PICO 1: In patients with HCC who failed LRT, are not eligible for LRT, or have metastatic disease with preserved liver function, what systemic therapy should be used?

First-Line Treatment

Sorafenib compared to no Sorafenib for HCC patients who are failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Sorafenib	With Sorafenib		Risk with no Sorafenib	Risk difference with Sorafenib
Mortality (follow up: range 19 months to 23 months)											
828 (2 RCTs) [1,2,a]	serious [b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	379 participants	449 participants	**HR 0.69** (0.57 to 0.83) [Mortality] [c]	**1-year**	
										670 per 1,000	**135 fewer per 1,000** (from 202 fewer to 68 fewer)
										Study Duration	
										590 per 1,000	**131 fewer per 1,000** (from 192 fewer to 67 fewer)
Disease progression (follow up: range 19 months to 23 months)											
828 (2 RCTs) [1,2]	not serious	not serious	serious [d,e]	not serious	none	⊕⊕⊕◯ MODERATE	379 participants	449 participants	**HR 0.58** (0.47 to 0.70) [Disease progression] [f]	**Study Duration**	
										520 per 1,000	**173 fewer per 1,000** (from 228 fewer to 118 fewer)
Quality of life (follow up: median 23 months)											
226 (1 RCT) [1]	serious [g]	not serious	not serious	serious [h]	none	⊕⊕◯◯ LOW	Cheng 2009 reported that "both treatment groups had similar total scores on the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index (FHSI-8) questionnaire and Functional Assessment of Cancer Therapy–Hepatobiliary (FACT–HP) questionnaire and showed no difference in QOL between the two groups (data not shown)."				
Harms: Serious adverse events											
823 (2 RCTs) [1,2]	not serious	not serious	not serious	serious [i]	none	⊕⊕⊕◯ MODERATE	198/377 (52.5%)	224/446 (50.2%)	**RR 0.97** (0.85 to 1.11)	525 per 1,000	**16 fewer per 1,000** (from 79 fewer to 58 more)
Harms: Discontinuation due to adverse events											
823 (2 RCTs) [1,2]	not serious	not serious	not serious	serious [i]	none	⊕⊕⊕◯ MODERATE	122/377 (32.4%)	142/446 (31.8%)	**RR 1.07** (0.88 to 1.31)	324 per 1,000	**23 more per 1,000** (from 39 fewer to 100 more)

Sorafenib compared to no Sorafenib for HCC patients who are failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings
Resource use - not reported							
-	-	-	-	-	-	-	AWP prices are the following: Sorafenib: $830 per 400 mg bid dosing. The median duration of therapy was 5.3 months in the Sorafenib group and 4.3 months in the Placebo group. Adjusted cost per course for Sorafenib is $132,034. The median overall survival was 10.7 months in the Sorafenib group and 7.9 months in the Placebo group. The estimated cost per life-year saved with Sorafenib is $565,858.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 25-54%, 1: 38-69%, 2: 2-8%; CP A 95-98%, B 2-5%; BCLC B 17-18%, C 82-96.1%
b. It was not clear if the decision for subsequent therapies after discontinuation of treatment was blinded or not. It was also not clear what therapies were given to each arm after discontinuation of treatment.
c. Median survival: SHARP trial 10.7 (9.4-13.3) vs 7.9 (6.8-9.1) months (difference 2.8 months) and AP trial 6.5 (5.6-7.6) vs 4.2 (3.8-5.5) months (difference 2.3 months).
d. Disease progression is an indirect measure of survival benefit.
e. Chen 2009 only reported progression as a composite of radiological progression or symptomatic progression.
f. Median time to progression: SHARP trial 5.5 (4.1-6.9) vs 2.8 (2.7-3.9) months (difference 2.7 months) and AP trial 2.8 (2.6-3.6) vs 1.4 (1.4-1.6) months (difference 1.4 months).
g. The study did not report details on survey response or response rates.
h. Small sample size.
i. Confidence interval shows both appreciable benefit and harm.

References

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2. Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J. F., de Oliveira, A. C., Santoro, A., Raoul, J. L., Forner, A., Schwartz, M., Porta, C., Zeuzem, S., Bolondi, L., Greten, T. F., Galle, P. R., Seitz, J. F., Borbath, I., Haussinger, D., Giannaris, T., Shan, M., Moscovici, M., Voliotis, D., Bruix, J., Group, Sharp,Investigators,Study. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med; Jul 24 2008.

Atezolizumab + Bevacizumab compared to Sorafenib for HCC patients who failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Sorafenib	With Atezolizumab + Bevacizumab	Relative effect (95% CI)	Risk with Sorafenib	Risk difference with Atezolizumab + Bevacizumab
Mortality (follow up: median 8.6 months)											
501 (1 RCT) [1,a]	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	65/165 (39.4%)	96/336 (28.6%)	**HR 0.66** (0.52 to 0.85) [d]	**1-year**	
										454 per 1,000	**125 fewer per 1,000** (from 184 fewer to 52 fewer)
										Study Duration	
										394 per 1,000	**113 fewer per 1,000** (from 165 fewer to 47 fewer)
Progression-free survival (follow up: median 8.6 months; assessed with: death or progression)											
501 (1 RCT) [1]	serious [b]	not serious	serious [e]	not serious	none	⨁⨁◯◯ LOW	109/165 (66.1%)	197/336 (58.6%)	**HR 0.59** (0.47 to 0.76) [f]	**Study Duration**	
										661 per 1,000	**189 fewer per 1,000** (from 262 fewer to 100 fewer)
Deterioration of quality of life (follow up: median 8.6 months; assessed with: ORTC QLQ-C30)											
501 (1 RCT) [1]	very serious [g,h]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	165 participants	336 participants	**HR 0.63** (0.46 to 0.85) [Deterioration of quality of life]	**Study Duration**	
										930 per 1,000	**117 fewer per 1,000** (from 224 fewer to 34 fewer)
Harms: Serious adverse events (follow up: median 8.6 months)											
485 (1 RCT) [1]	serious [g]	not serious	not serious	serious [i]	none	⨁⨁◯◯ LOW	48/156 (30.8%)	125/329 (38.0%)	**RR 1.23** (0.94 to 1.62)	308 per 1,000	**71 more per 1,000** (from 18 fewer to 191 more)
Harms: Discontinuation due to adverse events (follow up: median 8.6 months)											
485 (1 RCT) [1]	serious [g]	not serious	not serious	serious [i]	none	⨁⨁◯◯ LOW	16/156 (10.3%)	51/329 (15.5%)	**RR 1.51** (0.89 to 2.56)	103 per 1,000	**52 more per 1,000** (from 11 fewer to 160 more)

