JAMA Oncology | Original Investigation

Adjuvant Weekly Girentuximab Following Nephrectomy for High-Risk Renal Cell Carcinoma
The ARISER Randomized Clinical Trial

Karim Chamie, MD, MSHS; Nicholas M. Donin, MD; Pia Klöpfer, MD; Paul Bevan, PhD; Barbara Fall, MD; Olaf Wilhelm, MD; Stephan Störkel, MD; Jonathan Said, MD; Michael Gambla, MD; Robert E. Hawkins, MD; Gustavo Jankilevich, MD; Anil Kapoor, MD; Evgeny Kopyltsov, MD; Michael Staehler, MD; Kimmo Taari, MD; Alberto J. A. Wainstein, MD; Allan J. Pantuck, MD; Arie S. Belldegrun, MD

IMPORTANCE Girentuximab is a chimeric monoclonal antibody that binds carbonic anhydrase IX, a cell surface glycoprotein ubiquitously expressed in clear cell renal cell carcinoma (ccRCC). Its safety and activity in phase 2 studies prompted investigation into its use as adjuvant monotherapy in participants with high-risk ccRCC.

OBJECTIVE To evaluate the safety and efficacy of adjuvant girentuximab on disease-free survival (DFS) and overall survival (OS) in patients with localized completely resected high-risk ccRCC.

DESIGN, SETTING, AND PARTICIPANTS The ARISER trial (Adjuvant Rencarex Immunotherapy Phase 3 Trial to Study Efficacy in Nonmetastatic RCC) was a randomized, double-blind, placebo-controlled phase 3 clinical trial that took place between June 10, 2004, and April 2, 2013, at 142 academic medical centers in 15 countries in North and South America and Europe. Eligible adult patients had undergone partial or radical nephrectomy for histologically confirmed ccRCC and fell into 1 of the following high-risk groups: pT3/pT4Nx/NOM0 or pTanyN+M0 or pT1b/pT2Nx/NOM0 with nuclear grade 3 or greater. Patients were assigned via central computerized double-blind 1:1 randomization to receive either a single loading dose of girentuximab, 50 mg (week 1), followed by weekly intravenous infusions of girentuximab, 20 mg (weeks 2-24), or placebo, stratified by risk group and region. The data were analyzed from March 31, 2012, to April 2, 2013.

MAIN OUTCOMES AND MEASURES Co–primary end points were DFS and OS, based on imaging studies assessed by independent radiological review committee. Secondary end points included safety, assessed as the rate and grade of adverse events.

RESULTS A total of 864 patients (66% male; median [interquartile range] age, 58 [51-65] years) were randomized to girentuximab (n = 433) or placebo (n = 431). Compared with placebo, participants treated with girentuximab had no statistically significant DFS (hazard ratio, 0.97; 95% CI, 0.79-1.18) or OS advantage (hazard ratio, 0.99; 95% CI, 0.74-1.32). Median DFS was 71.4 months (interquartile range, 3 months to not reached) for girentuximab and never reached for placebo group. Median OS was never reached regardless of treatment. Drug-related adverse events occurred in 185 patients (21.6%), reported comparably between arms. Serious adverse events occurred in 72 patients (8.4%), reported comparably between arms. One drug-related serious adverse event occurred in a patient receiving placebo.

CONCLUSIONS AND RELEVANCE Girentuximab had no clinical benefit as adjuvant treatment for patients with high-risk ccRCC. The surprisingly long DFS and OS in these patients represent a challenge to adjuvant ccRCC drug development.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00087022

Editorial page 895

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Karim Chamie, MD, MSHS, David Geffen School of Medicine at UCLA, Department of Urology, 300 Jules Stein Plaza, Wasserman Building Third Floor, Los Angeles, CA 90095 (kchamie@mednet.ucla.edu).

JAMA Oncol. 2017;3(7):913-920. doi:10.1001/jamaoncol.2016.4419
Published online October 27, 2016.

While surgical resection is curative in the majority of patients who present with localized renal cell carcinoma (RCC), up to 30% will develop disease recurrence during follow-up, the majority within 5 years.[1] Once the disease progresses to a metastatic state, only high-dose interleukin 2 has been shown to produce durable complete and only in 7% to 10% of patients.[2,3] Thus, there is interest in developing well-tolerated adjuvant therapies for patients at high risk of recurrence following resection of localized RCC. Despite a number of trials evaluating agents for use in RCC in the adjuvant setting, only a single phase 3 adjuvant trial to date has demonstrated any progression-free survival benefit,[4] and that trial has been criticized for concerns regarding potential bias.[5] As such, at present, there remains no available clinically proven adjuvant therapy for patients with resected RCC who are at high risk of recurrence.[6]

Carbonic anhydrase IX (CAIX) is a cell surface glycoprotein member of the carbonic anhydrase family and is expressed in approximately 95% of clear cell RCC (ccRCC) but is absent from normal kidney and minimally expressed in nonrenal tissues[7] and is thus an attractive potential target for the diagnosis and treatment of patients with ccRCC. Interest in CAIX as a potential therapeutic target is supported by the central role that targeted therapies and companion diagnostics have assumed in other malignant neoplasms such as melanoma (*BRAF* V600E), non-small-cell lung cancer (*EML4-ALK*, *EGFR*), breast cancer (*ERBB2*), and chronic myeloid leukemia (*BCR-ABL*).[8]

