Results of the ADAPT Phase 3 Study of Rocapuldencel-T in Combination with Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma

Robert A. Figlin[1], Nizar M. Tannir[2], Robert G. Uzzo[3], Scott S. Tykodi[4], David Y.T. Chen[3], Viraj Master[5], Anil Kapoor[6], Daniel Vaena[7], William Lowrance[8], Gennady Bratslavsky[9], Mark DeBenedette[10], Alicia Gamble[10], Ana Plachco[10], Marcus S. Norris[10], Joe Horvatinovich[10], Irina Y. Tcherepanova[10], Charles A. Nicolette[10], and Christopher G. Wood[2], for the ADAPT study group

ABSTRACT

Purpose: Rocapuldencel-T is an autologous immunotherapy prepared from mature monocyte-derived dendritic cells (DC), coelectroporated with amplified tumor RNA plus CD40L RNA. This pivotal phase III trial was initiated to investigate the safety and efficacy of a combination therapy dosing regimen of Rocapuldencel-T plus sunitinib in patients with metastatic renal cell carcinoma (mRCC).

Patients and Methods: Patients received either Rocapuldencel-T plus standard of care (SOC) or SOC treatment alone. The primary objective compared overall survival (OS) between groups. Secondary objectives included safety assessments, progression-free survival (PFS), and tumor responses based on RECIST 1.1 criteria. Exploratory analyses included immunologic assessments and correlates with OS.

Results: Between 2013 and 2016, 462 patients were randomized 2:1, 307 to the combination group and 155 to the SOC group. Median OS in the combination group was 27.7 months [95% confidence interval (CI) 23.0–35.9] and 32.4 months (95% CI, 22.5–) in the SOC group HR of 1.10 (95% CI, 0.83–1.40). PFS was 6.0 months and 7.83 months for the combination and SOC groups, respectively [HR = 1.15 (95% CI, 0.92–1.44)]. The ORR was 42.7% (95% CI, 37.1–48.4) for the combination group and 39.4% (95% CI, 31.6–47.5) for the SOC group. Median follow up was 29 months (0.4–47.7 months). On the basis of the lack of clinical efficacy, the ADAPT trial was terminated on February 17, 2017. Immune responses were detected in 70% of patients treated with Rocapuldencel-T, and the magnitude of the immune response positively correlated with OS. In addition, we report the survival-predictive value of measuring IL-12 produced by the DC vaccine and the observation that high baseline numbers of T regulatory cells are associated with improved outcomes in DC-treated patients, but are associated with poor outcomes in patients receiving SOC treatment. No serious adverse events attributed to the study medication have been reported to date.

Conclusions: Rocapuldencel-T did not improve OS in patients treated with combination therapy, although the induced immune response correlated with OS. Moreover, we identified two potential survival-predictive biomarkers for patients receiving DC based immunotherapy, IL-12 produced by the DC vaccine and higher numbers of T regulatory cells present in the peripheral blood of patients with advanced RCC.

Introduction

Kidney cancer is among the 10 most common cancers in both men and women, with renal cell carcinoma responsible for up to 85% of all cases. In 2019, it is estimated that 73,820 people will be diagnosed in the United States (1). The 5 year relative survival rates at diagnosis have shown some improvement, however, the overall prognosis is still poor, particularly for patients who present with highstage disease and a primary tumor in place. Prior to the introduction of targeted therapies, cytokines, including high-dose IL-2 and IFN-α, were the standard of care (SOC) for metastatic renal cell carcinoma (mRCC; ref. 2). Although cytokines still form part of the treatment regimen, their use has been curtailed since the advent of tyrosine kinase inhibitors (TKI) and will likely be further diminished by the incorporation of checkpoint inhibitors (3).

At the time of initiation of the phase III ADAPT trial, sunitinib was a first-line SOC treatment option for patients with previously untreated, clear cell mRCC. In the pivotal phase III trial in previously untreated, primarily favorable and intermediate-risk patients with clear cell mRCC, sunitinib was associated with significantly longer PFS (11 vs.

[1]Cedars-Sinai Medical Center Los Angeles, California. [2]University of Texas, MD Anderson Cancer Center Houston, Texas. [3]Fox Chase Cancer Center, Temple University Health System, Philadelphia, Pennsylvania. [4]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington. [5]Emory University Department of Urology, Emory University Hospital, Atlanta, Georgia. [6]Urologic Cancer Centre for Research and Innovation, Hamilton, Ontario, Canada. [7]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa. [8]Huntsman Cancer Hospital, University of Utah, Salt Lake City, Utah. [9]SUNY Upstate Medical University, Syracuse, New York. [10]Argos Therapeutics Inc., now CoImmune Inc., Durham, North Carolina.

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Clinical trial registration: ADAPT is registered with clinicaltrials.gov, number NCT01582672.

Corresponding Author: Mark DeBenedette, CoImmune Inc., 4233 Technology Drive, Durham, NC 27704. Phone: 919-287-3428; E-mail: mdebenedette@coimmune.com

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Translational Relevance

Our results did not show a survival advantage of combining Rocapuldencel-T with first-line sunitinib. However, OS did exceed the expected target of the initial statistical model. Moreover, this study reaffirmed Rocapuldencel-T mechanism of action and excellent tolerability, reporting a correlation between induced memory CTLs and OS. In addition, we report the survival predictive value of measuring DC produced IL-12 and the presence of T regulatory cells in the peripheral blood as biomarkers for correlative studies. Furthermore, the ADAPT trial successfully deployed this cell-based reagent with few technical failures, manufacturing for >94% of enrolled patients.

5 months), and an improvement in overall survival (OS; median 26.4 vs. 21.8 months) versus IFNα therapy (4). At the time of ADAPT trial design, the international metastatic renal cell carcinoma database consortium (IMDC) risk model was validated using data from a cohort of 645 patients with naïve-VEGF therapy in naïve mRCC. Reported median OS for intermediate and poor risk patients was 27 months and 8.8 months, respectively (5). Further prospective analyses of trials with similar eligible intermediate/poor-risk patients to ADAPT established an OS of 14.7 months for VEGF-TKI and mTOR-targeted therapies (6). Subsequent trials after the start of ADAPT evaluating sunitinib as first-line therapy, CABOSUN and CHECKMATE-214, employing the IMDC risk score including intermediate/poor risk patients reported median OS of 21.2 months (7) and 26 months (8), respectively.