Resource Use - not reported

Atezolizumab + Bevacizumab compared to Sorafenib for HCC patients who failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings
-	-	-	-	-	-	-	AWP prices are the following: Atezolizumab/Bevacizumab: $16,573 per 1200 mg A +15 mg/kg Bev q3 weeks dose, Sorafenib: $830 per 400 mg bid dose. The median duration of therapy was 7.4 months in the Atezolizumab/Bevacizumab group and 2.8 months in the Sorafenib group. Adjusted cost per course for Atezolizumab/Bevacizumab is $175,199 and for Sorafenib is $69,754. The median overall survival was 19.2 months in the Atezolizumab/Bevacizumab group and 13.4 months in the Sorafenib group. The estimated cost per life-year saved with Atezolizumab/Bevacizumab is $218,162.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 62.5%, 1: 27.5; CP A 99%, B <1%; BCLC A 3%, B 15.5%, C 81.5%
b. The lack of blinding could have affected the decision to continue treatment (as it could be continued beyond disease progression at the discretion of the investigator, when there was observed evidence of clinical benefit and if symptoms and signs indicating unequivocal disease progression were absent) and could have led to differentially effective co-interventions in the post-discontinuation survival period.
c. Small number of events (total 161).
d. Median overall survival 19.2 vs 13.4 months (difference 5.8 months).
e. Progression-free survival is a surrogate for overall survival
f. Median progression overall survival 6.8 (5.7-8.3) vs 4.3 (4-5.6) months (difference 2.5 months).
g. We rated down for lack of blinding of participants and investigators.
h. The number of patient who completed the quality of life questionnaires is not clear. However, only “93% completed it by week 51, and at least 80% completed it thereafter until treatment discontinuation”. The 7% missing values may change the direction of effect in the confidence interval.
i. The CI includes both increased and decreased risk of AE.

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Lenvatinib compared to Sorafenib in HCC patients who failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Sorafenib	With Lenvatinib		Risk with Sorafenib	Risk difference with Lenvatinib
Mortality (follow up: median 27.2-27.7 months)											
954 (1 RCT) [1,a,b]	serious [c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	350/476 (73.5%)	351/478 (73.4%)	**HR 0.92** (0.79 to 1.06) [e]	**Study Duration** 735 per 1,000	**30 fewer per 1,000** (from 85 fewer to 20 more)
Progression-free survival (follow up: range up to 3.8 years; assessed with: death or progression)											
953 (1 RCT) [1]	not serious	not serious	serious [f]	not serious	none	⨁⨁⨁◯ MODERATE	367/475 (77.3%)	349/478 (73.0%)	**HR 0.64** (0.55 to 0.75) [g]	**Study Duration** 773 per 1,000	**160 fewer per 1,000** (from 215 fewer to 102 fewer)
Disease progression (follow up: range up to 3.8 months)											
953 (1 RCT) [1]	not serious	not serious	serious [f]	not serious	none	⨁⨁⨁◯ MODERATE	343/475 (72.2%)	308/478 (64.4%)	**HR 0.60** (0.51 to 0.71) [h]	**Study Duration** 722 per 1,000	**186 fewer per 1,000** (from 243 fewer to 125 fewer)
Decline in quality of life (EORTC QLQ-C30 clinically meaningful decline) (follow up: range up to 3.8 years)											
954 (1 RCT) [1]	serious [i]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	"Baseline scores on the EORTC QLQ-C30 and EORTC QLQ-HCC18 health questionnaires were similar in the lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. Analysis of time to clinically meaningful deterioration showed that role functioning (HR 0.83; 95% CI 0.71-0.97), pain (HR 0.82, 95% CI 0.70-0.95), and diarrhea (HR 0.53; 95% CI 0.45-0.63) from EORTC QLQ-C30, and nutrition (HR 0.81; 95% CI 0.68-0.95) and body image (HR 0.79; 95% CI 0.68-0.93) from EORTC QLQ-HCC18 were observed earlier in patients treated with sorafenib than in those treated with lenvatinib. For between-group comparison, the summary score was not significantly different between the treatment arms (HR 0·87, 95% CI 0·754–1·013)"				
Harms: Serious adverse events (follow up: range up to 3.8 years)											
951 (1 RCT) [1]	serious [j]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	144/475 (30.3%)	205/476 (43.1%)	**RR 1.42** (1.20 to 1.69)	303 per 1,000	**127 more per 1,000** (from 61 more to 209 more)
Harms: Discontinuation due to adverse events (follow up: range up to 3.8 years)											
951 (1 RCT) [1]	serious [j]	not serious	not serious	serious [k]	none	⨁⨁◯◯ LOW	43/475 (9.1%)	63/476 (13.2%)	**RR 1.46** (1.01 to 2.11)	91 per 1,000	**42 more per 1,000** (from 1 more to 100 more)

Lenvatinib compared to Sorafenib in HCC patients who failed/ineligible for resection/LRT with preserved liver function

