

Supplement materials

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Table 1. Baseline characteristics according to ePD until third disease progression

Characteristics	ePD free patients N=34 N (%)	ePD patients N=164 N (%)	P value *
Age:			
≥ 70 years	6 (18)	30 (18)	0.88
< 70 years	28 (82)	134 (82)	
ECOG PS:			
1	3 (9)	25 (15)	0.43
0	31 (91)	139 (85)	
Timing:			
Synchronous	28 (82)	143 (87)	0.64
Metachronous	6 (18)	21 (13)	
Resected primary tumor:			
Yes	21 (62)	109 (67)	0.74
No	13 (38)	55 (33)	
Sidedness:			
Left	25 (73)	116 (71)	0.91
Right	9 (27)	48 (29)	
Not available	0 (0)	0 (0)	
Nodal involvement:			
Yes	15 (44)	86 (52)	0.36
No	10 (29)	34 (21)	
Not available	9 (27)	44 (27)	
Baseline CEA level:			
> 200 ng/mL	13 (38)	36 (22)	0.09
≤ 200 ng/mL	14 (41)	89 (54)	
Not available	7 (21)	39 (24)	
Number of liver metastases:			
≥ 4	19 (56)	107 (65)	0.34
< 4	12 (35)	42 (26)	
Not available	3 (9)	15 (9)	
Liver metastases max diameter:			
> 30 mm	17 (50)	100 (75)	0.14
≤ 30 mm	14 (41)	42 (26)	
Not available	3 (9)	15 (9)	
Bilobar involvement:			
Yes	23 (68)	112 (68)	0.98
No	10 (29)	45 (28)	
Not available	1 (3)	7 (4)	
Liver involvement:			
> 6 segments	7 (21)	37 (23)	0.96
≤ 6 segments	25 (73)	116 (71)	
Not available	2 (6)	11 (6)	
RAS/BRAF status:			
Mutated	13 (38)	84 (51)	0.51
Wild-type	15 (44)	68 (42)	
Not available	6 (18)	12 (7)	
Microsatellite status:			
MSI High	0 (0)	3 (2)	1.00
MSI low/MSS	9 (27)	44 (27)	
Not available	25 (73)	117 (71)	
Induction CT:			
Triplet	15 (44)	95 (58)	0.19
Doublet	19 (56)	69 (42)	
Biological agent			
Anti EGFR	13 (38)	40 (25)	0.09
Anti VEGF	16 (47)	94 (57)	
Both	0 (0)	10 (6)	
None	5 (15)	20 (12)	

ePD: extrahepatic disease progression; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; CEA: Carcinoembryonic Antigen; MSI: microsatellite instability; MSS: microsatellite stable; CT: Chemotherapy; Anti EGFR: anti Epidermal Growth Factor antibodies; Anti VEGF: anti Vascular Endothelial Growth Factor antibodies.

* P value for Chi-squared of Fisher's exact test

Table 2. Competing risk uni- and multivariable analyses for ePD

Characteristics	Univariable analyses			Multivariable analyses		
	SHR	95% CI	Pvalue	SHR	95% CI	Pvalue
Age ≥ 70 years vs < 70 years	1.50	1.04-2.18	0.03	1.40	0.96-2.05	0.08
ECOG PS 1 vs 0	1.37	0.88-2.13	0.17	-	-	-
Synchronous vs metachronous	1.41	0.92-2.16	0.11	-	-	-
Resected primary tumor vs unresected	0.79	0.58-1.09	0.16	-	-	-
Left vs right primary	0.91	0.65-1.28	0.59	-	-	-
Nodal involvement vs no involvement	1.50	1.01-2.22	0.04	1.29	0.85-1.96	0.24
Number of liver metastases ≥ 4 vs < 4	1.79	1.28-2.52	0.001	1.63	1.12-2.36	0.01
Liver metastases max diameter > 30 vs ≤ 30 mm	1.26	0.88-1.78	0.20	-	-	-
Bilobar involvement yes vs no	1.21	0.87-1.68	0.24	-	-	-
Liver secondary resection	0.38	0.26-0.56	0.001	0.43	0.29-0.63	0.001

SHR: Subdistributed Hazard Ratio; CI: Confidence Interval; ePD: extrahepatic disease progression; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status.

