

## Challenge of lenvatinib application in HCC

**Supplementary Table 1.** The advances of lenvatinib combination therapy in advanced HCC

Therapy Regimens	mOS (months)	mPFS (months)	ORR (%)	DCR (%)	Efficacy Evaluation	References
LEN+TACE vs TACE (46 vs 57)	/	/	69.57 vs 40.35, (P<0.05)	/	mRECIST	[37]
LEN+TACE vs TACE (34 vs 32)	/	17.00 vs 14.00, (P=0.510)	64.7 vs 34.4, (P=0.014)	79.4 vs 59.4, (P=0.066)		[38]
LEN+TACE vs TACE (53 vs 51)	/	/	77.36 vs 56.36, (P<0.05)	94.34 vs 79.89, (P<0.05)		[39]
LEN+TACE vs TACE (34 vs 68)	27.7 vs 18.4, (P=0.043)	8.3 vs 4.6, (P=0.008)	64.1 vs 36.5, (P=0.002)	79.4 vs 69.1, (P=0.272)		[40]
LEN+TACE vs TACE (60 vs 60)	/	/	68.3 vs 31.7, (P<0.001)	93.3 vs 86.7, (P<0.224)		[41]
LEN+TACE vs LEN (170 vs 168)	17.8 vs 11.5, (P<0.001)	10.6 vs 6.4, (P<0.001)	54.1 vs 25.0, (P<0.001)	94.1 vs 73.2, (P<0.001)		[43]
LEN+TACE vs LEN (19 vs 19)	not reached vs 16.9, (P=0.007)	11.6 vs 10.1, (P=0.019)	63.2 vs 63.2, (P=1.0)	100 vs 100, (P=1.0)		[44]
LEN+DEB-TACE vs LEN (142 vs 69)	15.9 vs 8.6, (P=0.0022)	8.6 vs 4.4, (P<0.001)	46.48 vs 13.05, (P<0.001)	76.76 vs 56.52, (P<0.001)		[45]
LEN+DEB-TACE vs LEN (78 vs 78)	8.0 vs 5.0, (P=0.003)	/	57.7 vs 25.6, (P<0.001)	75.6 vs 56.4, (P=0.011)		[46]
LEN+TACE vs SOR+TACE (25 vs 24)	13.0 vs 8.0, (P<0.05)	10 vs 6.5, (P<0.05)	62.8 vs 46.3, (P=0.027)	86.0 vs 76.7, (P=0.03)		[48]
LEN+TACE vs SOR+TACE therapy (59 vs 57)	19.0 vs 10.8, (P=0.022)	8.4 vs 7.43, (P=0.081)	60.7 vs 38.9, (P=0.022)	96.4 vs 96.3, (P>0.05)		[49]
LEN+TACE vs SOR+TACE therapy (53 vs 59)	30.5 vs 20.5, (P=0.018)	10.7 vs 6.0, (P=0.002)	54.7 vs 44.1, (P=0.260)	81.1 vs 61.0, (P=0.020)		[50]
LEN+DEB-TACE vs SOR+DEB-TACE (50 vs 100)	14.9 vs 12.3, (P=0.043)	/	64.0 vs 33.3, (P=0.008)	76.0 vs 68.0, (P=0.310)		[51]
LEN vs ATEZ/BEV (181 vs 177)	/	7.3 vs 10.8, (P=0.019)	/	/		[56]
LEN vs ATEZ/BEV (152 vs 152)	20.2 vs not reached, (P=0.039)	6.0 vs 8.3, (P=0.005)	47.5 vs 44.2, (P=0.440)	80.8 vs 88.9, (P=0.013)		[57]
LEN vs ATEZ/BEV (66 vs 66)	20.6 vs not reached, (P=0.577)	5.2 vs 8.8, (P=0.012)	52.4 vs 43.8, (P=0.330)	82.5 vs 76.6, (P=0.404)		[58]
LEN vs ATEZ/BEV (170 vs 92)	17.9 vs 14.0, (P=0.7)	6.3 and 7.2, (P=0.2)	35.9 vs 33.7, (P=0.8)	62.9 vs 63.0, (P=1.0)		[59]
LEN vs ATEZ/BEV (152 vs 65, with Child-Pugh B)	13.8 vs 8.2, (P=0.005)	8.2 vs 6.9, (P=0.8443)	35.0 vs 18.0, (P=0.0185)	65.0 vs 55.0, (P=0.2213)		[60]
LEN+TACE vs ATEZ/BEV+TACE (34 vs 34)	/	6.03 vs 7.03, (P=0.545)	58.8 vs 61.8, (P=0.804)	85.3 vs 82.4, (P=0.742)		[63]
LEN+SBRT vs LEN (37 vs 77)	19.3 vs 11.2, (P<0.001)	10.3 vs 5.3, (P<0.001)	56.8 vs 20.8, (P<0.001)	91.9 vs 64.9, (P=0.005)		[73]
LEN+SBRT vs SBRT (35 vs 35)	16.8 vs 11.0, (P=0.043)	9.1 vs 3.7, (P<0.001)	54.29 vs 22.86, (P=0.007)	85.71 vs 46.43, (P=0.005)		[75]
LEN+TACE+RT vs LEN+TACE (51 vs 51, with PVTT)	22.8 vs 17.1, (P=0.031)	12.8 vs 10.5, (P=0.035)	56.9 vs 51.0, (P=0.551)	92.1 vs 90.2, (P=0.727)		[76]
LEN+PD-1+HAIC vs LEN+PD-1 (89 vs 53, with PVTT)	26.3 vs 13.8, (P<0.001)	11.5 vs 5.5, (P<0.001)	61.8 vs 20.8, (P<0.001)	/		[82]
LEN+PD-1+HAIC vs LEN+PD-1 (84 vs 86)	17.7 vs 12.6, (P=0.001)	10.9 vs 6.8, (P=0.001)	59.5 vs 41.9, (P=0.022)	88.1 vs 82.6, (P>0.05)		[83]
LEN+PD-1+HAIC vs LEN+PD-1 (45 vs 25)	15.9 vs 8.6, (P=0.0015)	8.8 vs 5.4, (P=0.032)	40.0 vs 16.0, (P=0.038)	77.6 vs 44.0, (P<0.001)		[84]
LEN+PD-1+HAIC vs LEN+PD-1 (58 vs 63, TACE-refractory uHCC patients)	24.0 vs 13.0, (P=0.001)	13.0 vs 7.2, (P<0.001)	48.3 vs 23.8, (P=0.005)	87.9 vs 69.8, (P=0.02)		[85]
LEN+PD-1+HAIC vs LEN+PD-1+TACE (34 vs 61)	25.0 vs 19.3, (P=0.035)	21.74 vs 8.74, (P=0.007)	52.9 vs 27.9, (P=0.03)	100 vs 88.5, (P=0.001)	RECIST v.1.1 criteria	[86].

