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Multicenter Phase II trial of lenvatinib plus hepatic intra-arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma: LEOPARD

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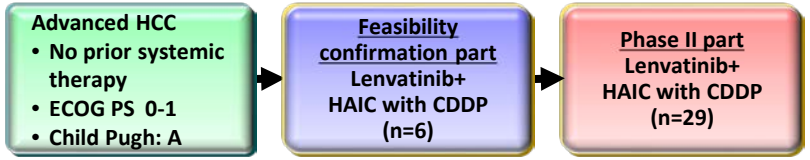
Trial design



Purpose

In patients with advanced hepatocellular carcinoma (HCC) who have no prior history of systemic therapy, the tolerability of the combination of lenvatinib and hepatic arterial infusion chemotherapy (HAIC) with cisplatin was confirmed in the first 6 patients, and the efficacy and safety were evaluate in the phase II part.

Primary endpoint:

Objective response rate (ORR) (central assessment: modified RECIST)

Secondary endpoints:

Progression-free survival (PFS), Overall survival (OS), frequency of adverse events, ORR (Central assessment: RECIST1.1), ORR (Investigator's judgement: mRECIST), etc.

Main eligibility criteria

- Advanced HCC patients who are not applicable for surgical resection, liver transplantation, local ablative therapy or TACE
- No prior systemic therapy for HCC
- Age 20-79 years old
- Presence of measurable lesions
- ECOG PS of 0-1
- Written informed consent

Treatment of Lenvatinib+HAIC with CDDP

HAIC with CDDP: a dose of 65 mg/m^2, every 4-6 weeks for up to 6 courses.

Lenvatinib: 12mg, qd for body weight of ≥60kg, 8mg, qd for body weight of <60kg

Statistical consideration

Expected ORR (mRECIST): 40%

Threshold ORR (mRECIST): 20%

Power: 80%, α: one-sided 5% (Two-sided 10%)

Number of required patients: 35 patients

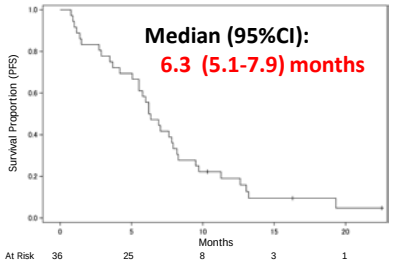
Patient characteristics (n=36) (Sep 2018-Mar 2020)

	n	%
Age (yrs), median (range)	68	(23-78)
Gender, male	33	91.7
ECOG performance status, 0	35	97.2
1	1	2.8
HBs Ag (+)	8	22.2
HCV Ab (+)	8	22.2
Child-Pugh score, A5	25	69.4
A6	11	30.6
Previous local treatments (+)	22	61.1
BCLC stage, B	20	55.6
C	16	44.4
Portal vein invasion (+)	16	44.4
Extrahepatic metastases (+)	8	22.2
AFP (ng/mL), median (range)	131.6	(1.4-108,160)

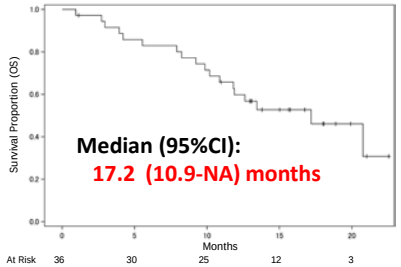
Tumor response

	Central assessment				Investigator	
	mRECIST		RECIST1.1		mRECIST	
Best Response	n	%	n	%	n	%
CR	10	29.4	3	8.6	6	16.7
PR	12	35.3	13	37.1	16	44.4
SD	4	11.8	10	28.6	8	22.2
PD	8	23.5	9	25.7	6	16.7
Not evaluable	2	—	1	—	—	—
ORR (CR+PR)	64.7% (22/34)		45.7% (16/35)		61.1% (22/36)	
Exact 95% CI	(46.5%, 80.3%)		(28.8%, 63.4%)		(43.5%, 76.9%)	
DCR (CR+PR+SD)	76.5% (26/34)		74.3% (26/35)		83.3% (30/36)	

Progression-free survival



Overall survival



Main adverse events (Worst grade)

Adverse events	G1	G2	G3	G4	G1-4 (%)	G3-4 (%)
Nausea	6	6	1	-	36%	3%
Fatigue	6	5	2	-	36%	6%
Malaise	11	10	-	-	58%	-
Appetite loss	11	14	2	0	75%	6%
Palmar-plantar erythrodysesthesia	9	7	0	-	44%	0%
Hypertension	3	10	4	0	47%	11%
Leukocytopenia	2	13	8	0	64%	22%
Neutropenia	3	13	7	0	64%	19%
Anemia (decreased hemoglobin)	12	9	3	0	67%	8%
Thrombocytopenia	7	18	2	0	75%	6%
Increased T-Bil	5	7	3	1	44%	11%
Increased AST	2	15	12	0	81%	33%
Increased ALT	14	8	7	0	81%	19%
Hypoalbuminemia	7	20	1	-	78%	3%
Increased Cr	11	3	0	1	42%	3%
Proteinuria	15	8	3	-	72%	8%

Comparison of LEOPARD results with standard first-line treatment

	Sorafenib	Sorafenib	Lenvatinib	Atezo+Bev	Lenva+CDDP
Trial name	SHARP	Asia-Pacific	REFLECT	IMbrave150	LEOPARD
ORR (mRECIST)	ND	ND	40.6%	35%	64.7%
ORR (RECIST)	2%	3.3%	18.8%	30%	45.7%
PFS (months)	5.5*	2.8*	7.3	6.9	6.3
OS (months)	10.7	6.5	13.6	19.2	17.2

*Time to Progression. ND, no data.

Conclusions

Len+CDDP yielded very favorable ORR and overall survival, and was well-tolerated in pts with advanced HCC. Further evaluation of this regimen in a phase III trial is warranted.

Acknowledgement

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Disclosure of Potential Conflicts of Interest

Ikeda M reports personal fees and other from Eisai, MSD, Eli Lilly Japan, Yakult, Ono, Chugai, Bristol-Myers Squibb, Novartis, Bayer, Takeda, outside the submitted work.