Sunitinib induces tumor regression through inhibition of VEGF activity, and nonspecific immune modulation effects, which consist of a well-documented decrease in T regulatory cells (9). Rocapuldencel-T is an autologous dendritic cell–based immunotherapy developed to capture and present a patient's tumor-specific antigens and direct the immune response to each patient's tumor. The addition of Rocapuldencel-T to the known efficacy of sunitinib could more effectively reconstitute the host immune response than either product alone. This is supported by both clinical and immune response data reported in the phase IIb trial, evaluating Rocapuldencel-T in combination with sunitinib in patients with intermediate or poor-risk mRCC. Increases in the numbers of CTLs between baseline and post fifth dose of Rocapuldencel-T was a statistically significant correlate to survival (10). The primary endpoint was complete response rate, and secondary endpoints included OS, progression-free survival (PFS), and safety. Approximately 62% of patients experienced a clinical benefit [9 partial response (PR) and 4 stable disease (SD)], but no complete responses (CR) were noted, and enrollment was terminated early. Nonetheless, the median PFS from registration was 11.2 months [95% confidence interval (CI) 6.0-19.4], the median OS was 30.2 months (95% CI, 9.4-57.1), and no significant AEs attributed to Rocapludencel-T were observed (10). This reported extension of OS benefit compared with other studies using first-line sunitinib, warranted continued development of Rocapuldencel-T. The rationale to combine sunitinib with Rocapuldencel-T, was based on antitumor activity of sunitinib and its potential to attenuate immune suppression in the tumor microenvironment observed in mRCC (9, 11). As a confirmatory study, the ADAPT phase III trial design randomized intermediate/poor-risk patients as defined by IMDC score, with newly diagnosed mRCC, to receive the combination of Rocapuldencel-T plus SOC versus SOC alone. The trial completed accrual of 462 patients with the goal of evaluating OS for the primary endpoint between the two groups.

Patients and Methods

Study design and participants

ADAPT is an open-labeled, randomized multicenter phase III trial conducted at 108 international sites. Participating countries included sites from the United States, Canada, Israel, the Czech Republic, United Kingdom, Hungary, Italy, and Spain. The ADAPT trial was approved by each institutional review board in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization. Patients provided written informed consent before participation. Patients were newly diagnosed with advanced disease histologically assessed as RCC, with predominantly clear cell histology. Remaining metastatic disease must have a clear cell component and be measurable according to RECIST 1.1. Patients were considered intermediate or poor risk by IMDC score. Favorable risk patients were not eligible for the study. All patients were newly diagnosed with advanced RCC presenting with a primary tumor in place, thus with at least one risk factor and not considered as favorable risk per IMDC risk criteria. Risk factors 5 and 6 were excluded because their poor performance status might not have allowed for the preparation of the vaccine before disease progression or death. Recent evidence from the CARMENA trial (12) further supports this group of patients with poor outcomes post-nephrectomy. The number of risk factors present included: a Karnofsky performance status score of <80%, time from initial diagnosis to treatment of <1 year and life expectancy of 6 months or greater, hemoglobin level below the lower limit of the normal range, corrected serum calcium concentration of >10 mg per deciliter, absolute neutrophil count above the upper limit of normal (ULN) range, and a platelet count above the ULN range (5). A total of 462 patients were randomized 2:1 to receive either Rocapuldencel-T plus SOC treatment or SOC treatment alone. For both groups, SOC treatment was initiated with sunitinib, administered per current labeling for mRCC. However, when intolerance to sunitinib or early progression (prior to week 48) was observed, a switch to other SOC treatments was permitted.

Efficacy endpoints

The primary objective of the ADAPT trial compared OS between the two study groups. Secondary objectives included safety assessments, PFS, objective response rate (ORR), and response duration based on RECIST 1.1 between study groups. Exploratory outcomes analyzed the immune response, based on the measurement of functional $CD28^+/CD45RA^-$ memory CTLs, and assessments of correlates with OS. Determination of the percentage of $CD4^+/FOXP3^+/CD25^+/CD127^-$ T regulatory cells in the peripheral blood at various time points was compared between the two groups and included assessments of correlates with OS.

Statistical analysis

The primary analysis of the study was conducted when 290 OS events were accrued. The analysis of the intent-to-treat (ITT) population is calculated on the basis of an assumed power of 80% with two-tailed alpha of 0.05, representing a 6 months or greater OS improvement between study groups. The efficacy assumption used a median OS for SOC of 16 months and a median OS for Rocapuldencel-T plus SOC treatment of 22.6 months. The allocation ratio of patients between the study groups was set at 2:1, accrual time for

the study was set at 18–24 months and total duration set at 2 years postaccrual. The ITT population included all randomized patients in the study. This population was used for the demographic and baseline characteristics and for the primary efficacy analyses. The mITT population included all randomized patients in the study who received at least one or more doses of sunitinib for the SOC group or at least one or more doses of Rocapuldencel-T for the combination group. This population was used for supportive efficacy analyses.

Rocapuldencel-T manufacturing

Rocapuldencel-T was manufactured at a centralized GMP compliant facility (Argos Therapeutics). Following screening and consent, autologous tumor total RNA was isolated from standard nephrectomy (partial or cytoreductive nephrectomy) tumor tissue confirmed having predominantly clear cell histology. Per protocol, after excision tissue was placed on ice and immediately placed in RNA preservative to maintain RNA integrity (13). mRNA was amplified using RT/PCR and *in vitro* transcription technologies as described previously (14). CD40L RNA was manufactured using *in vitro* transcription and a posttranscriptional capping method (15). DC product was matured from monocytes isolated from patient leukapheresis by elutriation and coelectroporated with amplified tumor RNA and CD40L RNA using a postmaturation electroporation protocol described previously (10). Final product was formulated as 1.4×10^7 DC/0.7mL in 80% autologous plasma, 10% dextrose (50% w/v; Hospira), and 10% DMSO (Sigma) and cryopreserved in liquid nitrogen vapor phase. Thawed samples of final product were assessed for sterility, *Mycoplasma*, endotoxin, and viability prior to release for clinical use. Rocapuldencel-T was administered into a single lymph node basin as three intradermal injections of 0.2 mL each (0.6 mL total volume). Rocapuldencel-T dosing was initiated after completion of at least one 6-week sunitinib cycle followed by one dose every 3 weeks for a total of five doses (induction phase). Booster phase dosing followed with one dose every 3 months until withdrawal criteria were met. Doses were administered through 48 weeks irrespective of disease progression, unless unacceptable toxicity occurred, or per patient/physician decision. OS was measured from the date of subject randomization until death or censoring. PFS was defined as the number of days from randomization to the date of the first documented disease progression/relapse or death, whichever occurred first as reported by each investigational site. Tumor response was assessed by RECIST 1.1 criteria.