Girentuximab is an IgG1 κ light chain chimeric version of a murine monoclonal antibody (mAb) and recognizes the antigen CAIX. The use of anti-CAIX antibodies in the setting of positron emission tomography–computed tomography imaging for diagnosis for both localized and advanced RCC[7,9-12] suggests their feasibility as a treatment agent. Several phase 2 nonrandomized trials of girentuximab in metastatic RCC demonstrated its safety and tolerability and suggested that it may slow disease progression.[13-15] The mechanism of antitumor activity of girentuximab is antibody-dependent cellular cytotoxicity (ADCC), although a contribution by other mechanisms cannot be ruled out.[16] Herein, we report the results of The ARISER trial (Adjuvant Rencarex Immunotherapy Phase 3 Trial to Study Efficacy in Nonmetastatic RCC), a randomized phase 3 clinical trial evaluating the efficacy and safety of girentuximab as an adjuvant treatment for high-risk clinically localized ccRCC following nephrectomy.

Key Points

Question Does adjuvant weekly girentuximab following complete resection of clinically localized, high-risk clear cell renal cell carcinoma improve disease-free and overall survival when compared with placebo?

Findings In this randomized clinical trial of 864 patients, there was no difference in disease-free or overall survival between patients receiving girentuximab and those receiving placebo. Girentuximab was well tolerated, and there was a nonsignificant disease-free survival benefit in patients with high carbonic anhydrase IX scores.

Meaning Adjuvant girentuximab failed to improve disease-free or overall survival vs placebo in a cohort of patients with fully resected, high-risk clear cell renal cell carcinoma.

Methods

Study Design

The ARISER study was a double-blind, placebo-controlled, randomized, parallel-group, international, phase 3 clinical trial designed to evaluate the efficacy and safety of adjuvant girentuximab treatment vs placebo in patients with ccRCC who have undergone surgery with no evidence of residual disease and with a high risk of recurrence. The study was carried out at 142 sites in 15 countries (Argentina, Brazil, Canada, Czech Republic, Finland, France, Germany, Netherlands, Norway, Poland, Russia, Sweden, Ukraine, United Kingdom, United States). Study procedures received ethics committee and institutional review board approval at each of the participating sites. All patients provided written informed consent. The study protocol is available in Supplement 1.

Patients

Eligible patients were 18 years or older and had undergone partial or radical nephrectomy for histologically confirmed ccRCC within 12 weeks of randomization, and were deemed to be at high risk for recurrence by meeting 1 of 3 pathologic criteria: pT3/pT4Nx/N0M0 or pTanyN+M0 or pT1b/pT2Nx/N0M0 with nuclear grade 3 or greater. These criteria were chosen based on historical RCC cohorts demonstrating patients with these pathologic characteristics to be at high risk for disease recurrence.[17] Patients with macroscopic or microscopic residual disease were excluded. The final clinical condition of the patients was obtained by routine telephone contact.

Randomization and Masking

To ensure appropriate treatment allocation balance, central computerized double-blind randomization using the minimization method was used to randomly assign patients to either girentuximab or placebo in a 1:1 ratio. Randomization was stratified for risk group (pT3/pT4Nx/N0M0 or pTanyN+M0 or pT1b/pT2Nx/N0M0 with grade ≥3) and region (US vs non-US). Study medications were packaged according to a computer-generated random code list.

Procedures

Patients allocated to girentuximab received a dose of intravenous 50 mg girentuximab (week 1) followed by weekly 15-minute intravenous infusions of 20 mg (weeks 2-24). Those randomized to placebo received an infusion of phosphate-buffered saline with polysorbate 20 diluted in 100 mL of normal saline on an identical schedule. Patients were observed for disease recurrence with computed tomographic imaging every 3 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter until final analysis—after 360 recurrence events. All radiographic images were independently reviewed by an independent radiological review committee (IRRC) using a backward read approach. An indepen-

dent data monitoring committee met throughout the trial and reviewed the safety and efficacy data. Relevant paraffin blocks of the tumor and, if applicable, lymph node metastases were provided for central pathology review. Two pathologists performed the staining and central review for tumor histologic analysis and grading: (1) J.S. for sites in North and South America and (2) S.S. for sites in Europe. The staining and central review for CAIX was performed by 1 central pathologist (S.S.) using an investigational immunohistochemistry assay based on the M75 mAb. The whole specimen was reviewed for distribution of normal and tumor tissue and for homogeneous and/or heterogeneous staining. The percentage of stained cells was evaluated by light microscopy with low-power magnification (5×-10×) whereas the intensity of staining was evaluated by high-power magnification (20×-40×). A CAIX score was derived by multiplying the intensity of staining (1-3) by percent positivity of cells (0%-100%), yielding a range of 0 to 300.[18]

Outcomes

The primary objective of the study was to detect a statistically significant difference in disease-free survival (DFS) and overall survival (OS) for the girentuximab arm relative to the placebo arm. Secondary end points included drug safety in patients receiving the drug, assessed by the number and grade of adverse events (AEs). Weekly documentation of AEs was performed following each infusion. In addition, the study included a preplanned immunohistochemical evaluation of quantitative CAIX expression for exploratory analysis as a potential prognostic and predictive biomarker.

