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Editorial

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# Prioritized Requirements for First-Line Systemic Therapy for Hepatocellular Carcinoma: Broad Benefit with Less Toxicity

Masatoshi Kudo

Department of Gastroenterology and Hepatology Kindai University Faculty of Medicine, Osaka-Sayama, Japan

**Keywords**
Hepatocellular carcinoma · Atezolizumab plus bevacizumab · Combination immunotherapy · Durvalumab plus tremelimumab

*Prof. M. Kudo*

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The results of the phase III LEAP-002 trial of pembrolizumab plus lenvatinib combination therapy [1] and a phase III trial of camrelizumab plus rivoceranib combination therapy [2] were presented at the European Society for Medical Oncology Congress in September 2022. The LEAP-002 study failed to yield the expected results. However, the results of clinical trials of combination immunotherapy (IO) are currently available for five regimens in advanced hepatocellular carcinoma (HCC), namely, four IO + tyrosine kinase inhibitor (TKI)/anti-vascular endothelial growth factor (VEGF) antibody combination regimens, including two regimens from the previously published IMbrave150 (atezolizumab + bevacizumab) [3, 4] and COSMIC312 (cabozantinib plus atezolizumab) [5] studies, as well as IO + IO combination therapy (anti-programmed death ligand-1 [PD-L1] antibody + anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] antibody) [6]. It is not appropriate to compare outcomes and toxicities among these studies because the patient populations had very different background characteristics. However, because all studies except LEAP-002 used sorafenib as the comparator, it might be meaningful, to some extent, to compare overall survival (OS) hazard ratios (HRs), progression-free survival (PFS) HRs, and objective response rates (ORRs) between these regimens. The OS HR was 0.62 for camrelizumab + rivoceranib [2], 0.66 for atezolizumab + bevacizumab [4], and 0.78 for durvalumab + tremelimumab [6], which shows that anti-programmed cell death protein-1 (PD-1)/PD-L1 antibody + TKI/anti-VEGF antibody yields a better OS benefit than the IO + IO regimen. The PFS HR and ORR were also better for anti-PD-1/PD-L1 antibody + TKI/anti-VEGF antibody than for the IO + IO regimen (Table 1). The progressive disease (PD) rate clearly differed between anti-PD-1/PD-L1 antibody + TKI/anti-VEGF antibody and the IO + IO regimen, at 16.2–19% versus 39.9%. OS was comparable between the IMbrave150 study popula-



Correspondence to:
Masatoshi Kudo, m-kudo@med.kindai.ac.jp

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**Table 1.** Efficacy results of four clinical trials of combination IO

| | LEAP-002* | | Cam+Rivo | | IMbrave150 | | IMb150 Non-VP4 | | HIMALAYA | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Len + pembro (*N* = 395) | Len + placebo (*N* = 399) | Cam + rivo (*N* = 272) | Sorafenib (*N* = 271) | Atezo + bev (*N* = 336) | Sorafenib (*N* = 165) | Atezo + bev (*N* = 288) | Sorafenib (*N* = 140) | T300 + D (*N* = 393) | Sorafenib (*N* = 389) |
| Median follow-up, mo | 32.1 | | 14.5 | | 15.6 | | 15.6 | | 33.18 | 32.23 |
| Age | 66 | 66 | 58 | 56 | 64 | 66 | — | — | 65 | 64 |
| VP4 | No | | Yes | | Yes | | No | | No | |
| MVI/EHS | 68 | 66 | 74 | 74 | 77 | 73 | — | — | 67 | 65 |
| Median OS, months | 21.2 | 19.0 | 22.1 | 15.2 | 19.2 | 13.4 | 21.1 | 15.4 | 16.4 | 13.8 |
| HR, *p* value | HR = 0.84 (0.71–0.99), *p* = 0.0227 | | HR = 0.62 (0.49–0.80), *p* < 0.0001 | | HR = 0.66 (0.52–0.85), *p* = 0.0009 | | HR = 0.67 (0.51–0.88), *p* = 0.003 | | HR = 0.78 (0.65–0.92), *p* = 0.0035 | |
| Median PFS | 8.2 | 8.0 | 5.6 | 3.7 | 6.9 | 4.3 | 7.1 | 4.7 | 3.78 | 4.07 |
| HR, *p* value | HR = 0.87 (0.73–1.02), *p* = 0.047 | | HR = 0.52 (0.741–0.65), *p* < 0.0001 | | HR = 0.65 (0.53–0.81), *p* = 0.0001 | | HR = 0.64 (0.51–0.81), *p* < 0.001 | | HR = 0.90 (0.77–1.05) | |
| ORR RECIST v1.1, % | 26.1 | 17.5 | 25.4 | 5.9 | 30 | 11 | 31 | 11 | 20.1 | 5.1 |
| CR, % | 1.5 | 1.5 | 1.1 | 0.4 | 8 | <1 | 8 | 0 | 3.1 | 0 |
| PR, % | 24.6 | 16.0 | 24.3 | 5.5 | 22 | 11 | 23 | 11 | 17.0 | 5.1 |
| SD, % | 55.2 | 60.9 | 52.9 | 48.0 | 44 | 43 | 46 | 47 | 39.9 | 55.5 |
| PD, % | 18.7 | 21.6 | 16.2 | 36.5 | 19 | 25 | 18 | 23 | 39.9 | 39.3 |
| DCR, % | 81.3 | 78.4 | 78.3 | 53.9 | 74 | 55 | 77 | 58 | 60.1 | 60.7 |

