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MEETING SUMMARY
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RENAL CELL CARCINOMA UPDATE

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PHASE I/II STUDY OF THE ORAL HIF-2α INHIBITOR MK-6482 IN PATIENTS WITH ADVANCED CLEAR CELL RENAL CELL CARCINOMA

Choueiri T, et al.
ASCO GU 2020. Abstract #611
Oral presentation

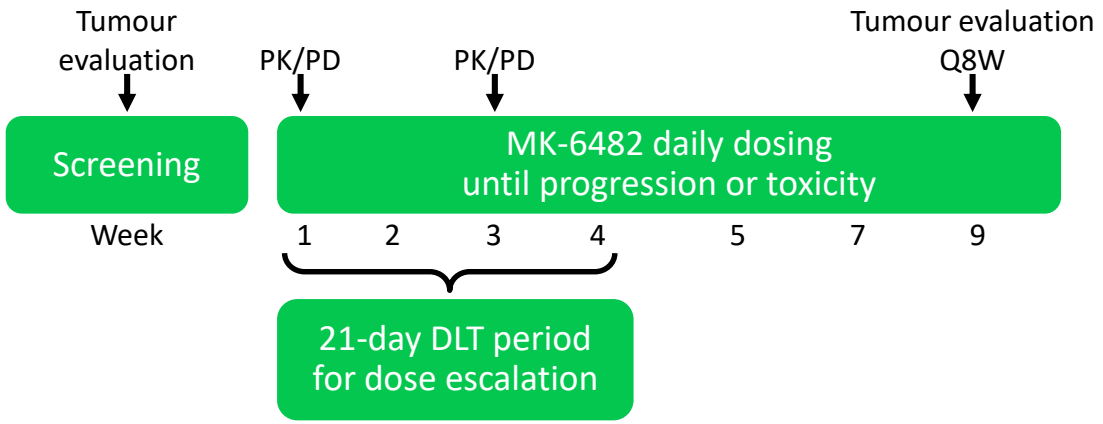
INTRODUCTION

- Hypoxia-inducible factor **(HIF)-2α is a transcription factor that is a key oncogenic driver in RCC**
- **90% of patients with sporadic ccRCC have defective pVHL**[1,2]
- Loss of pVHL function results in constitutive activation of HIF-2α[2]
- **MK-6482 is a** first-in-class **small molecule HIF-2α inhibitor** that blocks the heterodimerisation of HIF-2α with HIF-1β and induces regression in mouse xenograft RCC models

ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; RCC, renal cell carcinoma; pVHL, von Hippel–Lindau protein

1. Shen C, et al. Semin Cancer Biol 2013;23:18-25; 2. Sato Y, et al. Nat Genet 2013;45:860-7;
3. Choueiri T, et al. ASCO GU 2020. Abstract #611 Oral presentation

STUDY DESIGN



- Dose-escalation cohort for patients with advanced solid tumours
- Dose-expansion cohort for patients with advanced ccRCC who previously received ≥1 therapy
  - Key end points: Safety, ORR, duration of response, PFS

Data cut-off: 15 May 2019

Primary endpoint

- Safety

Key secondary endpoints

- ORR
- DOR
- PFS

- Dose of 120 mg QD selected for further clinical development from dose-escalation cohort
- 55 previously treated advanced ccRCC patients enrolled at 120 mg PO QD in dose expansion cohort
  - 39 (71%) discontinued
    - Mainly due to disease progression (55%)
  - 16 (29%) treatment ongoing
- Median (95% CI) follow-up: 13.0 (11.0-13.8) months

ccRCC, clear cell renal cell carcinoma; CI, confidence interval; DLT, dose limiting toxicity; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics;

