Liver Cancer

Liver Cancer , DOI: 10.1159/000532023
Received: May 17, 2023
Accepted: July 6, 2023
Published online: July 28, 2023

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Kudo M

ISSN: 2235-1795 (Print), eISSN: 1664-5553 (Online)
https://www.karger.com/LIC
Liver Cancer

Editorial

Drug-off Criteria in Patients with Hepatocellular Carcinoma who Achieved Clinical Complete Response after Combination Immunotherapy Combined with Locoregional Therapy

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Short Title: Drug-off Criteria in HCC Patients Achieving Complete Response

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Number of Tables: 3
Number of Figures: 3
Word Count: 1874

Keywords: hepatocellular carcinoma, systemic therapy, locoregional therapy, clinical complete response, drug-off criteria

1. Introduction

Hepatocellular carcinoma (HCC) is refractory to treatment under the following conditions: (1) a large number of tumors, (2) large tumor size, (3) vascular invasion or extrahepatic spread, and (4) poorly differentiated HCC[**1**]. Curative treatment options include liver transplantation, resection, and ablation, such as radiofrequency ablation (RFA) or microwave ablation (MWA), which yield the best outcomes in patients with HCC confined to the liver [**1,2**]. However, HCCs with a high tumor burden or microscopic vascular invasion, and confluent multinodular gross type or poorly differentiated pathological type HCCs, have a high recurrence rate after curative therapy, and achieving a complete cure is difficult in these cases [**1-5**].

Because of its high response rate and good tolerability, the combination of atezolizumab plus bevacizumab is the first-line systemic therapy regimen for HCC [**6-10**]. In cases in which bevacizumab is not indicated, durvalumab plus tremelimumab is the recommended treatment regimen (Fig. 1) [**11-15**]. In patients who are not eligible for or intolerant to combination immunotherapy, molecular targeted agents such as lenvatinib[**16**] are the first-line option (Fig. 1). In patients with intermediate-stage HCC not suitable for transarterial chemoembolization (TACE)[**17,18**], atezolizumab plus bevacizumab combination immunotherapy combined with locoregional therapy such as TACE, ablation, or resection can achieve high complete response (CR) rates, as well as a durable deep response (Fig. 2) [**19-22**]. One important issue that needs to be resolved is establishing the optimal time to discontinue systemic therapy after CR is achieved with systemic therapy alone or drugs plus locoregional therapy. However, there were no clear criteria prior to a recent report [**22**]. This Editorial introduces the recently proposed criteria of "Clinical CR" and the "Drug-off Criteria" after imaging CR is achieved and discusses their validity.

2. High Rate of Complete Response by Combination Treatment with Systemic and Locoregional Therapy

Until recently, TACE was the only recommended treatment for intermediate-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm [**23**] in addition to EASL [**24**] and AASLD [**25**] clinical practice guidelines. If liver function is preserved and there is no vascular invasion or extrahepatic spread, the Hepatocellular Carcinoma Clinical Practice Guidelines by the Japan Society of Hepatology (JSH)[**26**] recommends systemic therapy in addition to TACE for patients with a primary tumor >3 cm in diameter or more than four multifocal tumors. Intermediate-stage HCC comprises a heterogeneous population in terms of tumor number, tumor size, and liver function. Although TACE has been the standard of care for intermediate-stage HCC, achieving a cure with TACE alone is difficult. The concept of "TACE refractory" [**27,28**] or "TACE unsuitable" [**17,18**] was proposed in recent years, resulting in a gradual shift in treatment strategies that prioritize upfront systemic therapy followed by TACE over TACE alone for patients with good liver function and a high tumor burden who are not suitable for TACE [**17-19,21,29,30**].

Intermediate-stage HCC is a locally advanced cancer; therefore, it is important to maximize treatment efficacy while maintaining liver function and managing adverse events. If a deep response is achieved using systemic therapy, locoregional therapy should be added as soon as possible while the response is maintained to achieve a complete cure (Fig. 2.) [**22**].