Certainty assessment							Summary of findings
Resource Use - not reported							
-	-	-	-	-	-	-	AWP prices are the following: Levantinib: $787 per 8-12 mg daily dose, Sorafenib: $830 per 400 mg bid dose. The median duration of therapy was 5.7 months in the Levantinib group and 3.7 months in the Sorafenib group. Adjusted cost per course for Levantinib is $134,657 and for Sorafenib is $92,174. The median overall survival was 13.6 months in the Levantinib group and 12.3 months in the Sorafenib group. The estimated cost per life-year saved with Levantinib is $392,150.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Less than 1.08 was considered non-inferiority
b. ECOG 0: 63%, 1: 37%; CP A 99%, B 1%; BCLC B 20.5%, C 79.5%
c. It was not clear if the lack of blinding led to differentially effective co-interventions in the post-progression survival period.
d. The 95% confidence interval favors either drug
e. Median overall survival: 13.6 (12.1-14.9) vs 12.3 (10.4-13.9) months (difference 1.3 months).
f. Time to disease progression is an Indirect measure of survival.
g. Median progression free survival: 7.3 (5.6-7.5) vs 3.6 (3.6-3.7) months (difference 3.7 months).
h. Median time to progression: 7.4 (7.2-9.1) vs 3.7 (3.6-3.9) months (difference 3.7 months).
i. Open-label studies with no blinding of patients or investigators.
j. Open-label studies with no blinding of patients or investigators, and the investigators were responsible for determining if the adverse events were related to treatment or not.
k. Small number of events

References

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Second-Line Treatment

Regorafenib compared to no Regorafenib for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Regorafenib	With Regorafenib		Risk with no Regorafenib	Risk difference with Regorafenib
Mortality (follow up: range 3.7 months to 12.6 months)											
573 (1 RCT) [1,a]	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	169/194 (87.1%)	290/379 (76.5%)	**HR 0.61** (0.50 to 0.75) [c]	**1-year**	
										720 per 1,000	**180 fewer per 1,000** (from 249 fewer to 105 fewer)
										Study Duration	
										871 per 1,000	**158 fewer per 1,000** (from 230 fewer to 86 fewer)
Progression-free survival (follow up: range 3.7 months to 12.6 months; assessed with: death or progression)											
573 (1 RCT) [1]	not serious	not serious	serious [d]	not serious	none	⨁⨁⨁◯ MODERATE	194 participants	379 participants	**HR 0.46** (0.37 to 0.56) [Progression-free survival] [e]	**Study Duration**	
										920 per 1,000	**233 fewer per 1,000** (from 313 fewer to 163 fewer)
Disease progression (follow up: range 3.7 months to 12.6 months)											
573 (1 RCT) [1]	not serious	not serious	serious [d]	not serious	none	⨁⨁⨁◯ MODERATE	120/194 (61.9%)	149/379 (39.3%)	**HR 0.44** (0.36 to 0.55) [f]	**Study Duration**	
										619 per 1,000	**273 fewer per 1,000** (from 326 fewer to 207 fewer)
Quality of life (follow up: median 7 months)											
573 (1 RCT) [1]	serious [g]	not serious	not serious	serious [h]	none	⨁⨁◯◯ LOW	"No clinically meaningful differences were noted between the regorafenib and placebo groups in HRQoL. Overall changes from baseline in EQ-5D and FACT-Hep were similar in the two groups. In the LSM time-adjusted AUC analysis of the EQ-5D and FACT-Hep, the scores were lower in the regorafenib group than in the placebo group, and specifically the scores of the FACT-Hep Total and Trial Outcome Index (a subscale of the FACT-Hep) were statistically lower in the regorafenib group than in the placebo group (p=0·0006 and p<0·0001, respectively); however, minimally important thresholds for the differences as established in the literature were not met."				
Harms: Serious adverse events (follow up: median 7 months)											

Second-Line Treatment

Regorafenib compared to no Regorafenib for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function

Certainty assessment							Summary of findings				
567 (1 RCT) [1]	not serious	not serious	not serious	serious [i]	none	⊕⊕⊕◯ MODERATE	90/193 (46.6%)	166/374 (44.4%)	**RR 0.95** (0.79 to 1.15)	466 per 1,000	**23 fewer per 1,000** (from 98 fewer to 70 more)
Harms: Discontinuation due to adverse events (follow up: median 7 months)											
567 (1 RCT) [1]	not serious	not serious	not serious	serious [i]	none	⊕⊕⊕◯ MODERATE	37/193 (19.2%)	93/374 (24.9%)	**RR 1.30** (0.92 to 1.82)	192 per 1,000	**58 more per 1,000** (from 15 fewer to 157 more)
Resource Use - not reported											
-	-	-	-	-	-	-	AWP prices are the following: Regorafenib: $1,071 per 160 mg daily for 3 weeks every 4 weeks dose. The median duration of therapy was 3.6 months in the Regorafenib group and 1.9 months in the Placebo group. Adjusted cost per course for Regorafenib is $80,989. The median overall survival was 10.7 months in the Regorafenib group and 7.8 months in the Placebo group. The estimated cost per life-year saved with Regorafenib is $335,126				

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 66%, 1: 34%; CP A 98%, B 2%; BCLC A <1%, B 12.5%, C 87.5%
b. Blinding post discontinuation of treatment for subsequent therapies is unclear, and subsequent therapies were not reported. The possibility of placebo having earlier subsequent intervention with harms is present.
c. Median overall survival: 10.6 (9.1-12.1) vs 7.8 (6.3-8.8) months (difference 2.8 months).
d. Indirect assessment of survival
e. Median progression free survival: 3.1 (2.8-4.2) vs 1.5 (1.4-1.6) months (difference 1.6 months).
f. Median time to progression: 3.2 (2.9-4.2) vs 1.5 (1.4-1.6) months (difference 1.7 months).
g. Unclear response rate
h. The CI includes both improvement and worsening of quality of life.
i. The CI includes the minimally important different threshold for decision making.