* Negative study.

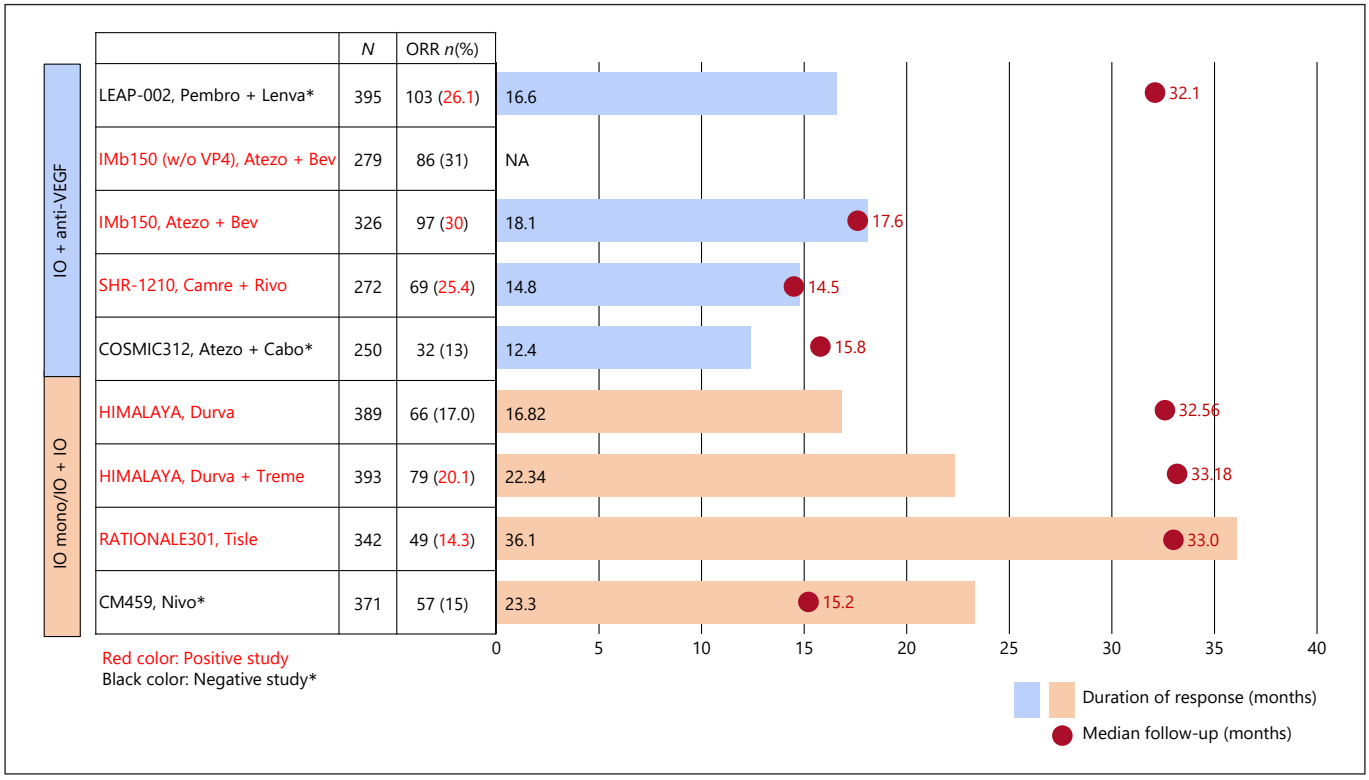


**Fig. 1** Duration of response.

tion, excluding those with main portal trunk and/or contralateral portal vein invasion (Vp4) [7], camrelizumab + rivoceranib, and lenvatinib + pembrolizumab, ranging from 21.1 to 22.1 months (Table 1). The ORR and PD rates were also comparable between these three regimens, ranging from 25.4% to 31% and 16.2–18.7%, respectively (Table 1). Therefore, anti-PD-1/PD-L1 antibody + TKI/anti-VEGF antibody has better ORR and PD outcomes than the IO + IO regimen (20.1% and 39.9%, respectively) (Table 1).

## Duration of Response

Another important factor in responders is how long the response is sustained. Response to tislelizumab was sustained for an extremely long duration of 36.1 months, which is the longest duration of response (DoR) among IO + anti-VEGF regimens and IO monotherapy/IO + IO regimens [8]. This durable response could be explained by the characteristics of the FCγ-portion of this anti-PD-1 antibody, which was specifically engineered to minimize FCγ receptor binding on macrophages. In other words, tislelizumab is characterized by a low response rate (14.3%) but an extremely long DoR in those who show a response. The durvalumab + tremelimumab combination (so called STRIDE regimen) also has a long DoR of 22.34 months. In addition, STRIDE regimen showed clear long-tail effect; the 3-year survival rate was 30.7%.

The atezolizumab + bevacizumab [4] and camrelizumab + rivoceranib [2] combinations, which showed positive results in clinical trials, have DoR of 18.1 months and 14.8 months, respectively. Pembrolizumab + lenvatinib also shows a somewhat long DoR at 16.6 months. Durvalumab monotherapy and nivolumab monotherapy also tend to have a long DoR; however, these agents have extremely low ORRs in monotherapy. Specifically, the response rates of nivolumab monotherapy [9] and durvalumab monotherapy [6] are approximately half of those of atezolizumab + bevacizumab. This indicates that both of DoR and ORR must be considered in evaluating the drug activity (Fig. 1) [10]. Atezolizumab + cabozantinib are associated with poor outcomes in terms of both ORR and DoR [5].