Statistical Analysis

Sample size calculations were based on historical data suggesting a median DFS of 18 months and 5-year OS of 40% in the placebo group.[17] The study was designed as a superiority trial with 80% power to detect a significant improvement of DFS by 35% and increase in 5-year OS by 30% among participants receiving girentuximab therapy compared with placebo. Based on these calculations, the study planned to enroll 856 patients, assigned equally to the 2 arms. A 2-sided log-rank test and the Kaplan-Meier method were used to compare differences in DFS and OS, with α of 5%. The potential effect of covariates on both DFS and OS was investigated using the Cox proportional hazards model. Sample size calculations were performed using Pass 2002 software. Data were analyzed with SAS, version 8.1. The study could be stopped early based on a planned futility analysis after 100 DFS events had occurred, or for unacceptable toxic effects. Final efficacy analysis for DFS was planned to take place after 360 locally reported DFS events had occurred, at which time an interim analysis of OS would be performed. A final OS analysis would be performed after 419 deaths, or 60 months after the last patient enrolled, whichever came later.

After the study was unblinded, exploratory analyses were performed to evaluate the relationship between treatment effect, CAIX score, patient and tumor characteristics. Score cutoffs of low (0-99), intermediate (100-199), and high (200-300) CAIX scores were used based on prior analyses demonstrating its utility as a prognostic biomarker.[18]

Results

From June 10, 2004, to August 27, 2008, 864 patients were enrolled and randomized to a treatment group, and made up the intention-to-treat (ITT) population. Of these, patients receiving at least 8 consecutive administrations of study medication (weeks 1-8) and without major protocol deviation were included in the per protocol population (eFigure 1 in Supplement 2). In total, 431 patients were assigned to placebo treatment and 433 to girentuximab treatment. Median follow-up was 54.1 months (interquartile range [IQR], 43.2-60.7 months) and 54.0 months (IQR, 42.5-60.6 months) for the girentuximab and placebo groups, respectively. Median age was 58 years (IQR, 51-65 years) in both the girentuximab and the placebo groups. Virtually all (834 [97%]) patients were centrally confirmed to have ccRCC. The majority of patients had high T stage (T3/T4) and high Fuhrman grade, with a well-balanced distribution of clinicopathologic characteristics between the treatment groups (**Table**).

The final DFS analysis was conducted after 360 locally reported DFS events and 181 deaths. According to the IRRC central reading assessment, 389 patients in the ITT population (45%) had a recurrence event at the time of cutoff for data analysis (March 31, 2012). The distribution of the overall DFS events was comparable between treatment arms: 5-year DFS was 53.9% and 51.6% for the girentuximab and placebo groups, respectively, and median DFS was 71.4 months (interquartile range, 3 months to not reached) for the girentuximab group and not reached for the placebo group (P = .74). The primary analysis for DFS based on the IRRC evaluation for the ITT population showed no statistically significant difference in median DFS between the treatment arms (**Figure 1**A) (hazard ratio [HR], 0.97; 95% CI, 0.79-1.18). Median OS was not reached for either treatment arm, and there was no difference in OS between treatment arms (Figure 1B) (HR, 0.99; 95% CI, 0.74-1.32). There was no statistically significant difference in DFS between treatment arms, regardless of pathologic risk group (pT3/pT4Nx/N0M0, HR, 0.91; 95% CI, 0.73-1.14; pTanyN+M0, HR, 1.58; 95% CI, 0.91-2.75; pT1b/pT2Nx/N0M0 with nuclear grade ≥3, HR, 1.00; 95% CI, 0.52-1.93). Disease-free survival differed significantly among the 3 pathologic risk groups (**Figure 2**), with node-positive patients demonstrating significantly worse median, 1-, and 5-year survival than those with clinically localized (pT1b/pT2Nx/N0M0 nuclear grade ≥3) or locally advanced (pT3/pT4Nx/N0M0) disease (eTable 1 in Supplement 2).

Adherence to treatment was excellent. The safety population was composed of 855 patients (girentuximab, n = 431; placebo, n = 424). Of a planned 24 treatments, the mean (SD) number of infusions per patient was 22.5 (4.22) and 22.1 (4.82) in the placebo and girentuximab arms, respectively. The safety profile was balanced between arms, and no safety signal was detected between girentuximab and placebo (eTable 2 in Supplement 2). During the study, AEs were reported by 569

Table. Intention-to-Treat Cohort Clinicopathologic Baseline Characteristics and Survival Events