For combination therapy consisting of systemic therapy and locoregional therapy including TACE, RFA, and resection, the conventional response evaluation criteria are not sufficient. For example, RECISTv1.1 does not account for complete pathologic necrosis of HCC with lipiodol deposition due to conventional TACE [**31**]. Furthermore, mRECIST criteria requires subtraction imaging to accurately assess complete pathologic necrosis [**32**].

A new criterion for clinical CR was recently proposed [**22**]. This criterion is defined as follows: (1) CR according to mRECIST/RECIST v1.1 assessed by CT/MRI, and (2) normalization of three tumor markers (AFP/AFP-L3/PIVKA-II) and maintenance of normal values for at least 6 weeks (Table 1). Although it remains to be validated compared with pathological findings, it is a simple diagnostic method that is associated with good treatment outcomes, as discussed later.

3. Complete Response Rates with Single Agent Systemic Therapy

Table 2 summarizes the outcomes of systemic therapies currently approved by the FDA, EMA, and Japan for unresectable HCC [**6,7,11,16,33-36**]. The CR rate by RECISTv1.1 is <1% for molecular targeted agents (lenvatinib, sorafenib, ramucirumab, cabozantinib, and regorafenib). HCC is currently the most common malignant neoplasm

among primary malignancies of the digestive system that regress spontaneously or go into remission (HCC accounts for 49.5%, 193/390 cases, of all digestive cancers) [**37**]. The number of cases of spontaneous regression exceeds the number of cases achieving CR after treatment with sorafenib. Therefore, achieving CR after monotherapy with molecular targeted agents is rare.
However, 7.7% of patients treated with atezolizumab plus bevacizumab and 3.1% of patients treated with durvalumab plus tremelimumab achieved a CR according to RECISTv1.1, which is a promising result in terms of CR in unresectable HCC after 2020, when combination immunotherapy became available in the routine clinical practice. However, CR by imaging alone is not an accurate indication of pathological CR without subsequent recurrence.

4. Complete Response Rate with the Combination of Systemic and Locoregional Therapy

Table 3 summarizes the results of combination treatment with drugs and locoregional therapy.
In intermediate-stage HCC, the TACTICS trial showed that the combination of TACE plus sorafenib yields a CR rate of 28.8% and median PFS of 25.2 months, which is significantly better than the outcomes of TACE alone [**38,39**]. In the TACTICS-L trial, lenvatinib plus TACE resulted in a CR rate of 66.1% and a median PFS of 28.0 months [**40**].
In patients with advanced-stage HCC, a multicenter randomized controlled trial (LAUNCH study) comparing lenvatinib alone with lenvatinib plus on-demand TACE (LEN+TACE) [**41**] showed a favorable ORR of 54.1% and a median PFS of 10.6 months. Downstaging with LEN+TACE enabled conversion surgery in 15.3% (26/170) of patients, and complete pathologic necrosis was observed in 1.2% (2/170) of patients. Similarly, the LEOPARD trial, which tested the combination of CDDP and lenvatinib in advanced-stage HCC, reported an ORR of 45.7% and PFS of 6.3 months according to RECISTv1.1 [**42**]. Thus, the combination of systemic therapy and locoregional therapy in both intermediate-stage HCC and advanced-stage HCC is gradually becoming a major trend worldwide due to its favorable outcomes [**30**].
A recent multicenter proof-of-concept study [**22**] reported the results of the combination of atezolizumab plus bevacizumab as initial therapy followed by curative conversion treatments such as resection, super-selective TACE, or ablation for TACE-unsuitable patients with early- to intermediate-stage HCC and good liver function (**A**tezolizumabp plus **B**evacizumab followed by **C**urative conversion therapy: **ABC conversion therapy**). The study reported a clinical CR rate of 34.5% (38/110 patients) based on the definition of clinical CR provided earlier (Table 1). In patients who achieved partial response (PR) or stable disease (SD) with Atezo/Bev, CR or deep PR can be achieved with the addition of locoregional therapy before the development of PD (Fig. 2.). Although the results cannot be simply compared, the percentage of patients achieving CR in response to the combination of systemic and locoregional therapy is increasing compared with that of patients treated with systemic therapy alone or locoregional therapy alone. In addition, in patients who fulfilled the drug-off criteria (Table 1), there was no recurrence during the 21.2 months follow-up period. In that sense, this drug-off criteria highly suggest pathological CR. A multicenter, prospective, randomized Phase 3 trial (IMPACT trial) is scheduled to start in Japan in the summer of 2023 to validate this favorable result [**22**] (shown in Fig. 3.).
Currently, several Phase 3 trials are ongoing to confirm the favorable results of the combination of TACE and immunotherapy in prospective randomized controlled trials. In particular, the TALENTACE trial, which evaluates the combination of TACE and atezolizumab plus bevacizumab [**43**], the ABC HCC trial [**44**], the EMERALD-1 trial, the EMERALD-3 trial [**45**], and the LEAP-012 study [**46**] are expected to show positive results (Fig. 3.).

