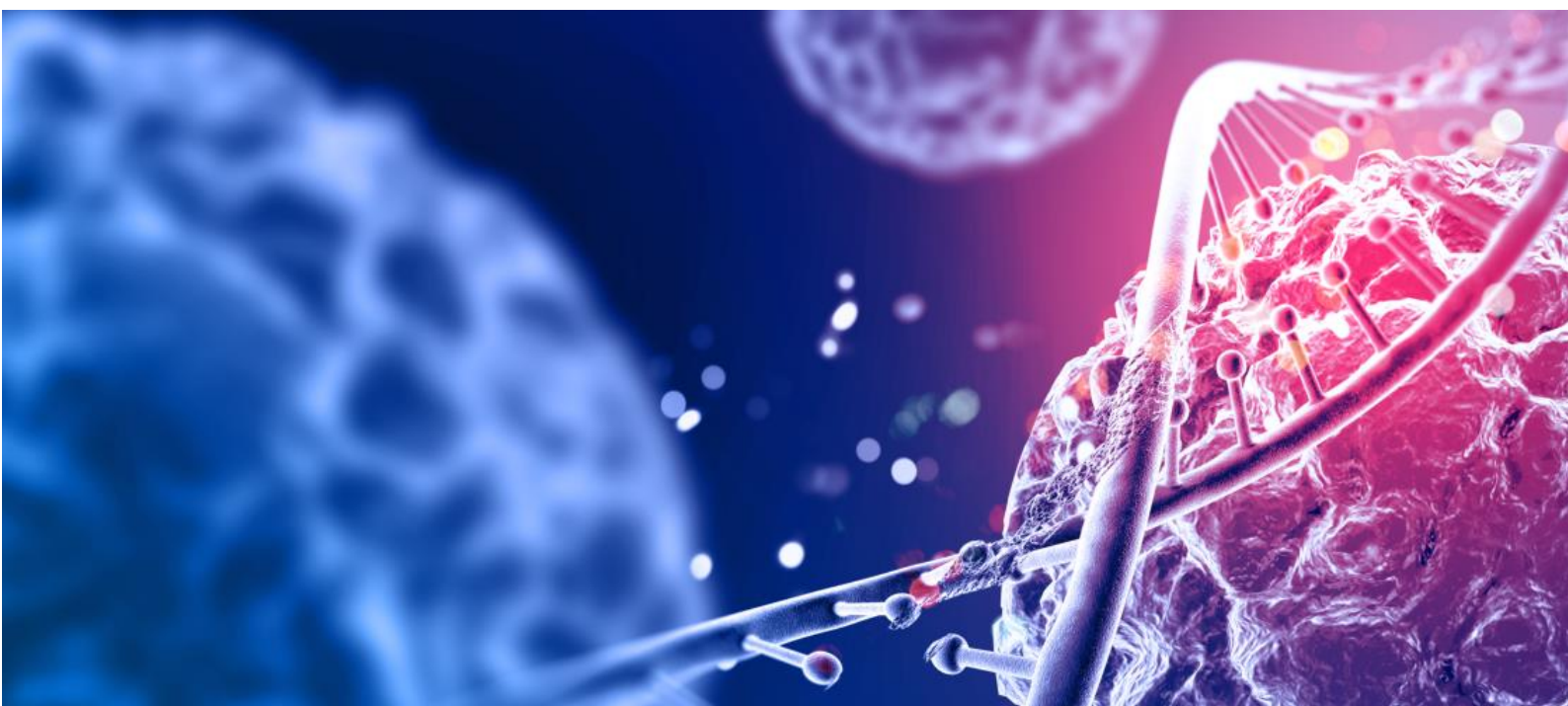


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ONCOLOGY FORECASTING



Biomarker-targeted therapy – Forecasting for pan-disease targets

Development of immunotherapy drugs have long been associated with broad use outside of the main label indications.

In a therapy area plagued with jargon and complex dynamics, most analysts when faced with one oncology forecast can find it quite daunting but forecasting across multiple indications can seem like an impossible task.

Let's break the problem down into bite sized chunks that we can digest more easily...

