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Key considerations in patient selection for the use of targeted therapy in metastatic renal cell carcinoma

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ABSTRACT

The number of treatment options for patients with renal cell carcinoma (RCC) and the extent of clinical evidence available to support treatment decisions are increasing. Targeted agents such as the tyrosine kinase inhibitors sunitinib and sorafenib have set new standards in this challenging condition and several are now approved for use in patients with metastatic RCC. Accurate prediction of prognosis in metastatic RCC is essential for counselling and understanding the potential implications of prognostic factors on treatment outcome can help guide therapeutic interventions. In metastatic RCC, key prognostic factors include performance status, histological subtype, and number and location of metastases. Data on the implications of these prognostic factors alone or as part of validated risk models will be presented and recommendations for treatment of key patient groups provided.

1. Introduction

Although the incidence of renal cell carcinoma (RCC) is increasing,[1] the outlook for patients with this condition has improved. In the period from 1954 to 1996, 5-year survival for patients with RCC of all stages has nearly doubled, from 34% to 62%.[2] In Europe, the long term rise in kidney cancer mortality observed in the early 1990s has come to an end, and a decline in mortality has been reported in most of Western Europe.[3]

In recent years, increased understanding of the complex natural history and molecular genetics of RCC[4] has provided better understanding of prognostic indicators and contributed to the introduction of new therapeutic interventions.[5] In particular, the development of clear-cell RCC has been linked to inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene.[5–7] The VHL gene product is essential in controlling the intracellular level of hypoxia-inducible factor 1α (HIF-1α) and VHL mutation or deletion induces accumulation of HIF-1α.[8] In turn, HIF-1α is central in regulating the expression of an array of genes essential to cancer cell functions in hypoxic conditions, such as angiogenesis, glucose transport, glycolysis and pH control.[5] For example, accumulation of HIF-1α leads to increasing levels of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF),[9,10] which enhance neovascularisation of proliferating renal tumours.[10–12] HIF-1α is therefore a central point in a pathway that includes many potential targets for drug intervention in RCC.

Several agents, with either single or multiple targets in this pathway, are now available to treat metastatic RCC (mRCC). Four of these new therapies have shown superior efficacy to traditional cytokine therapy or placebo in phase III studies. In first-line mRCC, the multitargeted tyrosine kinase inhibitor (TKI) sunitinib has shown su-

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perior efficacy compared with interferon-alpha (IFN-α).[13] As a result, sunitinib was recently approved for first-line mRCC. In poor-risk mRCC, the mammalian target of rapamycin (mTOR) kinase inhibitor temsirolimus has demonstrated activity versus IFN-α,[14,15] and was recently approved for the treatment of advanced RCC in the United States. Also in first-line mRCC, the monoclonal antibody bevacizumab has demonstrated significant activity when used in combination with IFN-α and compared with IFN-α alone.[16]

In second-line mRCC, sunitinib has demonstrated efficacy in two phase II studies of patients with cytokine-refractory disease.[17,18] In addition, in a placebo-controlled phase III trial of previously treated advanced RCC, the TKI sorafenib significantly prolonged progression-free survival (PFS).[19] In Europe, sorafenib is approved for the treatment of patients with advanced RCC who have failed prior IFN-α or interleukin-2 (IL-2) based therapy or are considered unsuitable for such therapy.[20]

In addition to these agents, selected patients with mRCC, with a good risk profile and clear-cell subtype histology have been shown to derive clinical benefit from immunotherapy with IL-2 or IFN-α.[21] In some circumstances surgery may be the recommended approach; however, it is beyond the scope of this article to address surgical intervention in detail.

There is currently a need for an understanding of the importance and implications of prognostic factors in patients with mRCC, to ensure clinicians achieve maximum benefit from the new targeted drugs available. This review presents current opinion on the implications of documented prognostic factors, and provides guidance for appropriate treatment strategies in key patient populations.

2. Key considerations in mRCC: patient characteristics

2.1. Age

Although age has been identified as an independent prognostic factor for survival in patients with localised RCC,[22,23] it does not appear to have value in patients with metastatic disease.[24,25] Nevertheless, it is particularly important in elderly patients to achieve a fair balance between the efficacy and safety of the selected treatment regimen.