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BASELINE CHARACTERISTICS

Characteristics	All patients N=55	IMDC risk category		
		Favorable N=5	Intermediate N=40	Poor N=10
Age, median (range), years	62 (39-75)	61 (50-71)	62 (39-75)	59 (41-75)
Sex, n (%)				
Female	11 (20)	3 (60)	7 (18)	1 (10)
Male	44 (80)	2 (40)	33 (82)	9 (90)
Prior systemic therapies, median (range), n	3 (1-9)	3 (1-5)	3 (1-6)	3 (2-9)
Prior systemic therapies, n (%)				
1	9 (16)	1 (20)	8 (20)	0 (0)
2	12 (22)	1 (20)	9 (23)	2 (20)
≥3	34 (62)	3 (60)	23 (58)	8 (80)
Prior anticancer therapies, n (%)				
VEGF/VEGFR	51 (93)	5 (100)	36 (90)	10 (100)
Immune checkpoint inhibitor	40 (73)	3 (60)	29 (73)	8 (80)
Investigational/other	15 (27)	2 (40)	10 (25)	3 (30)
mTOR inhibitor	12 (22)	1 (20)	8 (20)	3 (30)
Cytokine	7 (13)	0 (0)	4 (10)	3 (30)

- The majority of patients were male (80%)
- Patients were heavily pre-treated with 62% having received ≥3 prior systemic therapies

IMDC, International Metastatic RCC Database Consortium; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

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RESULTS

PRIMARY ENDPOINT – SAFETY

All-Cause adverse events ≥20%

AE, n (%)	MK-6482 N=55				
	Grade 1/2	Grade 3	Grade 4	Grade 5	All Grades
Anemia	27 (49)	14 (26)	0 (0)	0 (0)	41 (75)
Fatigue	34 (62)	3 (6)	–	–	–
Dyspnea	23 (42)	3 (6)	–	–	26 (47)
Nausea	17 (31)	1 (2)	–	–	18 (33)
Cough	17 (31)	0 (0)	–	–	17 (31)
Edema peripheral	16 (29)	0 (0)	–	–	16 (29)
Vomiting	16 (29)	0 (0)	–	–	16 (29)
Hypoxia	6 (11)	8 (15)	–	–	14 (26)
Arthralgia	13 (24)	0 (0)	–	–	13 (24)
Dizziness	13 (24)	0 (0)	–	–	13 (24)
Blood creatinine increased	11 (20)	1 (2)	–	–	12 (22)
Diarrhea	12 (22)	0 (0)	–	–	12 (22)
Constipation	11 (20)	0 (0)	–	–	11 (20)
Hyperkalemia	10 (18)	1 (2)	–	–	11 (20)

- Most common grade 3 AEs were anaemia (26%) and hypoxia (15%)
- No grade 4 or 5 drug-related AEs were observed
- 2 patients (4%) experienced a total of four grade 4 AEs: hypercalcaemia, sepsis, cardiac arrest and respiratory failure
- 4 patients (7%) experienced grade 5 AEs secondary to PD:
  - Acute kidney injury, disease progression, malignant neoplasm progression, ventricular fibrillation
- No patient died of a TRAE
- 2 patients (4%) discontinued after the TRAE hypoxia
- 5 patients (9%) required dose reductions to manage TRAEs

AE, adverse event; PD, progressive disease; TRAE, treatment-related adverse event

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RESULTS

Efficacy parameter, n (%) [95% CI]	All patients N=55	IMDC risk category		
		Favorable N=5	Intermediate N=40	Poor N=10
ORR	13 (24) [13-37]	2 (40)	10 (25)	1 (10)
PR	13 (24)	2 (40)	10 (25)	1 (10)
SD	31 (56)	3 (60)	22 (55)	6 (60)
Disease control rate (CR + PR + SD)	44 (80)	5 (100)	32 (80)	7 (70)
PD	9 (16)	0 (0)	7 (18)	2 (20)
Nonevaluable	2 (4)	0 (0)	1 (2)	1 (10)

Best confirmed objective response by RECIST v1.1 per investigator assessment

- 69% of patients experienced a tumour shrinkage
- Median DOR was not reached
- 81% of patients had a response ≥6 months per Kaplan-Meier estimate
- 16 patients (29%) continued treatment beyond 12 months

CR, complete response; DOR, suration of response; IMDC, International Metastatic RCC Database Consortium; RECIST, Response Evaluation Criteria In Solid Tumors; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

