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Editorial

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Nivolumab plus Ipilimumab: A Novel First-Line Combination Immunotherapy for Unresectable Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Combination immunotherapy · Nivolumab plus ipilimumab

Introduction

The systemic therapy regimens for hepatocellular carcinoma (HCC) currently approved as 1st line agents are sorafenib (SOR) [1], lenvatinib (LEN) [2], atezolizumab plus bevacizumab [3, 4], durvalumab plus tremelimumab [5], and durvalumab monotherapy [5]. Also approved as 2nd line agents are regorafenib, cabozantinib, and ramucirumab. The American Association for the Study of Liver Diseases (AASLD) [6], Barcelona Clinic Liver Cancer (BCLC) [7] treatment algorithms and the guidelines of the Japan Society of Hepatology [8] recommend atezolizumab plus bevacizumab and durvalumab plus tremelimumab equally as the 1st choice of 1st line treatment. Recently, CheckMate 9DW results of nivolumab plus ipilimumab were presented at the American Society of Clinical Oncology (ASCO) in 2024 as a new 1st line combination immunotherapy [9].

Prof. M. Kudo

Editor *Liver Cancer*

Nivolumab plus Ipilimumab from the CheckMate 9DW

Efficacy Outcome

The efficacy of nivolumab plus ipilimumab is summarized in Table 1, with a median overall survival (OS) of 23.7 months, the combination immunotherapy with the most extended OS to date, and better than the control arm. The hazard ratio (HR) was 0.79 compared to the control group (LEN 85%, SOR 15%). The OS HR of HIMALAYA trial [5] and the IMbrave150 trial [3, 4] cannot be compared with CheckMate 9DW as SOR is the control group in these two trials. The median PFS was 9.1 months, which is exceptionally long. The HR for progression-free survival (PFS) was 0.87. The objective

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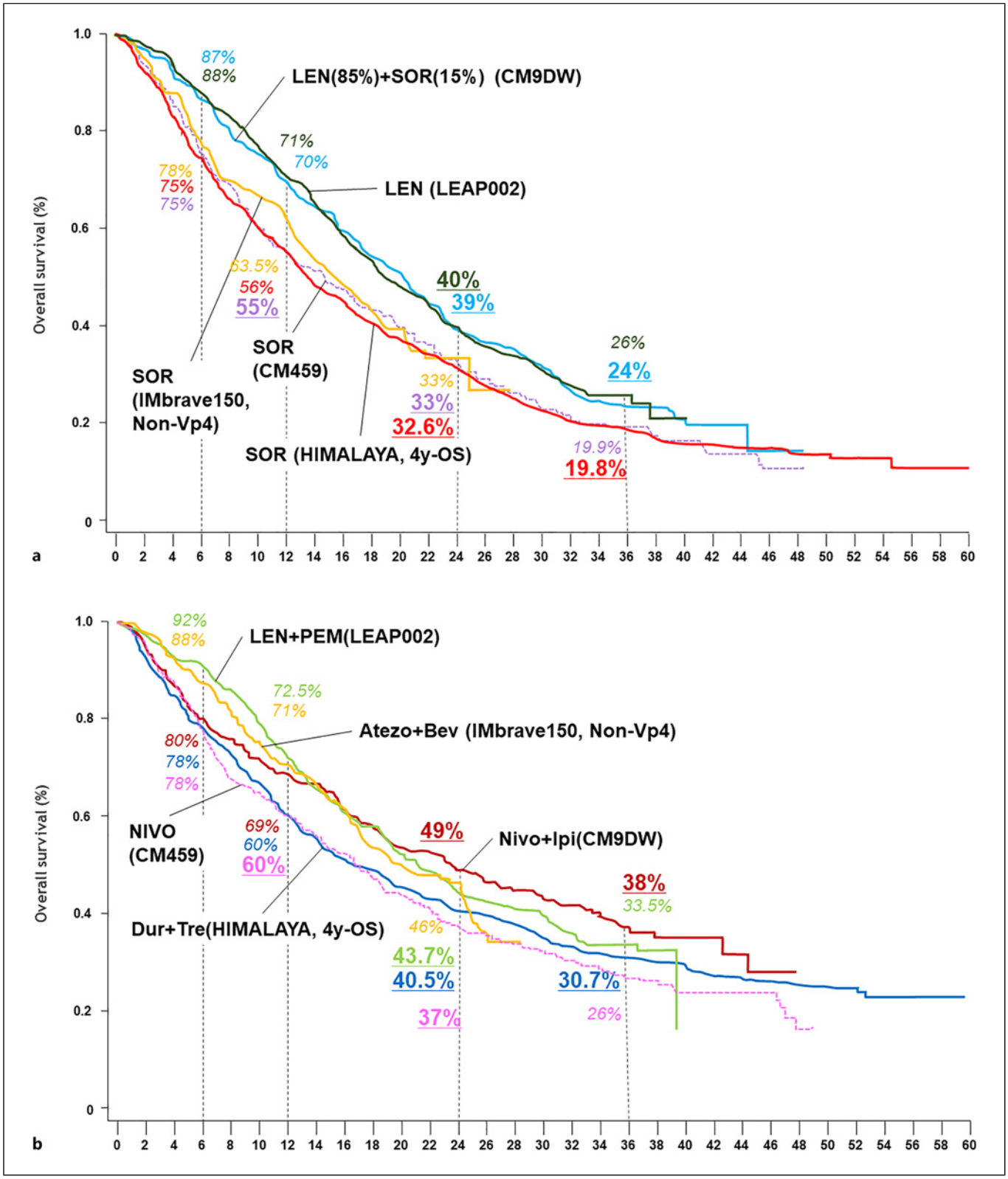
Table 1. Combination immunotherapy for unresectable HCC