Immune monitoring

Immune response assessments were predefined as exploratory objectives in the statistical analysis plan and performed on peripheral blood mononuclear cells (PBMC) isolated from peripheral blood samples collected from patients in North America who provided consent for immune monitoring. Pre- and post-Rocapuldencel-T treatment samples were collected at visit 1 (week 0), prior to initiation of sunitinib treatment or Rocapuldencel-T, Visit 2 (week 6) baseline, after the first cycle of sunitinib, but before Rocapuldencel-T, visit 6 (week 15) after the third dose of Rocapuldencel-T, Visit 9 (week 24), after the fifth dose of Rocapuldencel-T, and visit 12 (week 48), and after the seventh dose of Rocapuldencel-T. PBMCs were processed by Ficoll density gradient separation and stored frozen. When all blood draws were collected, memory $CD28^+/CD45RA^-$ CTL responses were assessed as described previously (10). Briefly autologous DC targets for *in vitro* PBMC stimulation were obtained from manufacturing and represent autologous product for each evaluable subject. After a 6-day incubation, cells were restimulated with autologous DCs for 5 hours in the presence of anti-CD107a antibody (BD Biosciences). After incubation, cells were stained for viability using a viability dye (Invitrogen) followed by surface staining with specific antibodies for detection of CD28, CD45RA, CD3, and CD8 expression, and intracellularly for IFN-γ, TNF-α, IL-2, and BrdU expression (BD Biosciences). A total of $4–6 \times 10^5$ cells collected in Trucount tubes (BD Biosciences) were acquired using a LSRII flow cytometer and data analyzed with FlowJo software (TreeStar). A positive immune response for a patient defined as an immune responder, was predefined as an increase in $CD28^+/CD45RA^-$ memory CTLs of at least two SDs from the patient-specific visit 2 (baseline) in the number of effector function CTLs measured from visit 2 to any time point after Rocapuldencel-T administration. The planned analyses included a correlation of the absolute change in effector function CTLs from visit 2 with clinical endpoints including OS assessed by the Spearman correlation coefficient (ρ).

T regulatory cell quantification

As predefined in the statistical analysis plan, comparison of percentage of T regulatory cells at each time point and the change from baseline to postbaseline time points were compared between treatment arms. The correlation between the change in T regulatory cells and the clinical endpoints were assessed. T regulatory cells were quantified in whole blood draws collected in heparin vacutainer tubes and shipped overnight to Argos Therapeutics Inc. Whole blood was stained with the following antibodies to CD25, CD127, CD3 (BioLegend), and CD4 (BD Biosciences). Red blood cells were lysed using BD FACS Lysing Solution (BD Biosciences) and mononuclear cells stored at -85°C until all patient visit blood collections were completed. Upon the patient's completion of the trial, stained frozen whole blood was thawed and stained with antibody to FoxP3 (BioLegend). Cells were analyzed on a LSRII flow cytometer and data analyzed with FlowJo software (TreeStar). Percentages of T regulatory cells represent the percentage of $CD4^+$ T cells in the peripheral blood with the following phenotype $FOXP3^+/CD25^+/CD127^-$.

IL-12 measurement

As a retrospective analysis based on our preclinical modeling of potency of Rocapuldencel-T (16), IL-12 secretion was determined postthaw from final product after DCs were incubated overnight at 1×10^6 DCs/mL in culture medium. Supernatants were collected and the IL-12p70 concentration was analyzed using the IL-12p70 Cytometric Bead Array kit (BD Biosciences) to test samples against a known standard. Samples were acquired on an LSRII Flow Cytometer and the data processed using FCAP array software (BD Biosciences) to generate IL-12 concentrations for each sample.

Results

Patient demographics

Between November 2012 and May 2016, the ADAPT trial randomized 462 patients to the two treatment groups. During systemic tumor removal, 1,131 tumors were collected, with 504 (44.5%) tumor screen failures, including specimens not having a predominantly clear cell histology, and a further 151 (13.3%) were subsequent screen failures. The ITT population included all randomized patients and was used for demographics, baseline characteristics, and primary efficacy analysis. This population included 462 patients, 307 (66.5%) were randomized to the combination group and 155 (33.5%) to the SOC group. At the time of data cutoff (February 02, 2017), 218 patients had died, 149

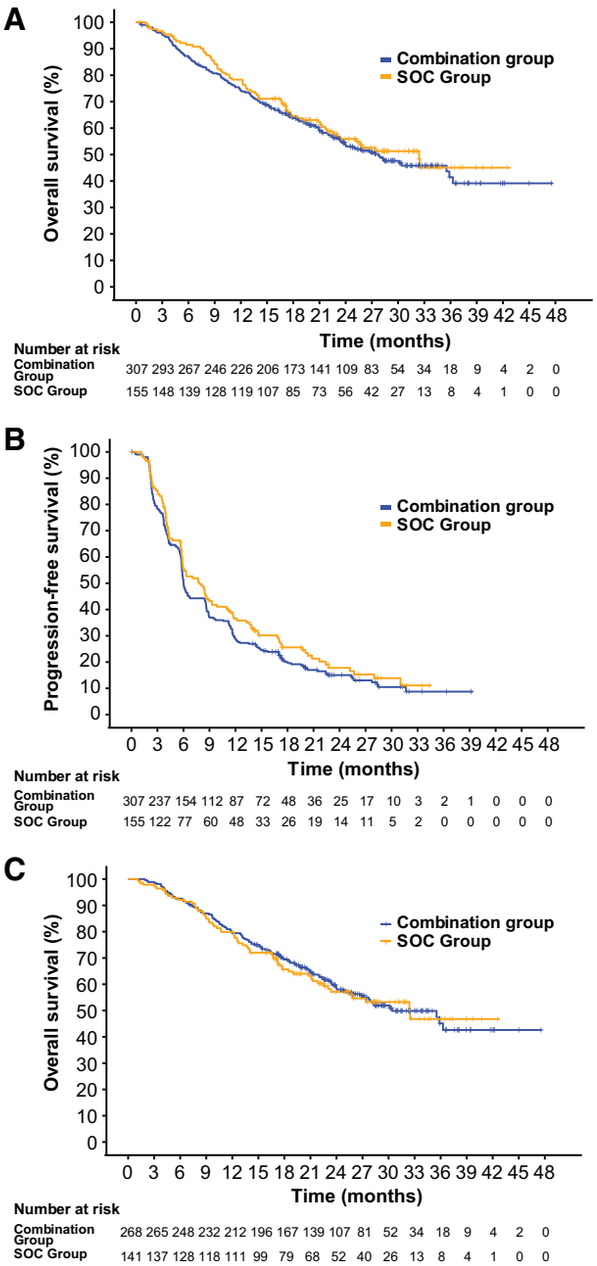

Figure 1.

