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Current Perspective

Nested and adjacent subgroups in cancer clinical trials: When the best interests of companies and patients diverge

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Abstract The design of clinical trials with outcomes reported in cohorts including nested subgroups is common in novel agents seeking new indications for approval. This structure represents a tension between drug companies that have an incentive to pursue broad biomarker-agnostic approvals and patients whose best interest is to identify the subgroup(s) most likely to benefit from the drug. Programmed death ligand 1 (PD-L1) and checkpoint inhibitors are a prominent example with early trials reporting efficacy of checkpoint inhibitors in cohorts with high levels of PD-L1. Subsequent analyses incrementally report outcomes in broader patient cohorts that include the nested subgroup of high PD-L1 expression which drives the positive outcome in the entire cohort. Comparing aggregate outcomes between groups of patients with known heterogeneous outcomes deters the effective analysis of all available data. Exploring the optimal treatment for individual patients with different levels of PD-L1 expression, whether it is checkpoint inhibitors only, checkpoint inhibitors combined with chemotherapy or chemotherapy only, requires a granular approach to trial design and reporting. Such grouping of patients with different biomarker findings is increasingly seen in the setting of adjuvant therapy, as well as in targeted therapies that show efficacy in a single gene mutation which however are studied in the setting of panels of mutations. Here we discuss the difference between nested and adjacent subgroups in oncology.

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CheckMate 649 was heralded as a practice changing study in the field of gastrointestinal cancer at the 2020 European Society of Medical Oncology Congress. Indeed, it was a large randomised phase III trial investigating the addition of nivolumab to chemotherapy in advanced gastric and gastroesophageal junction cancer and reported improvement in overall survival (OS) when compared with chemotherapy. The median OS was reported in three groups based on programmed death ligand 1 (PD-L1) combined positive score (CPS). The respective groups are PD-L1 CPS $\geq$5, PD-L1 CPS $\geq$1 and all randomised patients. This design of clinical trials where outcomes are reported in nested subgroups for which outcomes are separately known is increasingly common in novel agents seeking new indications for approval. Here, we argue that this structure represents a tension that has not existed before where drug companies have an incentive to pursue broad biomarker-agnostic approvals while it is in the patient's best interest to identify the subgroup that would benefit most from treatment. We discuss subpopulations that drive response to treatments and the interface between patient interests and pharmaceutical company incentives (See Fig. 1).

1. PD-L1 is a continuous biomarker with positive correlation to response to checkpoint inhibitors

1.1. Adjacent subgroups may have inferior outcomes when separated from nested subgroups

KEYNOTE-048 [1], a clinical trial for recurrent or metastatic head and neck cancer, is an example of a nested subgroup with superior response. This trial includes subgroups of PD-L1 CPS of 20 or more and PD-L1 CPS of 1 and also reports outcomes for the total population. There were 14 primary hypotheses comparing pembrolizumab alone or pembrolizumab with chemotherapy to cetuximab with chemotherapy in the different nested subgroups, as well as total population. Primary outcomes were both OS and progression-free survival (PFS), and the tested hypotheses included both superiority and non-inferiority comparisons. Despite a detailed statistical analysis and two interim analyses specified in the protocol, the study is still unable to inform patients whether pembrolizumab with or without chemotherapy is superior to cetuximab plus chemotherapy if PD-L1 CPS is less than 1 or 1–19, which may be described as adjacent subgroups as opposed to nested subgroups in the original study. In fact, Schoenfeld *et al.* [2] extracted information from the Kaplan–Meier curves and in fact found that, for the PD-L1 less than 1% population, the survival is worse in the pembrolizumab arm compared with the cetuximab arm. The design of the KEYNOTE-048 study resulted in a broad approval, but superior outcomes may be driven by select patients with higher PD-L1 expression, and certainly outcomes may be inferior for patients with PD-L1 <1%. Regardless, pembrolizumab with chemotherapy received a category 1 recommendation in the National Comprehensive Cancer Network guidelines for patients with any PD-L1 expression.

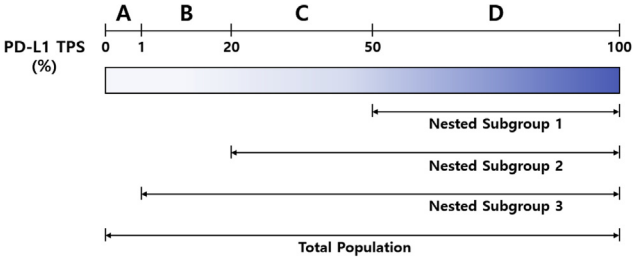

Fig. 1. Nested and adjacent subgroups in KEYNOTE-042. PD-L1 TPS as a continuous biomarker with adjacent subgroup A (less than 1%), B (1–19%), C (20–49%) and D (50% and above) and nested subgroups of 50% and above, 2% and above, 1% and above and total population. PD-L1, programmed death ligand 1; TPS, tumour proportion score.