Combination immunotherapy	Anti-PD-(L)1 plus anti-VEGF/TKI										Anti-PD-(L)1 plus Anti-CTLA-4			
Trial name	IMbrave150		IMbrave150 (non-Vp4)		ORIENT-32		CARES-310		LEAP-002		CheckMate 9DW		HIMALAYA	
Drugs	atezolizumab/ bevacizumab	SOR	atezolizumab/ bevacizumab	SOR	sintilimab/ bevacizumab biosimilar	SOR	camrelizumab/ rivoceranib	SOR	pembrolizumab/ LEN	LEN	nivolumab/ ipilimumab	LEN/ SOR (LEN 85%)	durvalumab/ tremelimumab	SOR
Subjects	uHCC (including Vp4)		uHCC (excluding Vp4)		uHCC (including Vp4)		uHCC (including Vp4)		uHCC (excluding Vp4)		uHCC (excluding Vp4)		uHCC (excluding Vp4)	
Liver function	Child-Pugh A		Child-Pugh A		Chile-Pugh A, B7		Child-Pugh A		Child-Pugh A		Child-Pugh A		Child-Pugh A	
n	336	165	288	140	380	191	272	271	395	399	335	333	393	389
mOS, months	**19.2**	13.4	**21.1**	15.4	**NE**	10.4	**23.8**	15.2	**21.2**	19.0	**23.7**	20.6	**16.4**	13.8
OS HR	0.66		0.67		0.57		0.64		0.84		0.79		0.78	
p value	0.0009		0.003		<0.0001		<0.0001		0.0227		0.018		0.0035	
mPFS, months	6.9	4.3	7.1	4.7	4.6	2.8	5.6	3.7	8.2	8.1	9.1	9.2	3.8	4.1
PFS HR (95% CI, *p* value)	0.65 (*p* = 0.0001)		0.64 (*p* = 0.0001)		0.56 (*p* < 0.0001)		0.52 (*p* <0.0001)		0.83 (0.71–0.98)		0.87 (0.72–1.06)		0.90 (0.77–1.05)	
ORR, %	**30**	11	**31.0**	11.0	**21**	4	**25.4**	5.9	**26.1**	17.5	**36.0**	13.0	**20.1**	5.1
CR, %	8	<1	8.0	0.0	0	0	1.1	0.4	1.5	1.5	7.0	2.0	3.1	0.0
PR, %	22	11	23.0	11	21	4	24.3	5.5	24.6	16.0	29.0	11.0	17.0	5.1
SD, %	44	43	46.0	47.0	52	60	52.9	48.0	55.2	60.9	32.0	62.0	39.9	55.5
PD, %	**19**	25	**18.0**	23.0	**27**	33	**16.2**	36.5	**12.2**	15.0	**20.0**	14.0	**39.9**	39.3
DCR, *n* (%)	74	55			72	64	78.3	53.9	81.3	78.4	68.0	75.0	60.1	60.7
TTR, months	**2.8**	2.6			**NA**	NA	**1.9**	3.7	NA	NA	**2.2**	3.7	**2.2**	3.8
DOR, months	**18.1**	14.9			**NE**	9.8	**14.8**	9.2	**16.6**	10.4	**30.4**	12.9	**22.3**	18.4
BCLC-C, %	82.0	81.0			85.3	85.9	86.0	85.2	78.5	75.7	73.0	73.0	80.0	83.0
BCLC ≤ B, %	**18.0**	19.0			**14.7**	14.1	**14.0**	14.8	**21.5**	23.8	**27.0**	26.0	**20.0**	17.0
AFP ≥400, %	38.0	37.0	35.0	31.0	43	42	35.3	36.9	30.1	33.1	32.0	34.0	36.9	31.9
Systemic steroid, %	**12.2**	0.0	NA	NA	NA	NA	16.0	NA	**9.6**	1.8	**29.0**[a]	NA	**20.1**[a]	1.9
TRAE leading to discontinuation, %	**10.0**	0.0			**14**	6	**3.7**	4.5	**5.6**	4.6	**18.0**	10.0	**8.2**	11.0
TRAE leading to death, %	**2.0**	<1			**3**	3	**0.4**	0.4	**1.0**	0.8	**4.0**	<1	**2.3**	0.8