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Cabozantinib compared to no Cabozantinib for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Cabozantinib	With Cabozantinib		Risk with no Cabozantinib	Risk difference with Cabozantinib
Mortality (follow up: range up to 45 months)											
707 (1 RCT) [1,a]	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	167/237 (70.5%)	317/470 (67.4%)	**HR 0.76** (0.63 to 0.92) [c]	**1-year**	
										660 per 1,000	**100 fewer per 1,000** (from 167 fewer to 31 fewer)
										Study Duration	
										705 per 1,000	**100 fewer per 1,000** (from 168 fewer to 30 fewer)
Progression-free survival (follow up: range up to 45 months; assessed with: death or progression)											
707 (1 RCT) [1]	not serious	not serious	serious [d]	not serious	none	⨁⨁⨁◯ MODERATE	205/237 (86.5%)	349/470 (74.3%)	**HR 0.44** (0.36 to 0.52) [e]	**Study Duration**	
										865 per 1,000	**279 fewer per 1,000** (from 351 fewer to 218 fewer)
Quality of life - not reported											
-	-	-	-	-	-	⨁◯◯◯ VERY LOW					
Harms: Serious adverse events (follow up: range up to 45 months)											
704 (1 RCT) [1]	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	87/237 (36.7%)	232/467 (49.7%)	**RR 1.35** (1.12 to 1.64)	367 per 1,000	**128 more per 1,000** (from 44 more to 235 more)
Harms: Discontinuation due to adverse events (follow up: range up to 45 months)											
704 (1 RCT) [1]	not serious	not serious	not serious	serious [f]	none	⨁⨁⨁◯ MODERATE	11/237 (4.6%)	98/467 (21.0%)	**RR 4.52** (2.47 to 8.27)	46 per 1,000	**163 more per 1,000** (from 68 more to 337 more)
Resource Use - not reported											
-	-	-	-	-	-	-	AWP prices are the following: Cabozantinib: $866 per 60 mg daily dose. The median duration of therapy was 3.8 months in the Cabozantinib group and 2 months in the Placebo group. Adjusted cost per course for Cabozantinib is $98,782. The median overall survival was 10.2 months in the Cabozantinib group and 8 months in the Placebo group. The estimated cost per life-year saved with Cabozantinib is $538,811 .					

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 53.5%, 1: 44.5%, 2: <1%; CP A 99%, B 1%; BCLC B 9.5%, C 90.5%
b. Due to imbalances in post-treatment co-interventions.
c. Median overall survival: 10.2 (9.1-12) vs 8 (6.8-9.4) months (difference 2.2 months).
d. Indirect measure of overall survival
e. Median progression-free survival: 5.2 (4-5.5) vs 1.9 (1.9 vs 1.9) months (difference 3.3 months).
f. Wide confidence interval

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Ramucirumab compared to no Ramucirumab for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function and high AFP

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Ramucirumab	With Ramucirumab		Risk with no Ramucirumab	Risk difference with Ramucirumab
Mortality (follow up: range up to 28 months)											
292 (1 RCT) [1,a]	serious [b,c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	74/95 (77.9%)	147/197 (74.6%)	**HR 0.71** (0.53 to 0.95) [e,f]	**Study Duration**	
										779 per 1,000	**121 fewer per 1,000** (from 228 fewer to 17 fewer)
Progression-free survival (follow up: range up to 28 months; assessed with: death or progression)											
292 (1 RCT) [1]	not serious	not serious	serious [g]	serious [d]	none	⨁⨁◯◯ LOW	86/95 (90.5%)	172/197 (87.3%)	**HR 0.45** (0.34 to 0.60) [h]	**Study Duration**	
										905 per 1,000	**252 fewer per 1,000** (from 354 fewer to 149 fewer)
Disease progression (follow up: range up to 28 months)											
292 (1 RCT) [1]	not serious	not serious	serious [g]	serious [d]	none	⨁⨁◯◯ LOW	77/95 (81.1%)	129/197 (65.5%)	**HR 0.43** (0.31 to 0.58) [i]	**Study Duration**	
										811 per 1,000	**300 fewer per 1,000** (from 408 fewer to 191 fewer)
Quality of life (follow up: range up to 28 months; assessed with: time to deterioration in FHSI-8)											
292 (1 RCT) [1]	serious [j]	not serious	not serious	serious [d,k]	none	⨁⨁◯◯ LOW	"Time to deterioration of FHSI-8 score from randomization to the first meaningful deterioration (greater than equal to 3 points) in total score Median time to deterioration 3.7 months (2.8 - 4.4) vs 2.8 months (1.6-2.9) HR: 0.799 (0.535-1.171). Time to deterioration performance status (ECOG): from randomization to performance status of 2 or higher: HR 1.08 (0.64-1.83)"				
Harms: Serious adverse events (follow up: range up to 28 months)											
292 (1 RCT) [1]	not serious	not serious	not serious	serious [d,l]	none	⨁⨁⨁◯ MODERATE	28/95 (29.5%)	68/197 (34.5%)	**RR 1.17** (0.81 to 1.69)	295 per 1,000	**50 more per 1,000** (from 56 fewer to 203 more)
Harms: Discontinuation due to adverse event (follow up: range up to 28 months)											
292 (1 RCT) [1]	not serious	not serious	not serious	serious [d,l]	none	⨁⨁⨁◯ MODERATE	10/95 (10.5%)	35/197 (17.8%)	**RR 1.69** (0.87 to 3.26)	105 per 1,000	**73 more per 1,000** (from 14 fewer to 238 more)

Resource Use - not reported

Ramucirumab compared to no Ramucirumab for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function and high AFP

Certainty assessment							Summary of findings
-	-	-	-	-	-	-	AWP prices are the following: Ramucirumab: $9,459 per 8 mg/kg every 2 weeks dose, The median duration of therapy was 2.8 months in the Ramucirumab group and 1.87 months in the Placebo group. Adjusted cost per course for Ramucirumab is $56,755. The median overall survival was 8.5 months in the Ramucirumab group and 7.3 months in the Placebo group. The estimated cost per life-year saved with Ramucirumab is $567,552.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 57.5%, 1: 42.5%; CP A 100%; BCLC B 19%, C 81%
b. Unclear blinding for allocation of subsequent therapies
c. The protocol was amended with concern for early stoppage of the trial for benefit.
d. Low event rate
e. Post-hoc sensitivity analyses with censoring for new anti-cancer therapy showed HR 0·65 (0.46 - 0.91)
f. Median overall survival: 8.5 (7-10.6) vs 7.3 (5.4-9.1) months (difference of 1.2 months)
g. Surrogate for overall mortality
h. Median progression-free survival: 2.8 (2.8-4.1) vs 1.6 (1.5-2.7) months (difference of 1.2 months)
i. Median time to progression: 3 (2.8-4.2) vs 1.6 (1.5-2.7) months (difference of 1.4 months)
j. High attrition
k. confidence interval crosses threshold for both appreciable harm and benefit
l. confidence interval crosses threshold for both harm and no harm

References

1. Zhu, A. X., Kang, Y. K., Yen, C. J., Finn, R. S., Galle, P. R., Llovet, J. M., Assenat, E., Brandi, G., Pracht, M., Lim, H. Y., Rau, K. M., Motomura, K., Ohno, I., Merle, P., Daniele, B., Shin, D. B., Gerken, G., Borg, C., Hiriart, J. B., Okusaka, T., Morimoto, M., Hsu, Y., Abada, P. B., Kudo, M., investigators, Reach-,study. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol; Feb 2019.