Characteristic	Girentuximab (n = 433)	Placebo (n = 431)	Total (N = 864)
Sex, No. (%)			
Male	276 (64)	298 (69)	574 (66)
Female	157 (36)	133 (31)	290 (34)
Ethnic origin, No. (%)			
White	405 (94)	405 (94)	810 (94)
Asian	10 (2)	9 (2)	19 (2)
Hispanic	8 (2)	8 (2)	16 (2)
African	10 (2)	5 (1)	15 (2)
Other	0 (0)	4 (1)	4 (1)
Age, median (IQR), y	58 (51-65)	58 (51-65)	58 (51-65)
ECOG performance status			
0	371 (86)	368 (85)	739 (86)
1	62 (14)	62 (14)	124 (14)
Histologic subtype, No. (%)			
Clear cell	421 (97)	413 (96)	834 (97)
Non-clear cell	10 (2)	16 (4)	26 (3)
Stage, No. (%)			
T1	25 (6)	30 (7)	55 (6)
T2	44 (10)	40 (9)	84 (10)
T3	353 (82)	348 (81)	701 (82)
T4	11 (3)	13 (3)	24 (3)
N+	32 (7)	33 (8)	65 (7)
Fuhrman grade, No. (%)			
G1	17 (4)	13 (3)	30 (4)
G2	133 (31)	135 (31)	268 (31)
G3	234 (54)	232 (54)	466 (54)
G4	45 (10)	48 (11)	93 (11)
CAIX Score, No. (%)			
0-99	74 (17)	87 (21)	161 (19)
100-199	162 (38)	134 (32)	296 (35)
≥200	190 (45)	202 (48)	392 (46)
Follow-up, median (IQR), mo	54.1 (43.2-60.7)	54.0 (42.5-60.6)	54.1 (43.0-60.7)
Independent radiology review, No. (%)			
Metastatic at baseline	50 (12)	46 (11)	96 (11)
Disease-free survival	142 (33)	151 (35)	293 (34)
Censored, No. (%)	241 (56)	234 (54)	475 (55)

Abbreviations: CAIX, carbonic anhydrase IX; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

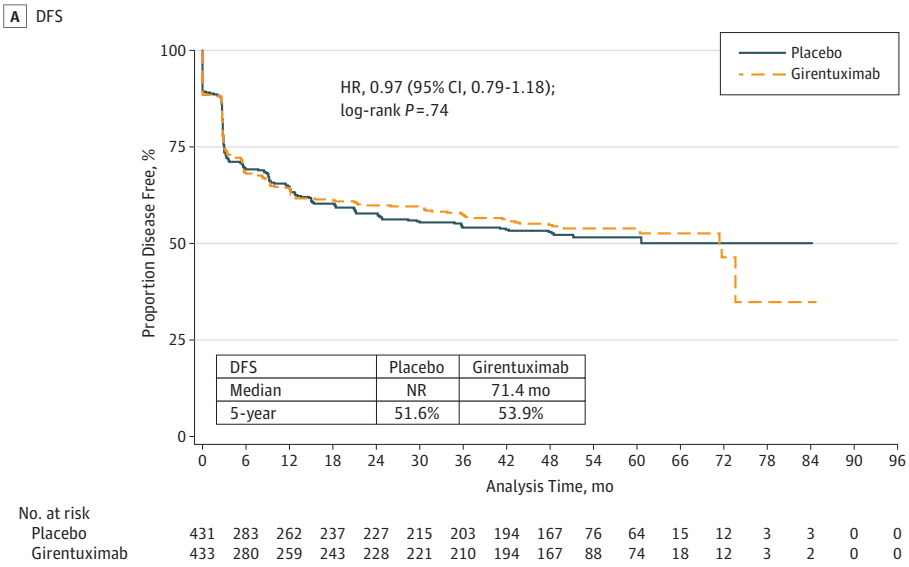
patients (67%), and were reported comparably between the treatment arms (girentuximab, n = 288 [67%]; placebo, n = 281 [66%]). The majority of these (n = 384 [67%]) were deemed unrelated or unlikely to be related to use of the study drugs. Serious AEs were reported by 8% of all patients (n = 72), divided evenly between the placebo (n = 36 [4%]) and girentuximab (n = 36 [4%]) groups. The single drug-related serious AE that occurred during the study was reported by a placebo patient. Deaths resulting from an AE were reported for 5 patients (0.6%). There were no reported drug-related deaths due to an AE throughout the course of the study.

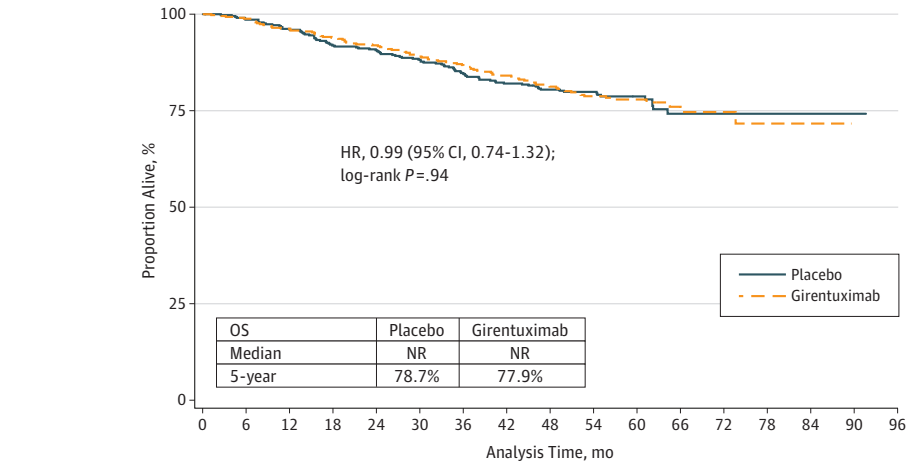
Pharmacokinetic data showed a mean steady state trough concentration of 8.7 µg/mL from week 8 on, meeting the required level for introducing the mode of action (ADCC), and confirming an appropriate dose. Thirty-seven patients treated with girentuximab (9%) developed neutralizing human antichimeric antibodies. Of these patients, 25 (68%) demonstrated no relevant influence of human antichimeric antibodies on serum levels of girentuximab.

