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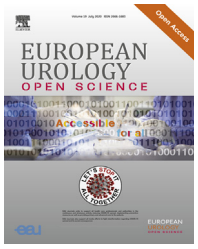

European Association of Urology

Review – Kidney Cancer

Treatment of Advanced Renal Cell Carcinoma: Immunotherapies Have Demonstrated Overall Survival Benefits While Targeted Therapies Have Not

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Abstract

Context: Current guidelines suggest several targeted therapies (TTs) and immunotherapies (ITs) in the treatment of advanced or metastatic renal cell carcinoma (mRCC). Ideal sequencing of these treatments is unclear.
Objective: The primary objective was to evaluate the overall survival (OS) data of the treatments approved for mRCC. Secondary objectives included evaluating other signs of efficacy and adverse events.
Evidence acquisition: We reviewed the current Food and Drug Administration–approved treatments for mRCC. Trials associated with approval were reviewed. We also included pre- and postapproval publications when appropriate.
Evidence synthesis: There is minimal evidence supporting OS benefit for the nine approved TTs. They result in adverse events and are a considerable economic burden. For these reasons, their future role in mRCC treatment should be re-evaluated, given the emergence of IT that have demonstrated OS benefits. Accumulating long-term survival data with high-dose interleukin-2 treatment suggests that this older treatment could still be considered for eligible patients. Checkpoint inhibitors have shown promising OS and durable responses; as such, the high cost of treatment might be justified. However, the available evidence does not suggest that adding TT to IT would increase efficacy over IT alone, but would add toxicity.
Conclusions: Trial data supporting OS benefit are much stronger for ITs than for TTs. Combining checkpoint inhibitors with TTs has not been shown to produce better OS than checkpoint inhibitors alone, while more adverse events are present. Granting drug approvals based on efficacy without demonstrated OS benefit should be revisited.

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Patient summary: Approved treatments for metastatic kidney cancer include targeted and immune-based therapies. The former commonly produces temporary tumour shrinkage, but survival benefits are unclear. All approved immunotherapies have increased survival, and a proportion of patients appear cured.

1. Introduction

According to the Food and Drug Administration (FDA; https://www.fda.gov/media/71195/download), "overall survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. – Bias is not a factor in endpoint measurement". Historically, the development of treatment of urological cancers was driven by improvement in overall survival (OS) [1]. This pattern changed in 2005 and 2006 when two large randomised phase 3 trials with sorafenib and sunitinib failed to provide OS benefit, but suggested significant progression-free survival (PFS) benefit and were approved by the FDA [2–6]. From this point on, FDA considered PFS as a valid surrogate endpoint leading to a total of nine targeted treatment (TT) approvals (Table 1). Interestingly, during recent years, several new immunotherapies (ITs) have demonstrated OS benefits.

With an annual incidence of 338 000 new cases and 144 000 deaths worldwide, kidney cancer is considered the most lethal cancer of the urinary tract. More than two out of five patients succumb to their disease [7]. However, during the last 2 decades, OS in advanced or metastatic renal cell carcinoma (mRCC) has been increasing in Western countries [8]. During this time period, indications for surgery have remained approximately the same. In contrast, a paradigm change in systemic treatments has occurred. After 2005, the use of cytokine therapies has plummeted, while the use of several TTs has gained popularity. The interpretation has been that TTs yield OS benefits, and further expansion of these treatments has been proposed [8]. Most reviews and publications during this time period conveyed the same message: before 2005 we had only "toxic" cytokine and chemotherapy treatments with limited efficacy, while from 2005 TTs have provided substantial patient benefits (Fig. 1). During the most recent years, immune checkpoint inhibitors have been added to the armament, making the sequencing of the treatments our biggest contemporary challenge. Guideline recommendations (European Association of Urology [9], National Comprehensive Cancer Network [10], and European Society for Medical Oncology [11]) have adapted accordingly, recommending a multitude of treatments. However, it is often forgotten that, during the same time period, the use of abdominal imaging has increased substantially, leading to earlier detection and treatment of mRCC (lead time bias and stage migration [8,12]). This translates to an increased incidence, earlier surgical interventions, and better OS results [8]. Therefore, increased use of TTs might not be the cause of improvement in survival.