OS and PFS among patients on the ADAPT study. Kaplan–Meier survival curves (**A**) and PFS curves (**B**) for patients in the ITT population, and survival curves (**C**) for patients in the mTT population. Blue lines represent patients on the combination group and yellow lines represent patients on the SOC group. Numbers of patients at risk are depicted below the graphs. (+) denotes censored patients.

(48.5%) in the combination group and 69 (44.5%) in the SOC group. 241 patients remained alive in the two groups, 156 (50.8%) in the combination group, and 85 (54.8%) in the SOC group. Of the patients alive at the time of data cutoff, 66 patients (42%) in the combination group and 28 (33%) in the SOC group remained on treatment. Ninety patients remained in follow up from the combination group and 57 remained in follow up from the SOC group (**Fig. 1S**). Thirty-nine (12.7%) of the 307 patients randomized to the combination group did not receive Rocapuldencel-T (17 due to manufacturing failures, five deaths prior to dosing, and 15 due to subject or principal investigator's decision). Fourteen (9%) of the 155 patients in the SOC group did not receive sunitinib, 241 patients (78%) completed induction phase dosing with Rocapuldencel-T (five doses), and 188 (61%) received at least seven doses. **Table 1** shows the demographics and disposition of the enrolled patients. According to the IMDC risk factors 76.5% and 77.4% of patients were intermediate risk and 23.5% and 22.6% were poor risk for the combination group and the SOC group, respectively. Assessment of baseline characteristics identified no significant differences between groups.

Clinical outcomes and safety assessment

Rocapuldencel-T was initiated after at least one cycle of sunitinib and combination patients received 5 doses (induction) irrespective of progression. Following completion of induction, booster dosing with Rocapuldencel-T continued unless two or more progression events accrued within the first 48 weeks. 221 of the 307 patients (72%) continued combination treatment with Rocapuldencel-T after the first progression and 90 of the 155 patients (58%) continued SOC treatment after the first progression. If discontinuation of sunitinib is indicated, either for toxicity or disease progression, second-line therapy was initiated, and patients continued with Rocapuldencel-T dosing in combination with second-line therapy. 194 patients received Rocapuldencel-T in combination with other SOC treatments as subsequent therapy and remained on study. Some patients received Rocapuldencel-T in combination with more than one other active agent (Supplementary Table 1S). The most common subsequent SOC treatments in both groups were axitinib, nivolumab, everolimus, pazopanib, cabozantinib, and bevacizumab; all others were used in less than 6% of patients. The proportion of patients in the two groups who received each of the subsequent treatments were comparable; the largest difference was in the use of nivolumab, which was higher in the combination group compared with the SOC group (29.0% vs. 17.4%; Supplementary Table 1S).

The ITT population included all randomized patients ($n = 462$). For the primary endpoint, median OS in the combination group was 27.7 months (95% CI, 23.0–35.9) and 32.4 months (95% CI, 22.5, -) in the SOC group with an unadjusted HR of 1.10 (95% CI, 0.83–1.46) and a HR of 1.06 (95% Cl, 0.79–1.40) after adjustment for randomization stratification factors (**Table 2**; **Fig. 1A**). PFS for the ITT population was 6.0 months (95% CI, 5.8-6.7) in the combination group and 7.83 (95% Cl, 5.87–9.3) in the SOC group with a HR of 1.15 (95% Cl, 0.92–1.44) in the ITT population (**Table 2**; **Fig. 1B**). The mITT population ($n = 409$) included all randomized patients who received at least 1 or more doses of Rocapuldencel-T ($n = 268$) or at least 1 or more doses of sunitinib ($n = 141$). Median OS in the combination group was 30.4 months (95% CI, 25.8-) and 32.5 months (95% CI, 23.0-) in the SOC group with an unadjusted HR of 0.97 (95% CI, 0.72–1.33), and a HR of 0.95 (95% CI, 0.70–1.29) after adjustment for randomization stratification factors (**Table 2**; **Fig 1C**). Objective response rates for both groups are shown in **Table 2**. There was a total of 9 (2.9%) CRs in the combination group and 3 (1.9%) in the SOC group; the number of PRs in the two groups was 122 (39.7%) and 58 (37.4%), respectively. The ORR was similar between the two groups, 42.7% (95% CI, 37.1–48.4) in the combination group and 39.4% (95% CI, 31.6–47.5) in the SOC group.

For the evaluation of safety data, patients who received at least one dose of Rocapuldencel-T or sunitinib were included in the safety summaries. A total of 299 patients in the combination group received

Table 1. Patient demographics and disease characteristics.

ITT Population	Combination group *n* = 307		SOC Group *n* = 155		Group comparability *P*
Median age	60 y		61 y		0.615
Gender, Male	227	73.9%	114	73.5%	>0.999
Race					0.114
White	288	93.8%	151	97.4%	
Non-White	19	6.2%	4	2.6%	
Time from Initial Dx	2.67 mo		2.63 mo		
Metastatic disease					0.866
Yes	305	99.3%	155	100.0%	
Measurable	273	88.9%	135	87.1%	
Nonmeasurable	32	10.4%	20	12.9%	
No	2	0.7%	0	0%	
IMDC Risk factors					
Intermediate risk	235	76.5%	120	77.4%	0.907
Poor risk	72	23.5%	35	22.6%	
1	84	27.4%	43	27.7%	0.993
2	151	49.2%	77	49.7%	
3	52	16.9%	26	16.8%	
4	20	6.5%	9	5.8%	
Karnofsky Performance status					0.934
100%	104	33.9%	55	35.5%	
90%	120	39.1%	61	39.4%	
80%	69	22.5%	32	20.6%	
70%	12	3.9%	7	4.5%	
60%	1	0.3%	1	0%	

Abbreviation: Dx, diagnosis.

Table 2. Clinical responses by treatment group.