CR, complete response; ORR, objective response rate; TRAE, treatment-related adverse event. [a]High-dose steroid (≥40 mg/day).



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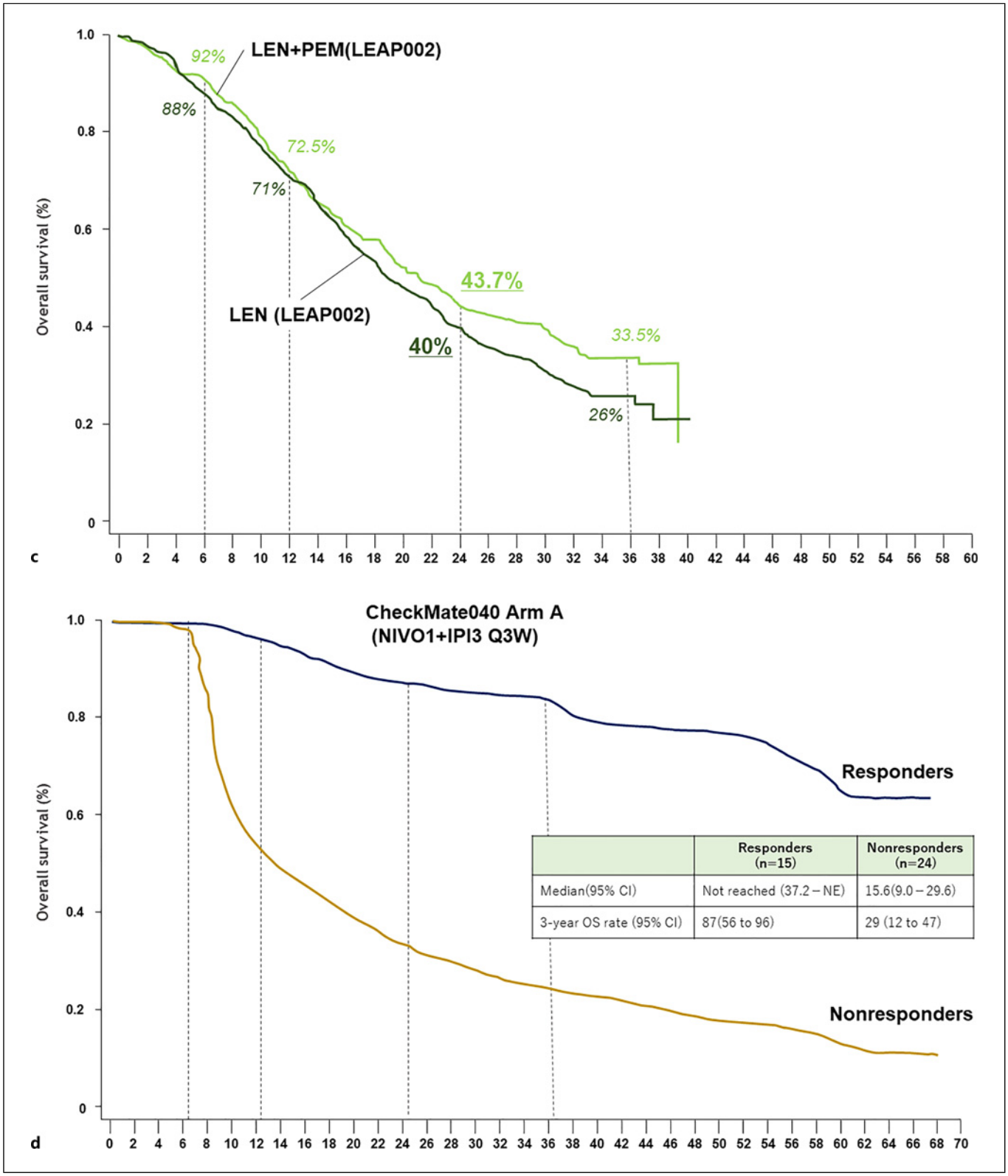