5. Can Drugs be Discontinued in Patients who fulfil Drug-off Criteria?

Drug-free status is important for patients' quality of life if pathological CR is truly obtained. In the LAUNCH trial, the recurrence rate of patients receiving LEN+TACE followed by curative resection was not described in detail, although drug discontinuation was reported in some cases [**41**].
A multicenter proof-of-concept study of ABC conversion therapy [**22**] proposed the following criteria for drug discontinuation: (1) mRECIST CR achieved by super-selective TACE/RFA/MWA, (2) sustained normalization of AFP/AFP-L3/PIVKA-II for at least 12-24 weeks, and (3) complete disappearance of arterial blood flow in the tumor determined by contrast-enhanced ultrasonography (CEUS), which has the highest sensitivity for detecting intra-tumor arterial blood flow [**47-60**]. Although 25 patients remained cancer-free with no recurrence of HCC after drug discontinuation, 3 of the 13 patients who did not meet the drug-off criteria and continued atezolizumab plus bevacizumab therapy had recurrence of HCC[**22**]. These data indicate that it is not adequate to discontinue the

drug simply because the criterion for clinical CR was met. Conversely, the drug-off criterion is useful for the clinical diagnosis of pathological CR.
However, this criterion is only feasible in countries such as Japan, where tumor markers other than AFP, such as PIVKA-II and AFP-L3, can be routinely measured in clinical practice. Cases in which AFP is negative and only PIVKA-II or AFP-L3 is abnormal, suggest non-pathological CR because cancer cells may be present somewhere. In such cases, it is necessary to detect intranodular arterial flow, and if it is detected, cancer-free status can be achieved by performing super-selective TACE or ablation. Although it is not necessary to perform CEUS in all cases for the management of HCC, CEUS is crucial for the decision of drug-off because CEUS is much more sensitive than CT/MRI for the detection of intranodular arterial blood flow. Thus, CEUS plays an important role in the diagnosis of pathological CR in addition to normalized AFP, AFP-L3, and PIVKA-II levels, and is thus important for determining when to discontinue the treatment drug.
There has been no proposal so far regarding the drug-off criteria for patients who have achieved CR per RECIST v1.1 (complete tumor disappearance on CT or MRI) after receiving combination immunotherapy alone. The following criteria may be used: (1) CR by CT/MRI (RECIST v1.1), (2) persistent negative results for all three tumor markers (AFP, AFP-L3, and PIVKA-II) for at least 12-24 weeks, and (3) complete disappearance of the nodule by fusion imaging technique with CT/MRI and ultrasound[**61-63**]. Drug-off is considered acceptable if no Kupffer defect is found on CEUS with Sonazoid at the site of the primary tumor or if no intratumoral arterial blood flow is detected by the re-injection technique [**64-67**] even if a Kupffer defect is found. On the other hand, if arterial flow remains within the Kupffer defect (Defect Reperfusion) by sonazoid CEUS, RFA under CEUS guideline[**55**] on fusion-image-guided ablation[**61-63**] can lead to true cancer-free status after drug discontinuation.