1.2. Immunotherapy versus immunotherapy plus chemotherapy in adjacent subgroups

Non-small-cell lung cancer (NSCLC) is a tumour type in which immunotherapy is widely used in the advanced setting. In 2016, KEYNOTE-024 [3] established the use of single agent pembrolizumab in stage IV NSCLC with PD-L1 tumour proportion score (TPS) of 50% or greater. KEYNOTE-189 was published in 2018 and described the outcomes of adding pembrolizumab to cytotoxic chemotherapy compared with cytotoxic chemotherapy alone across the entire spectrum of PD-L1 expression. KEYNOTE-042 further demonstrated improved OS with pembrolizumab monotherapy in patients with PD-L1 TPS of $\geq$50%, $\geq$20% and $\geq$1%. Patients with PD-L1 $\geq$1% are therefore eligible for both pembrolizumab monotherapy and pembrolizumab combined with chemotherapy. There remains a question, however, whether patients have better outcomes with pembrolizumab alone or combined with chemotherapy across the spectrum of PD-L1 expression. Aguilar *et al.* [4] found that response to pembrolizumab monotherapy is more likely with higher PD-L1 expression. Among patients with PD-L1 $\geq$50% who respond to pembrolizumab alone, the median PD-L1 is 90%. They compared groups of patients with PD-L1 of 50–89% with PD-L1 of 90–100% and found a response rate of 32.7% and 60%, respectively. Hence, patients with higher PD-L1 expression would likely benefit more from pembrolizumab monotherapy compared with pembrolizumab with chemotherapy; however, the transition point where pembrolizumab monotherapy becomes superior is unknown and is left to clinical judgement. To further explore this turning point, trials that report outcomes by adjacent subgroups are

required. For example, outcomes of pembrolizumab with and without chemotherapy should be reported in subgroups with PD-L1 of 1–19%, 20–49%, 50–89% and ≥90%. PD-L1 expression is a continuous biomarker, and analytic methods that do not use arbitrary cut-offs may also lead to findings that further inform medical decision-making. Despite strong evidence of the correlation between PD-L1 and response to immunotherapy, such comprehensive reporting is lacking due to incentives of drug companies to seek the broadest indications for approval.

1.3. For adjuvant immunotherapy, long-term outcomes in different levels of PD-L1 are key

The recent publication by Kelly *et al.* [5] reports outcomes of CheckMate 577 on adjuvant nivolumab in resected oesophageal or gastroesophageal junction cancer. The primary outcome was duration of response, and the patients receiving nivolumab had a longer median disease-free survival of 22.4 months compared with 11 months in the placebo arm. These results raise the questions of how heterogeneous the outcomes were among patients in the trial. Specifically, are patients with high PD-L1 expression driving the overall difference in outcomes? The trial enrolled patients regardless of tumour cell PD-L1 expression. PD-L1 expression was only described as positive (≥1%) or negative (<1%) in both baseline characteristics and subgroup analyses, and it is not possible to know if higher PD-L1 expression is associated with better outcomes. As adjuvant therapy inherently treats patients that may not need it, it is especially important to delineate the characteristics of patients that benefit the most. To further clarify the role of nivolumab in the adjuvant setting, there must be long-term follow-up and information about the PD-L1 expression in long-term survivors.

2. Trial end-points are changed to maximise treatment indications

KEYNOTE-042 [6] is notable for the change in primary end-points during the trial. The original protocol included OS for PD-L1 TPS ≥50% as a primary end-point. After KEYNOTE-010 [7] reported an OS benefit in PD-L1 TPS ≥ 1% in previously treated advanced NSCLC, the primary end-point was amended to OS in patients with PD-L1 TPS ≥ 50%, ≥20% and ≥1%. OS of patients with PD-L1 TPS of 1–49% was included as an exploratory end-point. The trial was published in Lancet as an original article that does not include results of the exploratory analysis for the PD-L1 TPS 1–49% subgroup. The exploratory analysis is only reported as an abstract publication with similar median OS in the pembrolizumab arm and chemotherapy arm (13.4 months versus 12.1 months) [8]. The addition of primary end-points that include nested subgroups with known outcomes and the selective reporting of outcomes of adjacent subgroups are problematic. KEYNOTE-048 is also notable for multiple changes in end-points and three primary hypotheses comparing superiority of pembrolizumab versus cetuximab-chemotherapy for PFS in PD-L1 strongly positive and total populations and superiority of pembrolizumab-chemotherapy versus cetuximab-chemotherapy for PFS in the PD-L1 strongly positive population. All together, the trial ended up with 14 primary hypotheses to test.

