Combined radiofrequency ablation and ipilimumab in uveal melanoma: Results from the SECIRA-UM trial

E.A. Rozeman, W. Prevoo, M.A.J. Meier, K. Sikorska, B.A. van de Wiel, A. Broeks, H. van Tinteren, E. Kapiteijn, J.V. van Thienen, J.B. Haanen, C.U. Blank

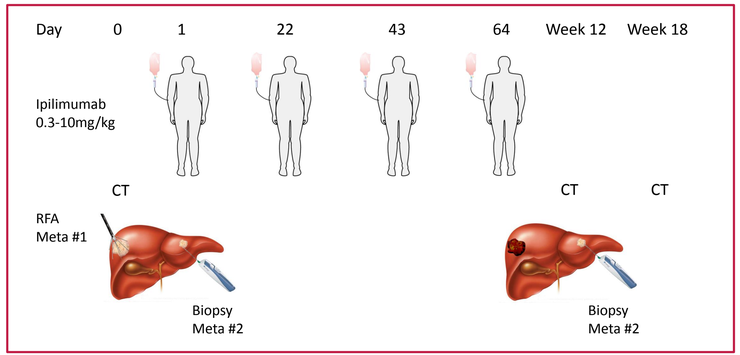
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Background

- Uveal melanoma (UM) is a rare disease (0.4-8 cases/1.000.000/year).[1]
- After enucleation or radiotherapy of the primary lesion, 50% of UM patients develop distant metastases.[2]
- Chemoembolization or intrahepatic artery perfusion improved local control, but failed to show convincing OS benefit.[3,4]
- So far, systemic therapies such as targeted therapies [5,6] or chemotherapy[7] have failed to prove OS benefit.
- In contrast to cutaneous melanoma the anti-CTLA-4 and anti-PD-1 antibodies ipilimumab (IPI), Nivolumab (NIVO) , and Pembrolizumab (PEM) showed only limited clinical activity in UM, thus combination therapies may be required.[8-12]
- Preclinical experiments in a murine melanoma model indicated that additional radiofrequency ablation(RFA) enhanced antigen presentation and induced durable responses,[13] and was synergistic with CTLA-4 blockade. [14]

Methods

- The SECIRA-UM trial is a phase 1b/2 study to assess safety and efficacy of the combination of RFA and IPI in UM patients with at least 2 unresectable liver lesions.
- In the phase 1b part patients underwent RFA of one liver lesion and received 4 courses IPI 0.3mg/kg, 3mg/kg or 10mg/kg q3wk in a 3+3 design.
- Primary endpoint of the phase 1b part was safety in terms of dose limiting toxicities per cohort to define the recommended phase 2 dose(RP2D).
- Primary endpoints of the phase 2 part were confirmed objective response rate (ORR) and disease control rate (DCR) according to RECIST 1.1 (only non-RFA lesions), secondary endpoints were progression free survival (PFS) and OS.



Results

- In the phase 1b part IPI 10mg/kg + RFA was defined as the RP2D.
- After 19 patients had been treated, the study was amended to adjust the RP2D to IPI 3mg/kg + RFA, because 9 patients (47%) had developed grade 3 colitis. In the 3mg/kg IPI + RFA cohort also 19 patients have been treated.

Table 1. Baseline characteristics

	All (n=41)	0.3mg/kg (n=3)	3mg/kg (n=19)	10mg/kg (n=19)
Age mean +/-SD	61 +/- 8,7	61 +/- 5,7	63 +/- 9,2	59 +/-8,4
Sex				
Male	24 (58%)	2 (67%)	12 (63%)	10 (53%)
Female	17 (42%)	1 (33%)	7 (27%)	9 (47%)
ECOG PS				
0	39 (95%)	2 (67%)	18 (94%)	19 (100%)
1	2 (5%)	1 (33%)	1 (5%)	0 (0%)
Extrahepatic disease	24(59%)	1(33%)	11(58%	11(58)
Lung	21 (50%)	1 (33%)	9 (48%)	10 (50%)
Skeletal	9(22%)	0(0%)	6(32%)	3 (17%)
Subcutaneous	4 (10%)	0(0%)	2(11%)	2(11%)
LDH median (range)	255 (130-757)	297 (130-531)	256 (139-757)	253(153-685)
<ULN	19 (46%)	1 (33%)	9 (47%)	9 (47%)
1-2 x ULN	15 (36%)	1 (33%)	7 (37%)	7 (37%)
> 2xULN	7 (17%)	1 (33%)	3 (16%)	3 (16%)
ALT median (range)	31 (9-156)	18 (9-57)	31 (18-156)	34 (17-131)
Previous treatment for metastatic disease	13 (32%)	2 (67%)	4(21%)	4(21%)

Table 2. Treatment disposition and treatment response

	All (n=40)*	0.3mg/kg (n=3)	3mg/kg (n=19)	10mg/kg (n=19)
Number of cycles				
1	5 (13%)		2 (11%)	3 (16%)
2	9 (23%)	1 (33%)	2 (11%)	6 (32%)
3	7 (18%)		4 (21%)	3 (16%)
4	19 (48%)	2 (67%)	11 (58%)	7 (37%)
Best overall response				
PR	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SD	6 (15%)	0 (0%)	2(11%)	4 (21%)
PD	35 (85%)	3 (100%)	17 (89%)	15 (79%)
Reason for treatment discontinuation				
- Progression or death	6 (15%)	1 (33%)	2 (11%)	3 (16%)
- Adverse events	14 (35%)	-	6 (32%)	9 (47%)