## Challenge of lenvatinib application in HCC

LEN+PD-1+HAIC vs LEN+HAIC (75 vs 74)	16.0 vs 9.0, (P=0.002)	11.0 vs 6.0, (P<0.001)	45.33 vs 33.78, (P=0.146)	78.66 vs 62.12, (P=0.027)	mRECIST	[87]
LEN+PD-1+HAIC vs LEN+HAIC (58 vs 87, HAIC refractory uHCC patients)	43.6 vs 18.9, (P=0.009)	35.6 vs 9.4, (P=0.009)	/	/		[88]
LEN+PD-1+HAIC+ TAE vs LEN+PD-1+HAIC (50 vs 50)	14.1 vs 11.3, (P=0.041)	5.6 vs 4.4, (P=0.037)	72.0 vs 52.0, (P=0.039)	88.0 vs 76.0, (P=0.118)		[89]
LEN+PD-1+HAIC vs LEN (71 vs 86)	not reached vs 11, (P<0.001)	11.1 vs 5.1, (P<0.001)	67.6 vs 13.6, (P<0.001)	90.1 vs 72.1, (P=0.005)		[90]
LEN+HAIC vs HAIC (110 vs 132)	/	19.4 vs 16.1, (P=0.092)	/	/		[93]
LEN+HAIC+ sequential ablation vs LEN+HAIC (53 vs 97)	30.0 vs 13.6, (P=0.010)	12.8 vs 5.6, (P<0.001)	/	/		[95]
LEN vs HAIC (52 vs 52)	7.9 vs 10.8, (P=0.106)	4.0 vs 3.6, P=0.706	23.1 vs 28.8, (P=0.502)	51.9 vs 73.1, (P=0.026)	RECIST v1.1 criteria	[96]
LEN vs PD-1+HAIC (65 vs 53)	10.1 vs 17.1, (P=0.005)	4.8 vs 9.3, (P=0.006)	9.2 vs 47.2, (P<0.001)	69.2 vs 86.8, (P=0.002)		[97]
LEN+PD-1 vs LEN+ placebo (395 vs 399)	21.2 vs 19.0, (P=0.023)	8.2 vs 8.0, (P=0.047)	26.1 vs 17.5	81.3 vs 78.4		[106]
LEN+PD-1 group vs LEN (54 vs 85)	21.7 vs 12.8, (P=0.0051)	11.3 vs 6.6, (P=0.0128)	38.9 vs 24.7, (P=0.076)	92.6 vs 74.1, (P=0.006)	mRECIST	[107]
LEN+PD-1 vs LEN group (40 vs 47)	22.9 vs 10.3, (P=0.01)	7.5 vs 4.8, (P=0.05)	45.0 vs 23.4, (P=0.03)	83.5 vs 76.6, (P=0.5)	RECIST v.1.1 criteria	[108]
LEN+PD-1 vs REG+PD-1 (32 vs 29)	5.3 vs 4.0, (P=0.512)	14.1 vs 13.7, (P=0.764)	12.5 vs 10.3, (P=0.557)	71.9 vs 58.6, (P=0.207)		[113]
LEN+PD-1 vs PD-1 (30 vs 39)	18.4 vs 8.5, (P=0.013)	10.6 vs 4.4, (P<0.001)	32.7 vs 10.3, (P=0.013)	80.0 vs 53.8, (P=0.012)		[115]