The CAIX score was quantified for 849 of 864 (98%) ITT participants. Median CAIX score for the entire ITT cohort was 190 (IQR, 120-240), with no significant difference in scores between the girentuximab and placebo groups (P = .13) (Table).

Subgroup analysis was undertaken to evaluate for an interaction between CAIX score and treatment efficacy. We observed a nonsignificant girentuximab treatment benefit with increasing CAIX score (eFigure 2 in Supplement 2). In the subgroup of patients with CAIX score of 200 or greater (n = 392), treatment with girentuximab was associated with a nonsignificant improved DFS (HR, 0.75; 95% CI, 0.55-1.04; P = .08). Forest plot analysis demonstrated that in patients with a CAIX score of 200 or greater, treatment with girentuximab

Figure 1. Kaplan-Meier Analysis According to Treatment Arm





DFS indicates disease-free survival; HR, hazard ratio; NR, not reached; and OS, overall survival.

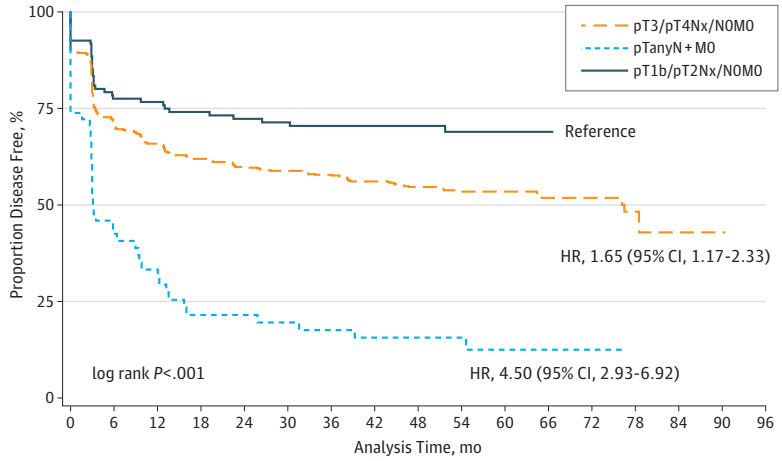
was associated with a decreased risk of disease recurrence in several subgroups, including patients younger than 65 years, patients with ECOG status of 0, and patients with G1/G2 tumors (**Figure 3**).

Discussion

In this large prospective trial, adjuvant girentuximab therapy did not improve DFS or OS in patients with ccRCC at high risk for recurrence. Girentuximab was well tolerated, with an excellent safety profile and no reported drug-related serious AEs. In the subgroup of patients with CAIX scores of 200 or greater, there was a nonsignificant DFS benefit.

Several potential explanations for the failure of girentuximab to produce benefits in the ARISER trial warrant discussion. Girentuximab is known to work via activation of ADCC,[16,19] and as such the potential therapeutic effects of girentuximab depend on an effective host immune function. A variety of immunologic data suggest that immune function may decline with age.[20] Consistent with this are studies of immunotherapeutic agents in which older patients with cancer demonstrate less effective responses.[21,22] Our finding that girentuximab was more effective in the subgroup of patients younger than 65 years is consistent with these observations and, while requiring prospective confirmation, suggests that an insufficient activation of ADCC could explain the failure of its efficacy. The growing understanding of mAb-based therapy, along with the technical and engineering capability to produce mAb-based products, has led to an expanded repertoire of potential products, and numerous modifications to mAbs have been described with the aim of improving their clinical

Figure 2. Kaplan-Meier Analysis of Disease-Free Survival According to Pathologic Risk Group



No. at risk

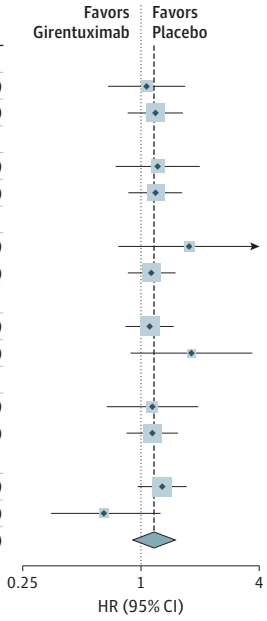
pT3/pT4Nx/N0M0	678	417	363	329	265	115	23	5
pTanyN + M0	65	15	11	9	7	4	1	0
pT1b/pT2Nx/N0M0	121	89	81	75	62	19	0	0

HR indicates hazard ratio.

