Progress and challenges of confirmatory trials for cancer drugs granted conditional approval in China

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In 2020, China National Medical Products Administration (NMPA) established the conditional approval (CA) pathway, similar to accelerated approval of the US Food and Drug Administration (FDA), for serious life-threatening diseases for which no effective treatment exists after a multi-year pilot program.[1] This expedited pathway allows for accelerated approval based on early trial data or surrogate endpoints, with the developer required to submit confirmatory trials within a set timeframe to determine whether the drug will receive full approval or be withdrawn.

Recently, several studies have reported uncertainty in the use of surrogate endpoints and failure to complete confirmatory trials in a timely manner in the US FDA accelerated approval pathway, which ultimately affects the clinical benefit to patients.[2–4] These issues have raised public concern that similar problems may occur during the implementation of the CA pathway in China. A previous study reported a limited trial–level correlation between surrogate endpoints and overall survival (OS) for CA cancer indications.[1] Hence, this study further extends the progress and challenges for confirmatory trials of cancer drugs granted conditional approval in China between 2020 and 2024, with a view to supporting policy optimization for this program.

We identified all cancer indications granted CA in China from the implementation of this expedited pathway (August 1, 2020) to September 1, 2024, and their regulatory status (e.g., converted to full approval or ongoing). For each indication, the requirements and projected completion time of confirmatory trials were extracted from the China NMPA Conditional Approval Database.[5] The status of confirmatory trials and the timing of first patient enrollment was assessed based on information of confirmatory trial requirements similar to the previous study.[6,7] Similar to the previous study, changes in full approval indications compared to CA indications were categorized as same, earlier line of therapy, broadened but not earlier line, or others.[2] The detailed methodology is shown in eAppendix 1, Table S1, Table S2 and Figure S1.

China granted 81 CA drugs together with 94 paired cancer indications in 2020–2024 (Figure S2). As described in Table S3, most pre-approval pivotal clinical trials were single-arm trial designs (76%) and had response rate as the primary efficacy endpoint. 49% of the CA indications were exclusive to China, while 51% were also approved by the US FDA. The highest number of conditional approval cancer indications occurred in 2021 (n = 29), declining to 13 by 2024 (Table S3 and Figure S3). The median projected time to complete a confirmatory trial was 4.0 years (IQR, 4.0–5.0), which was negatively correlated with time to CA date (Figure S4 and Figure S5). There was no significant difference between domestic and imported CA cancer indications in approvals per year, cancer sites, drug categories, indication types, or confirmatory trial timelines, but primary efficacy endpoints differed significantly in pivotal trials ($P = 0.004$; Table S5).

Of the 94 CA cancer indications, 18 (19%) were converted to full approval, 63 (67%) were in ongoing status, 11 (11%) had submitted supplemental applications, one (1%) was withdrawn and one (1%) was in other status (Table S3). Among the CA indications that were converted to full approval, 78% of these included OS evidence or QOL evidence while OS data of six CA indications were immature (Table S4). Furthermore, 9 (50%) CA indications showed significant improvement in OS or QOL, whereas the other 4 CA indications met the prespecified criteria for the primary efficacy endpoint but did not show significant improvement in OS (immaturity) or QOL (Table S4). For the 18 CA indications granted full approval, ten were in the same indications, seven were in earlier line of therapy and one was broadened but not earlier line when compared to CA indications (Table S4, Table S6 and Table S7). Four CA indications of the confirmatory trials were terminated or withdrawn (Table S8 and Table S9). For the three