Overall survival					
ITT	**Combination group**	**SOC Group**	**Modified ITT**	**Combination group**	**SOC Group**
n = 462	*n* = 307	*n* = 155	*N* = 409	*n* = 268	*n* = 141
Median OS	27.7 mo	32.4 mo	Median OS	30.4 mo	32.5 mo
95% CI	23.0–35.9	22.5, -	95% CI	25.8-	23.0-
HR (95% CI) Unadjusted	1.10, (0.83–1.46)		HR (95% CI) Unadjusted	0.97 (0.72–1.33)	
HR (95% CI) Adjusted	1.06, (0.79–1.40)		HR (95% CI) Adjusted	0.95 (0.70–1.29)	

Progression free survival		
	Combination Group	**SOC Group**
ITT Population	*N* = 307	*N* = 155
Median PFS	6.0 mo	7.83 mo
95% CI	5.83–6.73	5.87–9.3
HR (95% CI)	1.15 (0.92–1.44)	

ORR		
ITT Population	***n* = 307**	***n* = 155**
Best overall response, *n* (%)		
CR	9 (2.9%)	3 (1.9%)
PR	122 (39.7%)	58 (37.4%)
SD	121 (39.4%)	57 (36.8%)
PD	30 (9.8%)	10 (6.5%)
Not evaluable NE	25 (8.1%)	27 (17.4%)
ORR (CR + PR) *n* (%)	131 (42.7%)	61 (39.4%)
(95% CI)	(37.1–48.4)	(31.6–47.5)
Disease control rate (CR + PR + SD), *n* (%)	253 (82.4%)	118 (76.1%)
(95% CI)	(77.7–86.5)	(68.6–82.6)

Abbreviations: NE, not evaluable; PD, progressive disease.

Table 3. Overview of AEs.

Period AE category	Combination group ($N = 299$) *n* (%)	SOC Group ($N = 141$) *n* (%)	Total ($N = 440$) *n* (%)
Pretreatment period[a]			
Any AEs	10 (3.3)	2 (1.4)	12 (2.7)
Any SAEs	1 (0.3)	0 (0.0)	1 (0.2)
Any grade III/IV/V AEs	1 (0.3)	0 (0.0)	1 (0.2)
Randomized treatment period[b]			
Any AEs	296 (99.0)	139 (98.6)	435 (98.9)
Rocapuldencel-T–related AEs	174 (58.2)		
SOC-related AEs	285 (95.3)	134 (95.0)	419 (95.2)
Any grade III/IV/V AEs	214 (71.6)	98 (69.5)	312 (70.9)
Rocapuldencel-T–related grade III/IV/V AEs	6 (2.0)		
SOC-related grade III/IV/V AEs	144 (48.2)	74 (52.5)	218 (49.5)
Deaths	19 (6.4)	7 (5.0)	26 (5.9)
Any SAEs	129 (43.1)	47 (33.3)	176 (40.0)
Rocapuldencel-T–related SAEs	0 (0.0)		
SOC-related SAEs	48 (16.1)	24 (17.0)	72 (16.4)
Discontinuation of Rocapuldencel-T due to			
Any AEs	11 (3.7)		
Rocapuldencel-T–related AEs	0 (0.0)		
SOC-related AEs	4 (1.3)		
Discontinuation of SOC due to			
Any AEs	60 (20.1)	32 (22.7)	92 (20.9)
Rocapuldencel-T–related AEs	3 (1.0)		
SOC-related AEs	42 (14.0)	21 (14.9)	63 (14.3)

Note: Percentage is calculated using the number of subjects in the column heading as the denominator.
[a]AEs during pretreatment period include AEs occurring prior to the first dose of study medication.
[b]AEs during randomized treatment period include AEs occurring on or after the first dose of study medication.

either Rocapuldencel-T or sunitinib, of which 31 patients received sunitinib only and 268 patients received the combination therapy of Rocapuldencel-T and sunitinib. 141 patients in the SOC treatment group received at least one dose of sunitinib. Rocapuldencel-T administration was well tolerated with a total of 174 (58.2%) combination group patients reporting treatment-emergent adverse events (TEAE), considered to be related to Rocapuldencel-T. Of the 214 (71.6%) patients who experienced grade III/IV/V TEAEs in the combination group, 6 (2.0%) were assessed by investigators as related to Rocapuldencel-T. Serious adverse events (SAE) of any causality were reported in 129 (43.1%) patients. All causality TEAEs in the combination group leading to study withdrawal were reported in 11 (3.7%) patients, and all causality TEAEs leading to death were reported in 19 (6.4%) patients. None (0%) of these reported events were considered Rocapuldencel-T-related (**Table 3**).

The median Rocapuldencel-T exposure was 54.3 weeks with a median number of doses administered of 8. Median sunitinib exposure was the same in both groups, 36.1 weeks in the combination group, and 36.0 weeks in the SOC group. The number of dose modifications was comparable between the two groups. Per protocol, patients who experienced disease progression or intolerable toxicity with sunitinib in either group could start on second-line SOC treatment at the investigator's discretion. Patients on the combination group, who were still in the study treatment period, continued Rocapuldencel-T dosing in combination with second-line therapy. The duration of subsequent SOC treatments was longer in the combination group (20.3 weeks) compared with the SOC group (11.4 weeks), although the overall SOC treatment exposures were similar (53.6 vs. 48.0 weeks, respectively; Supplementary Table S1).

Correlative studies

Prior results from the phase IIb study of patients with mRCC treated in combination with Rocapuldencel-T and sunitinib revealed a correlation between increases in the numbers of functional $CD28^+/CD45RA^-$ memory CTLs after treatment and overall survival (10). As part of the exploratory objectives, the immune response in patients ($n = 146$) randomized to the combination group was assessed using a similar criterion. The numbers of functional $CD28^+/CD45RA^-$ memory CTLs measured at either visit 1 or visit 2 both prior to Rocapuldencel-T administration showed no differences. However, after the third, fifth, and seventh dose of Rocapuldencel-T administration, there was a statistically significant increase in the numbers of functional $CD28^+/CD45RA^-$ memory CTLs (**Fig. 2A**). Furthermore, the percentage of patients considered as immune responders per-protocol at any time point after Rocapuldencel-T administration was 72%, 79%, and 82% post 3, 5, and 7 doses of Rocapuldencel-T, respectively. Eighty-three of the 117 patients (71%) evaluated had received at least 7 doses and were included in the planned analyses comparing the induced immune response with OS. A weak linear relationship but statistically significant correlation ($r = 0.38$; $P \leq 0.001$) between the increased numbers of Rocapuldencel-T–induced functional $CD28^+/CD45RA^-$ memory CTLs and OS was demonstrated after the administration of seven doses. Furthermore, for any subject having a positive immune response to Rocapudencel-T, median OS was not reached at the time of data cutoff (**Table 4**).