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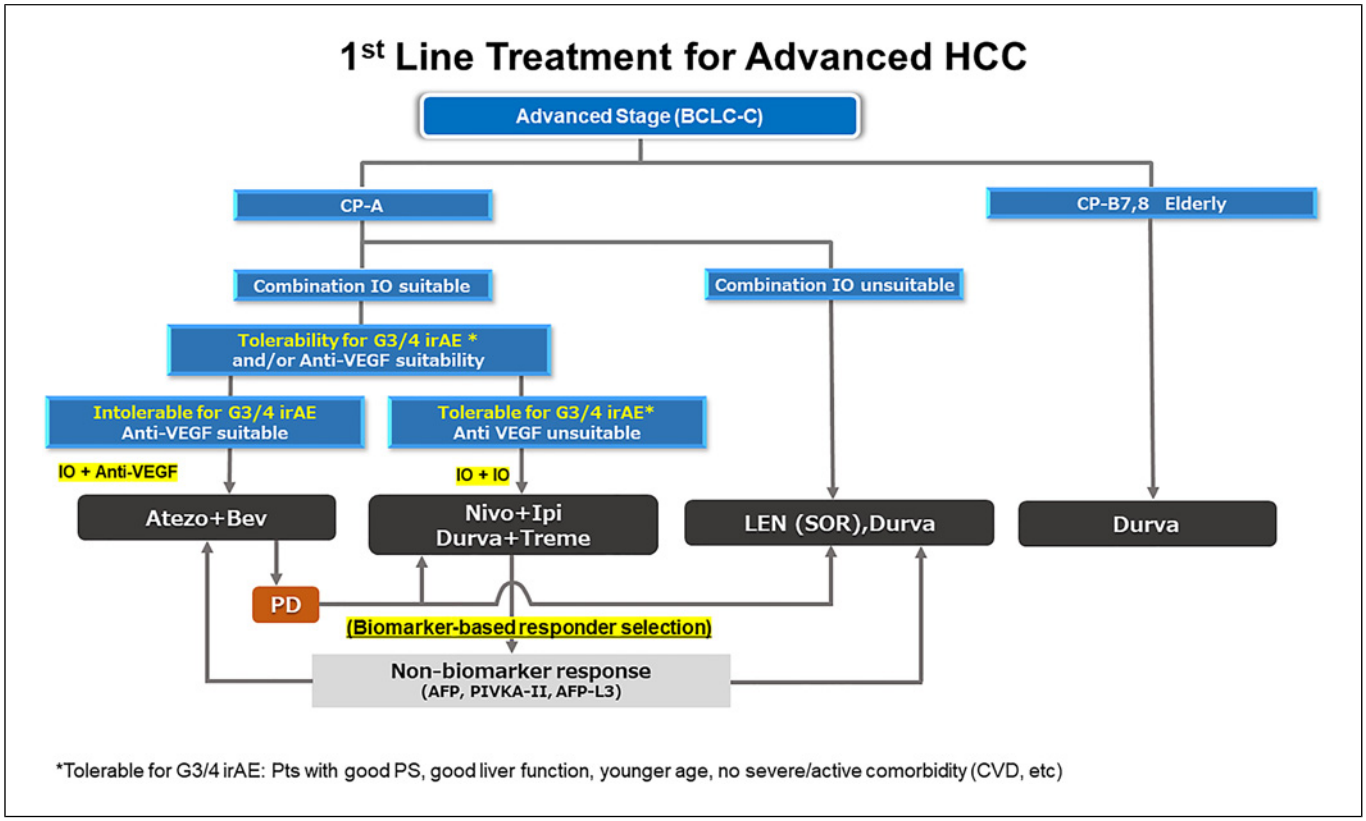