Evidence on the efficacy of targeted therapy in subgroups of young or elderly patients is limited. However, in the large, phase III clinical trial of sunitinib versus IFN-α in untreated patients with clear-cell mRCC, age at baseline (<65 years versus ⩾65 years) had no meaningful effect on outcome following treatment.[13] In addition, preliminary observations from a worldwide expanded-access study suggest the activity of sunitinib is unchanged in elderly patients. In an analysis of 2,341 patients enrolled in the study, the objective response rate (ORR) was 9.3% and clinical benefit was observed in 52.3% of patients.[26] In the subgroup of patients >65 years of age, the ORR was 8.1% and clinical benefit was seen in 52.1%. The tolerability of treatment in patients >65 years was similar to that reported in the overall population.

The use of sorafenib in elderly patients has also been investigated as part of a large, open-label, expanded-access trial in patients with advanced RCC.[27] In this trial, the efficacy and tolerability of sorafenib in patients >65 years of age were similar to that in the overall population.

2.2. Performance status

Performance status (PS) has been consistently identified as a significant prognostic factor in patients with RCC. Historically, low pretreatment Karnofsky PS was associated with shorter survival in patients with advanced RCC.[24,25] In a retrospective study of 670 patients with advanced, predominantly metastatic RCC, median survival time was 2.7 months, 6.1 months, 10.6 months and 14.4 months for patients with Karnofsky PS of 60%, 70%, 80% and 90%, respectively ($p < 0.0001$).[24] Following multivariate analysis, Karnofsky PS <80% was associated with shorter survival (risk ratio 1.53 (95% CI:1.20–1.85). As well, Négrier et al. identified Eastern Cooperative Oncology Group (ECOG) PS as an independent prognostic factor for survival in a multivariate analysis of 782 patients with mRCC treated with IL-2 or IFN or both.[28] Median survival in patients with ECOG PS 0 was 21 months (95% CI: 18.3–23.7) compared with 9.6 months (95% CI: 8.2–11.1) in patients with ECOG PS ⩾1 ($p < 0.001$). The risk ratio for ECOG PS (0 versus ⩾1) was 1.4 (95% CI: 1.2–1.7).

Baseline ECOG PS has been shown to be a prognostic factor for survival during treatment with targeted therapy. This has been demonstrated in analyses of sunitinib in cytokine-refractory (PS 0 versus 1; $p = 0.0034$),[29] and first-line mRCC (PS 0 versus PS 1; hazard ratio (HR) 0.700; 95% CI: 0.543–0.901; $p = 0.006$).[30] Subpopulation analysis of an international expanded-access trial also suggests that patients with ECOG PS 0 or 1 have longer median treatment duration (154 days versus 83 days) and lower mortality (15% versus 43%) than those with PS 2.[26] ECOG PS >0 has also been found to be an independent adverse prognostic factor for PFS in patients with clear-cell mRCC treated with VEGF-targeted therapy (sunitinib, axitinib, sorafenib or bevacizumab).[31,32]

2.3. Symptoms

Symptoms do not appear to affect prognosis in patients with mRCC.[24] Nevertheless, symptoms may be caused by the presence of a metastatic lesion and should

be considered when selecting a treatment regimen. In patients with symptomatic disease, the aim of treatment should be to reduce symptom severity. In this setting, a regimen expected to induce a high objective response is preferred to one associated with tumour shrinkage or stable disease. In patients with asymptomatic disease, considerations such as safety and tolerability or the expected extension in PFS or overall survival (OS) may become more important in treatment selection than the objective response rate; however, this position has never been established in a prospective clinical trial.

3. Key considerations in mRCC: tumour characteristics

3.1. Histology

The major histological subtypes of RCC are conventional or clear-cell RCC (75%), papillary (12%), chromophobe (4%), oncocytoma (4%) and collecting duct (<1%).[33] A further 3–5% of renal tumours are unclassified including sarcomatoid features.[33] The various histological subtypes of RCC have different biological and clinical behaviour and consequently vary in metastatic potential and patient survival.[34] For example, Cheville et al report significant differences in outcome for the different RCC subtypes. Cancer-specific survival rates at 5 years for patients with clear-cell, papillary, and chromophobe RCC were 68.9%, 87.4%, and 86.7%, respectively. Patients with clear-cell RCC had a poorer prognosis compared with patients with papillary and chromophobe RCC ($p < 0.001$).[35]

Non-clear cell RCC subtypes are generally considered insensitive to immunotherapy, with objective response rates of less than 5% reported.[36,37] There are limited data on the efficacy of targeted therapy in the various histological subtypes of mRCC. However, evidence suggests the TKIs sunitinib and sorafenib remain effective non-clear cell metastatic or advanced RCC and interesting results have been reported from a recent analysis of temsirolimus in advanced RCC.