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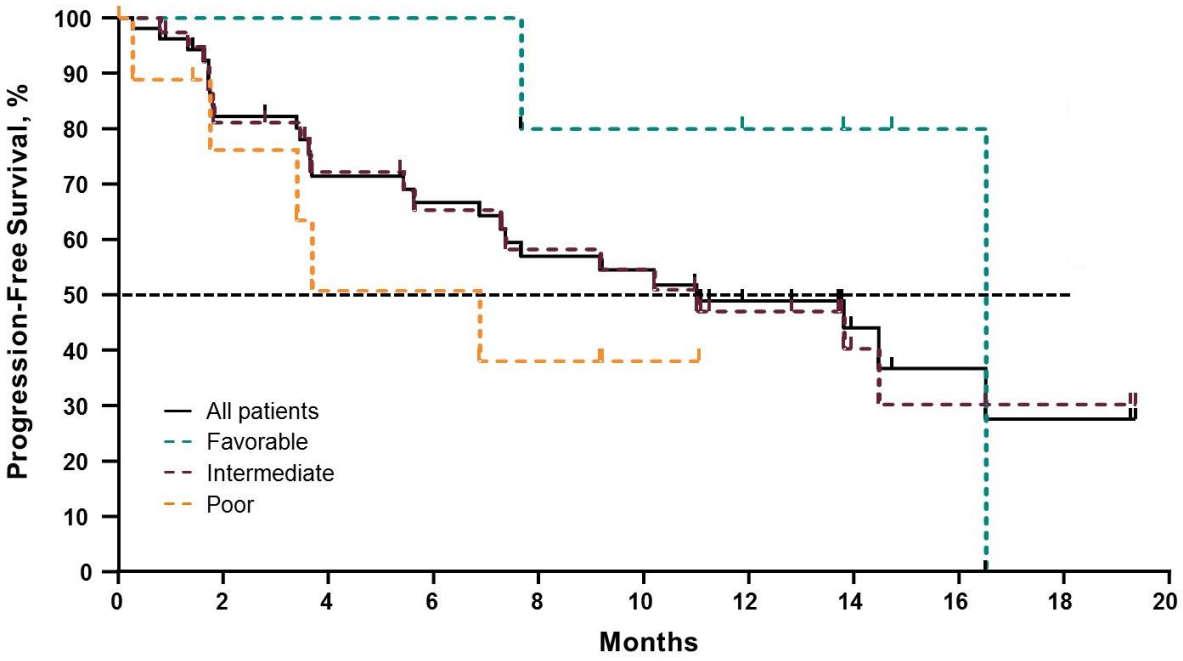
RESULTS

PROGRESSION FREE SURVIVAL



Patient population	Median PFS, months	12-month PFS Rate, %
All patients (N=55)	11.0	49
Favourable (n=5)	16.5	80
Intermediate (n=40)	11.0	47
Poor (n=10)	6.9	NR

PFS, progression free survival

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CONCLUSIONS

- **MK-6482 is well tolerated with a favourable safety profile**
  - Anaemia and hypoxia are on-target toxicities
- After a **median follow up of 13 months**, **promising clinical activity was observed** in patients with heavily pre-treated advanced ccRCC
- A phase 3 trial is ongoing to further investigate the effects of MK-6482 monotherapy in patients with advanced ccRCC

ccRCC, clear cell renal cell carcinoma

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OVERALL SURVIVAL AND INDEPENDENT REVIEW OF RESPONSE IN CHECKMATE-214 WITH 42-MONTH FOLLOW-UP: FIRST-LINE NIVOLUMAB + IPILIMUMAB VERSUS SUNITINIB IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