Figure 3. Forest Plots of Cox Proportional Hazard Ratios (HRs) for Disease-Free Survival of Subgroups Stratified by Carbonic Anhydrase IX (CAIX) Level

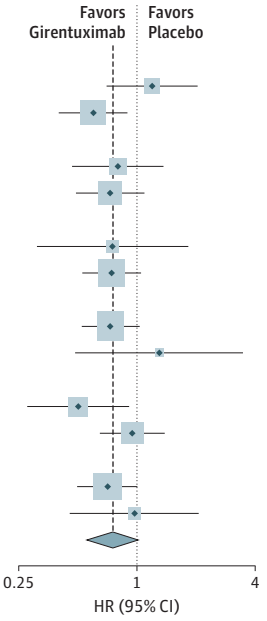
A CAIX <200

Subgroup	No.	HR (95% CI)
Age, y		
≥65	124	1.06 (0.67-1.66)
<65	333	1.18 (0.85-1.62)
Sex		
Female	156	1.21 (0.74-1.98)
Male	301	1.18 (0.86-1.61)
T stage		
T1/T2	76	1.75 (0.76-4.02)
T3/T4	381	1.12 (0.85-1.48)
N stage		
N0/NX	414	1.10 (0.83-1.46)
N1/N2	43	1.79 (0.88-3.67)
Grade		
G1/G2	133	1.13 (0.66-1.94)
G3/G4	324	1.13 (0.84-1.53)
ECOG performance status		
0	393	1.28 (0.96-1.70)
1	63	0.64 (0.33-1.25)
Overall	457	1.15 (0.88-1.49)



B CAIX ≥200

Subgroup	No.	HR (95% CI)
Age, y		
≥65	106	1.19 (0.70-2.03)
<65	286	0.60 (0.40-0.89)
Sex		
Female	129	0.80 (0.47-1.36)
Male	263	0.73 (0.49-1.09)
T stage		
T1/T2	62	0.75 (0.31-1.82)
T3/T4	330	0.75 (0.53-1.05)
N stage		
N0/NX	373	0.73 (0.52-1.03)
N1/N2	19	1.30 (0.49-3.46)
Grade		
G1/G2	163	0.50 (0.28-0.91)
G3/G4	229	0.95 (0.65-1.38)
ECOG performance status		
0	332	0.71 (0.50-1.01)
1	60	0.97 (0.46-2.07)
Overall	392	0.75 (0.55-1.04)



Size of the data marker corresponds to patient number within indicated strata. CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; and HR, hazard ratio.

efficacy. Such modifications include altering the amino acid sequence or modifying glycosylation of the Fc region to enhance interaction with effector cells,[23,24] linking radioisotopes[9,25,26] or drugs to the antibodies with the aim of delivering a cytotoxic payload, or the creation of bispecific antibodies that link tumor cells directly to cytotoxic effector cells.[27] Chimeric antigen receptor T cells targeted to CAIX have been successfully generated and administered to limited numbers of patients.[28] Given the high degree of specificity of CAIX expression for ccRCC, along with the substantial level of expression in a large proportion of tumors, CAIX remains a potentially valuable therapeutic and diagnostic target.

Another noteworthy finding of the ARISER trial was the excellent DFS characteristics of the study cohort, which exceeded expectations and resulted in a longer-than-expected study duration. Median DFS was almost 6 years in the girentuximab arm, and not reached for the placebo arm, with a median OS that was not reached for either treatment arm. After 5 years of

follow-up, more than half of patients remained free of recurrence. These excellent survival rates observed in ARISER may be driven in part by improvements in computed tomographic sensitivity, which may contribute to earlier and more thorough detection of previously occult disease, thereby excluding patients with rapidly progressing disease from study inclusion. As such, historical relapse rates, such as those used in the power calculations in ARISER, may no longer be consistent with contemporary clinical experience. The fact that virtually all trials of adjuvant therapy in high-risk RCC have failed to show a treatment benefit,[6] including the recently published ECOG-ACRIN (ASSURE) E2805 trial, illustrates the difficulty in successful adjuvant RCC therapeutic discovery.[29] The success of future adjuvant trials will require use of inclusion criteria sufficiently broad to meet accrual goals while limiting inclusion to patients who are most likely to benefit from therapy. Not surprisingly, we observed a strong association between survival and disease stage, with median survival for those with clinically localized, locally advanced, and node-positive disease of not reached, 71.2 months, and 2.9 months, respectively. Based on these observations, future trials should consider limiting enrollment to only those patients with locally advanced or node-positive disease to ensure an event rate that is sufficiently high to detect a treatment effect.

Predictive biomarkers and companion diagnostics represent a potential mechanism for enriching sample populations with patients most likely to benefit from therapy, and have emerged as central components in the treatment of multiple cancer types, including breast, colorectal, non-small-cell lung cancer, and others.[30] While not specified a priori, our subset analysis revealed a nonsignificant DFS benefit in those with a high CAIX score, and further study of CAIX score as a predictive biomarker is warranted given this observation. Future studies of CAIX-directed therapies should incorporate CAIX scoring a priori, as was done in ARISER, and consideration should be given to incorporating CAIX score into trial inclusion criteria.