Two expanded-access programmes have reported results on sunitinib and sorafenib in non-clear cell RCC. First, of more than 2,000 evaluable patients with mRCC refractory to at least 1 prior systemic therapy in the worldwide sunitinib expanded-access programme, 276 (11.8%) have non-clear cell histology.[26] The response rate in these patients is 5.4%, compared with 9.3% in the overall population. The rate of clinical benefit was similar in the two groups; 47.0% of patients with non-clear cell histology and 52.3% in the overall population.[26] Second, in an open-label, expanded-access trial of sorafenib in 2,488 patients with advanced RCC, 212 (8.5%) patients had non-clear cell RCC, classified as papillary, chromophobe, collecting duct or oncocytoma.[38] In patients with papillary RCC evaluable for response ($n = 118$), 4 (3.4%) had partial response and 91 (77.1%) stable disease. In evaluable patients with chromophobe RCC ($n = 18$), partial response and stable disease were seen in one (5.5%) patient and 16 (88.8%) patients, respectively. The majority of evaluable patients with collecting duct ($n = 5$) or oncocytoma ($n = 2$) had stable disease, and the authors conclude that sorafenib may have activity in papillary and chromophobe subtypes.[38]

The efficacy of sunitinib and sorafenib has also been evaluated in 53 patients with metastatic papillary and chromophobe RCC.[39] The majority (62%) of patients had received previous treatment, 79% with cytokines. They were then treated with sunitinib ($n = 20$; 38%) or sorafenib ($n = 33$; 62%). ORR was seen in 3/12 (25%) patients with chromophobe RCC and 2/41 (4.8%) patients with papillary RCC ($p = 0.07$). PFS was longer in patients with chromophobe RCC, 9.3 months versus 6.6 months in papillary RCC ($p = 0.07$). The ORR was higher in patients treated with sunitinib than those who received sorafenib, 15% versus 6% ($p = 0.3$). PFS was 11.9 in the sunitinib group compared with 5.5 months in the sorafenib group ($p = 0.002$). Hence, the TKIs sunitinib and sorafenib appear active in papillary and chromophobe subtypes of non-clear cell RCC. However, the efficacy of these agents in this setting is limited and less than that in clear-cell disease. Furthermore, there is no convincing evidence of the efficacy of TKIs in unclassified RCC, especially those with predominant sarcomatoid features.

In addition to these data, a recent analysis of temsirolimus versus IFN-α in previously untreated patients with advanced RCC suggests temsirolimus is effective in non-clear-cell and other histological subtypes of RCC.[40] In patients with clear-cell tumours ($n = 339$), median OS was longer in patients who received temsirolimus ($n = 169$) than IFN-α ($n = 170$), 10.7 months (95% CI: 8.5–13.0) versus 8.2 months (95% CI: 6.6–10.4). This was also the case in patients with non-clear cell RCC ($n = 73$), 11.6 months (95% CI: 8.9–14.5) versus 4.3 months (95% CI: 3.2–7.3). Similarly, temsirolimus was associated with longer median PFS than IFN-α in patients with clear-cell RCC, (5.5 months [95% CI: 3.8–7.1] versus 3.7 months [95% CI: 2.5–4.6]) and non-clear cell RCC, (7.0 months [95% CI: 3.9–8.9] versus 1.8 months [95% CI: 1.6–2.1]. The HR for median OS and PFS in patients with non-clear cell RCC were 0.49 and 0.38, respectively. However, data on the efficacy of temsirolimus or everolimus in a trial of papillary tumours are not yet available, and no conclusion can be made on whether this RCC subtype represents a suitable target for treatment with mTOR inhibitors.