6. Conclusion

The combination of atezolizumab-bevacizumab and locoregional therapy has shown promising results for achieving a high rate of clinical CR in TACE-unsuitable intermediate-stage and advanced-stage HCC, in which CR is rarely achieved with locoregional therapy alone or systemic therapy alone. An increasing number of patients who achieve clinical CR with systemic therapy-based multimodal therapy are facing the choice of whether to continue or discontinue the treatment drug. The criteria for drug discontinuation remain to be sufficiently validated, and there is a lack of data on recurrence rates after drug discontinuation. Although the recently reported criteria are reliable [**22**], further validation study is needed.

Conflict of Interest Statement

Lecture: Eli Lilly, Bayer, Eisai, Chugai, Takeda, AstraZeneca; Grants: Taiho, Otsuka, EA Pharma, AbbVie, Eisai, Chugai, GE Healthcare; Advisory Consulting: Chugai, Roche, AstraZeneca, Eisai.
Masatoshi Kudo is the Editor-in-Chief of Liver Cancer.

Funding Sources

There is no funding for this Editorial.

Author Contributions

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

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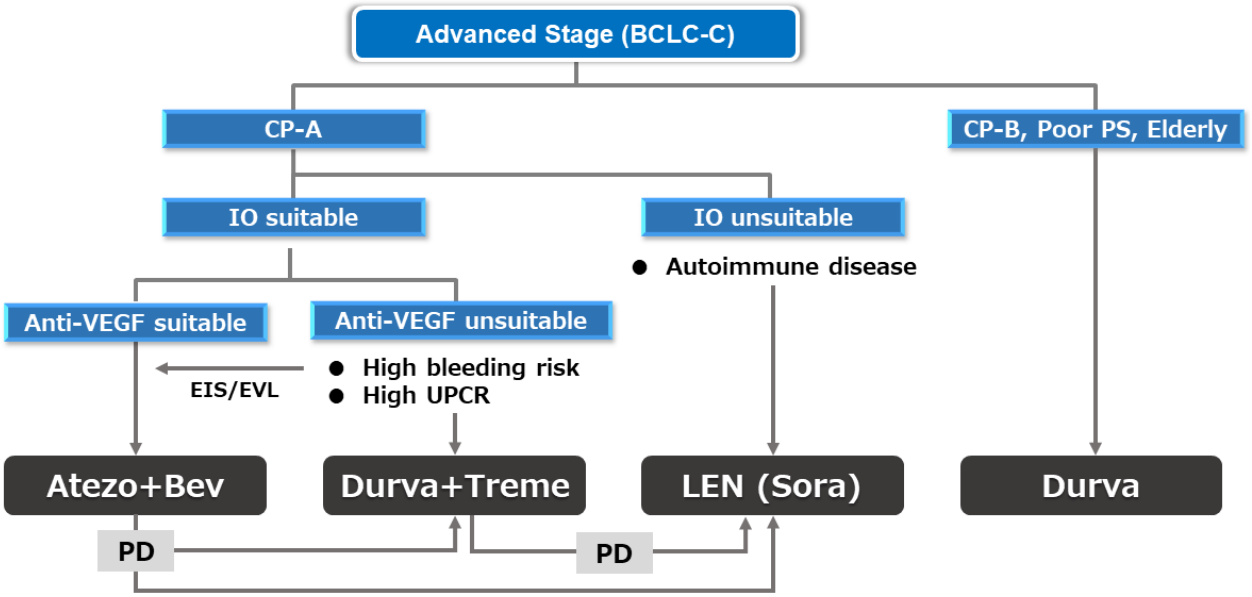
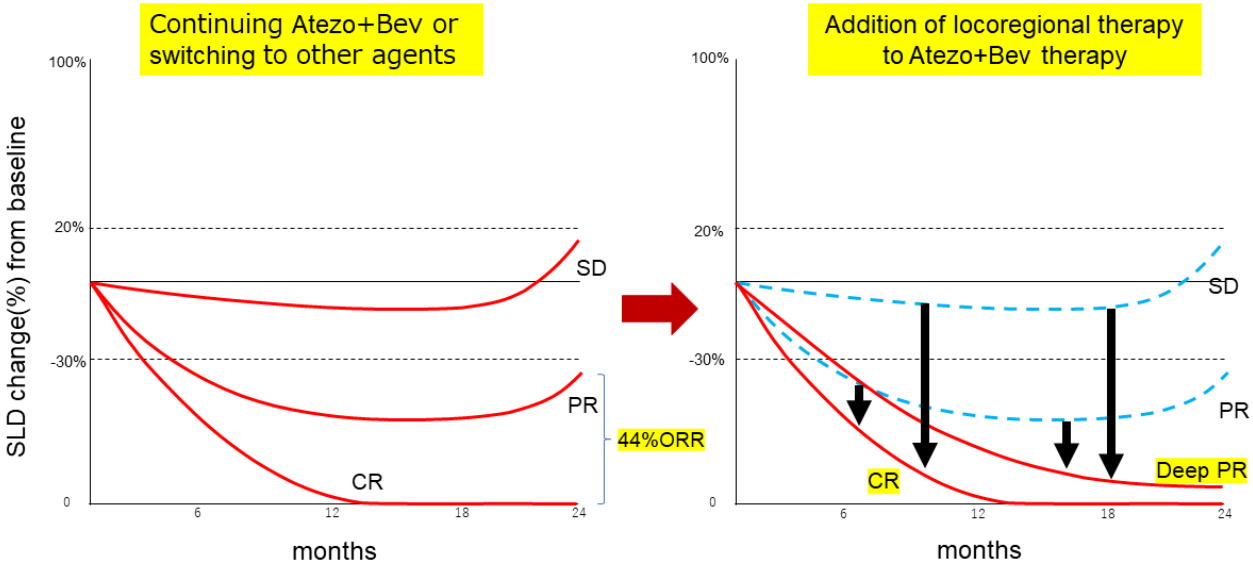
Figure Legends