RCC has long been known to be relatively resistant to chemotherapy [13] and radiation [14]. Before approval of TTs, ITs with cytokines has shown effects even with some rare long-lasting complete responses (CRs). Especially, interferon-alpha and interleukin-2 seemed to benefit some mRCC patients [1,15–20]. The mechanism of action for the former includes its known ability to increase the activity of natural killer cells and cytotoxic T cells [21], while the latter has been regarded a T-cell growth factor [22]. The pooled results of four randomised control trials comparing interferon-alpha with non–interferon-alpha showed a difference in response rates (12.5% vs 1.5%), especially a notable 3.8-mo weighed average survival benefit [1]. Long-lasting CRs were rare with interferon-alpha [1,15,16], while these were more common with interleukin-2 [17,16–20]. High-dose interleukin-2 (HD-IL2) became the first FDA-approved treatment for mRCC, and these cytokine treatments were standard treatments of mRCC for 3 decades. No randomised study comparing HD-IL2 and interferon-alpha has been conducted [1], but the latter was suggested to be a suitable control arm for TT studies as it was considered safer and proved to provide survival benefit [1,15,16].

Guidelines [9–11] have stratified mRCC treatment depending on International Metastatic RCC Database Consortium (IMDC) [23] risk. Several subgroups have been proposed in the mRCC literature; it is, however, important to keep in mind that none of these have been proved to be predictive, but there is a clear prognostic difference in median survival (43.2 mo favourable, 22.5 mo intermediate, and 7.8 mo poor risk) [23,24]. This point is important to understand, as not all randomised trials discussed had balanced groups. In general, there is little biological rationale why these subgroups would predict treatment benefit with TTs or ITs. The complexity of cancer and immune system in these models might have been underestimated.

To understand the typical treatment algorithm and the economic impact of TTs, a recent publication from Canada is available [25]. Most patients were treated with first-line sunitinib (81%), while 19% were treated with pazopanib (regarded generally as a "more tolerable" treatment [26]). The median first-line treatment duration was 7.7 mo for patients receiving sunitinib and 4.6 mo for those receiving pazopanib. Of the patients, 40% received additional second-line therapy lasting a median of 3 or 8 mo. The average drug cost for first-line sunitinib only was $72 675 (interquartile range $12 784–100 420).

Table 1 – All FDA-approved drugs (March 2020; www.cancer.gov/about-cancer/treatment/drugs/kidney) for the treatments of advanced RCC or mRCC.

Names	1st-line treatment approval	Pharma company	FDA approval	EMA approval	Target	MOA TT/IT	Molecule	Trial completed/ mature data reported	QoL benefit published
Interferon-alpha [a]	–	Several	–	2009 biosimilar guidance (revision 2016)	Increased natural killer cell and cytotoxic T-cell activity	IT	Cytokine	Yes/yes	No (few long-term AEs)
Aldesleukin (IL-2, proleukin)	Yes	Novartis, Clinigen Group	1992	Pre-EMA approved in 9 (1990) and 15 (2018) EU countries	T-cell growth factor	IT	Cytokine	Yes/yes	No (few long-term AEs)
Sorafenib tosylate (Nexavar)	Only after interferon-alpha/IL-2	Bayer and Onyx Pharmaceuticals	2005	2006	RAF kinase, VEGFR-2, VEGFR-3, PDGFR-?, KIT, and FLT-3	TT	TKI	Yes/no	Yes
Sunitinib malate (Sutent)	Yes	Pfizer	2006	2006	PDGFRs, c-KIT, RET, CD114, CD135	TT	TKI	Yes/yes, but no mature OS	Yes
Temsirolimus (Torisel)	Yes	Pfizer	2007	2007	mTOR	TT	mTOR	Yes/no	No
Bevacizumab (Avastin, Mvasi) + interferon-alpha [a]	Yes	Roche	2009	2007	VEGF-A	TT + IT	Antibody	–/Yes	No
								Yes/yes	
Everolimus (Afinitor)	Yes	Novartis	2009	2009	mTOR	TT	mTOR	Yes/no	No
Pazopanib hydrochloride (Votrient)	Yes	Novartis	2009	2010	VEGFR, PDGFR, c-KIT, FGFR	TT	TKI	Yes/no	No
								No/no	Yes
Axitinib (Axitinib)	No (with avelumab)	Pfizer	2012	2012	VEGFR-1, VEGFR-2, and VEGFR-3	TT	TKI	Yes/yes No/no	No
Nivolumab (Opdivo)	No (with ipilimumab)	BMS	2015	2015	PD-1	IT	Antibody	No/yes	Yes
Cabozantinib-S-malate (Cabometyx)	Yes	Ipsen	2016	2016	VEGFR-2, MET, and AXL	TT	TKI	No/no	No
								No/no	
Lenvatinib mesylate (Lenvima) + everolimus	No	Eisai	2016	2016	VEGFR-1–3 and FGFR-1–4, PDGFRα, RET, and KIT	TT	TKI	Yes/no	No
Ipilimumab (Yervoy) + nivolumab	Yes	BMS	2018	2019	CTLA-4 + PD-L1	IT	Antibody	No/yes (only median 32 mo follow-up)	Yes
Pembrolizumab (Keytruda) + axitinib	Yes	Merck/Pfizer	2019	2019	PD-1 + VEGFR-1, VEGFR-2, and VEGFR-3	TT + IT	Antibody	No/no	No
Avelumab (Bavencio) + axitinib	Yes	Pfizer	2019	2019	PD-L1 + VEGFR-1, VEGFR-2, and VEGFR-3	TT + IT	Antibody	No/no	No