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Biomarker-targeted therapy – forecasting for pan-disease targets

Development of immunotherapy drugs have long been associated with broad use outside of the main label indications, since many autoimmune conditions shared common disease pathways and mechanisms through which drugs such as Humira (adalimumab) and MabThera (rituximab) worked. This deeper understanding of disease pathways and better identification of what made patients more or less likely to respond to a treatment started to change the way in which drug discovery and development was approached. It introduced the idea that there might be pan-disease targets for certain drugs, and that these drugs could be used to treat a range of conditions that were previously thought of as separate diseases, but which shared a common mechanism of dysfunction.

Better identification and segmentation of tumours has been leading us down the path of truly targeted agents that treat a specifically expressed marker regardless of tumour location for some years. The very first drug of this type was Roche's Avastin (bevacizumab), a VEGF inhibitor which experienced a lengthy drug development cycle as additional tumour indications (by location) were added to the label over the course of many years. Additionally, Herceptin (trastuzumab - a HER2+ targeted treatment) also gained a licence for treatment of gastric tumours that were also HER2+. More recently, Keytruda and Opdivo (pembrolizumab and nivolumab) have been steadily expanding their use base across different tumour locations but are not yet fully 'pan-tumour'. With the advancement of imaging and diagnostic techniques and companion diagnostics, diseases are becoming clearer, we have more data than ever before. Disease are being redefined at the molecular level, which is great for targeted therapies and should mean the most appropriate treatment being prescribed for the patients that will benefit the most from it.

In fact, viewing tumours by location is a very hierarchical, taxonomic way to look at the problem, which from a treatment perspective (with the exception of surgery) no longer makes much sense. At some point in the future we will most likely see a shift away from the traditional ICD-10 classification of cancers by location and perhaps to one that defines the cancer according to the expression of specific biomarkers, mutations or histopathology.

Meanwhile, the first ever tumour-agnostic drug (Bayer's Vitrekvi - larotrectinib) was launched in late 2019. This could be seen to hail the dawn of a new era of oncology treatment and drug development.

It is an increasing trend which is gaining acceptance but which at the same time brings a host of challenges within the current drug development and valuation frameworks.

Firstly, clinical development of these assets and defining the data required for regulatory submission and approval is a challenge – how do you prove efficacy against a specific target which can occur in multiple tumour sites in an environment which is used to seeing data for specific sites rather than against mutation targets? It is exceedingly costly to run phase III trials, but for some pan-tumour targets which can be found in 20+ tumour sites, this would effectively mean running 20 + trials to provide data in each site. How should the data be collected for regulatory bodies to show sufficient evidence across those cancers but with an acceptable number of trials / R&D expenditure? Not to mention the current physician base that is treating these cancers – it's no longer going to be just breast cancer specialists, urologists or skin cancer specialists, but any and all physicians that treat patients with cancer that would need to be targeted in order to gain market adoption.

Secondly, valuing these assets also becomes a challenge since now the asset is viable in many tumour sites, each with their own individual standard of care, patient outcomes, treatment algorithms and price comparators. It is often difficult enough to produce a forecast valuation for one asset in one or two indications, let alone one asset whose valuation needs to be built up from 20+ forecasts for example. In oncology, this is not an insignificant amount of work, data or market understanding to pull together.

Clinical development and regulatory issues aside, we are going to focus on how the commercial valuation of these assets can be done, what should be considered and included within a forecast, where the areas of risk may reside and how a true pan-tumour or tumour agnostic forecast could be achieved in a practical way when markets across different tumour types are so fundamentally different and complex.



Recap of fundamental drivers of oncology forecasts

We previously wrote a whitepaper on forecasting in oncology markets with greater accuracy and robustness, let's remind ourselves of some of the essential components of a predictive oncology forecast model:

- Eligible patient population
 - Stage of patients at diagnosis & relapse / progression patterns
 - Staging classification that should be applied (if different from AJCC)
 - Histopathology (if relevant)
 - Age and co morbidity status
 - Other exclusion or inclusion criteria (e.g. symptoms, fitness for treatment, tumour size & position etc)
- Prevalence / frequency of specific / relevant biomarkers
- Treatment algorithm (aligned with staging and relevant risk factors / prognosis)
- Line of therapy / therapy setting
- Duration of therapy
- Current standard of care

Challenges for pan-tumour / pan disease forecasts and valuations

There is sufficient complexity in any single oncology forecast, but we need to align many forecasts across many disparate and seemingly divergent markets in order to be able to forecast for a pan-tumour target. Within oncology, this process is somewhat more straightforward as diseases can be forecast in similar architectures, allowing physician management standards and algorithms to redirect patients as needed through the treatment cascade. More issues will be felt where the disease management is not so aligned (e.g. in autoimmune markets).