Tannir N, et al.
ASCO GU 2020. Abstract #609
Oral presentation

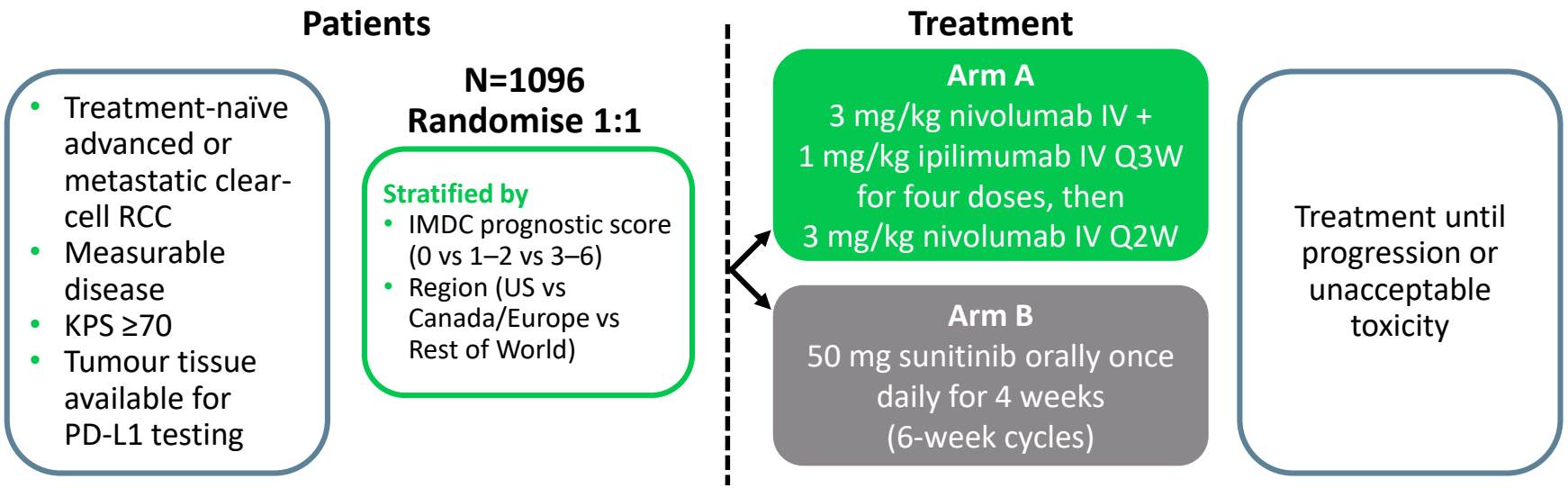
INTRODUCTION

- **Sunitinib**, a small molecule that inhibits multiple receptor tyrosine kinases, **is standard of care for first-line treatment of advanced renal-cell carcinoma**
- Approximately **75% of patients with advanced RCC have intermediate- or poor-risk disease and have worse outcomes than those with favourable-risk disease**[1,2]
- **Nivolumab** (a PD-1 immune checkpoint inhibitor antibody) **is approved for patients with intermediate or poor-risk, previously untreated advanced RCC, in combination with ipilimumab** (an anti–cytotoxic T-lymphocyte–associated antigen 4 antibody) based on the results of the Checkmate-214 study[3]
- **In the Checkmate-214 study, nivolumab and ipilimumab demonstrated superior overall survival and objective response rate compared to sunitinib in patients with advanced RCC**[4]
  - This benefit was observed in the ITT population as well as patients with intermediate /poor-risk classification[1]
- This presentation reports OS and response outcomes per independent radiology review committee (IRRC) and safety with extended follow up (minimum of 42 months)

IDMC, International Metastatic Renal Cell Carcinoma Database Consortium; IRRC, independent radiology review committee; ITT, intention-to-treat; OS, overall survival; PD-1, Programmed cell death protein 1; RCC, renal cell carcinoma;

1. Heng DY, et al. J Clin Oncol 2009;27:5794-9; 2. Heng DY, et al. Lancet Oncol 2013;14:141-8; 3. Nivolumab prescribing information Sep 2019; 4. Motzer RJ, et al. NEJM 2018;378:1277-90; 5. Tannir N, et al. ASCO GU 2020 Abstract #609 Oral Presentation

CHECKMATE-214 STUDY DESIGN



Co-primary endpoints

- In IMDC intermediate and poor risk patients:
  - ORR
  - PFS
  - OS

Secondary endpoints

- In ITT population:
  - ORR
  - PFS
  - OS

Exploratory endpoints

- ORR, PFS, OS in favourable-risk patients

IMDC, International Metastatic RCC Database Consortium; ITT, intent-to-treat; IV, intravenous; KPS, karnofsky performance status; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; RCC; renal cell carcinoma; US, United States of America

Escudier, B. ESMO 2017, Abstract ~ LBA5, Oral presentation; Motzer RJ, et al. NEJM 2018;378:1277-90