3.2. Metastases

At initial presentation, 25–30% of patients have overt metastases.[41] In patients with metastatic disease,

frequent sites include the lung parenchyma (50–60%), bone (30–40%), liver (30–40%) and brain (5%).

The use of antiangiogenic agents has been explored in patients with bone or central nervous system (CNS) metastases. In a single-centre study of patients with mRCC and CNS metastases ($N = 23$), 13 patients received sunitinib 50 mg once daily for 4 weeks followed by 2 weeks off (4/2 schedule) and 10 patients received sorafenib 400 mg twice daily continuously. [42] All patients had known CNS lesions at treatment initiation and had surgery, whole brain radiation therapy, radiotherapy or a combination of interventions. Median treatment duration for sunitinib or sorafenib (including sequential therapy), was 5.6 months (range: 0.3–20.3 months). Overall, the median time to progression (TTP) was 6.5 months (0.9–20.3 months). No evidence of CNS intratumoural bleeding or other haemorrhagic complications was observed and these agents appear suitable for administration to patients with pretreated CNS metastases. [42]

Subgroup analysis of a worldwide expanded access study also support the tolerability and efficacy of sunitinib in RCC patients with brain metastases. [26] In these patients ($N = 182$), the ORR was 7.1% and clinical benefit was seen in 39.5%. Median PFS was 5.5 months, compared with 8.9 months in the overall population. The tolerability of treatment in patients with brain metastases appeared similar to that reported in the overall population.

The safety and efficacy of sorafenib in RCC patients with brain metastases was also investigated in a subset analysis of an open-label, community-based, expanded-access program. [43] Patients with ECOG PS of 0 or 2 and prior local treatment of their brain lesions ($n = 65$) received sorafenib 400 mg twice daily. The safety and efficacy of sorafenib in patients with brain metastases were comparable to those observed in the whole study population. [43] Grade 3 adverse events (AEs) occurring in more than 2% of patients were fatigue and seizure (6.2% each); and hand-foot skin reaction, diarrhoea, haemoglobin, mucositis, dehydration, vomiting, hyperglycaemia, and thrombosis (3.1% each). No CNS-related bleeding events were reported. Overall, grade 3 AEs occurred in 26.2% of patients with brain metastases versus 35.2% of the total study population. Grade 4 AEs occurred in 9.0% of patients with brain metastases versus 6.1% of the overall population. Of the 50 patients with brain metastases evaluable for response, partial response was reported in 2 (4%), stable disease in 35 (70%), and progressive disease in 13 (26%). [27] Overall, TKI treatment in patients with brain metastases seems reasonable, with acceptable tolerability. The majority of patients involved in published studies in this setting had already undergone treatment with brain surgery, radiotherapy or radiosurgery. The efficacy of TKI treatment in patients with untreated brain metastases is unknown and there is an urgent need to address this issue, justifying worldwide effort in designing and implementing a prospective clinical trial in this specific patient population.

The effect of sunitinib, sorafenib or IFN-α on the occurrence and progression of metastatic bone lesions was assessed in a retrospective analysis of data from four randomized phase II and III clinical trials. [44] The correlation between treatment and progressive disease in the skeleton and median TTP of pre-existing or new metastatic bone lesions was assessed. In this analysis, sunitinib appeared more effective than sorafenib or IFN-α in prolonging TTP of pre-existing bone lesions. In patients receiving first-line treatment with sunitinib, sorafenib or IFN-α, progressive disease in pre-existing lesions was seen in 0/4 patients (0%), 5/5 patients (100%) and 2/8 patients (25%), respectively (sunitinib versus sorafenib, $p = 0.0003$). Similarly, progressive disease in new lesions occurred in 1/7 patients (14%), 3/19 patients (16%) and 4/30 patients (13%), respectively (sunitinib versus sorafenib, $p = 0.0012$). Sunitinib was also associated with significantly longer TTP than sorafenib in pre-existing ($p = 0.0014$) and new ($p = 0.017$) bone lesions. Although these results appear promising, these data are from a single centre and further evaluation of the emergence and progression of bone metastases during TKI treatment or immunotherapy is required.