AE = adverse event; EMA = European Medicines Agency; FDA = Food and Drug Administration; IL = interleukin; IT = immunotherapy; MOA = mechanism of action; mRCC = metastatic renal cell carcinoma; OS = overall survival; QoL = quality of life; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; TT = targeted therapy.

[a] Interferon-alpha has not been approved by the FDA, but it has been listed as a treatment option for metastatic renal cell carcinoma in several guidelines and with interleukin-2 it has been regarded as the historic standard treatment for mRCC.

Fig. 1 – Infographics of mRCC treatments. CR = complete response; HD-IL2 = high-dose interleukin-2; mRCC = metastatic renal cell carcinoma; OS = overall survival; TT = targeted therapy.

In this review, we have evaluated the OS data of the treatments approved for mRCC. We question whether drug approvals granted based on overall response rate and PFS responses without OS benefit still make sense in 2020, given the dramatic accelerated changes in the therapeutic landscape in the last years. We mainly focused on differences between IT and TT. Treatments were divided into ITs or TTs according to their main mechanism of action. ITs include interferon-alpha and interleukin-2 cytokines and modern checkpoint inhibitors (antibodies that specifically target the interaction between PD1/PD-L1 or block the CTLA-4 receptor in T cells). TTs refer to tyrosine kinase inhibitors or antibodies that target the vascular endothelial growth factor and related pathways, or mTOR inhibitors that affect cell growth factors and metabolism.

2. Evidence acquisition

In this review, we have focused on FDA-approved therapies for mRCC. These treatments were also approved by the European Medicines Agency (EMA), generally within 1 yr (Table 1). Our primary objective is to address the OS of these treatments. Our secondary objective was to address other signs of efficacy and adverse events. The National Cancer Institute (https://www.cancer.gov/about-cancer/treatment/drugs/kidney) lists cancer drugs approved by the FDA for mRCC. This list was reviewed in March 2020. It included generic and brand names linked to 32 NCI Cancer Drug Information summaries. Generic names and combination treatments were merged, leading to 15 approved drugs or drug combinations (Table 1). We included all trials that were associated with FDA approvals. This approach favours inclusion of trials with positive results, while trials with negative results are less likely to be included, as they may not have been published [27]. We reviewed trial publications associated with approvals and also explored other relevant postapproval studies. Primarily, we used clinicaltrials.gov and automatically linked publications therein. Additional PubMed searches were performed using generic names of the drugs. A lack of postapproval studies especially with TTs was noted, and the few that existed were industry sponsored. A predesigned electric table (Tables 1 and 2) was used for data collection. Some of the trial results were reported in several publications, and data maturity affected some results. We reported the most mature data published so far. For adverse events, we concentrated on collecting grade 3–4 adverse events. We performed a cost per saved life year estimation by dividing the cost of treatment by the life years gained (Table 3). Here, we used the (gained median OS [mOS]) or the (% of durable responses × time of response) as the denominator. Drug costs vary, but we believe that the approximate magnitude is correct (see the Supplementary material for details). However, we acknowledge that there is a need for specific unbiased cost analysis studies.

Table 2 – Analysis of the trial results.