RESULTS

Arm; n	ITT		IP	
	Niv+Ipi N=550	Sun N=546	Niv+ Ipi N= 425	Sun N=422
OS, HR (95% CI)	0.72 (0.61-0.86)		0.66 (0.55-0.80)	
OS, %				
24 mo	71	61	66	52
36 mo	59	51	55	44
48 mo	53	44	50	36
ORR per IRRC, % (95% CI)	39 (35-43)	33 (29-37)	42 (37-47)	26 (22-31)
CR, %	11	2	10	1
PFS per IRRC, HR (95% CI)	0.89 (0.76-1.05)		0.76 (0.63-0.91)	
PFS per IRRC, %				
24 mo	38	34	37	26
36 mo	34	25	35	20
48 mo	34	17	35	13
PFS per IRRC in responders, %	**N=215**	**N=178**	**N=179**	**N=111**
24 mo	70	63	68	55
36 mo	66	44	65	40
48 mo	66	34	65	33

CI, confidence interval; CR, complete response; IP, intermediate/poor risk; Ipi, ipilimumab; IRRC, independent radiology review committee ; ITT, intention-to-treat; mo, months; Niv; nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression free survival; Sun, sunitibib

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RESULTS

- **ORR per IRRC was higher and more responses were ongoing with Niv + Ipi vs Sun**
  - 68% vs 53% (ITT) and 68% vs 52% (IP)
- **More patients achieved CR with Niv + Ipi and these were ongoing in 86% (ITT) and 84% (IP) of patients**
- **PFS probability with Niv + Ipi stabilised after 24 months at ~35% in ITT and IP patients,** whereas probabilities declined over time with Sun
- **Among FAV patients:**
  - ORR was 29% with Niv + Ipi vs 54% with Sun
  - More patients achieved CR (13% vs 6%) and more responses were ongoing (69% vs 54%) with Niv + Ipi vs Sun
  - 94% of CRs were ongoing with Niv + Ipi
  - OS benefits were similar across treatment arms and PFS probabilities are stabilising with Niv + Ipi and declining with Sun
- **Incidence of grade 3-4 TRAEs was consistent with previous reports**
- No new drug-related deaths occurred in either treatment arm

CR, complete response; FAV, favourable risk patients; IP, intermediate/poor risk; Ipi, ipilimumab; IRRC, independent radiology review committee ; ITT, intention-to-treat; mo, months; Niv; nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression free survival; Sun, sunitibib; TRAE, treatment-related adverse event

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CONCLUSIONS

- **Superior OS and ORR with Niv + Ipi vs Sun** was maintained in ITT and IP patients
- **More patients treated with Niv + Ipi experienced CR compared with S**, responses and CRs were durable
- PFS probabilities stabilised with Niv + Ipi after extended follow up
- **No new safety signals** emerged during extended follow-up

IP, intermediate/poor risk; Ipi, ipilumumab; ITT, intention-to-treat; Niv, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Sun, sunitinib

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NIVOLUMAB IN COMBINATION WITH STEREOTACTIC BODY RADIOTHERAPY IN PRETREATED PATIENTS WITH METASTATIC RENAL CELL CARCINOMA: FIRST RESULTS OF PHASE II NIVES STUDY

Masini C, et al.