3.3. *Combinations of risk factors*

Understanding how complex interactions between multiple prognostic factors contribute to the clinical behaviour of mRCC is essential for patient assessment, prediction of outcome and appropriate management. In the prognostic model developed at the Memorial Sloan-Kettering Cancer Center, risk factors associated with shorter survival in patients with advanced RCC were low serum haemoglobin, elevated serum corrected calcium (>10 mg/dL), elevated serum lactate dehydrogenase (>1.5 times the upper limit of normal), low Karnofsky performance status (<80%), and an interval between diagnosis to treatment of less than one year. [45] These risk factors were used to create a risk model and three risk groups were defined: favourable risk (0 risk factors), intermediate risk (1–2 risk factors) and poor risk ($\geqslant$3 risk factors). This model has been validated and the risk groups defined are now extensively used in risk stratification of RCC patients and interpreting the results of clinical trials.

More recently, analysis of patients with clear-cell mRCC treated with VEGF-targeted therapy (sunitinib, axitinib, sorafenib or bevacizumab) identified the following independent adverse prognostic factor for PFS: ECOG PS >0, time from diagnosis to current treatment <2 years, baseline platelet count >300 K/muL, neutrophil count >4.5 K/muL, and baseline corrected serum calcium <8.5 mg/dL or >10 mg/dL. [31,46]

Subsequently, using data from an international, phase III trial, Motzer et al have developed and internally validated a nomogram for predicting the probability of 12-month PFS following systemic therapy with sunitinib in treatment-naïve mRCC patients.[30] This is the first prognostic tool specifically developed to predict patient outcome to systemic therapy for mRCC and it is hoped that this will further improve our ability to individualize treatment strategies and optimise clinical outcomes in patients with mRCC.

3.4. Molecular markers

In addition to the time-tested and well understood prognostic factors, other markers, such as molecular markers, are generating great interest. It is beyond the scope of this article to review in detail the evidence on the prognostic importance of the various molecular markers; however, it appears that few supply relevant independent information and to date, there are no molecular markers that can reliably predict outcome in patients with RCC.

Nonetheless, the role of carbonic anhydrase IX (CAIX) has been a special focus in RCC and one of the most significant results in this area is the relationship between decreased levels of CAIX and poor survival in mRCC.[47] These results suggest CAIX status may potentially aid patient selection. CAIX expression has been shown to be an important predictor of outcome in a small group of RCC patients receiving IL-2-based therapy[48]; however, these results require confirmation. Of particular interest is the role of CAIX status as a predictor of outcome during treatment with targeted agents that affect pH balance, such as antiangiogenic agents and mTOR inhibitors.

Another interesting result was provided by an analysis of VHL gene status and clinical outcome in mRCC patients receiving VEGF-targeted therapy.[49] Although there was no association between the presence of a VHL mutation or methylation and either objective response ($p = 0.53$) or overall tumour shrinkage ($p = 0.99$), patients with a VHL methylation or a mutation that truncated or shifted the VHL reading frame had a median TTP of 13.3 months, versus 7.4 months in patients with none of these features ($p = 0.06$). Because VEGF-targeted therapy has clear and substantial antitumour effects and has become a standard therapy in advanced RCC, these results are of particular interest. While additional analysis is required for greater understanding of these and other molecular markers, it appears they may have potential to expand the benefit of existing agents.

4. Alternatives to targeted therapies

Although targeted agents represent a major development in the treatment of mRCC, more conventional strategies such as cytokine therapy or surgical intervention maintain a role in the treatment of this condition.

Recommendations on the use of cytokines are available in the recently updated European Association of Urology (EAU) guidelines on RCC.[21] The authors state that only selected patients with mRCC, with a good risk profile and clear-cell subtype histology, derive clinical benefit from immunotherapy with IL-2 or IFN-α (grade B recommendation). In these patients, immunotherapy can provide a prolonged objective and occasionally complete response.[50–53] In comparison, TKIs have not been shown to cure mRCC and require prolonged administration. There is therefore a need to identify patients likely to benefit from immunotherapy and implement treatment where appropriate.