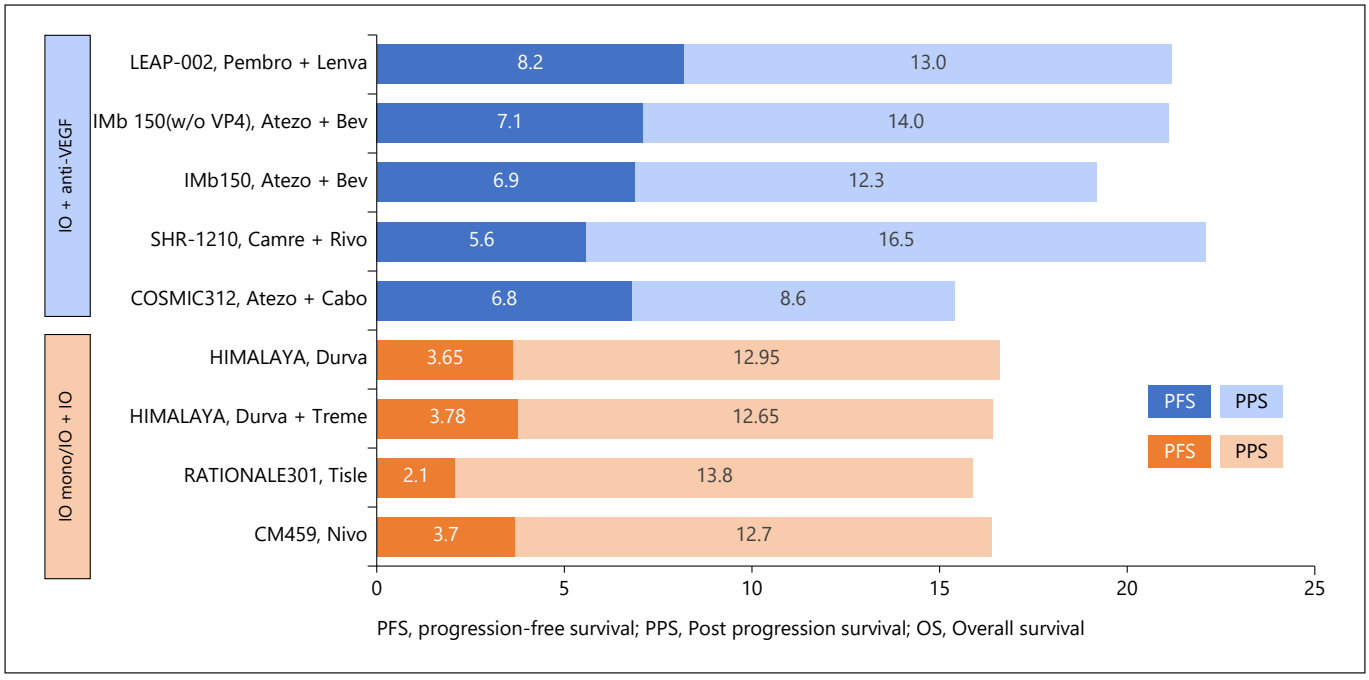


**Fig. 2** PFS, PPS, and OS in combination/single IO.

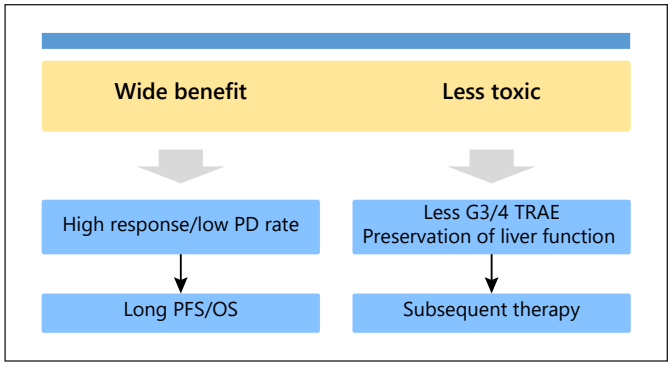


**Fig. 3** Prioritized requirements for first-line systemic therapy regimens.

### PFS, PPS, and OS in Combination and Single Agent IO

Figure 2 shows the PFS, PPS, and OS for IO + anti-VEGF, IO + IO, and IO monotherapy. Overall, IO + anti-VEGF regimens result in longer OS than IO + IO or IO monotherapy, and this effect is clearly attributable to a longer PFS. PPS is consistently in the range of 12–14 months in all studies, which supports that OS extension indeed depends on PFS extension. Therefore, extending PFS is also crucial for extending OS. Clinical studies of immune checkpoint inhibitors confirm that OS correlates well with other outcomes such as PFS and ORR [11].

### Relationship between Efficacy Outcomes and Toxicity Outcomes

Efficacy outcomes and toxicity outcomes are both important. In the IMbrave150 study [3, 4], atezolizumab + bevacizumab combination therapy had low toxicity and was associated with good quality of life (QOL), with preserved hepatic functional reserve [12]. QOL and toxicity outcomes are correlated with OS and PFS [13], and OS and PFS are in turn correlated with outcomes such as ORR and a low PD rate. In addition, studies show that among patients who tolerate the first-line regimen and show good QOL with preserved hepatic functional reserve, a large percentage (70–90%) who develop PD on first-line therapy can transition to subsequent therapy [14, 15]. This indicates that low toxicity, good QOL, and preserved liver function are important requirements for first-line treatment. A high response rate and a low PD rate are also important because they correlate with outcomes such as OS and PFS (Fig. 3, 4). A higher ORR is also likely to lead to curative conversion [16, 17].