Time

Models for these types of assets are large (often an aggregation of individual market forecasts) and require significant time and detailed understanding of the market, future dynamics, current treatment patterns etc, etc. They take time to build and sanity check. For example, for a product implicated in 20 tumour types, this may take 10x as much time to forecast to the same level of detail as a product implicated in only 2.

Data

These types of valuations are also often data-heavy – we need 10x as much information for 20 tumour types as we did for 2. For pan-tumour forecasts, while a lot of data may be relatively easily available (especially for larger, more studied tumour), there may not be so much information available for some of the smaller, niche cancers.

Cost

And of course, with many times the workload and data requirement, these forecasts are likely to cost more. This can be a challenge especially if the asset is preclinical or currently seeking investment (a forecast is generally required ahead of an investment decision).

Simplicity

The biggest challenge will be to keep the forecast simple and usable. If it is simply an aggregation of 20+ market models, managing the simple act of changing a market share becomes 20x more involved as it has to be done in each one of 20+ models.



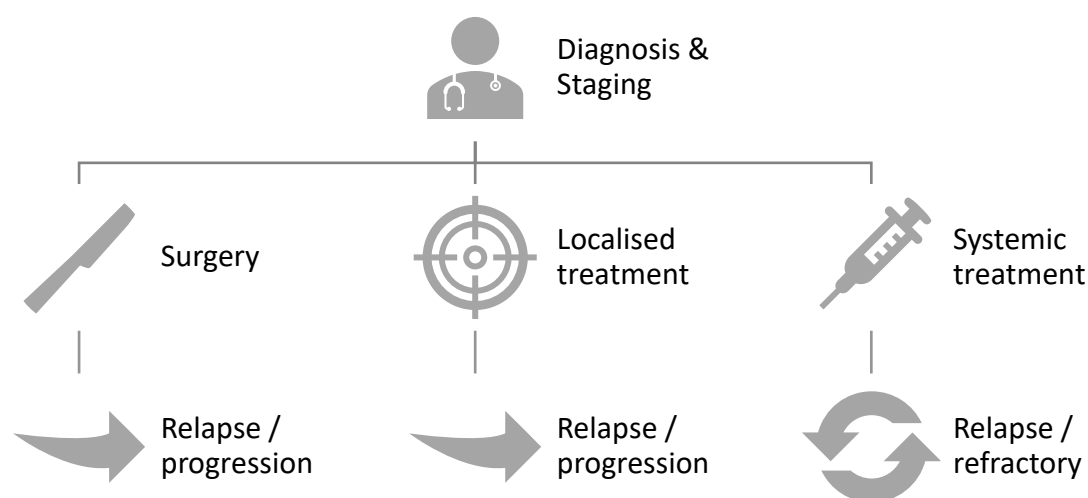
Solving the complexity

Here's how we do it in oncology.

Focus on the core fundamentals that are the **SAME** across any indication as follows:

Patients – incidence, staging, relapse and progression

In any oncology market, patients are all determined as incident patients (newly diagnosed in any year time frame). These patients are staged (often using AJCC criteria) and this staging, along with other relevant metrics, drives an initial treatment decision. While individual staging schemas may differ between tumours, patients will often follow this basic triage for initial treatment:



Different cancers have different progression algorithms, but broadly can be aligned to a similar flow with similar components adding extra steps where needed (e.g. maintenance or remission settings, additional lines of therapy, adjuvant, neoadjuvant or other treatment options into the flow where needed and relevant).

Once patients can be aggregated at the 'systemic treatment' pool, we can draw these patients through to a forecast model.

