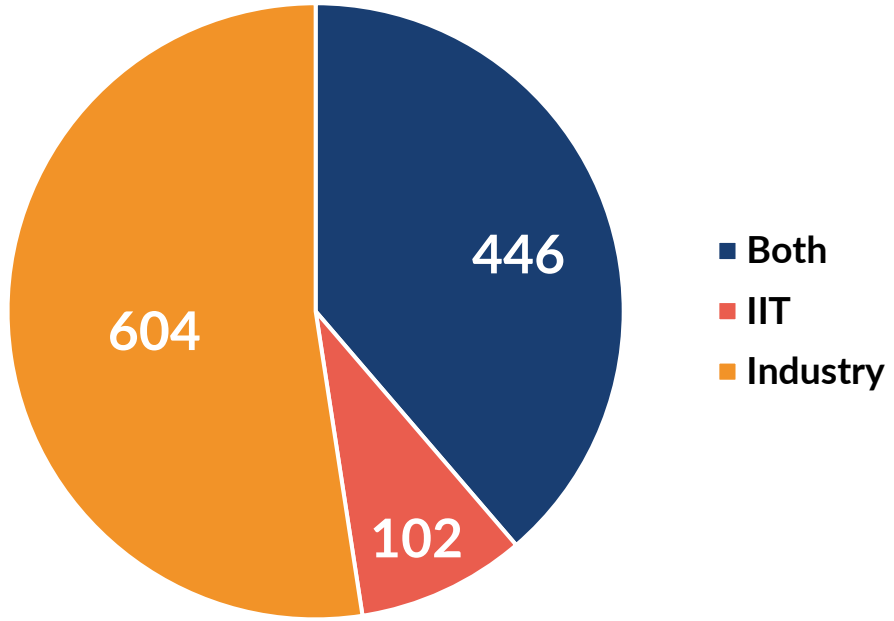


Clinical trial activities of Immuno-Oncology Products: Sponsor & Status

What do we know about the status of the associated clinical trials and their sponsors?



Trial status and sponsorship for records of Immuno-oncology Products



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Revised Scanning Criteria

Following the first iteration of the immuno-oncology scan, the scanning criteria was revised to narrow down on indications which were in phase III clinical trials and therefore might be closer to regulatory approval. Technology records that had the NIHR-IO status 'Finished and 'Other' were excluded as some of these might already be licensed in the UK.