Fig. 1. First-line treatment strategy for advanced-stage hepatocellular carcinoma
EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; UPCR, urine protein creatinine ratio; CP-A, Child-Pugh grade A, CP-B, Child-Pugh grade B, IO, immuno-oncology

Fig. 2. Effect of adding locoregional therapy to systemic therapy in intermediate-stage hepatocellular carcinoma (HCC)
Systemic therapy alone cannot achieve pathological complete response (CR) even in intermediate-stage HCC. During the best response is maintained, addition of locoregional therapy (resection, ablation, superselective TACE) can achieve high rate of pathological CR.
Even though CR is not achieved deep and durable response is achieved from stable disease (SD) and partial response (PR)

Fig. 3. Current ongoing Phase 3 clinical trials in hepatocellular carcinoma





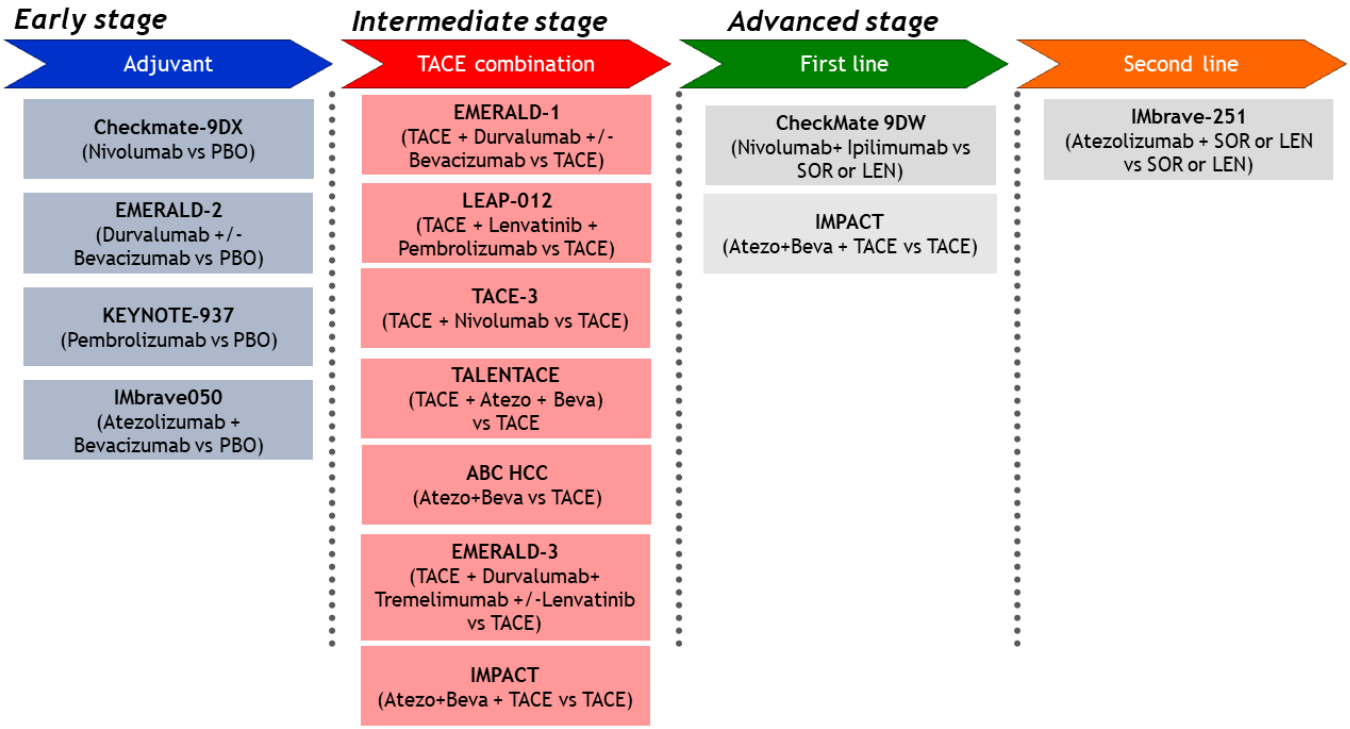


Table 1. Definition of Clinical CR and Drug-off Criteria in Immunotherapy Combined with Locoregional Therapy

Definition of Clinical CR
Fulfilling the following 2 conditions; 1. Achievement of CR per mRECIST/RECISTv1.1 evaluated by CT/MRI 2. Continuous normalization of 3 tumor markers (AFP/AFPL-3/PIVKA-II) more than 6 weeks
Drug-off Criteria
Fulfilling the following 3 conditions; 1. Achievement of CR per mRECIST (RECISTv1.1) by super-selective TACE/RFA/MWA 2. Continuous normalization of 3 tumor markers (AFP/AFP-L3/PIVKA-II) more than 12-24 weeks 3. Complete disappearance of intra-nodular arterial flow by CEUS

CR; Complete response, AFP; Alpha-fetoprotein, AFP-L3; Alpha-fetoprotein isoform, lectin affinity, PIVKA-II; Protein induced by vitamin K absence or antagonist-II, CEUS; Contrast-enhanced ultrasonography

