Rare cancers: A growing focus of early-stage clinical trials

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The proportion of early-stage drug trials tackling the biggest cancer killers has declined sharply since the early 1990s as less common tumour types receive increasing attention, according to new research to be presented during the International Congress on Targeted Anticancer Therapies (TAT) 2019, taking place from today to 27 February in Paris, France. The analysis highlights the changing treatment landscape, with doctors and pharmaceutical companies evaluating an expanding range of molecularly-targeted anticancer drugs and immunotherapy.

"Our study clearly shows the common cancer types are decreasing as a proportion of the patients in phase 1 studies and the uncommon types are increasing," said Dr. Jun Sato of the National Cancer Center Hospital, Japan, lead author of the latest research.

"The development of new treatment options means there are now multiple approaches to address an increasingly broad spectrum of different types of cancer."

Sato and his colleagues pooled results from 866 oncology phase 1 trials conducted worldwide for their analysis. These trials, published between 1991 and 2015, involved more than 29,000 patients enrolled to test novel medicines in the first stage of clinical testing.

They found that the proportion of phase 1 trials in which patients with either colorectal or lung cancer accounted for at least half of the enrolled group declined markedly over time, from 46.3% in 1991-95 to just

16.7% in 2011-15. The trend was consistent across North America, Europe and Asia.

Importantly, the absolute number of trials involving a majority of colorectal or lung cancer patients still rose over the period, from 31 to 41, but this was far less than the increase in trials focused on rarer cancer types.

Lung and colorectal cancer are the most common causes of cancer death globally, accounting for 2.6 million of an estimated 9.6 million cancer deaths in 2018, according to the World Health Organization.

The 1991-2015 timespan chosen for the analysis coincides with a revolution in cancer therapy, driven by the development of molecularly-targeted anticancer drugs and application of comprehensive molecular profiling techniques for patient selection in clinical trials. Initially, from 1990s to early 2000s, scientists used these advances to investigate large cancer populations with frequent genomic mutations, but over time, the focus of genomic-driven clinical trials has shifted to less common mutations and rarer tumour types.

"There has been a natural evolution to infrequent tumour types, such as biliary tract cancers, due to a better understanding of the genomic drivers and altered pathways in these malignancies. Besides, common cancers like lung adenocarcinomas are now classified into multiple rarer subtypes based on genomic markers," said Dr. Rodrigo Dienstmann of the Oncology Data Science unit at the Vall d'Hebron Institute of Oncology, Barcelona, Spain.

Still, the new study does not tell the full story, since it fails to fully reflect a second much more recent revolution in cancer medicine—the arrival of immunotherapy. Because the data analysed comes from trials published up to 2015, when immuno-oncology was in its infancy, it does

not include the rapid growth in immunotherapy clinical trials over the last few years.

"This study won't have really captured the explosion in immunotherapy trials that we have seen," Dienstmann said.

Lung cancer is one notable field where new immunotherapy treatments like PD-(L)1 targeting checkpoint inhibitors have proven particularly promising. As a result, Dienstmann believes there has been a bounce back in the proportion of phase 1 trials addressing lung tumours since 2015.

Overall, the clinical trial landscape is increasingly biased towards immunotherapy, with more than 2,200 trials now evaluating PD-(L)1 inhibitors, according to the U.S.-based Cancer Research Institute.

Interestingly, both targeted therapies and immunotherapies have proven largely ineffective in colorectal cancer, except immune checkpoint inhibitors in microsatellite-unstable tumours.

"We get a lot of colorectal patients who have run through standard treatments and it is very difficult to put them into phase 1 trials because there are not many new options," said Dr. Markus Joerger, responsible for the phase 1 unit at the St Gallen Cancer Centre, Switzerland.

Despite such challenges, the latest analysis shows there is a vibrant field of clinical research into new approaches for tackling cancer, with the picture proving particularly positive for patients with rare tumour types that have typically received limited attention in the past.

"Across all cancer types, what we are seeing is more and more phase 1 trials, reflecting the latest waves of innovation," Joerger concluded.

More information: Abstract 30P "Dynamic change in the distribution of cancer types in oncology phase I trials" will be presented by Jun Sato during the Selected Posters session on Tuesday, 26 February 2019, 17:30-18:00. *Annals of Oncology*, Volume 30, 2019 Supplement 1. DOI: 10.1093/annonc/mdz025

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