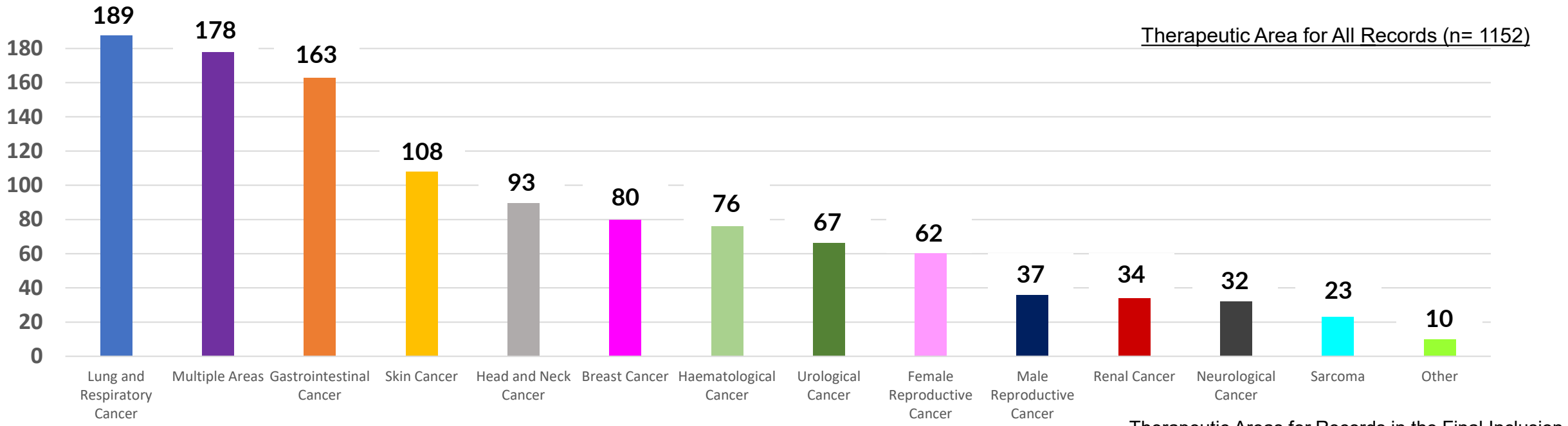
Inclusion Criteria

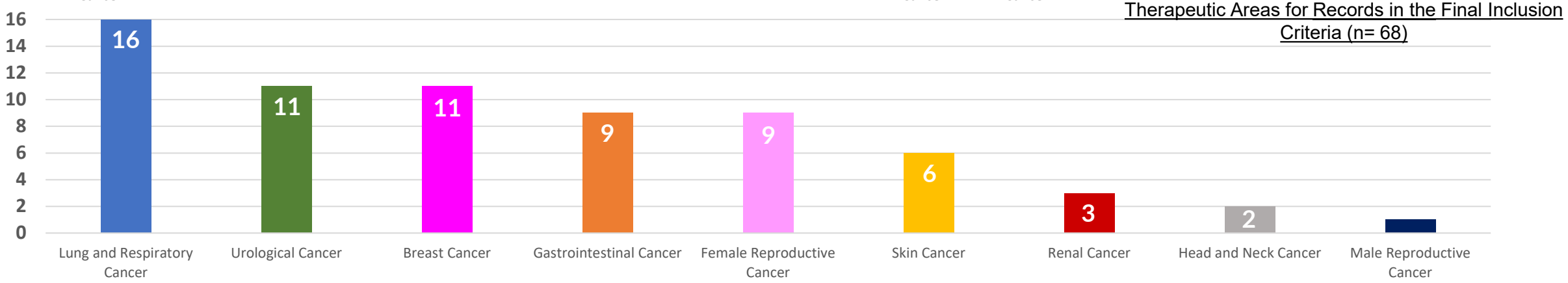
- Technology records ('Topics') on MInD associated with Pembrolizumab, Nivolumab and Atezolizumab
- Oncology indications
- Clinical trials information associated with each technology record were included
- **Only phase III trials**

Exclusion Criteria

- Technology records marked as 'No plans to launch in the UK', and 'No development reported'
- Non-oncology indications