ASCO GU 2020. Abstract #613
Oral presentation

INTRODUCTION

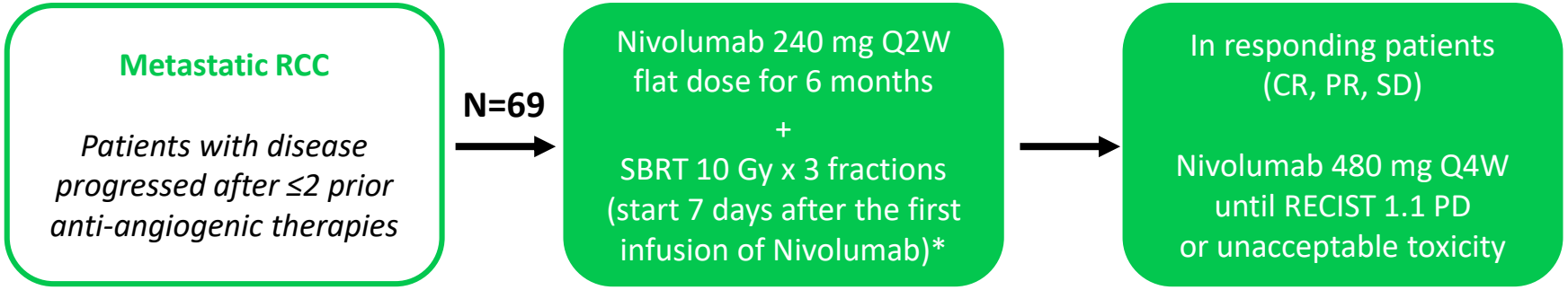
- **Despite advances in treatments for patients metastatic RCC (mRCC), the 5-year survival rate of these patients remains approximately 10%**
- Stereotactic body radiotherapy **(SBRT) is a focussed radiation therapy**, **delivering high-dose radiation directly to the tumour** resulting in more tumour cells being destroyed and less damage to adjacent healthy tissue
- Several preclinical studies have documented **an increase in peripheral anti-tumour immunity following radiation**. **SBRT may trigger increased tumour antigen release, promote T-cell infiltration, and result in increased anti-tumour immunity**
- **Radiation has been shown to induce tumour PD-L1 expression**
- Inhibition of the PD-1/PD-L1 axis with nivolumab has been demonstrated to improve anti-tumour immunity by blocking the tumour-mediated suppression of cytotoxic T cells
- **Nivolumab is a monoclonal antibody directed against PD-1**. Combining this drug with radiotherapy might have a synergistic effect. The combination of SBRT with nivolumab could potentially enhance the anti-tumour immune response and might improve clinical outcomes
- **This study attempted to ascertain whether the anti-tumour immunity of anti-PD1 therapy, in the form of nivolumab, can be enhanced by radiotherapy (SBRT)**

mRCC, metastatic renal cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; SBRT, stereotactic body radiotherapy

Masini C, et al. ASCO GU 2020. Abstract #613 Oral presentation; Masini C, et al. Journal of Clinical Oncology 2018;36.

STUDY DESIGN

- Phase 2, single-arm, multicentre study



* First cycle = Nivolumab 240 mg + SBRT + Nivolumab 240 mg
One cycle = 4 weeks

Primary endpoints
- ORR

Secondary endpoints
- PFS
- OS
- ORR of irradiated and non-irradiated metastases
- DOR
- Safety profile

Exploratory endpoints
- PD-L1 expression and analysis of genomic profile of tumour sample
- cfDNA (analysis of genomic alterations)

cfDNA, Circulating cell-free DNA; CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PD-L1; programmed death ligand-1; PFS, progression free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors ; RCC, renal cell carcinoma; SBRT, stereotactic body radiotherapy; SD, stable disease

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EFFICACY RESULTS

Patient characteristics:

- Clear cell histology: 79.7%
- Males: 82.6%
- IMDC intermediate/poor: 79.7%
- Median age: 67 (range 43-85)
- 2 prior lines of therapy: 18.8%
- Non-nephrectomy: 21.7%

Most frequent sites of SBRT:

- Lung: 37.7%
- Lymph nodes: 11.6%
- Bone: 11.6%

	N=69 (ITT)	N=63* (PP)
ORR, No (%)	12 (17.4)	12 (19.0)
95% CI	[9.3-28.4)	[10.25-30.9)
Best overall response No (%)		
CR	1 (1.4)	1 (1.6)
PR	11 (16.0)	11 (17.4)
SD	28 (40.6)	28 (44.5)
PD	23 (33.3)	23 (36.5)
Not evaluable	6 (8.7)	–
Disease control rate No (%)	40 (58.0)	40 (63.5)

*2 patients didn't receive SBRT; 4 pts didn't receive 2nd dose of nivolumab (first cycle not concluded)
Median number of nivolumab doses received was 12 (range 1-32)

- There was no statistically significant difference between site of SBRT and ORR
- Patients with clear cell histology achieved the greatest ORR benefit

CI, confidence interval; CR, complete response; IMDC, International Metastatic RCC Database Consortium; ITT, intention-to-treat; ORR, overall response rate; PD, progressive disease; PR, partial response; SBRT, stereotactic body radiotherapy; SD, stable disease