Treatment dynamics within oncology, especially in the systemic setting

In all oncology markets, patients are placed on a treatment / regimen (combination of products) and treated with that regimen for a certain amount of time depending on the cancer setting (this may be a defined number of cycles or treatment to progression). The important point to note is that patients are on that treatment until it finishes, they tend not to be switched out before they have completed the course or as long as they are still responding.

While each tumour type is likely to have its own treatment duration and specifics, the mechanisms of the forecast model can be the same, but with different duration assumptions for different tumour locations (e.g. breast cancer may have a long treatment duration than kidney cancer for example).

Once a patient has discontinued on a treatment, they enter a decision point where they can be moved to the next stage or removed from the treatment flow. Again, this will be the same for any tumour – where the patient goes next may differ, but the decision will remain.

Patients can then flow to the next treatment setting (or remission if relevant) and remain there for a specified duration of time.

Eventually, all patients will exit treatment, but the model structure will be similar across any and all tumours.

Of course, this all sounds very simple, but there is still a lot of work that needs to be done and a lot of data and assumptions that need to be collated even just to get to the initial patient number eligible for starting treatment. And with often 20+ tumours to consider, it would be easy to

overlook something fundamental in the forecast – there just isn't the time to scrutinise in the same level of detail the data and assumptions for 20+ forecasts as there would be if an asset were only covering say 2 forecasts.

Deciding on product assumptions

This is also a significant amount of information to generate in order to forecast the asset. Regardless of getting the market size, structure and flow accurate and reflective, we now need to specify the assumptions for our asset including:

1. Treatment setting – first line or relapse /refractory? Is it to be used following or in conjunction with another therapy/product? Is it a maintenance product?
2. How long will the product be used for? Is this treatment to progression, defined cycles or both? Does this vary by cancer location or treatment setting?
3. Will all patients respond in the same way across all tumour locations? i.e. are all patients with this biomarker / mutation likely to respond in the same way and for the same duration of time or will this vary depending on tumour location?
4. Are there current or future competing technologies / drug classes that could disrupt or take our market? Are these different by tumour location?
5. How will our product be adopted to the market?
 - a. What's the current standard of care and unmet need within the market? Does this vary by tumour location?
 - b. How will this affect the uptake of our product? Will this vary by tumour location? (e.g. if other products are already in market and physicians are happy with how to use / patient outcomes etc, how likely will they be to use this new, unknown product?)
6. How should the product be priced? What should it be priced against? If based on value-based methods, which tumour should be selected and could this price limit uptake in other cancer locations?

We may need different assumptions for each and every tumour, treatment setting or country which is not a small amount of information to gather and input to a forecast model.

Aligning the product against a % improvement over the “current standard of care” (whatever that may be in each tumour setting) may assist with some parameters (such as duration of treatment).