- **All technology records with NIHR-IO status 'Finished'**
- **All technology records with NIHR-IO status 'Other'**
- **All technology records in which the primary treatment was not Pembrolizumab, Nivolumab and Atezolizumab**

Therapy Areas of Immuno-Oncology Products





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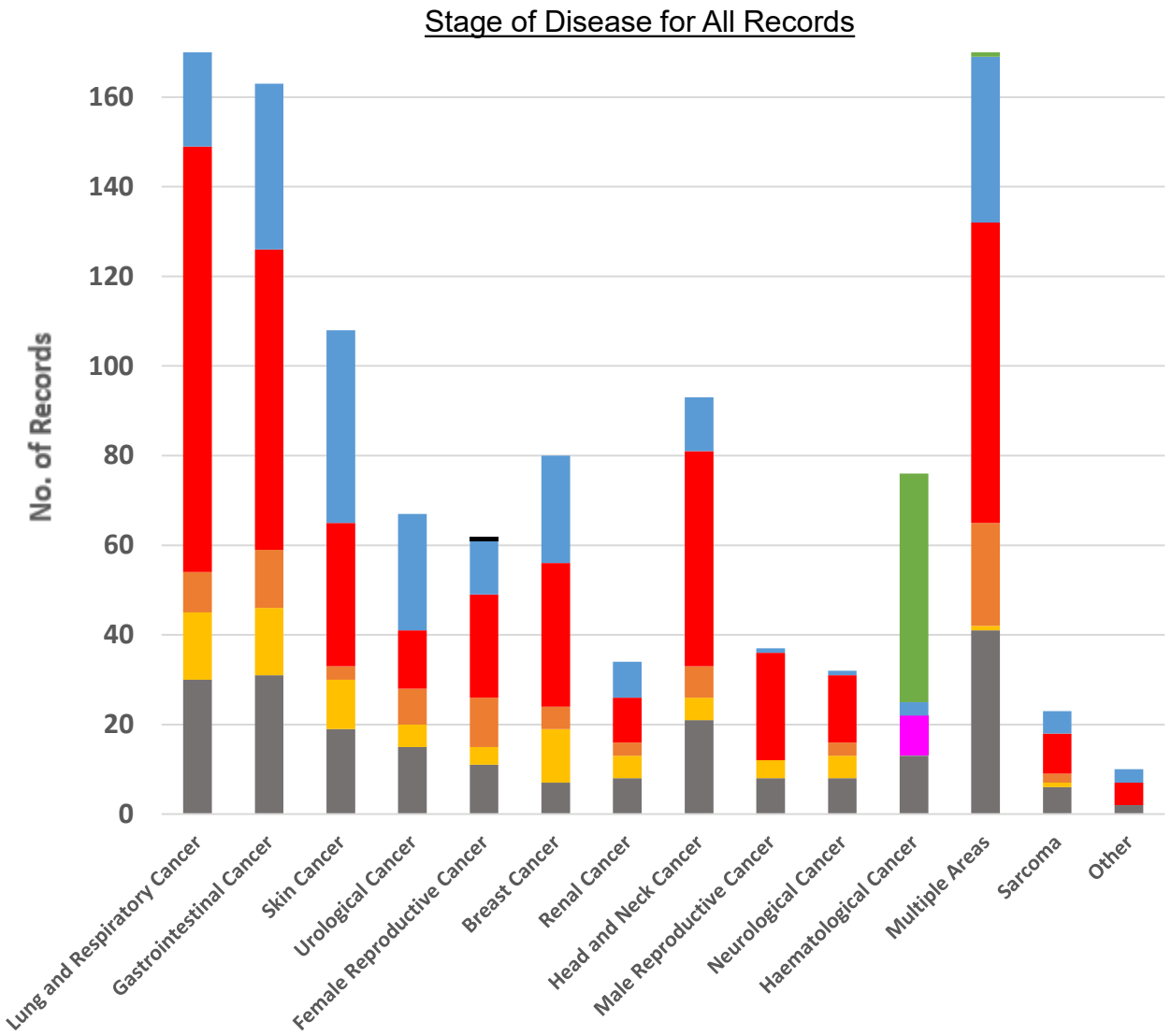
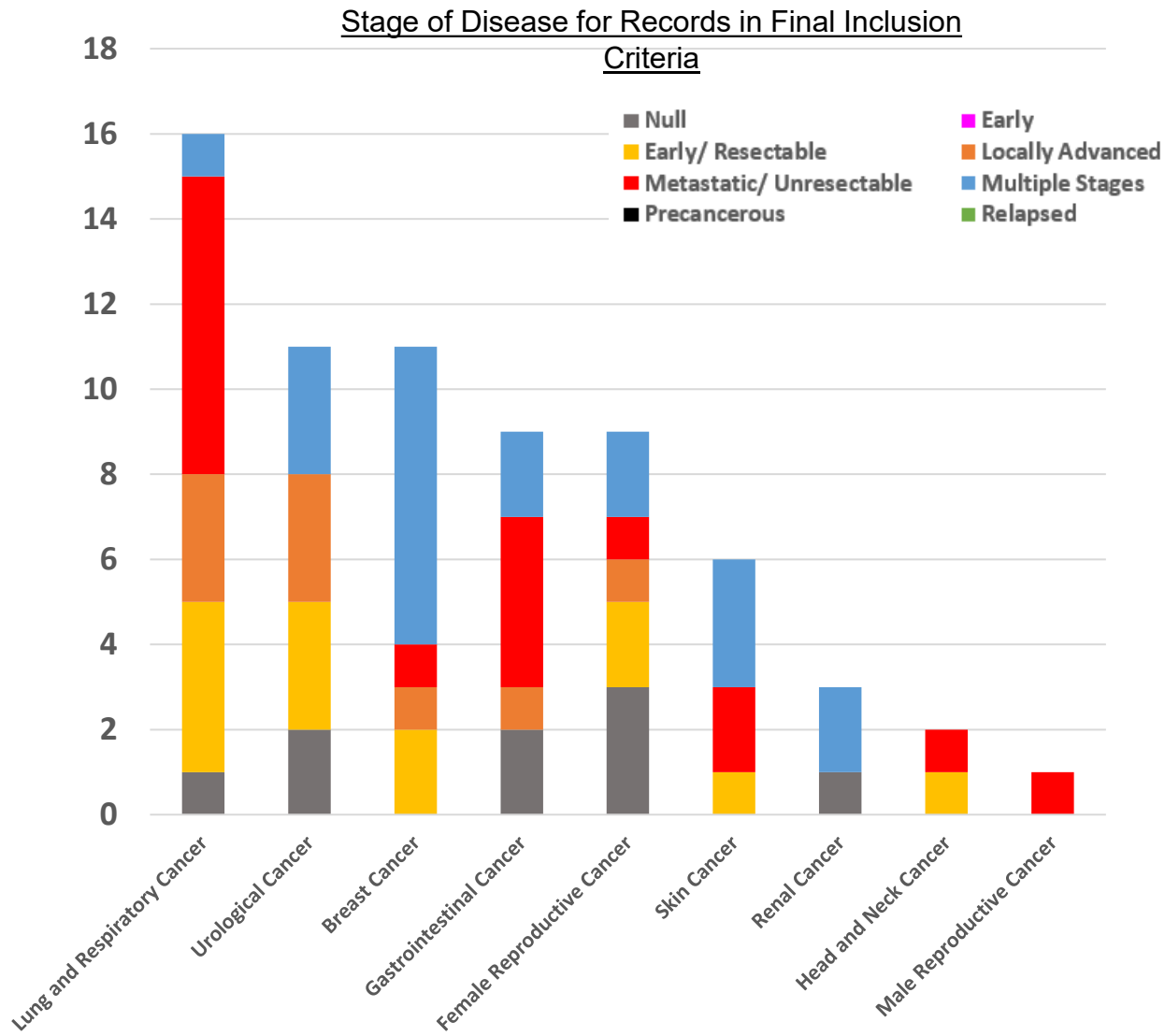
Stage of Disease by Therapy Areas of Immuno-Oncology Products