Pembrolizumab compared to no Pembrolizumab for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Pembrolizumab	With Pembrolizumab		Risk with no Pembrolizumab	Risk difference with Pembrolizumab
Mortality (follow up: range up to 30 months)											
413 (1 RCT) [1,a]	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	101/135 (74.8%)	180/278 (64.7%)	**HR 0.78** (0.61 to 0.99) [d,e]	**Study Duration**	
										748 per 1,000	**89 fewer per 1,000** (from 179 fewer to 3 fewer)
Progression-free survival (follow up: range up to 30 months; assessed with: death or progression)											
413 (1 RCT) [1]	not serious	not serious	serious [f]	not serious	none	⨁⨁⨁◯ MODERATE	135 participants	278 participants	**HR 0.72** (0.57 to 0.90) [Progression-free survival] [g]	**Study Duration**	
										810 per 1,000 [h]	**112 fewer per 1,000** (from 198 fewer to 34 fewer)
Disease progression (follow up: range up to 30 months)											
413 (1 RCT) [1]	not serious	not serious	serious [f]	not serious	none	⨁⨁⨁◯ MODERATE	100/135 (74.1%)	173/278 (62.2%)	**HR 0.69** (0.54 to 0.88) [i]	**Study Duration**	
										741 per 1,000	**135 fewer per 1,000** (from 223 fewer to 46 fewer)
Quality of life (assessed with: EORTC QLQ-C30 and QLQ-HCC18)											
398 (1 RCT) [1]	serious [j]	not serious	not serious	serious [k]	none	⨁⨁◯◯ LOW	"The change from baseline to week 12 in EORTC QLQ-C30 GHS/QoL and functional domain scores and symptom domain scores were similar between the pembrolizumab and placebo arms. The proportions of patients who improved, remained stable, or deteriorated according to EORTC QLQ-C30 GHS/QoL and domain scores were generally similar between pembrolizumab and placebo. The least squares mean change from baseline to week 12 in EORTC QLQ-HCC18 scores was similar between pembrolizumab and placebo. The proportions of patients reporting improved, stable, or deteriorated EORTC QLQ-HCC18 GHS/QoL and domain scores were generally similar between pembrolizumab and placebo. Time to deterioration was not significantly different between the pembrolizumab and placebo arms based on the prespecified analysis of the EORTC QLQ-HCC18 subscales: abdominal swelling (HR, 1.08; 95% CI, 0.76-1.54; P = .6552), fatigue (HR, 0.92; 95% CI, 0.71-1.20; P = .2795), and pain (HR, 0.97; 95% CI, 0.74-1.27; P = .4078)."				
Harms: Serious adverse events (follow up: range up to 30 months)											
413 (1 RCT) [1]	not serious	not serious	not serious	serious [c,l]	none	⨁⨁⨁◯ MODERATE	37/134 (27.6%)	104/279 (37.3%)	**RR 1.35** (0.99 to 1.85)	276 per 1,000	**97 more per 1,000** (from 3 fewer to 235 more)
Harms: Discontinuation due to adverse events (follow up: range up to 30 months)											

Pembrolizumab compared to no Pembrolizumab for second line treatment for HCC patients who failed/ineligible for resection/LRT and progressed on sorafenib with preserved liver function

Certainty assessment							Summary of findings				
413 (1 RCT) [1]	not serious	not serious	not serious	serious [c,m]	none	⨁⨁⨁◯ MODERATE	12/134 (9.0%)	48/279 (17.2%)	**RR 1.92** (1.06 to 3.49)	90 per 1,000	**82 more per 1,000** (from 5 more to 223 more)

Resource Use - not reported

-	-	-	-	-	-	-	AWP prices are the following: Pembrolizumab: $12,081 for 200 mg per 3 weeks dose. The median duration of therapy was 3.5 months in the Pembrolizumab group and 2.8 months in the Placebo group. Adjusted cost per course for Pembrolizumab is $60,404. The median overall survival was 13.9 months in the Pembrolizumab group and 10.6 months in the Placebo group. The estimated cost per life-year saved with Pembrolizumab is $219,652.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 0: 56%, 1: 44%; CP A 99%, B 1%; BCLC B 21%, C 79%
b. Unclear blinding and selection for subsequent treatments post study intervention
c. Low event rate
d. “Post hoc sensitivity analyses of OS accounting for the use of subsequent anticancer therapies, using inverse probability censored weighting model and two-stage survival analysis model, resulted in similarly lower HRs for the treatment differences (range, 0.67-0.68).”
e. Median overall survival: 13.9 (11.6-16.0) vs 10.6 (8.3 vs 13.5) months (difference of 3.3 months)
f. Surrogate measure for overall survival
g. Median progression-free survival: 3.0 (2.8-4.1) vs 2.8 (1.6-3.0) months (difference of 0.2 months)
h. Control rate for progression free survival was extrapolated from combined intervention and placebo total event rate.
i. Median time to progression: 3.8 (2.8-4.4) vs 2.8 (1.6-2.9) months (difference of 1 month)
j. Compliance rate was around 90% with completion rate around 68%. If the data for the missed questionnaires were available, they may lead to different conclusions.
k. Small number of events, as well as wide confidence interval that includes both appreciable improvement and worsening in quality of life.
l. Confidence interval crosses both appreciable harm and no harm.
m. Wide confidence interval

References

1. Finn, R. S., Ryoo, B. Y., Merle, P., Kudo, M., Bouattour, M., Lim, H. Y., Breder, V., Edeline, J., Chao, Y., Ogasawara, S., Yau, T., Garrido, M., Chan, S. L., Knox, J., Daniele, B., Ebbinghaus, S. W., Chen, E., Siegel, A. B., Zhu, A. X., Cheng, A. L., investigators, Keynote-. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol; Jan 20 2020.