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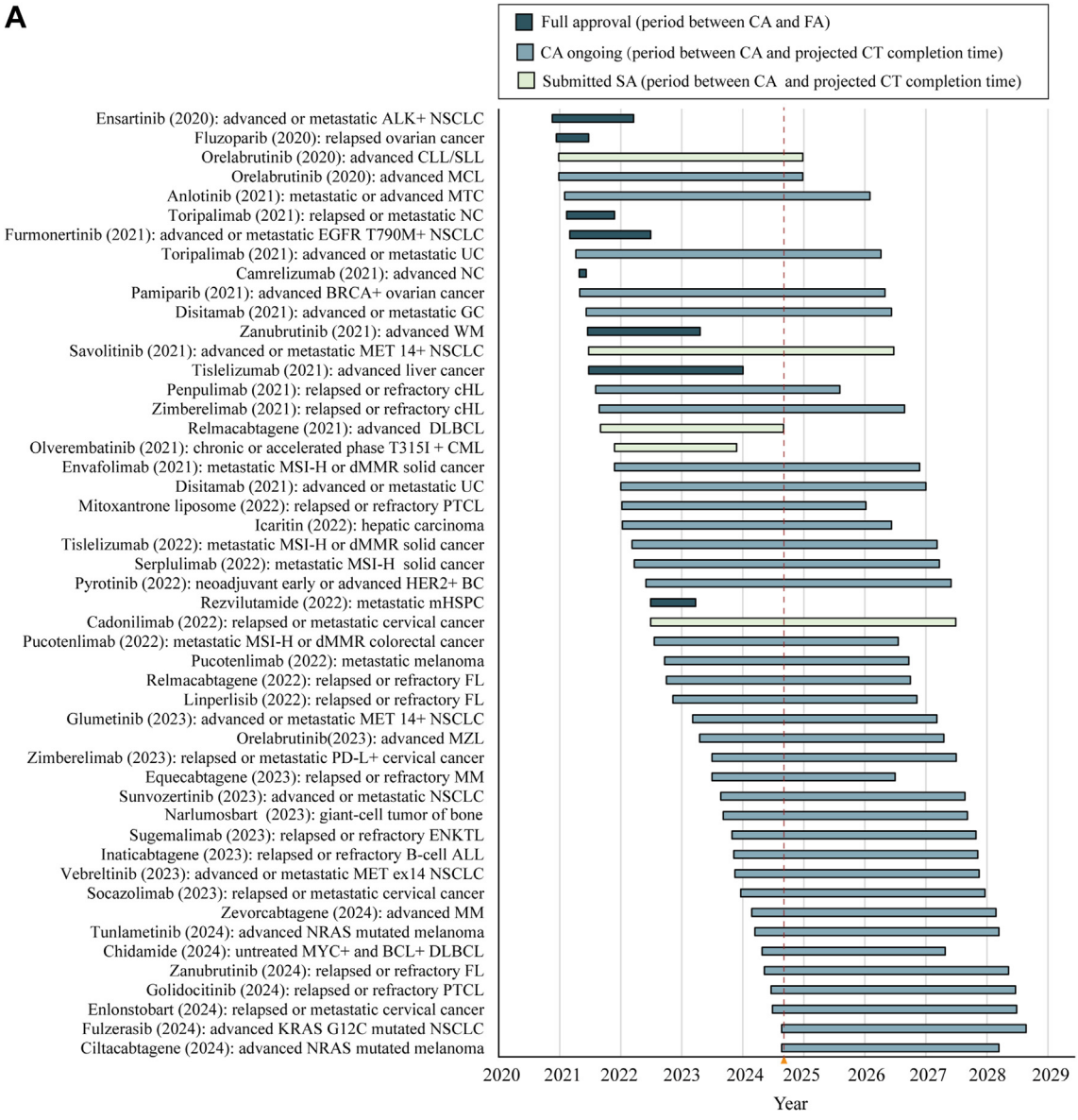

Fig. 1: **Regulatory status of conditional approval for cancer indications in China (n = 94). (A) Cancer indications developed by the domestic MAH (n = 49). (B) Cancer indications developed by the imported MAH (n = 45).** The yellow dotted lines indicate a cut-off date of September 1, 2024. CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; MTC, medullary thyroid carcinoma; NC, nasopharynx cancer; NSCLC, non-small cell lung cancer; UC, urothelium carcinoma; GC, gastric cancer; cHL, Classic Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; CML, chronic myelogenous leukemia; MSI-H, microsatellite instability high; dMMR, deficient mismatch repair; PTCL, peripheral T cell lymphoma; BC, breast cancer; FL, follicular lymphoma; MZL, marginal zone lymphoma; ENKTL, extranodal NK/T-cell lympho; MM, multiple myeloma; ALL, acute lymphocytic leukemia; HNSCC, head and neck squamous cell carcinoma; AML, acute myelocytic leukemia; NM-CRPC, nonmetastatic castration-resistant prostate cancer; CRC, colorectal cancer; TNBC, triple negative breast cancer; mHSPC, metastatic hormone sensitive prostate cancer; WM, waldenstrom macroglobulinemia; TC, thyroid cancer; MAH, marketing authorization holder; PC, prostate cancer; CT, confirmatory trials; CA, conditional approval; FA, full approval; SA, supplement application.

terminations of confirmatory trials, two were due to failure to meet the prespecified primary efficacy endpoints, and one was terminated by the sponsor (Table S9). For the withdrawal, it was attributed to logistical challenges encountered during the clinical trial. In addition, the confirmatory trials for five CA indications did not initiate patient recruitment with a median time of 2.4 years since CA date (range: 1.6–3.1) (Table S8).