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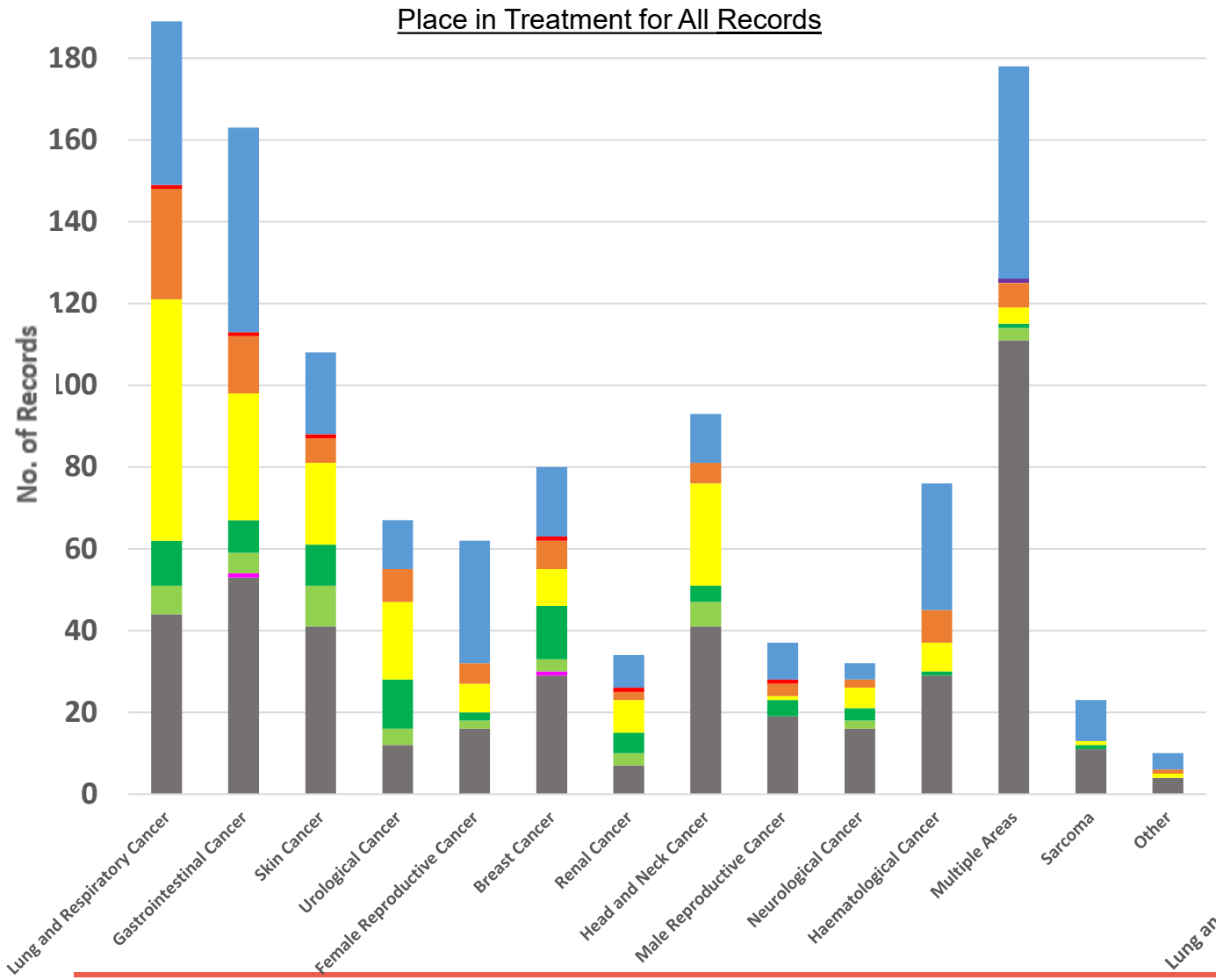
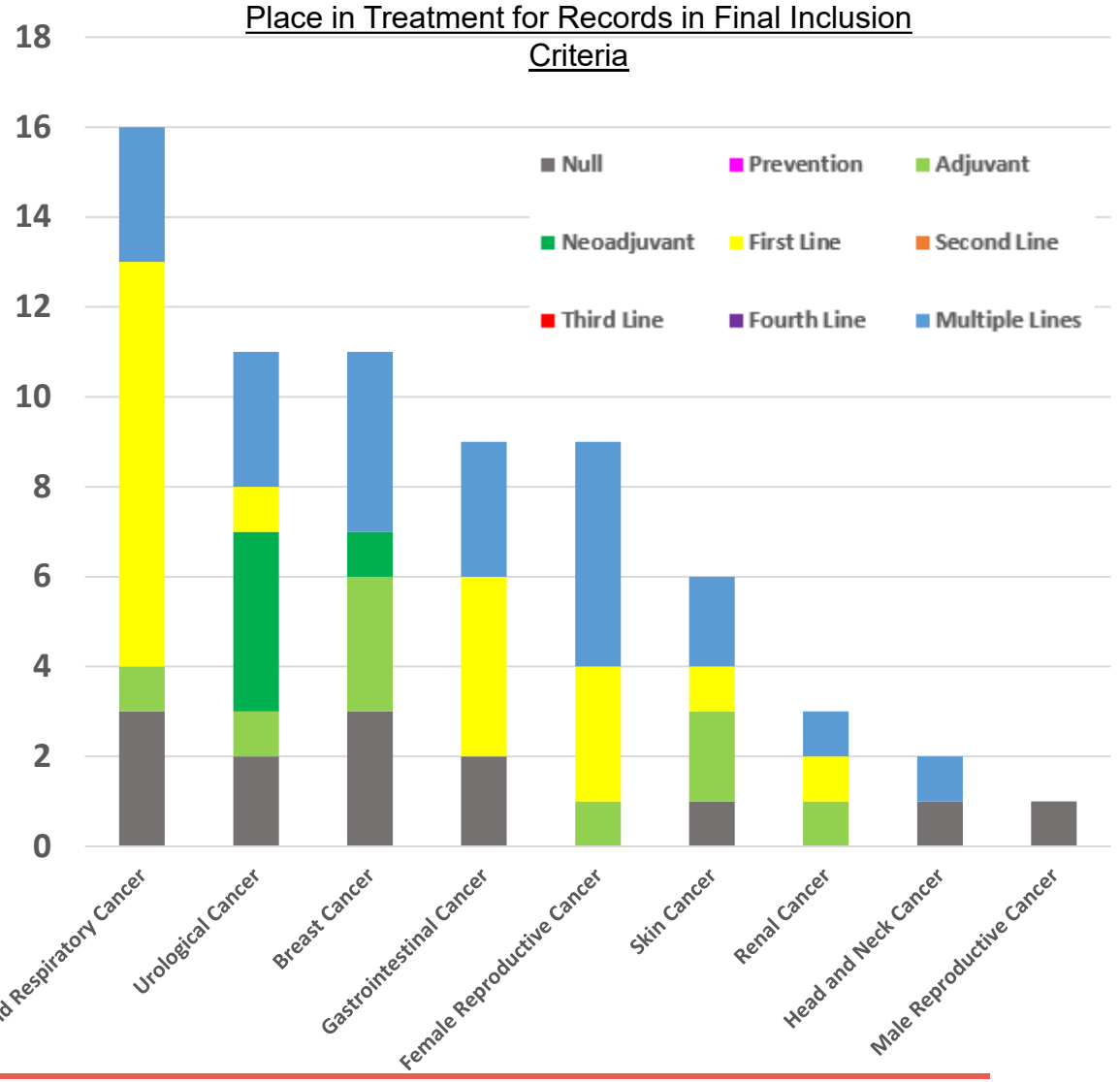
Place in Treatment by Therapy Areas of Immuno-Oncology Products