PICO 2: In patients with HCC with poor liver function who are not liver transplant candidates, should systemic therapies be used?

Sorafenib compared to no Sorafenib for HCC patients who are failed/ineligible for resection/LRT with poor liver function

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Sorafenib	With Sorafenib		Risk with no Sorafenib	Risk difference with Sorafenib
Mortality											
189 (1 RCT) [1,a]	very serious [b,c]	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	75/94 (79.8%)	64/95 (67.4%)	**HR 0.48** (0.35 to 0.68) [e]	**Trial Duration**	
										798 per 1,000	**262 fewer per 1,000** (from 369 fewer to 135 fewer)
Progression-free survival											
189 (1 RCT) [1]	serious [c,d]	not serious	serious [f]	serious [d]	none	⨁◯◯◯ VERY LOW	94 participants	95 participants	**HR 0.55** (0.40 to 0.75) [Progression-free survival] [g]	**SHARP Trial Duration**	
										590 per 1,000 [h]	**202 fewer per 1,000** (from 290 fewer to 102 fewer)
Quality of life (assessed with: FHSI-8)											
0 (1 RCT) [1]	very serious [b,c]	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	The authors state that the "quality of life of the 2 groups did not differ significantly at baseline or during the treatment, according to the response to the FHSI-8 questionnaire"				
Harms: Discontinuation due to adverse events											
180 (1 RCT) [1]	very serious [b,c,i]	not serious	not serious	serious [j]	none	⨁◯◯◯ VERY LOW	0/91 (0.0%)	2/89 (2.2%)	**RR 5.10** (0.25 to 105.00)	0 per 1,000	**22 more per 1,000** (from 8 fewer to 53 more) [k]
Resource Use - not reported											
-	-	-	-	-	-	-	AWP prices are the following: Sorafenib: $830 per 400 mg bid dose. The median duration of therapy (imputed from progression free survival) was 2.2 months in the Sorafenib group and 1.9 months in the Placebo group. Adjusted cost per course for Sorafenib is $54,806. The median overall survival was 4 months in the Sorafenib group and 3.5 months in the Placebo group. The estimated cost per life-year saved with Sorafenib is $1,315,354.				

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. ECOG 1: 27%, 2: 73%; CP B 75%, C 25%; BCLC B 12.5%, C 87.5%
b. No blinding applied
c. Unclear allocation concealment
d. Low event rate and sample size
e. The median overall survival was 4 months in the Sorafenib group and 3.5 months in the Placebo group (difference of 0.5 months).

f. Surrogate measure for overall survival
g. Median progression-free survival: 2.2 vs 1.9 months
h. Control event rate extrapolated from the SHARP trial
i. The discontinuation rate of 2.2% appears a significantly underestimation as the SHARP trial showed a discontinuation rate above 30%
j. Confidence interval includes threshold for both appreciable harm and no harm
k. 0 event in the control group and thus absolute risk was utilized

References

1. Ji, Y. X., Zhang, Z. F., Lan, K. T., Nie, K. K., Geng, C. X., Liu, S. C., Zhang, L., Zhuang, X. J., Zou, X., Sun, L., Zhang, Z. C.. Sorafenib in liver function impaired advanced hepatocellular carcinoma. Chin Med Sci J; Mar 2014.

PICO 3: Should we use systemic therapies in patients undergoing curative surgical resection for HCC?

Sorafenib compared to no Sorafenib for adjuvant therapy in patients with HCC who underwent curative surgical resection

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Sorafenib	With Sorafenib		Risk with no Sorafenib	Risk difference with Sorafenib
Mortality (follow up: range up to 4 years)											
1114 (1 RCT) [1]	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	113/558 (20.3%)	104/556 (18.7%)	**HR 0.995** (0.761 to 1.300)	203 per 1,000	**2 more per 1,000** (from 77 fewer to 94 more)
Recurrence-free survival (follow up: range up to 4 years; assessed with: death or recurrence)											
900 (1 RCT) [1]	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	450 participants	450 participants	**HR 0.937** (0.759 to 1.156) [Recurrence-free survival] [c]	484 per 1,000	**22 fewer per 1,000** (from 89 fewer to 51 more)
Disease recurrence (follow up: range up to 4 years)											
1114 (1 RCT) [1]	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	558 participants	556 participants	**HR 0.891** (0.735 to 1.081) [Disease recurrence] [d]	281 per 1,000	**26 fewer per 1,000** (from 66 fewer to 19 more)
Harms: Serious Adverse Events (follow up: range up to 4 years)											
1107 (1 RCT) [1]	not serious	not serious	not serious [e]	serious [f]	none	⨁⨁⨁◯ MODERATE	228/554 (41.2%)	225/553 (40.7%)	**RR 0.989** (0.860 to 1.140)	412 per 1,000	**5 fewer per 1,000** (from 58 fewer to 58 more)
Harms: Discontinuation due to adverse events (follow up: range up to 4 years)											
1107 (1 RCT) [1]	not serious	not serious	not serious [e]	serious [b]	none	⨁⨁⨁◯ MODERATE	41/554 (7.4%)	133/553 (24.1%)	**RR 3.25** (2.34 to 4.52)	74 per 1,000	**167 more per 1,000** (from 99 more to 261 more)

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Mortality estimate not only included patients after HCC resection, but also patients who underwent ablation; a possible differential effect is unknown.
b. Wide confidence interval that accounts for both appreciable benefit and harm. The confidence interval includes the threshold for clinical importance difference
c. Median recurrence-free survival 41.7 vs 38.7 months (difference 3 months).
d. Median time to recurrence 38.5 (30.4-NE) vs 35.8 (30.3-41.4) months (2.7 months).
e. The denominator is both resection and ablation, but this is a RCT and thus is less likely to impact the relative effects as it was stratified
f. Wide confidence interval that accounts for both appreciable harm and no harm.