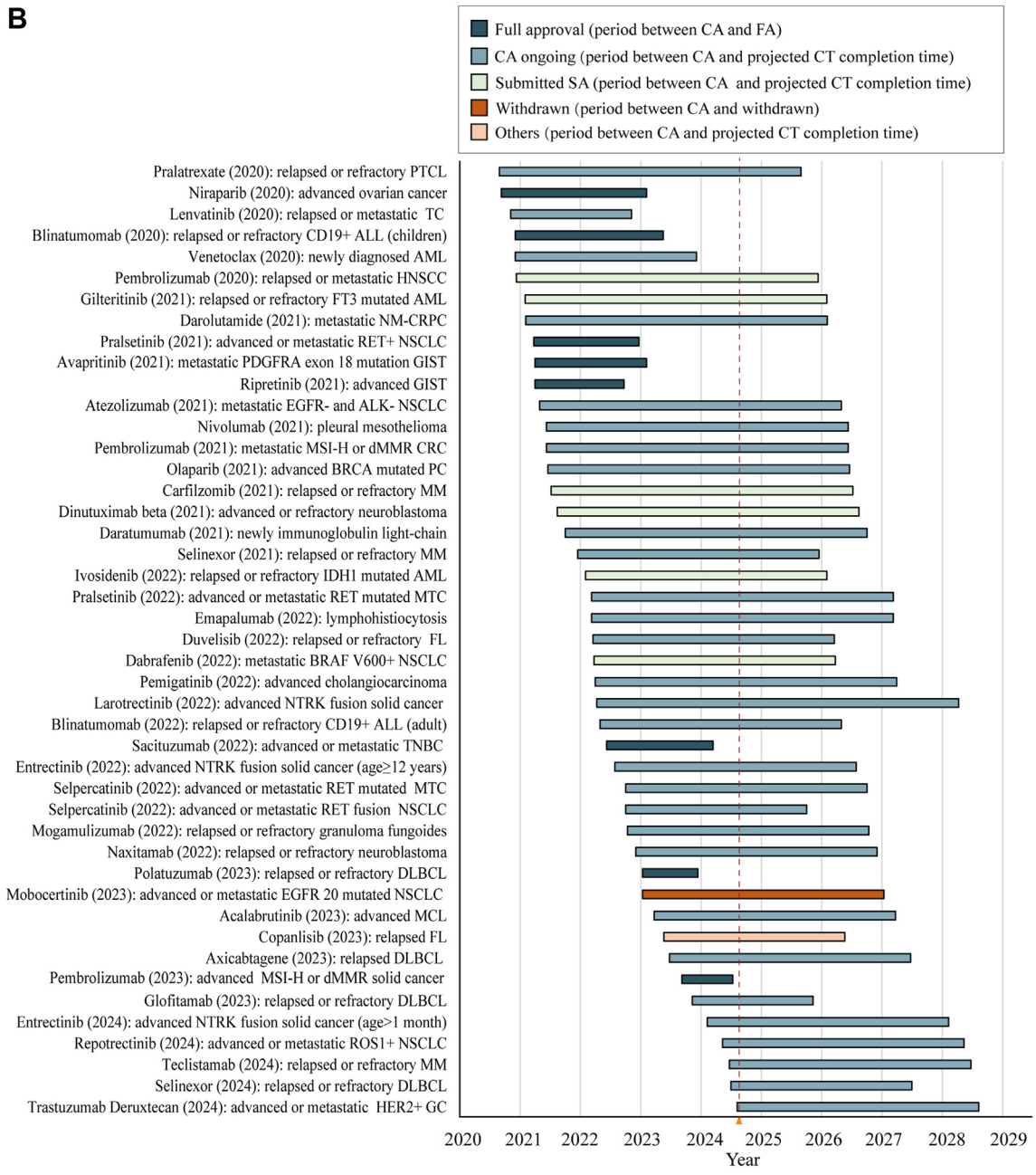

Fig. 1: Continued.