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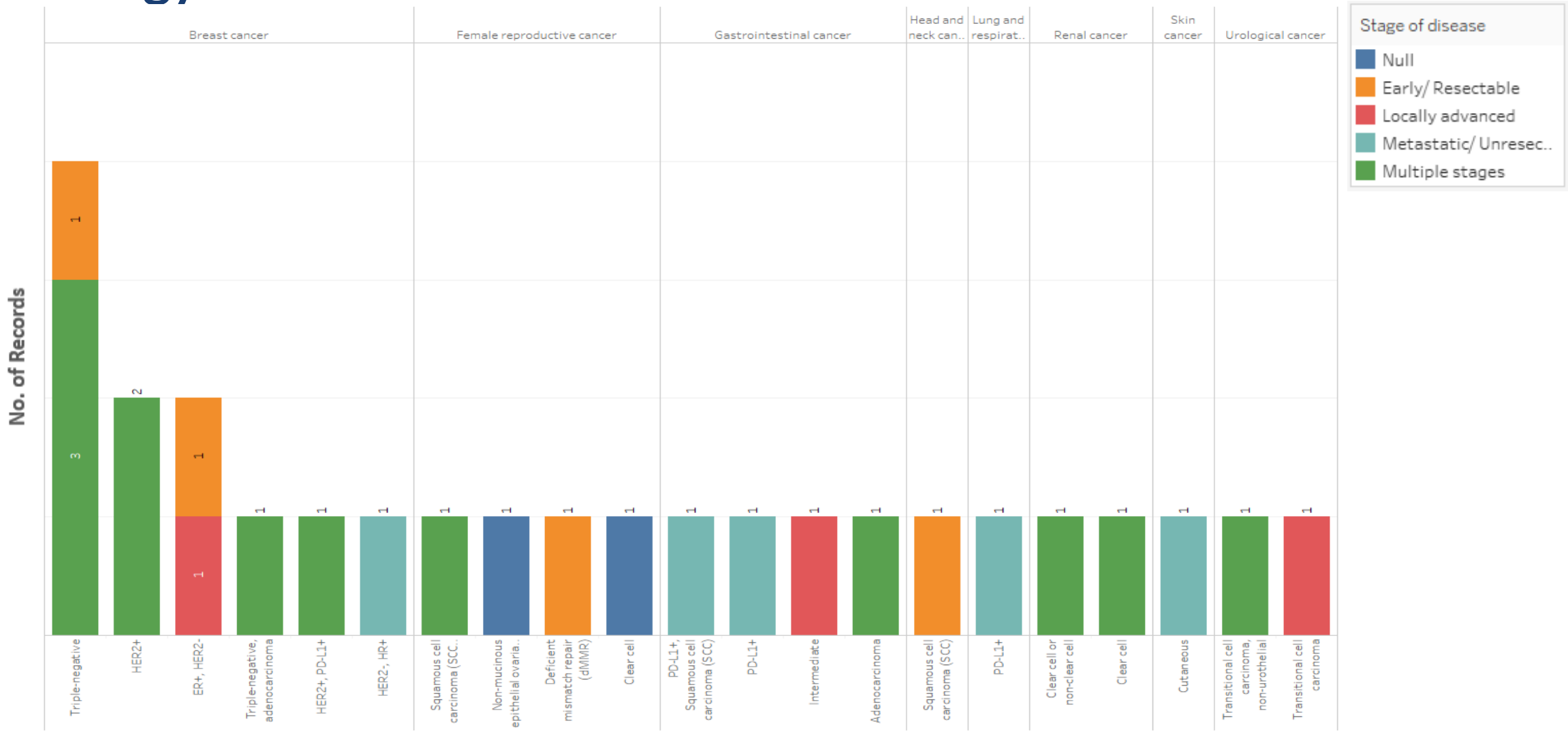
Subgroups and Stage of Disease by Therapy Areas of Immuno-Oncology Products