Summary of the considerations for the forecast

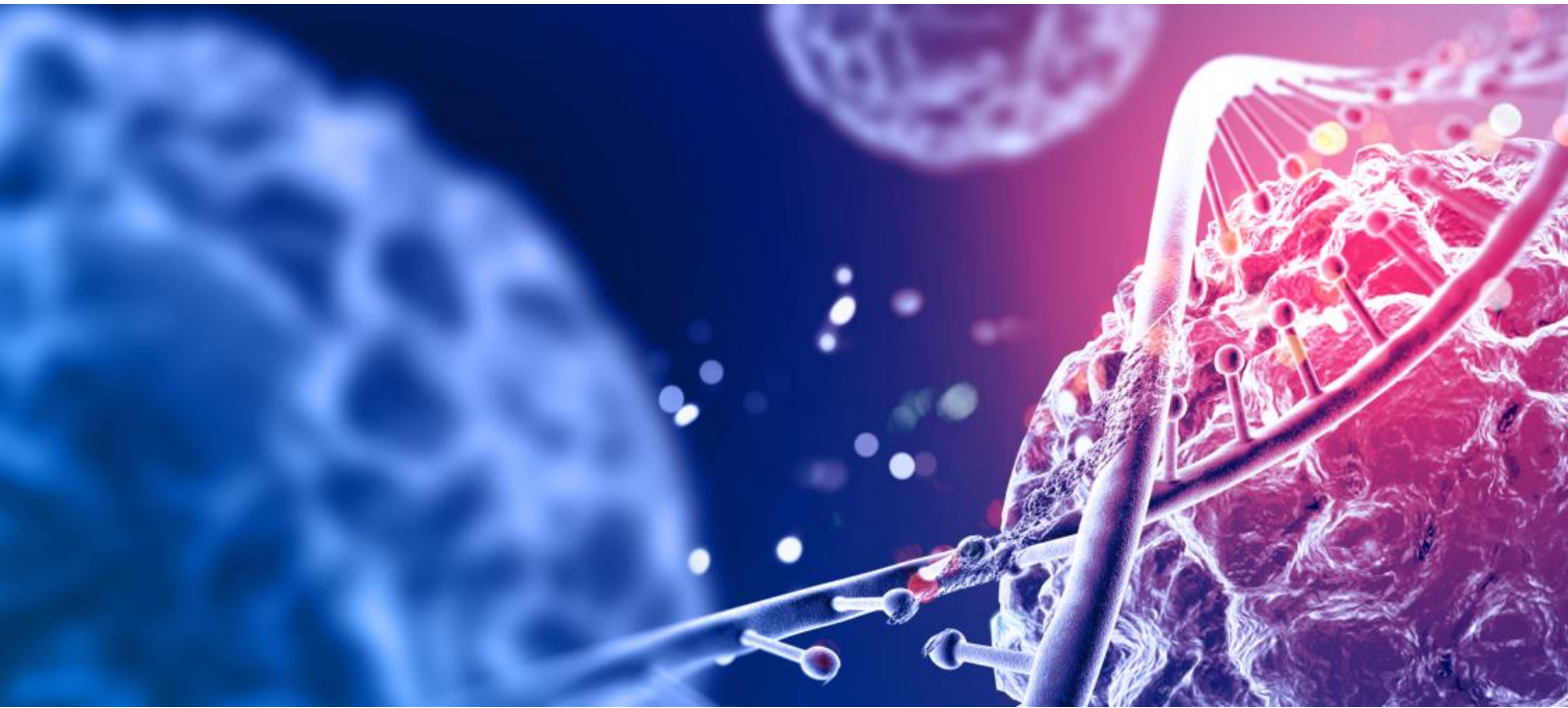
1. Identification of the mutation / biomarker of interest & definition of the tumours that are associated with that mutation / biomarker.
2. Identification of the relevant / eligible patient populations within those tumours
3. Current progress / physician management of the patient populations – this is likely to vary by disease and even by segment within that disease – where are these patients currently distributed and how are they currently treated? What are the alternative treatment options?
4. Where does this new agent fit in with the algorithm? What will be the comparative standard of care? Does this vary by disease?
5. What drivers and events are likely to impact the access to your patient population in each of the identified disease areas? Are these different?

6. Setting aside clinical trials which are likely to need their own set of considerations, what is the target product profile likely to be? How attractive is this asset going to be as a therapeutic option for this patient group?
7. Duration of therapy – how long are patients likely to be on therapy for? Will this vary by disease? What will drive this?
8. Dosing – how will the product be dosed across the different diseases? Is it likely to be the same or need to be different? Could dosing be site specific? (e.g. Avastin for wet AMD, same target, different site)
9. Price – how will this be set to optimise return on investment? Is the price going to have to be flat across the diseases? Could it end up being cost prohibitive if price was based on the smallest target population or the smallest clinical dose? (e.g. if Avastin & Lucentis had been launched in reverse – even though they are different products targeting the same process, their dosing and pricing is completely different)



Forecasts for tumour-agnostic products will undoubtedly involve much legwork to understand and model out individual diseases where potential target patients reside, there are no shortcuts! But determining how patients are likely to respond to therapy and aligning on core market drivers and variables will allow seemingly disparate tumour forecasts to be aggregated to one cohesive model and set of outputs so that investment decisions can be made in the most informed way to bring such assets to market.

If you would like any more information on pan-tumour forecasting or how we may be able to help forecast your asset, please do not hesitate to get in touch with a member of the team.



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