Limitations

Given the randomized, blinded, placebo-controlled trial design and the high level of adherence to treatment, the findings reported herein have a high likelihood of internal validity. The patient cohort clinicopathologic characteristics are similar to those of other randomized trials of agents in this clinical stage,[6] and the international multicenter nature of the trial suggests that the findings are generalizable to patients with resected high-risk ccRCC.

Conclusions

Girentuximab did not improve DFS or OS in patients with resected localized RCC at high risk of recurrence in this prospective randomized phase 3 trial. Tolerance of the medication was excellent, and AEs were minimal. Unplanned subset analysis demonstrated a nonsignificant girentuximab treatment effect in patients with high CAIX scores. The potential role of CAIX score as a predictor of response to girentuximab would require prospective analysis.

ARTICLE INFORMATION

Accepted for Publication: August 10, 2016.

Published Online: October 27, 2016. doi:10.1001/jamaoncol.2016.4419

Author Affiliations: Department of Urology, David Geffen School of Medicine at University of California, Los Angeles (Chamie, Donin, Pantuck, Belldegrun); Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at University of California, Los Angeles (Chamie, Pantuck, Belldegrun); Institute of Urologic Oncology, David Geffen School of Medicine at University of California, Los Angeles (Chamie, Donin, Pantuck, Belldegrun); Wilex AG, Munich, Germany (Klöpfer, Bevan, Fall, Wilhelm); MorphoSys AG, Munich, Germany (Klöpfer); Therawis Pharma GmbH, Munich, Germany (Fall, Wilhelm); Institute of Pathology, University of Witten/Herdeke and Helios Hospital, Wuppertal, Germany (Störkel); Department of Pathology, David Geffen School of Medicine at University of California, Los Angeles (Said); Central Ohio Urology Group, Columbus (Gambla); Christie Hospital NHS Trust, University of Manchester, Manchester, England (Hawkins); Clinical Oncology, Carlos G Durand Hospital, Buenos Aires, Argentina (Jankilevich); Department of Clinical Oncology, McMaster University, Hamilton, Ontario, Canada (Kapoor); State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia (Kopyltsov); Department of Urology, University Hospitals Munich, Campus Grosshadern, Munich, Germany (Staehler); Department of Urology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland (Taari); Faculty of Medical Sciences of Minas Gerais (FELUMA), Belo Horizonte, Brazil (Wainstein).

Author Contributions: Drs Chamie and Belldegrun had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis
Study concept and design: Chamie, Bevan, Wilhelm, Pantuck, Belldegrun.
Acquisition, analysis, or interpretation of data: Chamie, Donin, Klöpfer, Bevan, Fall, Störkel, Said, Gambla, Hawkins, Jankilevich, Kapoor, Kopyltsov, Staehler, Taari, Wainstein, Pantuck, Belldegrun.
Drafting of the manuscript: Chamie, Donin, Kopyltsov, Staehler, Pantuck.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chamie, Donin, Kopyltsov.
Administrative, technical, or material support: Donin, Bevan, Störkel, Said, Hawkins, Jankilevich, Kapoor, Pantuck.
Study supervision: Klöpfer, Bevan, Fall, Gambla, Kapoor, Pantuck, Belldegrun.

Conflict of Interest Disclosures: Dr Chamie receives research support from and serves as a consultant for UroGen Pharma, receives grant support from Phase 1 Organization, Stop Cancer Foundation, and is a consultant for Cold Genesys and a scientific advisory board member of Altor. Drs Klöpfer, Bevan, Fall, and Wilhelm are employees of Wilex, AG. Dr Staehler receives honoraria and research support from, and serves as an advisor to Pfizer, Roche, Bayer, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, and Wilex. Dr Taari receives honoraria from Abbvie, receives research support from Medivation, and receives travel and accommodation support from Orion and Astellas. Dr Wainstein receives travel and accommodation support, speakers bureau compensation, and compensation for consulting in an advisory role from MDS, Bristol-Myers Squibb, and Roche. Dr Pantuck receives compensation as a consultant and advisor for Kite Pharma. Dr Belldegrun is president and CEO of Kite Pharma, serves on the scientific advisory board of UroGen Pharma, and is a consultant for Teva Pharmaceutical. No other disclosures are reported.

Funding/Support: Wilex, AG, funded the study.

Role of the Funder/Sponsor: Wilex, AG, had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol*. 2005;173(1):48-51.

2. Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Fyfe G. High-dose aldesleukin in renal cell carcinoma: long-term survival update. *Cancer J Sci Am*. 1997;3(suppl 1):S70-S72.

3. Saigal CS, Deibert CM, Lai J, Schonlau M. Disparities in the treatment of patients with IL-2 for

metastatic renal cell carcinoma. *Urol Oncol*. 2010;28(3):308-313.

4. Jocham D, Richter A, Hoffmann L, et al. Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. *Lancet*. 2004;363(9409):594-599.