*Excluding null values where no subgroup/ mutation was specified

**Final inclusion criteria of Phase III and excluding 'other', 'finished', and records where the examined immuno-oncology medicines weren't the primary treatment records applied

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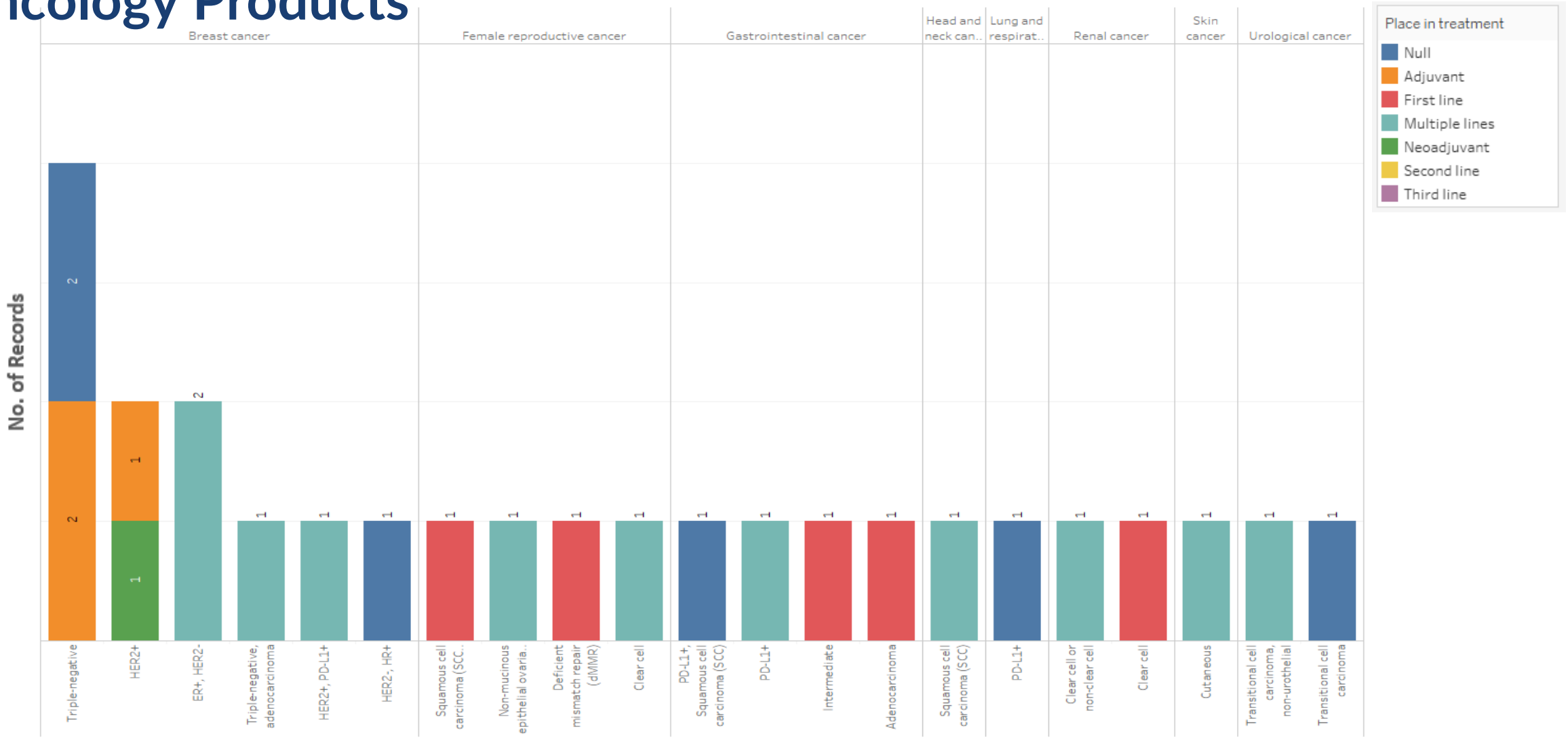
Subgroups and Place in Treatment by Therapy Areas of Immuno-Oncology Products