We had preclinically defined the secretion of IL-12 from Rocapuldencel-T as a potency marker for product release based on its requirement for the induction of memory T cells (16, 17). Given clinical precedents using delivery of IL-12 or DCs engineered to secrete IL-12 to mediate both immune and clinical responses (18, 19), this relationship

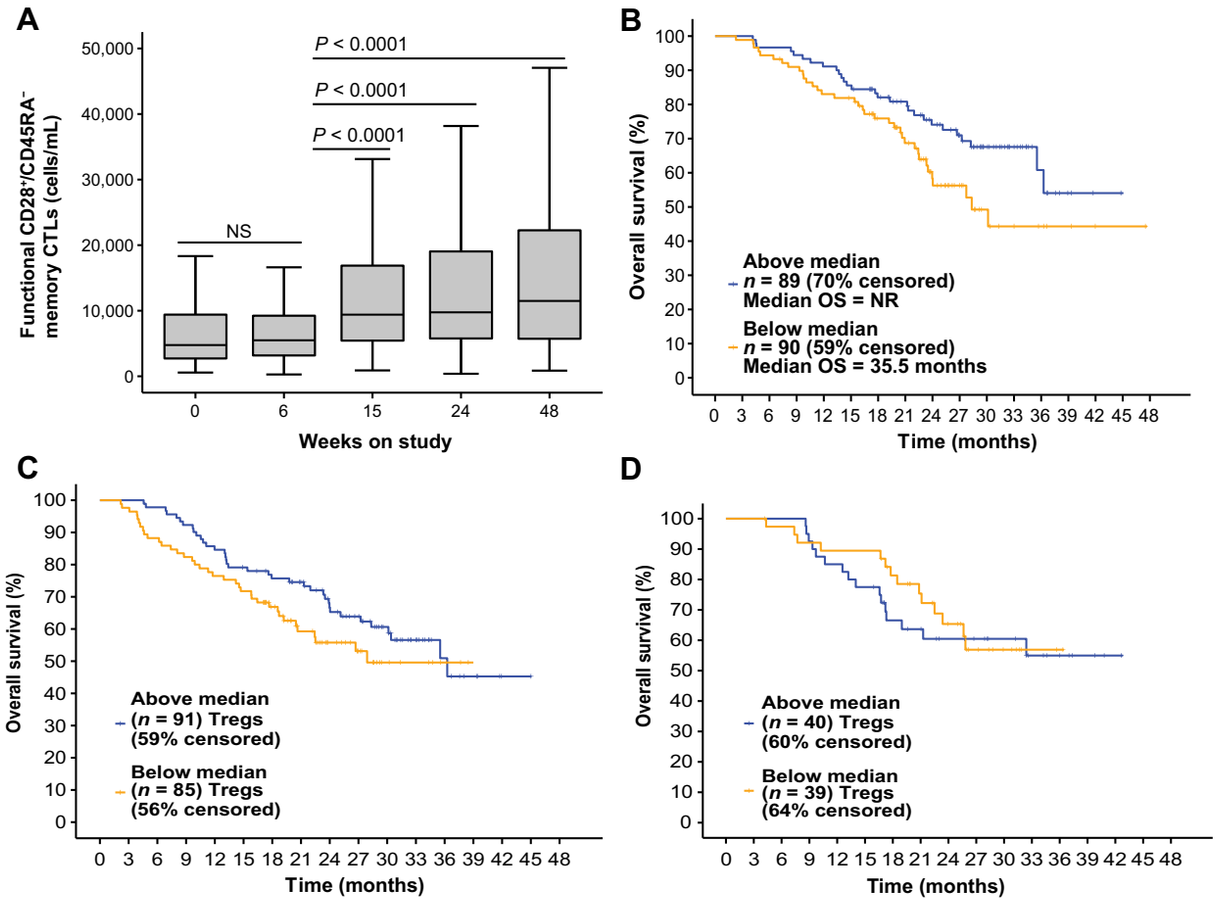

Figure 2.

Rocapuldencel-T–induced memory CTL response and immune correlates with overall survival. Number of functional $CD28^+/CD45RA^-$ memory CTLs (cells/mL) measured at each timepoint (**A**), from PBMCs collected from patients in the combination group ($n = 146$). Number of cells/mL was calculated using the following formula; (number of cellular events collected/number of beads collected) × (bead concentration)/collected volume) × 1,000. The number of viable $CD8^+/CD3^+$ T cells characterized as positive for CD28 and negative for CD45RA and expressing any of the following five functional markers, IFN-γ, TNF-α, IL-2, GrB, CD107a, or the expression of the proliferation marker, BrdU were identified as functional $CD28^+/CD45RA^-$ memory CTLs (cells/mL). Weeks 0 represents pretreatment with sunitinib and pre-dosing with Rocapuldencel-T ($n = 142$). Week 6 represents post the 1st cycle of sunitinib but predosing with Rocapuldencel-T ($n = 142$). Weeks 15, 24, and 48 represent timepoints after 3 ($n = 140$), 5 ($n = 136$), and 7 ($n = 103$) doses of Rocapuldencel-T, respectively. Kaplan–Meier survival analysis of combination group by IL-12 concentration (**B**). Measurement of IL-12 secreted from DC products ($n = 179$). Patients were stratified by above the median or below the median. Yellow lines represent patients below the median and blue lines represent patients above the median. Median IL-12 = 394 pg/mL. Percentage of T regulatory cells before the first dose of Rocapuldencel -T and OS (**C** and **D**). The percentage of T regulatory cells measured in the peripheral blood at visit 2 (V2) are defined as the percentage of $CD4^+$ T cells with the following phenotype $CD25^+/FoxP3^+/CD127^-$ (%Tregs). The T regulatory cell population in the combination treatment group or SOC-treated groups of patients was stratified by above the median or below the median. Censored patients are designated by dots on the lines. Yellow lines represent patients below the median and blue lines represent patients above the median for patients on the combination group (**C**) and the SOC group (**D**).

was explored using manufactured material collected in the ADAPT trial. IL-12 concentration was determined in Rocapuldencel-T products manufactured for 179 unselected patients in the combination group. The concentration of IL-12 produced for each patients' product exhibited a weak linear relationship but statistically significant correlation with OS ($r = 0.27$, $P < 0.0002$) and with the magnitude of the Rocapuldencel-T–induced immune response corresponding to changes from baseline in the number of functional $CD28^+/CD45RA^-$ memory CTLs at each time postdosing. The strongest correlation, with a moderate linear relationship ($r = 0.43$, $P < 0.0001$), was seen after the seventh dose, where 95 of 179 (53.0%) products were assayed. Moreover, there was no correlation between a product's IL12 concentration and the number of functional $CD28^+/CD45RA^-$ memory CTLs measured at baseline ($r = 0.03$, $P < 0.694$; **Table 4**).