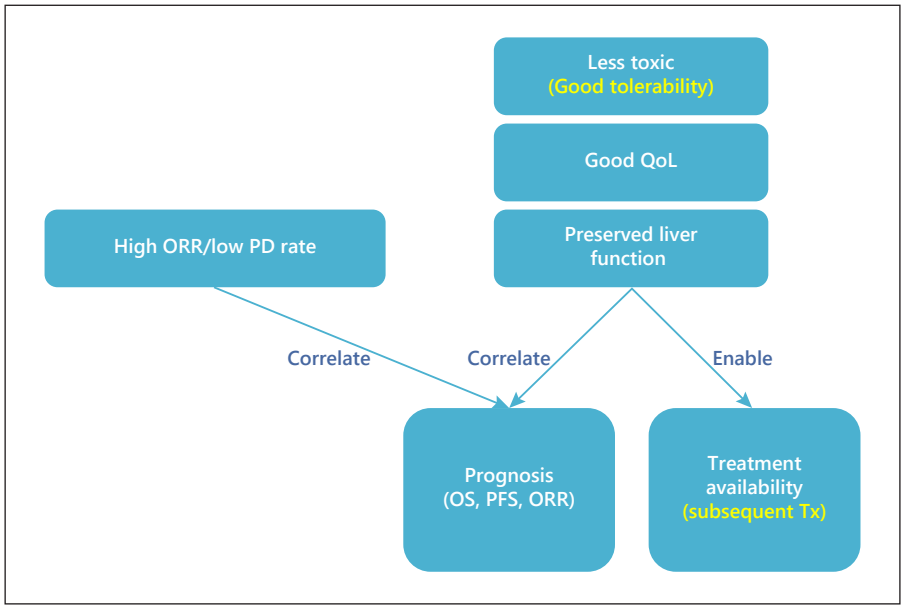


**Fig. 4** Relationship of efficacy and toxicity outcomes of first-line systemic therapy agents.

### Broad Benefit and Less Toxicity May Be Preferable for First-Line Systemic Agents

Two important prioritized requirements for first-line systemic therapy regimens are that the regimen can benefit a large percentage of patients (i.e., has a broad benefit) and that it has low toxicity. Therefore, the key phrase "broad benefit, less toxicity" is an important priority in the selection of first-line systemic therapy regimens for HCC. "Broad benefit" means a high response rate and a low PD rate, which lead to longer PFS and OS. Less toxic regimens cause fewer grade 3 and 4 treatment-related adverse events and allow a large percentage of patients to transition to the subsequent treatment because their liver function is preserved. Consequently, these factors should be considered when selecting a first-line treatment regimen. Among the currently available regimens, atezolizumab + bevacizumab best satisfies the requirements for first-line systemic therapy. However, only drawback of this regimen is that protein urea is sometimes induced by bevacizumab, which causes a difficultly to applying subsequent targeted agents with anti-VEGF activity. Even so, atezolizumab + bevacizumab is currently the ideal first-line regimen because it has the lowest rate of immune-related AEs requiring systemic steroids (12.2%). STRIDE regimen required 20.1% of systemic steroid. Considering risk-benefit balance of STRIDE regimen, biomarker to predict its efficacy may be necessary to use this regimen as a first-line systemic therapy.

### Conclusion

When selecting a first-line systemic therapy regimen for HCC, the most important requirements that should be prioritized are "broad benefit, less toxicity." However, a CTLA-4-containing regimen should be included in the systemic treatment of HCC because IO-IO regimens show a clear tail plateau in the Kaplan-Meier curve. To establish the role of CTLA-4-containing regimens, the development of a reliable biomarker to predict their efficacy is essential.

### Conflict of Interest Statement

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### Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

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