Table 3. Ipilimumab-related adverse events

	3mg/kg (n=19)		10mg/kg (n=19)	
Adverse event	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All	17 (90)	7 (37)	18(95)	10 (53)
Diarrhea	7 (37)	3(16)	11 (58)	4 (21)
Colitis	5 (26)	4 (21)	9 (47)	9 (47)
Rash	3 (16)	1 (5)	8 (42)	0 (0)
Fatigue	6 (32)	0 (0)	5 (26)	1 (5)
Pruritus	6 (32)	0 (0)	3 (16)	0 (0)
Nausea	6 (32)	0 (0)	2 (11)	0 (0)
Fever	0 (0)	0 (0)	5 (26)	0 (0)
Vomiting	1 (5)	0 (0)	3 (16)	0 (0)
Weight loss	1 (5)	0 (0)	2 (11)	0 (0)
Hyperthyroidism	2 (11)	0 (0)	1 (5)	0 (0)
Chills	1 (5)	0 (0)	1 (5)	0 (0)
Hypothyroidism	1 (5)	0 (0)	1 (5)	0 (0)
Anorexia	2 (11)	0 (0)	0 (0)	0 (0)
Hypophysitis	2 (11)	2 (11)	0 (0)	0 (0)
Adrenal insufficiency	2 (11)	0 (0)	1 (5)	0 (0)
Pneumonitis	0 (0)	0 (0)	1 (5)	0 (0)
Uveitis	0 (0)	0 (0)	1 (5)	0 (0)

RFA related adverse events

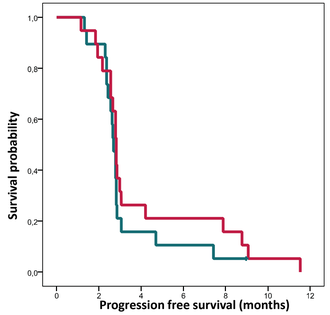
- The most common RFA related toxicities were transient elevation of liver enzymes and flank pain.
- The frequency of RFA-related side effects did not differ between the different dosing cohorts.

Subsequent treatments

There was no significant difference in the number of patients(pts) that were treated with systemic and/or local subsequent treatments between both cohorts.

- In the 3mg/kg cohort 5 patients (26%) received subsequent systemic treatments [2 pts PKC inhibitor (PKCi), 1 pt TCR therapy, 1 pt combination of IPI + NIVO, 1 pt PKCi and DTIC and Lubrinectidin and radiotherapy(RT)] and 2 pts were treated with RT only.
- In the 10mg/kg cohort 6 patients (32%) received subsequent systemic treatments [2 pts combination of PKCi+MEKi, 1 pt NIVO and PKCi, 1 pt NIVO and RT, 1 pt PKCi and embolization with yttrium and 1 pt PKCi], 2 pts were treated with RT only, and 1 pt had surgery and RT.

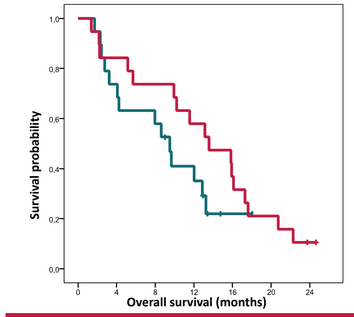
Figure 2. Progression free survival and overall survival per cohort



3mg/kg
Median PFS:
2.6 months, (95% CI: 2.5-2.9)

10mg/kg
Median PFS:
2.8 months (95% CI: 2.6-3.0)

HR: 0.72 (95% CI: 0.37-1.40)
P=0.31



3mg/kg
Median OS:
9.4 months, (95% CI: 7.2-11.8)

10mg/kg
Median OS:
13.6 months (95% CI: 7.4-19.6)

HR:0.59 (95% CI:0.28-1.29)
P=0.18

Conclusions

- The combination of IPI 3mg/kg +RFA was safe but showed limited clinical activity in UM.
- IPI 10mg/kg + RFA had a higher toxicity rate but there seems to be a trend towards longer overall survival.
- Further exploration of combination regimens in randomized clinical trials is warranted.

References

1 Krantz Clin Opht 2017, 2 Kujala Inv Opht Vis Sci 2003, 3 Leyvraz Ann Onc 2014, 4 Eschelman Semin Int Rad 2013, 5 Scheulen ASCO 2017, 6 Carvajal JAMA 2014, 7 Kivela EJC 2003, 8 Maio Ann Onc 2013, 9 Luke Cancer 2013, 10 Kelderman ACTA onc 2013, 11 Algazi Cancer 2016, 12 van der Kooij ACTA onc 2017, 13 den Brok Cancer res 2004, 14 den Brok BJC 2006

E.A.(Lisette) Rozeman, l.rozeman@nki.nl; C.U.(Christian) Blank, c.blank@nki.nl

MADRID 2017 ESMO congress