LEN+PD-1+TACE vs LEN+TACE (41 vs 40)	16.9 vs 12.1, (P=0.009)	7.3 vs 4.0, (P=0.002)	56.1 vs 32.5, (P=0.033)	85.4 vs 62.5, (P=0.019)	mRECIST	[146]
LEN+PD-1+TACE vs LEN+TACE (33 vs 49)	16.4 vs 11.0, (P<0.01)	9.4 vs 5.9, (P<0.01)	51.7 vs 47.9, (P>0.05)	81.8 vs 77.6, (P=0.429)		[147]
LEN+PD-1+TACE vs LEN+TACE (31 vs 52)	18.9 vs 13.9, (P<0.001)	12.5 vs 6.6, (P<0.001)	71.0 vs 42.3, (P=0.023)	93.5 vs 80.8, (P=0.195)		[148]
LEN+PD-1+TACE vs LEN+PD-1 (60 vs 58)	29.0 vs 17.8, (P<0.01)	16.2 vs 10.2, (P<0.01)	76.7 vs 44.9, (P<0.01)	96.7 vs 75.9, (P<0.01)		[152]
LEN+PD-1+TACE vs LEN+PD-1 (86 vs 86)	20.5 vs 12.8, (P=0.013)	12.1 vs 7.8, (P=0.030)	55.8 vs 30.2, (P=0.017)	86.0 vs 65.1, (P=0.024)		[153]
LEN+PD-1+TACE vs LEN+PD-1 (75 vs 39)	not reached vs 14.0, (P=0.0039)	11.1 vs 5.1, (P=0.033)	44.0 vs 23.1, (P=0.028)	62.7 vs 43.6, (P=0.051)		[154]
LEN+PD-1+TACE vs SOR+PD-1+TACE (80 vs 85)	21.7 vs 15.6, (P=0.0027)	6.3 vs 3.2, (P<0.001)	41.25 vs 30.59, (P=0.008)	86.25 vs 62.35, (P=0.008)		[156]
LEN+PD-1+TACE vs PD-1+TACE (57 vs 41)	19.8 vs 15.7, (P<0.001)	11.4 vs 8.4, (P<0.001)	57.9 vs 41.5, (P=0.108)	75.4 vs 58.5, (P=0.076)		[157]
LEN+PD-1+TACE vs TACE (57 vs 43)	19.8 vs 9.4, (P<0.001)	11.4 vs 4.8, (P<0.001)	57.9 vs 32.6, (P=0.012)	75.4 vs 55.8, (P=0.039)		[157]
LEN+PD-1+TACE vs PD-1+TACE (56 vs 47)	26.0 vs not reached, (P=0.0045)	22.5 vs 14.0, (P=0.0013)	64.3 vs 38.3, (P=0.010)	85.7 vs 57.4, (P=0.002)		[158]
LEN+PD-1+TACE vs TACE (56 vs 54)	23.9 vs 15.3, (P<0.001)	11.9 vs 6.9, (P=0.003)	67.9 vs 29.6, (P<0.001)	92.9 vs 83.3, (P=0.122)		[159]
LEN+PD-1+TACE vs LEN+TACE (23 vs 29)	26.7 vs 14.4, (P=0.007)	8.2 vs 6.0, (P=0.005)	86.96 vs 34.48, (P<0.001)	100 vs 48.28, (P<0.001)		[160]
LEN+PD-1+TACE vs SOR+TACE (23 vs 32)	26.7 vs 17.9, (P=0.031)	8.2 vs 6.6, (P=0.047)	86.96 vs 46.88, (P<0.001)	100 vs 75, (P<0.001)		[160]