References

1. Bruix, J., Takayama, T., Mazzaferro, V., Chau, G. Y., Yang, J., Kudo, M., Cai, J., Poon, R. T., Han, K. H., Tak, W. Y., Lee, H. C., Song, T., Roayaie, S., Bolondi, L., Lee, K. S., Makuuchi, M., Souza, F., Berre, M. A., Meinhardt, G., Llovet, J. M., investigators, Storm. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol; Oct 2015.

PICO 5: In patients with liver-confined HCC undergoing locoregional therapy, should systemic therapies be used?

Sorafenib vs no Sorafenib as adjuvant to curative locoregional ablation (including RFA)

Sorafenib compared to no Sorafenib for adjuvant therapy in patients with HCC who received curative locoregional ablation treatment
Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Sorafenib	With Sorafenib		Risk with no Sorafenib	Risk difference with Sorafenib
Mortality (follow up: range up to 4 years)											
1114 (1 RCT) [1]	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	113/558 (20.3%)	104/556 (18.7%)	**HR 0.995** (0.761 to 1.300)	**Study Duration** 203 per 1,000	**2 more per 1,000** (from 77 fewer to 94 more)
Recurrence-free survival (follow up: range up to 4 years; assessed with: death or recurrence)											
900 (1 RCT) [1]	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	450 participants	450 participants	**HR 0.970** (0.656 to 1.434) [Recurrence-free survival] [c]	**Study Duration** 484 per 1,000	**10 fewer per 1,000** (from 132 fewer to 129 more)
Disease recurrence (follow up: range up to 4 years)											
1114 (1 RCT) [1]	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	558 participants	556 participants	**HR 0.891** (0.735 to 1.081) [Disease recurrence] [d]	**Study Duration** 281 per 1,000	**26 fewer per 1,000** (from 66 fewer to 19 more)
Harms: Serious adverse events (follow up: range up to 4 years)											
1107 (1 RCT) [1]	not serious	not serious	serious [a]	serious [e]	none	⨁⨁◯◯ LOW	228/554 (41.2%)	225/553 (40.7%)	**RR 0.989** (0.860 to 1.140)	412 per 1,000	**5 fewer per 1,000** (from 58 fewer to 58 more)
Harms: Discontinuation due to adverse events (follow up: range up to 4 years)											
1107 (1 RCT) [1]	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	41/554 (7.4%)	133/553 (24.1%)	**RR 3.25** (2.34 to 4.52)	74 per 1,000	**167 more per 1,000** (from 99 more to 261 more)

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Data is combined for patients who underwent resection and ablation and thus indirect
b. Wide confidence interval that accounts for both appreciable benefit and harm. The confidence interval includes the threshold for clinical importance difference
c. Median recurrence-free survival 19.6 vs 22.1 months (difference -2.5 months).
d. Median time to recurrence: 38.5 (30.4-NE) vs 35.8 (30.3-41.4) months (2.7 months).
e. Wide confidence interval that accounts for both appreciable harm and no harm.

References

1. Bruix, J., Takayama, T., Mazzaferro, V., Chau, G. Y., Yang, J., Kudo, M., Cai, J., Poon, R. T., Han, K. H., Tak, W. Y., Lee, H. C., Song, T., Roayaie, S., Bolondi, L., Lee, K. S., Makuuchi, M., Souza, F., Berre, M. A., Meinhardt, G., Llovet, J. M., investigators, Storm. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol; Oct 2015.

Sorafenib vs no Sorafenib in conjunction with TACE

Sorafenib compared to no Sorafenib for patients with HCC in conjunction with TACE locoregional therapies

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Sorafenib	With Sorafenib		Risk with no Sorafenib	Risk difference with Sorafenib
Mortality (follow up: range 23 months to 33 months)											
1234 (4 RCTs) [1,2,3,4]	serious [a,b,c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	614 participants	620 participants	**HR 0.92** (0.76 to 1.10) [Mortality] [e]	**2-year**	
										262 per 1,000	**18 fewer per 1,000** (from 56 fewer to 22 more)
										Study Duration	
										180 per 1,000	**13 fewer per 1,000** (from 40 fewer to 16 more)
Progression-free survival (follow up: range 23 months to 28 months; assessed with: death or progression)											
519 (3 RCTs) [1,3,5]	serious [a,f]	not serious [g]	serious [h]	serious [g]	none	⨁◯◯◯ VERY LOW	Kudo et al 2019 reported improvement in progression-free survival (PFS) in patients who received sorafenib and TACE compared to TACE alone (HR 0.66, 95% CI 0.47-0.94; median 25.2 vs 13.5 months). Meyer et al 2017 also reported comparable PFS in both arms (HR 0.99, 95% CI 0.8-1.3; 7.9 vs 7.8 months). Hoffman et al 2015 reported comparable PFS in both arms as well (HR 1.3, 95% CI 0.5-3.3). [i]				
Disease progression (follow up: range 23 months to 33 months)											
1284 (5 RCTs) [1,2,3,4,5]	serious [a,b,f]	not serious	serious [h]	not serious	none	⨁⨁◯◯ LOW	Most of the studies reported improvement in time to progression in patients who received sorafenib and TACE compared to TACE alone: Kudo 2011 (HR 0.87, 95% CI 0.70-1.09; median 5.4 m vs 3.7 months), Kudo 2019 (HR 0.54, 95% CI 0.35-0.83; median 22.8 m vs 13.5 months), Lencioni 2016 (HR 0.80, 95% CI 0.59-1.08; median 5.6 vs 5.5 months), Meyer 2017 (HR 0.88, 95% CI 0.67-1.17; median 10.9 vs 10.7 months). Hoffmann 2015 reported worse progression in patients who received sorafenib with TACE compared to TACE alone (HR 1.211 95% CI 0.39-3.16; median 2.4 vs 2.8 months). [j]				
Quality of life (assessed with: EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D questionnaire)											
313 (1 RCT) [1]	serious [k]	not serious	not serious	serious [l]	none	⨁⨁◯◯ LOW	The authors state: "140/157 vs 149/156 returned at least one QOL questionnaire form. According to multilevel regression of QLQ-C30 score over 12 months, both the mean social and role functioning scales were found to be up to 6% lower (p=0·045 and p=0·050) for patients in the sorafenib group. Of the symptom scales, mean diarrhea score was up to 13% higher on average in the sorafenib group (p=0.0095) and mean appetite loss score was up to 10% higher (p=0.0018). According to HCC18, mean nutritional problem scores were up to 7% worse in the sorafenib group (p=0.0084). No evidence of non-zero interactions was observed. No significant differences were observed in other QOL scales."				
Harms: Serious adverse events											