Fig. 2. First-line treatment for advanced HCC. For the choice between IO+anti-VEGF and IO + IO regimens, it is essential to consider whether the patient can tolerate grades 3–4 irAEs and then consider anti-VEGF suitability. Intolerable for grade 3/4 irAE to the CTLA-4 containing regimen or are anti-VEGF suitable, the IO+anti-VEGF Atezo/Bev is recommended. For patients who would tolerate grades 3–4 irAE to the CTLA-4 containing regimen, i.e., those with good PS, good liver function, relatively young and without severe or active complications such as cardiovascular disease (CVD) or anti-VEGF unsuitable, IO + IO regimens are indicated; however, patients should be switched to Atezo/Bev or LEN as early as possible in non-responders for biomarkers such as AFP, PIVKA-II, and AFP-L3%. For PD with Atezo/Bev, switching to IO + IO or LEN is recommended. VEGF: vascular endothelial growth factor. AFP; alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AFP-L3%, alpha-fetoprotein rectin fraction; PS, performance status.

Fig. 1. a Cross-trial comparison is basically not recommended. However, just for a reference purpose, checking the tendency of the KM curve of several trials may give a very good insight. Computer-simulated KM curves for the control arms in the CheckMate 9DW, LEAP-002, CheckMate 459, IMbrave150 (non-VP4), and HIMALAYA (4-year OS) trials, respectively. KM simulation curves for the LEN arm of LEAP-002 and the CheckMate 9DW control arm (85% LEN/15% SOR) are almost identical. This is a survival curve almost exclusively due to LEN. The three SOR arms of CheckMate 459, the SOR arm of IMbrave150 non-VP4, and the SOR arm of the 4-year survival of the HIMALAYA trial are also almost identical. **b** Cross-trial comparison is basically not recommended. However, just for a reference purpose, checking the tendency of the KM curve of several trials may give a very good insight. Simulated KM curves for the testing drug groups; KM curves for regimens including anti-VEGF actions such as LEN and bevacizumab are relatively better for the first 6 months to a year or so than the CheckMate 459 nivolumab alone and better than durvalumab plus tremelimumab in the HIMALAYA trial and nivolumab plus ipilimumab in the CheckMate 9DW. From this point of view, drugs with anti-VEGF activity have a better early OS. **c** The LEAP-002 trial also showed KM curves overlapping the LEN group and the LEN plus pembrolizumab group for almost 1 year. **d** Computer-simulated KM curves for responder and non-responder in arm A in the nivolumab plus ipilimumab group of the CheckMate 040 trial. Nivo 1 Ipi3 arm shows a significantly better OS in responder than non-responder with a 3-year OS rate of 87% for the responders and a 3-year OS rate of 29% for the non-responder, clearly showing a large difference between responder and non-responder to Nivol Ipi 3 treatment.

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response rate was 36%, including a 7% complete response rate, which is exceptionally high and is higher than the 30% for atezolizumab plus bevacizumab [4] and 20.1% for durvalumab plus tremelimumab [5] (Table 1). Notably, the progressive disease (PD) rate was 20%, half of durvalumab plus tremelimumab (40%), despite the immune-oncology (IO)-IO combination regimen. Time to response (TTR) was rapid, 2.2 months. This TTR was comparable to that of durvalumab plus tremelimumab. This quick TTR is a unique feature for anti-CTAL-4 antibodies. Duration of response (DOR) was 30.4 months, much longer than durvalumab plus tremelimumab (22.3 months), which is the longest among the currently available combination immunotherapy. Incidentally, the DOR for atezolizumab plus bevacizumab was 18.1 months. However, the nivolumab plus ipilimumab population is somewhat different from other trial populations in that it includes 27% of BCLC-B HCCs, which is slightly more than the HIMALAYA [4] and IMbrave150 trials [2, 3] (Table 1). Sintilimab plus bevacizumab in ORIENT-32 trial [10] and camrelizumab plus rivoceranib from CARES-31 trial [11] are not FDA-approved agents.