5. Fishman M, Antonia S. Specific antitumour vaccine for renal cancer. *Lancet*. 2004;363(9409):583-584.

6. Pal SK, Haas NB. Adjuvant therapy for renal cell carcinoma: past, present, and future. *Oncologist*. 2014;19(8):851-859.

7. Oosterwijk E, Bander NH, Divgi CR, et al. Antibody localization in human renal cell carcinoma: a phase I study of monoclonal antibody G250. *J Clin Oncol*. 1993;11(4):738-750.

8. Ong FS, Das K, Wang J, et al. Personalized medicine and pharmacogenetic biomarkers: progress in molecular oncology testing. *Expert Rev Mol Diagn*. 2012;12(6):593-602.

9. Steffens MG, Boerman OC, Oosterwijk-Wakka JC, et al. Targeting of renal cell carcinoma with iodine-131-labeled chimeric monoclonal antibody G250. *J Clin Oncol*. 1997;15(4):1529-1537.

10. Brouwers AH, Buijs WC, Oosterwijk E, et al. Targeting of metastatic renal cell carcinoma with the chimeric monoclonal antibody G250 labeled with (131)I or (111)In: an intrapatient comparison. *Clin Cancer Res*. 2003;9(10 pt 2):3953S-3960S.

11. Divgi CR, Uzzo RG, Gatsonis C, et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. *J Clin Oncol*. 2013;31(2):187-194.

12. Muselaers CH, Boerman OC, Oosterwijk E, Langenhuijsen JF, Oyen WJ, Mulders PF. Indium-111-labeled girentuximab immunoSPECT as a diagnostic tool in clear cell renal cell carcinoma. *Eur Urol*. 2013;63(6):1101-1106.

13. Bleumer I, Knuth A, Oosterwijk E, et al. A phase II trial of chimeric monoclonal antibody G250 for advanced renal cell carcinoma patients. *Br J Cancer*. 2004;90(5):985-990.

14. Bleumer I, Oosterwijk E, Oosterwijk-Wakka JC, et al. A clinical trial with chimeric monoclonal antibody WX-G250 and low dose interleukin-2 pulsing scheme for advanced renal cell carcinoma. *J Urol*. 2006;175(1):57-62.

15. Siebels M, Rohrmann K, Oberneder R, et al. A clinical phase I/II trial with the monoclonal antibody cG250 (Rencarex) and interferon-alpha-2a in metastatic renal cell carcinoma patients. *World J Urol*. 2011;29(1):121-126.

16. Surfus JE, Hank JA, Oosterwijk E, et al. Anti-renal-cell carcinoma chimeric antibody G250 facilitates antibody-dependent cellular cytotoxicity with in vitro and in vivo interleukin-2-activated effectors. *J Immunother Emphasis Tumor Immunol*. 1996;19(3):184-191.

17. Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. *J Clin Oncol*. 2002;20(23):4559-4566.

18. Chamie K, Klopfer P, Bevan P, et al. Carbonic anhydrase-IX score is a novel biomarker that predicts recurrence and survival for high-risk, nonmetastatic renal cell carcinoma: data from the phase III ARISER clinical trial. *Urol Oncol*. 2015;33(5):204.e225-233.

19. Liu Z, Smyth FE, Renner C, Lee FT, Oosterwijk E, Scott AM. Anti-renal cell carcinoma chimeric antibody G250: cytokine enhancement of in vitro antibody-dependent cellular cytotoxicity. *Cancer Immunol Immunother*. 2002;51(3):171-177.

20. Tomihara K, Curiel TJ, Zhang B. Optimization of immunotherapy in elderly cancer patients. *Crit Rev Oncog*. 2013;18(6):573-583.

21. Oddens JR, Sylvester RJ, Brausi MA, et al. The effect of age on the efficacy of maintenance bacillus Calmette-Guérin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC genito-urinary group study 30911. *Eur Urol*. 2014;66(4):694-701.

22. Joudi FN, Smith BJ, O'Donnell MA, Konety BR. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. *J Urol*. 2006;175(5):1634-1639.

23. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood*. 2012;119(22):5126-5132.

24. Bowles JA, Wang SY, Link BK, et al. Anti-CD20 monoclonal antibody with enhanced affinity for CD16 activates NK cells at lower concentrations and more effectively than rituximab. *Blood*. 2006;108(8):2648-2654.

25. Muselaers CH, Boers-Sonderen MJ, van Oostenbrugge TJ, et al. Phase 2 study of lutetium 177-labeled anti-carbonic anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma. *Eur Urol*. 2016;69(5):767-770.

26. Stillebroer AB, Boerman OC, Desar IM, et al. Phase 1 radioimmunotherapy study with lutetium 177-labeled anti-carbonic anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma. *Eur Urol*. 2013;64(3):478-485.

27. Zugmaier G, Gökbuget N, Klinger M, et al. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. *Blood*. 2015;126(24):2578-2584.

28. Lamers CH, Sleijfer S, Vulto AG, et al. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience. *J Clin Oncol*. 2006;24(13):e20-e22.

29. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387(10032):2008-2016.

30. La Thangue NB, Kerr DJ. Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat Rev Clin Oncol*. 2011;8(10):587-596.