Cited from ref #22

Table 2. Efficacy results of systemic therapy

	IMbrave150 trial Atezolizumab plus bevacizumab (Ref. 6,7)	**HIMALAYA trial** Durvalumab plus Tremelimumab (Ref. 11)	**REFLECT trial** Lenvatinib (Ref. 16)	**SHARP trial** Sorafenib (Ref. 33)	**REACH-2 trial** Ramucirumab (Ref. 34)	**CELESTIAL trial Cabozantinib** (Ref. 36)	**RESORSE trial** Regorafenib (Ref. 35)
Median OS (months)	19.2 (95%CI：NA)	16.4 (95%CI：14.2-19.6)	13.6 (95%CI：12.1-14.9)	10.7 (95%CI：9.4-13.3)	8.5 (95%CI：7.0-10.6)	10.2 (95%CI：9.1-12.0)	10.6 (95%CI：9.1-12.1)
Median PFS (months)	6.9 (95%CI：NA)	3.8 (95%CI：3.68-5.32)	7.4 (95%CI：6.9-8.8)	(TTP) 5.5 (95%CI：4.1-6.9)	2.8 (95%CI：2.8-4.1)	5.52 (95%CI：4.0-5.5)	3.1 (95% CI：92.8-4.1)
CR RECISTv1.1	**7.7 % (n=25)**	**3.1 % (n=12)**	**<1 % (n=2)**	**0 % (n=0)**	**0 % (n=0)**	**0 % (n=0)**	**1 % (n=2)**
ORR (%) RECISTv1.1	29.8 % (95%CI：24.8-35.0)	20.1 % (95%CI：NA)	24.1 % (95%CI：20.2-27.9)	2 % (95%CI：NA)	4.6 % (95%CI：1.7-7.5)	4.0 % (95%CI：2.8-7.7)	10 % (95%CI：7-14)
DCR (%) RECISTv1.1	73.6 % (95%CI：NA)	60.1 % (95%CI：NA)	75.5 % (95%CI：71.7-79.4)	43 % (95%CI：NA)	59.9 % (95%CI：53.1–66.7)	64 % (95%CI：NA)	65 % (95%CI：NA)

NA; not available, TTP; thrombotic thrombocytopenic purpura, CR; Complete Response, ORR; overall response rate, DCR; disease control rate, OS; overall survival, PFS; progression-Free Survival.

Table 3. Efficacy Results by Combination of Systemic plus Locoregional Therapy

	TACTICS trial Sorafenib＋TACE (Ref.38,39)(n=80)	**TACTICS-L trial** Lenvatinib＋TACE (n=62) (Ref. 40)	**ABC conversion** Atezolizumab plus Bevacizumab ＋TACE/RFA/resection (n=110) (Ref. 22)	**LAUNCH trial** Lenvatinib＋TACE (n=170) (Ref. 41)	**LEOPARD trial** Lenvatinib＋CDDP HAIC (n=36) (Ref. 42)
	Intermediate stage	**Intermediate stage**	**Intermediate stage**	**Advanced stage**	**Advanced stage**
Median OS (months)	36.2 (95%CI: 30.5-44.1)	NR (90%CI: 35.5-NR)	NR	17.8 (95%CI：16.1-19.5)	17.2 (95% CI: 10.9-NR)
Median PFS (months)	22.8 (95%CI：18.4-27.5))	28.0 (90%CI：25.1-31.0)	NR	10.6 (95%CI：9.5-11.7)	6.3 (95% CI: 5.1-7.9)
CR(%) (mRECIST)	**28.8 (n=23)**	**66.1 (n=41)**	**NA**	**2.9 (n=5)**	**NA**
Clinical CR*(%)	**NA**	**NA**	**34.5 (n=38) (drug-free in 23%)**	**15.3 (n=26) ****	**NA**
ORR (%) **(mRECIST)**	71.3 (95%CI：NA)	85.5 (90%CI：76.0 – 92.2)	NA	54.1 (95%CI：NA)	61.1 (95%CI: 43.5-76.9)
DCR (%)	83.8 (95%CI：NA)	91.9 (90%CI：NA)	81.8 (95%CI：NA)	94.2 (95%CI：NA)	83.3 (95%CI：67.2-93.6)

NA, not available; NR, not reached; AFP; Alpha-fetoprotein, AFP-L3; Alpha-fetoprotein isoform, lectin affinity, PIVKA-II; protein induced by vitamin K absence or antagonist-II

*mRECIST CR with normalized AFP, AFP-L3 and PIVKA-II levels>6 weeks
* *Curative resection after downstaging by LEN+TACE