Most confirmatory trials for CA indications were completed or projected within the targeted timeframe (Fig. 1 and Table S7). For the 18 cancer indications that converted from conditional approval to full approval, the median time was 1.4 years (IQR, 0.9–1.9). Notably, the conversion time for domestic indications was shorter than for imported ones (1.1 vs. 1.8 years; $P = 0.101$; Table S4), although this difference was not statistically significant. The results of the univariate analysis revealed no factors affecting the time to conversion to full approval (Figure S6). It was observed that all these CA indications converted to the full approval had their first patient enrollment for confirmatory trials completed prior to the CA date (Table S7). For the 76 cancer indications that did not convert to full approval, patient enrollment in confirmatory trials occurred before the CA date for 19 indications, after the approval date for 34 indications, and the timing for the remaining

indications was uncertain due to a lack of publicly available information (Table S8).

Usually, OS and QOL are considered to be the most significant indicators for evaluating the therapeutic benefit of cancer drugs. Our findings suggested that half of the CA indications showed improvement in OS or QOL, a percentage that appears to be higher than the FDA's accelerated approval of the cancer indications.[2] Previous studies have shown a relatively poor correlation between surrogate endpoints and OS, making it particularly important to include evidence of OS or QOL in confirmatory trials.[1,8–11] It should admit that the OS evidence for some CA indications was immature at the time of conversion to full approval, which may complicate the interpretation of clinical benefit for the cancer drugs.[12] Therefore, it is suggested that timely updating of the label with final OS evidence will help clinicians and patients in their decision-making.

The conversion time for CA indications to full approval in China appeared to be shorter than the time from accelerated approval to full approval in the US (median: 1.4 vs 3.4 years).[13] The previous study reported that confirmatory trials initiated prior to the accelerated approval date in the US have been shown to facilitate faster completion of confirmatory trials, thereby reducing patient exposure to the drugs with uncertain clinical benefits.[4,14] This study found that the confirmatory trials for 34 CA indications enrolled their first patient after the time of CA, suggesting that these CA indications may require a longer period of time to complete a confirmatory trial. In addition, we identified a number of indications for which there had been terminations, withdrawals, or non-initiation of patient recruitment in confirmatory trials following the several months after granted of CA, which may potentially delay the completion of confirmatory trials. Therefore, dynamic regulation of confirmatory trials for these CA indications is warranted. On August 24, 2023, China NMPA issued a draft guidance for comment requiring that confirmatory trials should be the first patient enrolled at the time of CA, which is expected to shorten the duration of confirmatory trials.[15]

This study did not find a significant difference in the status of confirmatory trials and the time to conversion to full approval between domestic and imported CA cancer indications. The previous study showed a portion of the imported cancer indications granted the CA were due to the lack of trial data in the Chinese population.[1] Therefore, confirmatory trials for these CA cancer indications may be required to conduct bridging trials in the Chinese population. In this study, we found that three imported cancer indications were converted to full approval after conducting a bridging trial in the Chinese population, with a median time of 1.85 years (between CA date and full approval date). This implied that the implementation of the CA policy is of great significance and could benefit more patients in advance of time.

This study has some limitations. First, we determined the status of confirmatory trials for CA cancer indications mainly based on clinicaltrials.gov and chinadrugtrials.org. If the companies did not keep the status of the trial up to date on these websites, it might affect the assessment of the results. Secondly, immature OS was based on the latest NMPA labelling, review report, published article, or meeting abstract. However, it was possible that the final OS evidence of some indications was not published in the agency.

Overall, incorporating OS or QOL in confirmatory studies is crucial for reducing uncertainty around the clinical benefits for patients, especially since most cancer drugs are approved based on surrogate endpoints. Furthermore, regulation of cancer drugs that potentially delay the timing of completion of confirmatory trials, including confirmatory trials that are not initiated in a timely manner, terminated, or withdrawn, should be rigorously strengthened to ensure that patients avoid being exposed to drugs without proven clinical benefit.

Contributors

XXL contributed to study design, data interpretation, data analysis and drafted the manuscript. YX contributed to data analysis and data interpretation. XD contributed to study design, data collection, data analysis and data interpretation. XFL contributed to data collection, data analysis and data interpretation. SC contributed to data collection, data analysis and data interpretation. YY contributed to study design, data analysis and data interpretation. LH contributed to study design, data collection, data analysis and data interpretation. XHZ contributed to study design, data collection, data analysis and data interpretation. All authors were involved in each stage of the preparation and revision of the manuscript. XXL, XD and LH have accessed and verified the data. YY, LH and XHZ were responsible for the decision to submit the manuscript.

Data sharing statement

All the data used in this study are from publicly accessible databases.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101238.

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