Generic name	Comparator	Prognostic risk group, MSKCC favourable %, both values presented if >1% difference	Prior nephrectomy, both values presented if >1% difference	mPFS (mo)	ORR (%)	CR (%)	Durable responses reported	Survival benefit shown, mOS (mo)	Primary endpoints (not met)	Gr 3–4 AEs	Trial number, references
Targeted therapies											
Sorafenib	placebo	52% vs 50%	93% vs 95%	5.5 vs 2.8	10% vs 2%	0.2% vs 0	No	No 17.8 vs 15.2 (p = 0.15)	(OS)	34% vs 24%	NCT00073307 [2–4]
Sunitinib	Interferon-alpha	38% vs 34%	91% vs 89%	11.0 vs 5	31% vs 6%	0 vs 0	No	No 28.6 vs 23.7 (p = 0.051)[a]	PFS [a]	46% vs 26%	NCT00083889 [5,6]
Temsirolimus	Interferon-alpha + temsirolimus	0% (poor risk 76% interferon and combination, 69% temsirolimus)	67%	3.1 interferon, 5.5 temsirolimus, 4.7 combination	4.8% interferon, 8.6% temsirolimus, 8.1% combination	NA	No	Yes [b] 7.3 interferon, 10.9 temsirolimus, (8.4 combination)	(OS)	67% temsirolimus, 78% interferon, 87% combination	NCT00065468 [39]
Everolimus	Placebo (2nd line)	52%	96%	4.9 vs 1.9	1.8% vs 0%	0 vs 0	No	No 14.8 vs 14.4	PFS	% not reported	NCT00410124 [33,34]
Pazopanib hydrochloride	Placebo	39%	89%	9.2 vs 4.2	30% vs 3%	<1% vs 0	No	No 22.9 vs 20.5	PFS	% not reported	NCT00334282 [35,36]
	Sunitinib	Not addressed	82% vs 84%	8.4 vs 9.5 (noninferiority trial)	31% vs 25% (p = 0.03)	0.2% vs 0.5%	No	No 28.4 vs 29.3	PFS	% not reported	NCT00720941 [26]
Axitinib	Sorafenib (2nd line)	28%	91% total but not specified for different arms	6.8 vs 4.7 (investigator assessed 8.3 vs 5.7)	19% vs 9%	0 vs 0	No	No 20.1 vs 19.2	PFS	More with axitinib, % not available	NCT00678392 [62–65]
	Sorafenib (1 st line)	?, ECOG 0–1	85% vs 90%	10.1 vs 6.5	32% vs 15%	Missing	No	No 21.7 vs 23.3	(PFS)	34% vs 25% (serious AE)	NCT00920816 [37]
Cabozantinib-S-malate	Sunitinib (phase II)	0%	72% vs 77%	8.2 vs 5.6 8.6 vs 5.3 (IRC)	33% vs 12% 20% vs 9% (IRC)	1% vs 0 0 vs 0 (IRC)	No	No 26.6 vs 21.2 [c] (HR 0.8)	PFS (OS)	67% vs 68%	NCT01835158 [66,67]
	Everolimus (2nd line)	45%, (IMDC favourable 20%)	86%	7.4 vs 3.8	17% vs 3%	0 vs 0	No	Yes [d] 21.4 vs 16.5	PFS	68% vs 60%	NCT01865747 [31,32]
Lenvatinib mesylate (Lenvima) + everolimus	Everolimus (2nd line)	24%	86% vs 96%	14.6 vs 5.5 mo	43% vs 6%	2% (one patient)	No	No (post hoc analysis suggested)	PFS	71% vs 50%	NCT01136733 [68]
Immunotherapies											
Interferon-alpha	Several RCTs	–	–	25% “decrease in tumour progression risk”	12.5% vs 1.5% (pooled results form 4 trials)	1–9%	Yes 4.1% vs 0% alive at 5 yr	Yes 3.8 mo weighed average (Cochrane review)	Several RCTs addressed OS	26–78% (vs comparator 46–87%)	– [1,15,16]
High-dose interleukin-2, aldesleukin, proleukin	Phase II, 255 patients	–	–	–	15% (14–48% in contemporary series)	7% (up to 22% in contemporary series)	Yes (response duration 3–131 mo, median duration of CR > 80 mo)	Yes 10–20% (30–50% in contemporary series) alive 5–10 yr after treatment	–	Short-term intensive treatment, Gr 3 100%, mortality 4% (<1% in contemporary series)	– [17–20]

Table 2 (*Continued*)