Table 3. Uni- and multivariable analyses for ePFS in [the subgroup of 61 never resected patients](#)

Characteristics	Univariable analyses			Multivariable analyses		
	HR	95% CI	P value	HR	95% CI	P value
Age ≥ 70 years vs < 70 years	1.13	0.62-2.06	0.067	-	-	-
ECOG PS 1 vs 0	2.19	0.95-5.06	0.01	2.68	1.14-6.30	0.02
Synchronous vs metachronous	1.36	0.67-2.77	0.44	-	-	-
Resected primary tumor vs unresected	0.60	0.34-1.05	0.05	0.87	0.43-1.75	0.70
Left vs right primary	0.56	0.30-1.01	0.03	0.49	0.22-1.09	0.08
Nodal involvement vs no involvement	1.08	0.48-2.43	0.86	-	-	-
Baseline CEA level > 200 vs ≤ 200 ng/mL	1.82	0.91-3.64	0.04	1.40	0.72-2.71	0.32
Number of liver metastases ≥ 4 vs < 4	2.61	1.34-5.09	0.03	1.59	0.57-4.48	0.38
Liver metastases max diameter > 30 vs ≤ 30 mm	2.62	1.48-4.63	0.002	3.03	1.29-7.12	0.01
Bilobar involvement yes vs no	1.69	0.90-3.16	0.14	-	-	-
Liver involvement > 6 vs ≤ 6 segments	1.32	0.74-2.36	0.33	-	-	-
RAS/BRAF mutation vs RAS/BRAF wild type	1.25	0.72-2.17	0.43	-	-	-
MSI high vs MSS	_*	_*	_*	_*	_*	_*
Triplet vs doublet induction	0.85	0.49-1.47	0.55	-	-	-
Anti EGFR vs Anti VEGF	1.15	0.59-2.23	0.76	-	-	-

HR: Hazard Ratio; CI: Confidence Interval; ePFS: extrahepatic progression free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CEA: Carcinoembryonic Antigen; MSI: microsatellite instability; MSS: microsatellite stable; Anti EGFR: anti Epidermal Growth Factor antibodies; Anti VEGF: anti Vascular Endothelial Growth Factor antibodies.

*no MSI high patients

Table 4. Uni- and multivariable analyses for ePFS in [the subgroup of 164 patients who underwent at least one liver-directed treatment](#)

Characteristics	Univariable analyses			Multivariable analyses		
	HR	95% CI	P value	HR	95% CI	P value
Age ≥ 70 years vs < 70 years	1.24	0.71-2.15	0.067	-	-	-
ECOG PS 1 vs 0	1.05	0.59-1.87	0.85	-	-	-
Synchronous vs metachronous	1.34	0.82-2.22	0.29	-	-	-
Resected primary tumor vs unresected	1.06	0.72-1.56	0.78	-	-	-
Left vs right primary	1.17	0.78-1.75	0.46	-	-	-
Nodal involvement vs no involvement	1.55	1.02-2.36	0.04	1.79	0.74-4.33	0.19
Baseline CEA level > 200 vs ≤ 200 ng/mL	0.95	0.59-1.55	0.85	-	-	-
Number of liver metastases ≥ 4 vs < 4	1.29	0.88-1.88	0.19	-	-	-
Liver metastases max diameter > 30 vs ≤ 30 mm	1.06	0.71-1.59	0.78	-	-	-
Bilobar involvement yes vs no	0.94	0.64-1.39	0.75	-	-	-
Liver involvement > 6 vs ≤ 6 segments	0.87	0.50-1.53	0.55	-	-	-
<i>RAS/BRAF</i> mutation vs <i>RAS/BRAF</i> wild type	0.94	0.65-1.37	0.75	-	-	-
MSI high vs MSS	3.03	0.43-21.15	0.049	1.68	0.33-8.51	0.53
Triplet vs doublet induction	1.29	0.90-1.85	0.17	-	-	-
Anti EGFR vs Anti VEGF	0.91	0.60-1.40	0.16	-	-	-
Liver retreatments	0.31	0.19-0.52	< 0.001	0.41	0.16-1.08	0.07

HR: Hazard Ratio; CI: Confidence Interval; ePFS: extrahepatic progression free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CEA: Carcinoembryonic Antigen; MSI: microsatellite instability; MSS: microsatellite stable; Anti EGFR: anti Epidermal Growth Factor antibodies; Anti VEGF: anti Vascular Endothelial Growth Factor antibodies.