For further analysis, the 179 products were stratified into two groups: those with IL-12 concentrations greater than the median ($n = 89$) and those with IL-12 less than or equal to the median ($n = 90$). The median IL-12 concentration was 394 pg/mL. At the time of data cutoff, median OS was not reached in the combination subgroup (70% censored) with IL-12 concentrations above the median and 35.5 months in the combination subgroup with IL-12 production below the median (59% censored). Kaplan–Meier survival analysis comparing these two combination subgroups showed the two survival curves to be well separated (**Fig. 2B**).

For a direct immunologic comparison between the two groups, we measured the percentage of T regulatory cells present in the peripheral blood of 196 patients on the combination group and 86 patients on the SOC group. Unexpectedly, a positive correlation between the percentage of T regulatory cells and OS was seen for patients on the

Table 4. Correlation between OS by Rocapuldencel-T dose and the immune response.

Correlation between the change in functional $CD28^+/CD45RA^-$ memory CTL count and OS					
			Change (cells/mL)		
Time point	***N***	**Median OS**	**Median (min–max)**	**Spearman ρ**	***P***
Post 3rd dose	114	Not reached	4,265 (−3,372–82,536)	0.21	0.030
Post 5th dose	112	Not reached	5,368 (−4,735–80,142)	0.06	0.544
Post 7th dose	83	Not reached	5,330 (−8,865–37,821)	0.38	0.001

IL-12 correlation with memory CTLs			
	N	**Spearman ρ**	***P***
Baseline	139	0.03	<0.6940
Post 3rd dose	130	0.26	<0.0031
Post 5th dose	127	0.39	<0.0001
Post 7th dose	95	0.43	<0.0001

IL-12 correlation with OS			
Combination group	179	0.27	<0.0002

T regulatory cell correlation with OS						
	Combination group			**SOC Group**		
	N	**Spearman ρ**	***P***	***N***	**Spearman ρ**	***P***
Prior to any treatment	196	0.34	<0.0001	86	0.13	<0.2358
Prior to 1st cycle sunitinib	176	0.27	<0.0003	79	0.01	<0.9235
Post 3rd dose	161	0.20	<0.0110	75	0.09	<0.4602
Post 5th dose	157	0.27	<0.0007	61	0.12	<0.3486
Post 7th dose	116	0.20	<0.0390	51	0.06	<0.6689

combination group at all time points. Even at the two baseline time points prior to any Rocapuldencel-T treatment ($P < 0.0001$ and $P < 0.003$, respectively). In contrast, no correlation between OS and the percentage of T regulatory cells in patients on the SOC group at any time point analyzed was detected (**Table 4**). The 176 patients in the combination group, representing data collected after sunitinib treatment but prior to Rocapuldencel-T treatment (visit 2), were stratified into two groups: those with T regulatory cell percentages greater than the median ($n = 91$) and those with percentages of T regulatory cells below the median ($n = 85$). Median T regulatory cell percentages were 2.0% in whole blood. Kaplan–Meier survival analysis comparing these two precombination treatment subgroups showed good separation between the survival curves (**Fig. 2C**). In contrast, when the same analysis was performed in the SOC group ($n = 79$), at the same time point the survival curves were inverted. Where those patients with percentages of T regulatory cells above the median ($n = 40$) had poor OS while those with percentages of T regulatory cells below the median ($n = 39$) had better OS (**Fig. 2D**). Median T regulatory cell percentages were 2.1% in whole blood. This observation is more in line with reported observations that patients with mRCC with higher percentages of T regulatory cells correlated with poor prognosis (20). Similar numbers of censored patients were in both groups.

Discussion

The results of the ADAPT trial showed that the combination of Rocapuldencel-T and SOC therapy for mRCC did not improve OS in the ITT population as outlined in the protocol. However, the OS endpoint for the combination group did exceed the expected target of the initial statistical model based on historical outcomes with sunitinib as monotherapy. What was unexpected was a reported median OS of 32.4 months in the SOC group, which was nearly double as estimated at the time of the ADAPT trial design (median OS of 14.7 months), and much higher than reported in several recent randomized studies (21), including those including checkpoint inhibitors available during the course of the ADAPT trial (8, 22, 23). More recently, the OS reported for treatment with sunitinib at a median follow up of 32.4 months for intermediate/poor-risk patients from the CHECKMATE-214 trial was 26.6 months (24). A potential limitation of this trial was the expansion of second- and third-line therapies available to treating clinicians including other TKIs, mTOR inhibitors, and checkpoint inhibitors (21, 25), which may have impacted the OS determination for SOC group. Prior to the initiation of ADAPT, TKI monotherapy had been the SOC, and in the subsequent validation study of the IMDC risk model, the median OS for the entire population including favorable-, intermediate-, and poor-risk patients was 22 months (5). The CABOSUN trial for patients with intermediate/poor-risk mRCC stratified by IMDC reported an OS of 21.2 months for patients treated with sunitinib (7). More recently, the contribution of nephrectomy to clinical outcome was recently reported for the CARMENA trial (12). In this study, 450 participants with clear cell RCC were randomized to sunitinib therapy with or without nephrectomy. The results for patients that did not receive nephrectomy (median OS = 18.4 months) were noninferior to patients that received nephrectomy (median OS = 13.9 months). Once again, these data stand in striking contradiction to the clinical outcome of the SOC group of the ADAPT trial, where all patients received nephrectomy. In these studies, all patients were treatment naïve at the time of randomization. Comparisons of OS are influenced by the ratio of intermediate- to poor-risk patients included in the analysis. It is important to note that the CARMENA trial classified patients by risk group using the MSKCC risk model and the ADAPT trial used the IMDC risk model. Furthermore, strict adherence to sunitinib therapy only throughout the CARMENA trial verses cycling between approved therapies after initiating with sunitinib in the ADAPT trial may also account for the survival discrepancy. Analysis of the therapies deployed in the ADAPT trial may provide further guidance on maximizing clinical benefit with the existing SOCs for mRCC. Moreover, the treatment options for patients with previously untreated advanced RCC is continually evolving with promising results from trials employing combination of pembrolizumab plus axitinib (26) or nivolumab plus ipilimumab (8) in the first-line setting. Thus, any subsequent trial design will have to take into account the deployment of these agents into first-line setting.