Surgery should be considered in patients with solitary metastatic lesions, and appears particularly effective following a long disease-free interval. In a retrospective analysis of 141 patients who underwent surgery with curative intent for the first recurrence of RCC between 1980 and 1993, the 5-year overall survival rate was 44%. The factors found to have a favourable impact on survival included disease-free interval >12 months versus $\leqslant$12 (5-year OS 55% versus 9%; $p < 0.0001$) and solitary versus multiple sites of metastases (5-year OS rate 54% versus 29%; $p < 0.001$).[54]

5. Recommended treatment of key patient populations

Accurate prediction of survival in RCC is essential for counselling, design of an appropriate follow-up schedule and treatment selection. Treatment selection has become particularly important now that new effective agents such as the TKIs are available. Recommendations for the use of targeted therapy in key patient populations are described in Table 1.

6. Conclusions

Progress in understanding the genetic features of RCC have led to the development of new targeted therapeutic agents. Several of these agents have demonstrated activity in patients with mRCC and their availability has revolutionised treatment of this condition. Prognostic factors can help define patients more likely to benefit from these therapies, as well as assisting in the interpretation of clinical effectiveness of treatment once initiated. In mRCC, key prognostic factors include performance status, histological subtype, and number and location of metastases. In addition, validated risk models provide useful tools for risk stratification and planning treatment. Validation of more accurate predictive models is ongoing and in the future, such models may include factors including circulating or tumour biomarkers and/or functional radiological information adapted to the target.

Table 1 – Recommendations for the use of targeted therapy in mRCC

Factor	Prognostic value	First-line treatment	Second-line treatment
Age	–	Sunitinib* IFN-α plus bevacizumab† Immunotherapy in very selected patients ⩽80 years old (good PS, 1 metastatic site)	Sunitinib Sunitinib/sorafenib* when following immunotherapy Clinical trial
Performance status	+++		
ECOG PS 0		Sunitinib* IFN-α plus bevacizumab*† Immunotherapy in very selected patients ⩽80 years old (good PS, 1 metastatic site)	Sunitinib Sunitinib/sorafenib* when following immunotherapy Clinical trial
ECOG PS 1		Sunitinib* IFN-α plus bevacizumab*† If tolerability is a concern, discuss sorafenib If ⩾2 other poor prognostic factors are present, treat as ECOG PS 2	Sunitinib Sunitinib/sorafenib* when following immunotherapy Clinical trial
ECOG PS 2		If ⩾2 other poor prognostic factors are present, temsirolimus*	Clinical trial Best supportive care
Histological subtype	+++		
Type 1. Clear-cell		Sunitinib* IFN-α plus bevacizumab*† Immunotherapy in very selected patients ⩽80 years old (good PS, 1 metastatic site)	
Type 2. Papillary and chromophobe		Antiangiogenic agents may be useful, but efficacy is less than that in clear-cell RCC Clinical trial with antiangiogenic agent or mTOR inhibitor Immunotherapy is ineffective	
Type 3. Undifferentiated including sarcomatoid features		Clinical trial Immunotherapy is ineffective Antiangiogenic agents also seem ineffective	
Metastases	+		
Brain		Surgery, radiosurgery or radiotherapy If rapid tumour progression in the brain is seen, treatment decisions become complex and it may be worth starting antiangiogenic treatment without local treatment of brain metastases	Antiangiogenic agent
MSKCC risk group	+++		
Good		Sunitinib IFN-α plus bevacizumab† Immunotherapy in very selected patients ⩽80 years old (good PS, 1 metastatic site) If tolerability is a concern, discuss sorafenib	Sunitinib Sunitinib/sorafenib when following immunotherapy Clinical trial Immunotherapy
Intermediate		Sunitinib IFN-α plus bevacizumab† If tolerability is a concern, discuss sorafenib	Immunotherapy (clinical trial) Sorafenib
Poor		Temsirolimus Sunitinib	Sorafenib

*Based on data from a phase III trial.
†Not approved in this setting.
IFN-α = interferon-alpha; PS = performance status; ECOG = Eastern Cooperative Oncology Group; RCC = renal cell carcinoma; mTOR = mammalian target of rapamycin; MSKCC = Memorial Sloan-Kettering Cancer Center.

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Conflict of interest

A. Ravaud: member of the Global, European and/or French advisory boards of Pfizer, Bayer, GSK and Wyeth. Member of RCC clinical trial steering committees for Pfizer and Novartis. Principal investigator for the S-TRAC trial sponsored by Pfizer.

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