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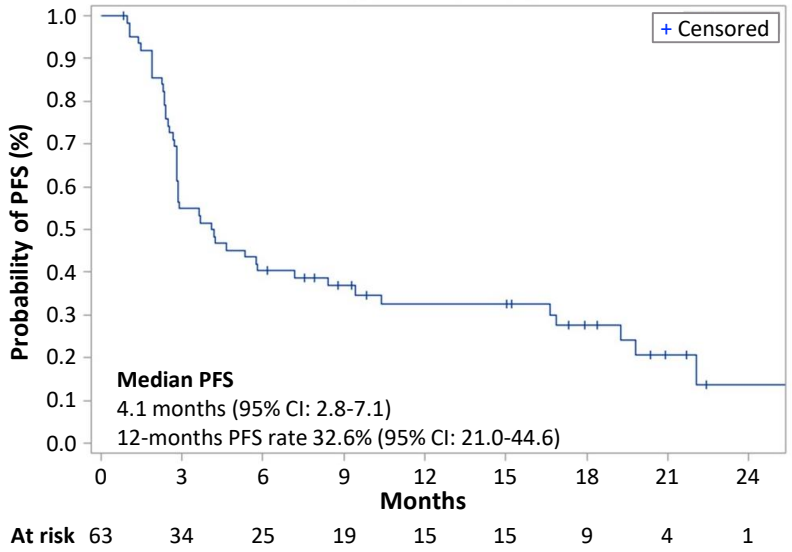
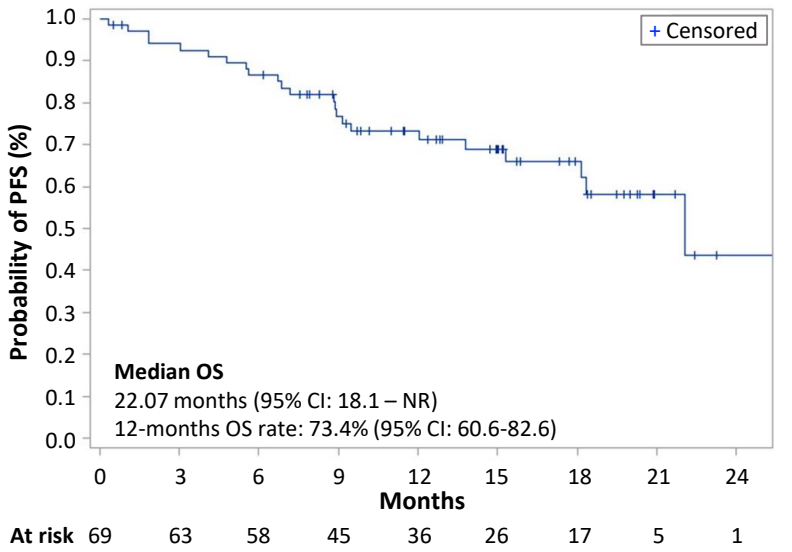
EFFICACY RESULTS

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



- Median follow up of 15 months (range 0-25.6)

CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression free survival;

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SAFETY

	Grade 1-2 (%)	Grade 3-4 (%)
Dermatologic		
Rash	13 (18.8%)	2 (2.9%)
Pruritus	6 (8.7%)	–
Renal		
Elevated creatinine	1 (1.4%)	–
Respiratory		
Pneumonia	8 (11.6%)	–
GI		
Anorexia	1 (1.4%)	–
Diarrhoea	1 (1.4%)	4 (5.8%)
Nausea-vomiting	4 (5.8%)	–
Colitis	1 (1.4%)	1 (1.4%)
Bowel obstruction	–	1 (1.4%)
Gastric pain	2 (2.9%)	–
Hyperamilasemia/hyperlipasemia	3 (4.3%)	3 (4.3%)
Hypertransaminasemia	3 (4.3%)	–
Neurologic disorders	0	1 (1.4%)
Endocrine immune disorders	4 (5.8%)	–
Cardiologic disorders	1 (1.4%)	–
Haematologic	–	2 (2.9%)
Fatigue	11 (15.9%)	3 (4.3%)
Others	7 (10.1%)	–

- 7 patients discontinued treatment due to AE
- Treatment-related grade 3-4 toxicities were experienced in 17 patients (24.6%)
- All grade 3-4 toxicities were outside of the irradiated area
- 6 patients (8.7%) were hospitalised due to treatment related SAEs

AE, adverse event; GI, gastrointestinal; SAEs, serious adverse events

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CONCLUSIONS

- **NIVES is the first prospective trial of nivolumab plus SBRT in mRCC patients**
- The **combination of nivolumab and SBRT had an acceptable safety profile** in pre-treated mRCC patients
- A high DCR and survival rate was observed with the combination of nivolumab and SBRT but **the primary endpoint of ORR was not reached**
- The results of this study suggest that the combination of nivolumab and SBRT warrant further investigation in future studies