In the Kaplan-Meier (KM) curve, OS in the nivolumab plus ipilimumab group was slightly below that of the control group for 12 months, crossing from there to a long tail plateau. The reasons for this are clear: Figure 1a, b show computer-simulated KM curves for the control arms of the various phase 3 trials. The simulated KM curves almost overlapped with the LEN arm of LEAP-002 [12] and the control arm (LEN 85%/SOR 15%) of CheckMate 9DW [9]. Also, the SOR arm from the CheckMate 459 [13], the SOR arm in IMbrave150 [3, 4] non-Vp4 group [14], the SOR arm in the HIMALAYA trial (the 4-year update OS data) [15] showed almost overlapping curves as well (Fig. 1a).

This fact clearly showed that the control arm had a better KM curve for LEN than for SOR, with SOR having a lower OS (Fig. 1a). The cross-trial comparison is basically not recommended. However, as the control arm in several trials showed almost identical OS curves, it might be insightful to look at the testing arms just for reference purposes. The testing arm showed that drugs with anti-VEGF effects, such as LEN plus pembrolizumab and atezolizumab plus bevacizumab, showed a better OS curve in the first year; nivolumab monotherapy, durvalumab plus tremelimumab and nivolumab plus ipilimumab show slightly inferior OS curves compared with drugs with anti-VEGF effects for around 12 months, especially first 6 months (Fig. 1b).

From this, it can be inferred that combination immunotherapy with anti-VEGF activity clearly prevents early mortality at an earlier period from treatment than IO monotherapy or IO + IO combination immunotherapy. This suggests that in nivolumab plus ipilimumab and durvalumab plus tremelimumab therapy, it is preferable to detect non-responders earlier than image PD using tumor markers such as AFP and PIVKA-II, and in biomarker non-responders, an anti-VEGF-containing regimen should be initiated earlier than imaging PD (biomarker-based responder selection).

From the above, it can be understood that nivolumab plus ipilimumab has a slightly inferior OS for the first year or so compared to LEN, which is a common feature of IO + IO combination immunotherapy and IO monotherapy (Fig. 1b). Indeed, in the LEAP-002 study, the simulated KM curve of LEN plus pembrolizumab completely overlapped with that of the LEN arm for the first 12 months [16].

Subsequent therapy was obtained in 45% of patients in the nivolumab plus ipilimumab group and 65% in the LEN (85%)/SOR (15%) group. Immunotherapy was given in 13% of the nivolumab plus ipilimumab and 35% of the LEN/SOR group.

Safety Outcome

Treatment-related adverse events leading to drug discontinuation occurred in 18% of patients with nivolumab plus ipilimumab, compared with 8.2% for durvalumab plus tremelimumab (Table 1); treatment-related deaths also occurred in 12 of 332 patients (4%), slightly more than in durvalumab plus tremelimumab or atezolizumab plus bevacizumab (Table 1). Grade 3/4 adverse events included diarrhea, pruritus, and liver dysfunction. In addition, 29% of patients received high-dose steroid treatment due to immune-related adverse events (irAE), which was also slightly higher than other combination immunotherapies, including hepatitis in 12%, diarrhea, and colitis in 8%, rush in 3%, and proteinuria in 3%. For ipilimumab, as with other organ cancers, irAE liver damage should be of particular caution.

The FACT-HEP total score, a measure of quality of life, also tended not to decrease in the nivolumab plus ipilimumab group. HRQOL showed a clinically meaningful decline in the LEN/SOR group after 29 weeks but not in the nivolumab plus ipilimumab group.

Nivolumab plus Ipilimumab from the Results of CheckMate 040

After SOR treatment, results of 2nd line nivolumab plus ipilimumab have already been published [17, 18]. The objective response rate for nivolumab plus ipilimumab was

as high as 32% in the Nivo 1 mg/kg and Ipi 3 mg/kg group despite being second line. However, the PD rate was 40%. Overall survival showed a long tail plateau but very short in stable disease (SD) and PD patients at 14.5 and 8.3 months, respectively (Fig. 1d). This suggests that responders to nivolumab plus ipilimumab have a very long OS, and some patients may be almost cured. Other patients, i.e., with SD and PD, have an overall poor clinical course. Also, although the results of a 5-year follow-up data have been published [18], the response rate for the Nivo 1+Ipi 3 patients ($n = 50$) was 34%, and the PD rate of 32%, good as second-line treatment. As expected, the Nivo 1+Ipi 3 combination is better with a median OS of 22.2 months than the other Nivo 3+Ipi 1 combination and Nivo 3 every 2 weeks+Ipi 1 every 6 weeks group, so it is easy to understand that Nivo 1+Ipi 3 every 3 weeks is the best regimen and this regimen was chosen for phase 3 trial, CheckMate 9DW.