The ADAPT trial successfully deployed a cellular reagent with few technical failures, manufacturing for >94% of enrolled patients. Furthermore, we confirmed biological activity of Rocapuldencel-T in patients who received combination therapy. The intended mechanism of action of Rocapuldencel-T induces functional $CD28^+/CD45RA^-$ memory CTLs against patient-specific tumor antigens. An immune response to Rocapuldencel-T was scored as positive for >70% of the treated patients. Of those patients with immunologic activity a positive correlate with improvement in OS was detected after Rocapuldencel-T dosing. In addition, this analysis confirmed data from the phase IIb study that demonstrated a statistically significant correlation of this same population of CTLs with OS after 5 doses of Rocapuldencel-T, suggesting a survival benefit in the patients who demonstrate an increase in newly induced, functional $CD28^+/CD45RA^-$ memory CTLs. These data are consistent with this immunotherapy's proposed mechanism of action (10, 17). We have extended these immunologic findings to include the concentration of IL-12 produced by each DC product as a correlate with the induced immune response, reaching strong statistical significance after five and seven doses of Rocapuldencel-T. Others have shown a positive correlation between time to progression and the concentration of IL-12 produced by the respective DC vaccine. However, no correlation was observed between IL-12 and the immune response nor the immune response and OS (18, 27). To the best of our knowledge, this is the first report of IL-12 as a potency marker for a DC product correlating with OS. Moreover, the correlation of IL-12 levels with the magnitude of the Rocapuldencel-T–induced immune response and its association with OS, could make it a potential candidate for a predictive biomarker used to preidentify Rocapuldencel-T responders and patients with the potential for clinical benefit after Rocapuldencel-T administration. This trial and others deploying DC vaccines for the treatment of cancer extends our understanding of the importance of DC therapy in stimulating cell mediated immunity and builds on the development of Rocapuldencel-T.

Interestingly, we identified a strong positive correlation between OS and patients treated with Rocapuldencel-T who had greater percent of T regulatory cells at baseline and at each subsequent time point measured. Higher than the median percent of T regulatory cells predicted better clinical outcome in these patients. There was no correlation with OS and T regulatory cell percentages in the SOC group, at any time point analyzed. In fact, patients in the SOC group who had T regulatory cell percentages above the median performed worse than those with T regulatory cells below the median. The exact opposite was seen for patients who received Rocapuldencel-T. This is in direct contrast with previously reported studies that higher percentages of T regulatory cells are a poor prognostic indicator for mRCC (20). The exact underlying mechanism for this relationship is unknown; however, this data lends credence to the deployment of Rocapuldencel-T in the field of immuno-oncology.

Targeted therapies have yielded some improvements for the treatment of mRCC, but durable responses and long-term survival are still rare in patients with intermediate-/poor-risk mRCC. In this study, Rocapuldencel-T was evaluated in combination with sunitinib for the treatment of patients with newly diagnosed mRCC with intermediate-/poor-risk as defined by IMDC risk score. Overall no statistically significant improvement in OS was achieved using the combination therapy. However, patients treated with Rocapludencel-T did reveal an enhanced immune response and the magnitude of the immune response correlated with OS. Furthermore, the advantage of deploying Rocapuldencel-T as a targeted immune therapy is priming against both mutated and nonmutated tumor antigens in rapid production timeline with robust biomarker endpoints for T-cell activation. Therefore, these data presented from the ADAPT trial extend this technology platform to other cancer types, including high mutation burden tumors like NSCLC and melanoma in combination with checkpoint blocking antibodies used for these cancers. Taken together, data provided from the ADAPT trial identify immune correlates with clinical outcomes and two potential survival-predictive biomarker for patients receiving DC-based therapy provides evidence for future DC based immunotherapeutic interventions for cancer treatment.

Disclosure of Potential Conflicts of Interest

N.M. Tannir reports receiving other commercial research support from Bristol-Myers Squibb, Nektar, Calthera Biosciences, Lilly, Pfizer, Arrowhead, Mirati Therapeutics, Takeda, Epizyme, Inc., Eisai and Exelixis Inc., and reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Nektar, Pfizer, Oncorena, Novartis, Lilly, Surface Oncology, Ono Therapeutics, Ipsen, Neoleukin Therapeutics, and Eisai. R.G. Uzzo reports receiving speakers bureau honoraria from Janssen. S.S. Tykodi reports receiving commercial research grants from Clinigen, and reports receiving other commercial research support from Bristol-Myers Squibb, Calithera Biosciences, Jounce Therapeutics, Merck, Pfizer, Exelixis, and Nektar Therapeutics. A. Kapoor reports receiving speakers bureau honoraria from Ipsen, Pfizer, Novartis, BMS, Merck, Eisai. D. Vaena is an employee/paid consultant for AstraZeneca, Bristol-Myers Squibb, and Bayer. M. DeBenedette is an employee/paid consultant for and holds ownership interest (including patents) in CoImmune Inc. A. Gamble, A. Placho, M.S. Norris, J. Horvatinovich, and I.Y. Tcherepanova are employees/paid consultants for CoImmune. C.A. Nicolette is an employee/paid consultant for Argos Therapeutics. C.G. Wood reports receiving speakers bureau honoraria from Pfizer and is an advisory board member/unpaid consultant for Kidney Cancer Association. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: R.A. Figlin, N.M. Tannir, R.G. Uzzo, V. Master, M. DeBenedette, C.A. Nicolette, C.G. Wood

Development of methodology: R.A. Figlin, N.M. Tannir, M. DeBenedette, I.Y. Tcherepanova, C.A. Nicolette

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.A. Figlin, N.M. Tannir, R.G. Uzzo, S.S. Tykodi, D.Y.T. Chen, V. Master, A. Kapoor, D. Vaena, W.T. Lowrance, G. Bratslavsky, M. DeBenedette, A. Gamble, A. Plachco, M.S. Norris, J. Horvatinovich, C.A. Nicolette, C.G. Wood

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.A. Figlin, N.M. Tannir, R.G. Uzzo, S.S. Tykodi, V. Master, W.T. Lowrance, G. Bratslavsky, M. DeBenedette, A. Gamble, M.S. Norris, J. Horvatinovich, I.Y. Tcherepanova, C.A. Nicolette, C.G. Wood

Writing, review, and/or revision of the manuscript: R.A. Figlin, N.M. Tannir, S.S. Tykodi, D.Y.T. Chen, V. Master, A. Kapoor, D. Vaena, W.T. Lowrance, G. Bratslavsky, M. DeBenedette, M.S. Norris, J. Horvatinovich, I.Y. Tcherepanova, C.A. Nicolette, C.G. Wood

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Gamble, A. Plachco, C.A. Nicolette

Study supervision: R.A. Figlin, N.M. Tannir, R.G. Uzzo, D. Vaena, I.Y. Tcherepanova, C.A. Nicolette, C.G. Wood

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