DCR, disease control rate; mRCC, metastatic renal cell carcinoma; ORR, overall response rate; SBRT, stereotactic body radiotherapy

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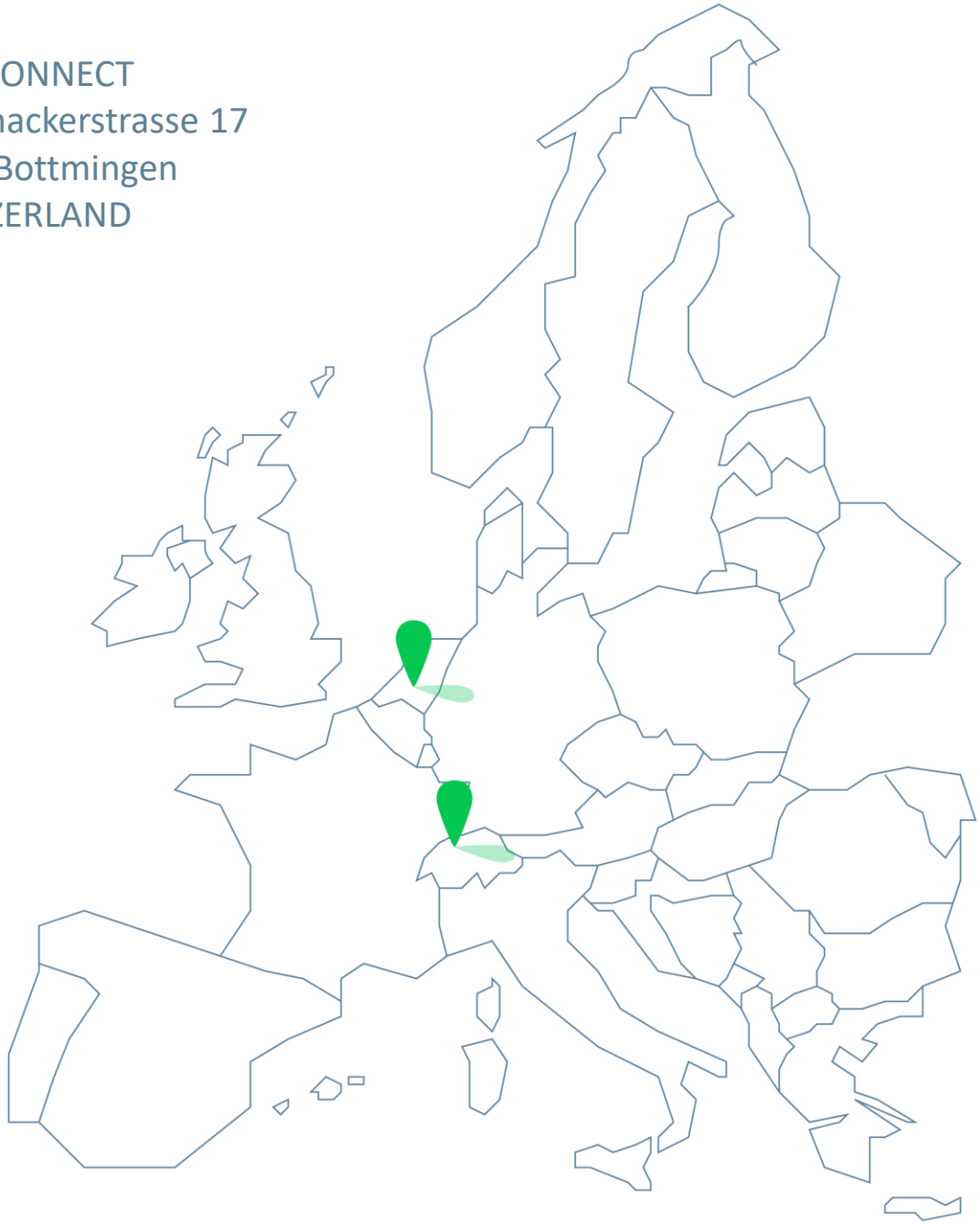

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