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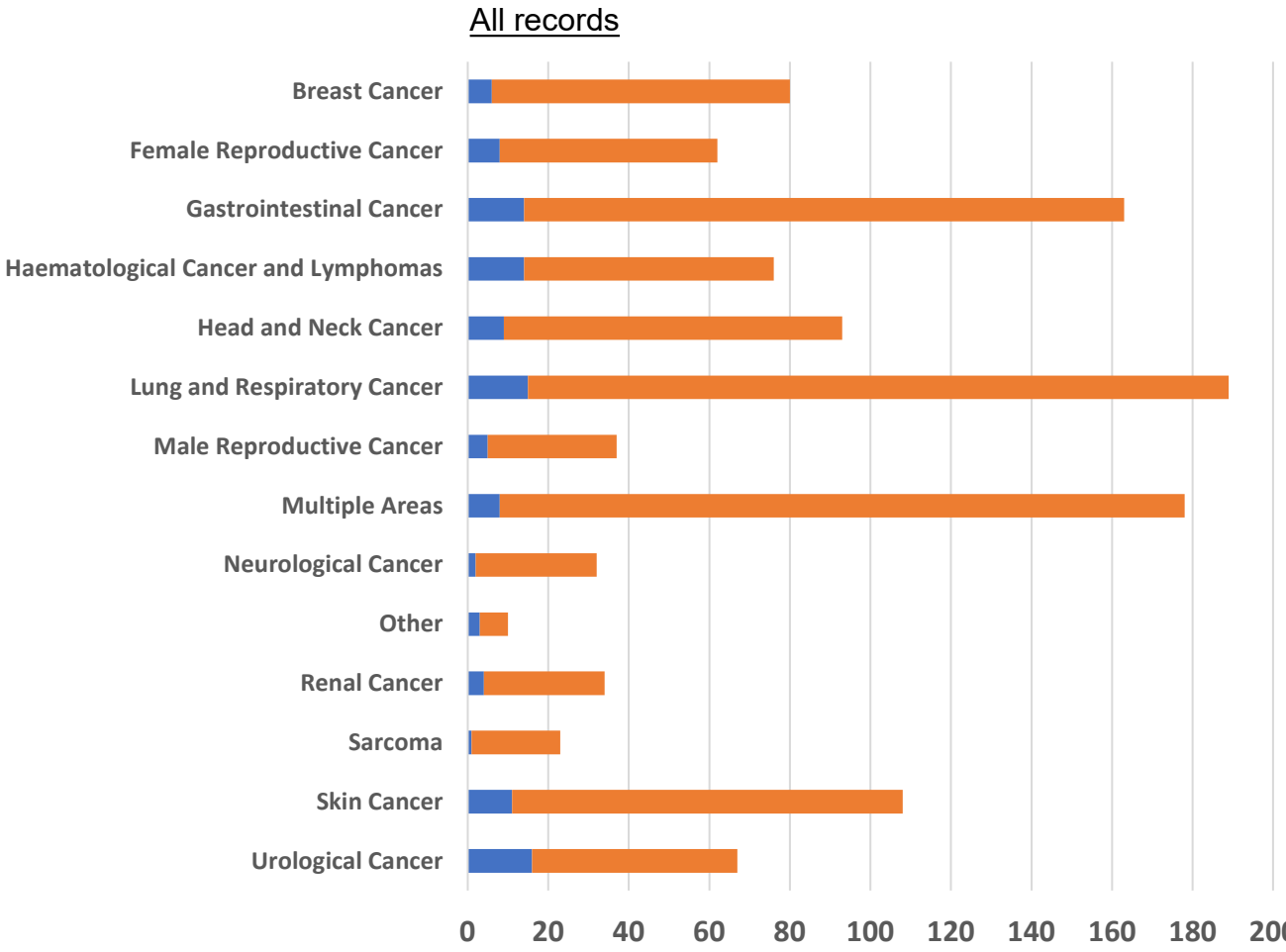
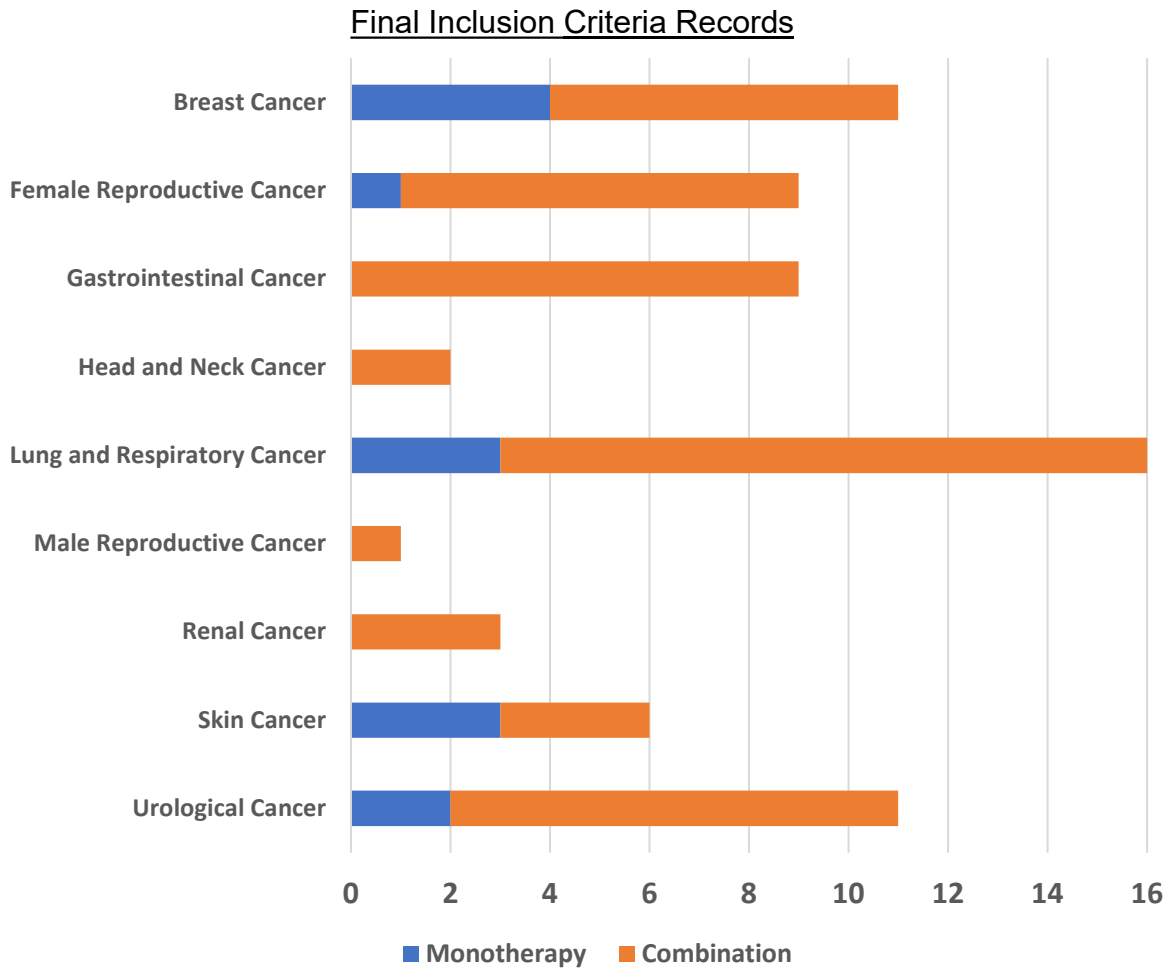
*Excluding null values where no subgroup/ mutation was specified

**Final inclusion criteria of Phase III and excluding 'other', 'finished', and records where the examined immuno-oncology medicines weren't the primary treatment records applied