Sorafenib compared to no Sorafenib for patients with HCC in conjunction with TACE locoregional therapies

Certainty assessment							Summary of findings				
1123 (4 RCTs) [1,2,4,5]	serious [b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	130/560 (23.2%)	198/563 (35.2%)	**RR 1.48** (1.24 to 1.77)	232 per 1,000	**111 more per 1,000** (from 56 more to 179 more)

Harms: Discontinuation due to adverse events

1073 (3 RCTs) [1,2,4]	serious [b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	63/534 (11.8%)	115/539 (21.3%)	**RR 1.81** (1.36 to 2.40)	118 per 1,000	**96 more per 1,000** (from 42 more to 165 more)

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. No blinding in Kudo 2019, and the patients were unmasked at the time of progression in Meyer 2017 based on the investigator's assessment, rather than central review.
b. Allocation concealment was no clear in Kudo 2011 and Lencioni 2016.
c. It was also not clear if subsequent interventions, after progression and discontinuation of sorafenib, led to any differential effect in overall survival.
d. The confidence interval includes both benefits and harms.
e. Median overall survival: Kudo 2011 29.7 months vs not reached, TACTICS 36.2 vs 30.8 months (difference 5.4 months), SPACE not reached, TACE-2 21.0 (14.6-29.3) vs 19.9 (16.7-23.2) months (difference 1.1 months).
f. Decision regarding disease progression was made by local review in 22% of the patients in Meyer 2017, rather than central review.
g. Borderline decision for both imprecision and inconsistency.
h. Indirect assessment of survival
i. The studies defined progression using different methods, thus we did not pool them: Kudo et al 2019 used unTACEable progression, Meyer et al 2017 used RECIST v1.1, and Hoffman et al 2015 used mRECIST.
j. The studies defined progression using different methods, thus we did not pool them: Kudo 2011 used recurrence in patients with complete remission and increase in size/development of new lesion in patients with incomplete remission, Kudo 2019 used untreatable progression, Lencioni 2016 and Hoffmann 2015 used mRECIST, and Meyer 2017 used RECIST v1.1.
k. Unclear attrition bias with no reporting of how many patients completed the pre and post assessment in each group. Also, 10% in the sorafenib group did not complete any form vs 4% in the placebo group.
l. Total sample size is less than 400 for continuous outcome and event rate is less than 300 for dichotomous outcome

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Bevacizumab vs no Bevacizumab in conjunction with TACE

Bevacizumab compared to no Bevacizumab in patients with HCC in conjunction with TACE locoregional therapy

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no Bevacizumab	With Bevacizumab		Risk with no Bevacizumab	Risk difference with Bevacizumab
Overall survival											
62 (2 RCTs) [1,2]	serious [a]	serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	"2 randomized controlled trials involving total of 62 patients were identified. Birtten et al reported improvement in overall survival in patients who received bevacizumab versus observation (median survival 61 months vs 49 months). Pinter et al reported worse overall survival in patients who received bevacizumab compared to placebo (median survival 5.3 months vs 13.7 month; HR 1.7, 95% CI 0.8-3.6)."				
Progression-free survival (follow up: median 16 weeks; assessed with: death or progression)											
30 (1 RCT) [2]	serious [a]	not serious	serious [d]	very serious [e]	none	⨁◯◯◯ VERY LOW	3/15 (20.0%)	12/15 (80.0%)	**RR 4.0** (1.4 to 11.3)	**Study Duration**	
										200 per 1,000	**600 more per 1,000** (from 80 more to 1,000 more)
Disease progression (follow up: median 1 years)											
32 (1 RCT) [1]	serious [a]	not serious	serious [d]	very serious [c]	none	⨁◯◯◯ VERY LOW	16 participants	16 participants	**HR 0.9** (0.3 to 2.4) [Disease progression] [f]	**Study Duration**	
										900 per 1,000	**26 fewer per 1,000** (from 401 fewer to 96 more)
Harm: Discontinuation due to adverse events (follow up: median 16 weeks)											
30 (1 RCT) [2]	serious [a]	not serious	not serious	very serious [e]	none	⨁◯◯◯ VERY LOW	0/15 (0.0%)	1/15 (6.7%)	**RR 3.0** (0.1 to 68.3) [g]	0 per 1,000	**67 more per 1,000** (from 60 fewer to 193 more) [h]
Harms: Death related to the intervention (follow up: median 1 years)											
32 (1 RCT) [1]	serious [a]	not serious	not serious	very serious [e]	none	⨁◯◯◯ VERY LOW	1/16 (6.3%)	8/16 (50.0%)	**RR 11.0** (1.6 to 75.5)	63 per 1,000	**625 more per 1,000** (from 38 more to 1,000 more)

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Unclear allocation concealment, and unclear if central blinded assessment was used.
b. Studies showed contradicting findings.
c. Small number of patients
d. Progression and progression-free survival are surrogates for survival.
e. Very small number of events
f. Median time to progression 7.2 (4.1-10.3) vs 11.7 (4.9-18.6) months (difference -4.5 months),
g. Relative risk estimated using 0.5 continuity correction
h. The absolute effects were estimated using the absolute risk difference because the baseline risk in the placebo arm was 0%.

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