3. Targeted agents are also approved for panels of mutations when results are driven by a nested subgroup

The phenomenon of nested subgroups is also seen with categorical biomarkers such as somatic or germline mutations. Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved for a broad range of gene mutations based on the PROfound study [9]. It is approved for germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC). HHR genes included in the PROfound study are *BRCA1, BRCA2, ATM* and an additional 12 prespecified genes. Cohort A included *BRCA 1, BRCA 2* and *ATM* mutations, and cohort B included the remaining 12 gene mutations. The primary outcome of radiological PFS was reported for cohort A and also the total population of cohort A+B with a statistically significant difference favouring the study drug. This trial design follows a similar pattern seen in immunotherapy trials with nested subgroups likely driving the outcomes of the larger group. Rucaparib is another PARP inhibitor approved for *BRCA* mutated prostate cancer. The TRITON2 [10] study demonstrated a response rate of 44% in *BRCA* mutated mCRPC and 10.5% in the *ATM* mutated subgroup. Despite differences in response rates of each gene mutation, the PROfound study reports outcomes with the nested subgroup of BRCA gene-mutated patients that are able to drive positive outcomes in both cohort A and cohort A+B. These concerns regarding the PROfound study trial design have been raised previously [11,12]. This is evidence for the lack of incentives for drug companies to identify the subgroup of patients that would benefit most from a new drug as broader approvals lead to larger profits.

The practice of nested subgroups in clinical trials where a subset of patients drives the positive outcomes works against the goals of precision medicine, and recently, others have also noted this phenomenon [13]. We want to find the best treatment for each individual patient, and this means designing clinical trials that look into which subset of patients benefit most from a treatment. We propose the use of adjacent subgroups in place of the nested subgroups seen in the aforementioned

examples. KEYNOTE-042 should report outcomes of patients with PD-L1 of >50%, 20–50% and 1–19%. KEYNOTE-048 should describe outcomes in subgroups with PD-L1 ≥20%, 1–19% and less than 1%. PROfound study should provide a detailed analysis of cohort B and also for *ATM* mutated patient in cohort A. This would help identify the tipping point in continuous biomarker such as PD-L1, where a certain treatment becomes more effective, and also identify subgroups that likely have ride-along benefit and may actually be harmed by that treatment. How does pembrolizumab monotherapy compare to pembrolizumab with chemotherapy with PD-L1 of 60% of 40%? This can only be answered by analysed adjacent subgroups. The Federal Drug Administration (FDA) should also require drug companies to report post-marketing studies on subgroups to refine the approval indications. A practicing physician cannot analyse all the new data supporting a drug approval with the depth and breadth of the field of oncology. Once a drug is approved for a certain indication, it will be used in such patients even if there is limited evidence. Pembrolizumab will be given to patients with NSCLC and PD-L1 40% if it is approved for that indications.

4. Conclusion

We view this as a modern phenomenon and are not criticising a certain study or a single drug company. Financial incentives can be very effective in bringing drugs that help patients to market. However, we should recognise this tension that exists now in designing and interpreting trials. Drug companies are incentivised to maximise market share while patients are best served by identifying the characteristics most likely to lead to good outcomes. The example of cetuximab in *K-ras*–mutated colorectal cancer is reason for optimism. After the approval of cetuximab for *EGFR*-expressing colorectal cancer in 2007 based on a randomised controlled trial [14], the trial groups (National Cancer Institute of Canada Trials Group, Australasian Gasto-Intestinal Trials Group) and the pharmaceutical company (Bristol-Myers Squibb) collaborated and looked into outcomes in *K-ras*–mutated advanced colorectal cancer. This study led to recognition that cetuximab is not effective in the subpopulation of colorectal cancer with *K-ras* mutation. Proper incentives and improved regulatory guidance for participants in drug development can lead to high-quality information from clinical trials that can inform patients and improve their outcomes.

Authors' contributions

The contributions to this manuscript are as follows. Dr. Vinay Prasad's contribution are conceptualization, supervision and writing-review & editing. Dr. Myung Sun Kim's contributions are conceptualization and writing-original draft.

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