Monotherapy vs Combination by Therapy Area

Combination therapies were more prevalent than monotherapies at any stage of development and in all therapeutic areas





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Summary

- The initial dataset contained 1,152 technology records associated with 1,225 clinical trials
  - Pembrolizumab had the highest number of technology records (496) followed by Nivolumab (435) and then Atezolizumab (221)
  - Lung and respiratory cancers was the most common therapy area being investigated followed by Multiple areas and Gastrointestinal cancers
  - Nearly 18% of the technology records (n=206) have estimated license date suggesting potential for UK/EU license and/or launch within 5 years
- The second iteration, which narrowed down phase III indications, showed that all therapy areas were not at the same level of clinical development.
  - Lung and respiratory cancers was the most common therapy area along with by Breast and Urological cancers
  - Phase II was the highest level of a few therapy areas such as Sarcomas and Neurological cancers which highlights a gap in clinical development

Limitations & Challenges

- Standardization of data fields due to heterogeneity from clinical trial registries
- Collating the most relevant data fields that would be most useful for future decision making
- Discerning which product was the primary treatment (or comparator) and company responsible for each trial when companies were collaborating (i.e. not the primary sponsor)
- For records associated with multiple trials, decisions on which trials to include and/or prioritize e.g., most advanced phase vs terminated/withdrawn status

Recommendations: Ongoing and future work

- This dataset provides an initial 'spine' of data to NHSE/AAC - further stakeholder (e.g. clinical, commercial) and enrichment activities of the dataset will further enhance the findings
- Further analysis could be done to better understand which technologies are now licensed and approved in the UK and which are still in the development pipeline
- Ongoing work with NHSE Commercial Medicines Analytical Team and oncology clinicians to translate data into actionable intelligence by:
    - Reorganising the dataset into specialist indications/therapy areas to support specialist oncology teams in the NHS
    - Preparing further analysis and insight to support NHSE/I Commercial Team Advisory Board(s) in decision-making
    - Clinical development in paediatric cancers appears to be a gap which might require further discussions with pharmaceutical companies by the NHSE
- This dataset may support NICE with topic selection challenges for products with large number of indications
- As with all horizon scanning information - the data will require refreshing to keep up with the rapid pace of development in this field – timing of any refreshing should be targeted to coincide with major conferences (e.g. ASCO)

Acknowledgement

We would like to acknowledge and thank the following members of the project team

Name	Job title	Organisation	Role in IO project
Dapo Ogunbayo	Medicines Programme Lead	NIHR IO	Project Oversight
Sarah Khan	Research Associate	NIHR IO	Project Lead
Rhiannon Potter	Research Assistant	NIHR IO	Horizon scanner / Researcher
Oshin Sharma	Analyst	NIHR IO	Data Support
Alex Inskip	Information Specialist	NIHR IO	Information/data support
John Spoors	Head of Commercial Medicines Policy Analysis	NHSE	Working Group
Nisha Rajendran	Senior Analytical Lead | Epidemiologist	NHSE	Working Group
Luke Wainwright	AAC Research Lead	NHSE/AAC	AAC Programme Support

We also appreciate the contribution made by Steve Williamson (NHS England Lead Cancer Pharmacist) and Cherry Chung (NHS England Policy and Project Manager).

Description of selected data fields (1/2)

Data field	Description	Additional notes/comments
NIHR-IO Status	Status of the topic on MInD: Indicative of the stage of regulatory development in the UK	- 'Active' = currently in NICE topic selection process, i.e. has MA/MAA within the next three years - 'Monitoring' = still in clinical trials - 'Finished' = Completed the NICE TS process, i.e. has MA/MAA and/or could have been approved already - 'Other' = Development was discontinued, or company advised to close record
NICE TSID	NICE Topic Selection ID: The topic has been notified to NICE via a filtration form and/or a Technology Briefing.	The topic submission process for NICE changed in November 2021, so this field will not apply to some records
UKPS ID	UKPS is a database of information on new medicines, indications and formulations in the pharmaceutical pipeline where pharma companies provide date on a confidential and secure platform accessible only to key UK-wide users	UK PharmaScan ID is used as proxy to indicate UK readiness by company
Intervention(s)	List of interventions associated with the technology record	Majority of the records were for Pembrolizumab, Nivolumab and Atezolizumab in combination with other therapeutics interventions

*MA=Marketing Authorisation, MAA= Marketing Authorisation application

Description of selected data fields (2/2)

Data field	Description	Additional notes/comments
Primary treatment?	Whether or not the immuno-oncology product is the primary treatment being tested in the clinical trial	
Potential HIT	Potential Histology Independent Therapy (HIT)	These have been classed as Tumour Agnostic Therapies (TATs) on IO's MInD
Trial Status	Status as record on trial protocol on the registry	
Highest Phase	The highest phase of topics with multiple trials	
Regulatory status	Technology records checked for the current status of regulatory development (in development, EU licence, others)	Actual dates are not included due to CIC information
Regulatory Awards	Proxy to indicate innovation and/or accelerated regulatory development	- UK (MHRA) – PIM/EAMs, ILAP - EU (EMA): Orphan, accelerated assessment, PriMe, - US (FDA): Orphan, Fast track, priority review, breakthrough therapy, Project Orbis
Sponsor	Whether the trial is sponsored by a pharmaceutical company or it is an Investigator Initiated Trial (IIT)	

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- The views expressed are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care