Even more interesting is the responder analysis curve for Nivo 1+Ipi 3 (Fig. 1d), which shows that responders and non-responders have significantly different prognoses, with a sharp decline in OS from 6 months for non-responders. Given this, it is essential to identify responders regarding IO + IO regimens. Conversely, it is reaffirmed that it is essential to detect non-responders by tumor markers linked to tumor response, such as AFP, PIVKA-II, and AFP-L3%, before waiting until imaging PD. Biomarker-based responder selection is essential.

It is well known that PIVKA-II cannot be used as therapeutic monitoring for treatments with anti-VEGF activity as it generally shows a paradoxical result of hypoxia-induced increase in response to anti-VEGF action, if any. However, PIVKA-II can monitor the therapeutic effect of nivolumab plus ipilimumab and durvalumab plus tremelimumab. Therefore, it is essential whether there is an AFP response or a PIVKA-II response, and if, based on this biomarker response, it can be determined that the patient is a responder or non-responder to IO-IO regimens within 4–8 weeks after the start of treatment, then if the patient is judged to be a non-responder within 4–8 weeks of starting treatment, immediate transition to atezolizumab plus bevacizumab or LEN, which contain anti-VEGF effects, may prevent early-term death (biomarker-based responder selection).

Updated Treatment Algorithm in Advanced HCC

Previously, the selection of 1st line regimen has been determined by anti-VEGF as suitable or unsuitable [6, 19–22]. However, with the advent of highly effective combination immunotherapies such as nivolumab plus ipilimumab in addition to durvalumab plus tremelimumab, the tolerability to the high-grade (grade 3 or 4) irAE and its management of CTLA-4 antibodies should also be an essential selection criterion for the choice of 1st line agent (Fig. 2). In other words, good performance status, good liver function, relatively young age and absence of severe or active comorbidities to tolerate grades 3–4 irAE should be essential selection criteria for the choice of IO-IO agents (Fig. 2).

Biomarker-Based Responder Selection

When IO-IO regimens are used as first-line treatment, the characteristics of the response need to be known. It is clear that non-responders receive almost no benefit from the IO-IO regimen (Fig. 1d), and it can be said that the IO-IO regimen is an all-or-nothing regimen. There are specific populations for whom the IO-IO regimen should be used as it certainly provides a very high-quality response in terms of quick response, long DOR, and deep depth of response. Three tumor markers, AFP, PIVKA-II, and AFP-L3, are essential in detecting non-responders earlier than image PD in the population not benefiting from these IO-IO regimen. As these tumor markers always show a decreasing trend for responders within 2–4 weeks compared to the baseline, early introduction of a regimen with anti-VEGF activity, such as atezolizumab plus bevacizumab or LEN, in the non-responder population may be crucial in the clinical practice setting (Fig. 2). In this case, biomarker-based responder selection will be crucial for early detection of non-responder to IO-IO regimens. Although PIVKA-II and/or AFP-L3 cannot be measured routinely or are not reimbursed by medical insurance in some countries, it is necessary to monitor all three tumor markers whenever possible as elevated AFP-L3 can be seen even in the absence of elevated PIVKA-II or AFP. Thus, the measurements of PIVKA-II and AFP-L3 are an urgent global need [23].

Conclusion

Nivolumab plus ipilimumab is a novel first-line treatment option with a very high efficacy profile for unresectable HCC. Its relatively high irAEs will be well managed since management of AEs against anti-CTLA-4 antibodies was trained based on clinical experience with durvalumab plus tremelimumab so far. Combination immunotherapy including nivolumab plus ipilimumab will continue to improve the outcome of unresectable HCC [22, 24].

Statement of Ethics

No statement is needed because this study was based exclusively on published data.

Conflict of Interest Statement

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Author Contributions

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

Data Availability Statement

Data are not applicable because this is not a research article.

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