Generic name	Comparator	Prognostic risk group, MSKCC favourable %, both values presented if >1% difference	Prior nephrectomy, both values presented if >1% difference	mPFS (mo)	ORR (%)	CR (%)	Durable responses reported	Survival benefit shown, mOS (mo)	Primary endpoints (not met)	Gr 3–4 AEs	Trial number, references
Nivolumab	Everolimus (2nd line)	36%	89% vs 87%	4.2 vs 4.5	25% vs 5%	1% vs 0.5%	Yes (26/94 of responses on-going at 60 mo)	Yes 25.8 vs 19 (26% vs 18% alive at 60 mo)	OS	19% vs 37%	NCT01668784, JCO.2020.38.6_suppl.617 [43]
Ipilimumab + nivolumab	Sunitinib	IMDC 23%	80% vs 76% (82% vs 80% ITT)	11.6 vs 8.4 (9.7 vs 9.7 ITT)	42% vs 26% (39% vs 33% ITT)	10% vs 1% (11% vs 2% ITT)	Yes (88% on-going CRs; 59% on-going ORs)	Yes NR vs 26.6 (NR vs 37.9 ITT)	OS, ORR, PFS	46% vs 63%	NCT02231749 [45,46,48,53]
Combination of targeted therapy and immunotherapy											
Bevacizumab + interferon-alpha	Interferon-alpha	29%	100%	10.2 vs 5.4	31% vs 13%	–	–	No	(OS)	–	centerwatch.com, BO17705E [69,70]
		26%	85%	8.5 vs 5.2	25.5% vs 13.1%	–	–	No 18.3 vs 17.4	(OS)	80% vs 63%	NCT00072046 [71,72]
Pembrolizumab + axitinib	Sunitinib	IMDC 31%	83%	15.1 vs 11.1	59% vs 36%	5.8% vs 1.9%	–	Yes 90% vs 78% alive, HR 0.53	OS, PFS	75.8% vs 70.6%	NCT02853331 [73]
Avelumab + axitinib	Sunitinib	IMDC 20% PD-L1 positive (22% all)	86% (80% all)	13.8 vs 7.2 (13.8 vs 8.4 all)	55.2% vs 25.5% (51% vs 26% all)	4.4% vs 2.1% (3.4% vs 1.8% all)	–	No "OS data were immature", HR 0.80	PFS (OS), among PD-L1–positive tumours	71.2% vs 71.5%	NCT02684006 [59,60]

AE = adverse event; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IMDC = International Metastatic RCC Database Consortium; IRC = independent review committee; ITT = intention to treat; mOS = median OS; mPFS = median PFS; MSKCC = Memorial Sloan Kettering Cancer Center; NA = not applicable; NR = not reported; OR = overall response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial.

[a] Imbalance in randomisation; sunitinib patients had better prognostic MSKCC (38% vs 32%). When considering favourable-risk patients only, more patients died in the sunitinib group than in the interferon-alpha group at 2 yr (72% vs 76%) [6].

[b] Imbalance in randomisation; patients in the temsirolimus arm were younger, had a better performance score, and had better prognostic MSKCC risk classification.

[c] Graphs overlapping for 6 mo before; censoring affects mOS.

[d] Only 18-mo unplanned survival analyses, representing 78% of the 408 deaths planned for the prespecified final analysis (these data have not been published).

Table 3 – FDA-approved drugs for the treatment of mRCC that have shown survival benefit and a clinically meaningful (>5%) amount of CR and/or durable multiyear responses.

												Cost analyses [a]	
Generic name	Comparator	Patient risk group	mPFS	ORR	CR rate	Durable responses reported	Survival benefit shown	Primary endpoints (not met)	Gr 3–4 AEs (comparator)	QoL benefit published	References	Cost of treatment (cost per month)	Cost of saved life year (survival benefit used in calculations)
Interferon-alpha	Several trials	–	25% "decrease in tumour progression risk"	12.5% vs 1.5% (pooled results form 4 trials)	1–9% 4.1% vs 0% alive at 5 yr	Yes	Yes, 3.8 moth weighted average (Cochrane)	Several RCTs addressed OS	26–78% (46–87%)	–	[[1], [15]], [16]] [74],]	$11 000 ($1000) [28]	$36 000 (mOS)
High-dose interleukin-2, aldesleukin, proleukin	Phase II, 255 patients	–	–	15% (14–48% in contemporary series)	7% (up to 22% in contemporary series)	Yes response duration 3–131 mo, median duration of CR > 80 mo	Yes 10–20% (30–50% in contemporary series) alive 5–10 yr after treatment	–	Short-term intensive treatment, Gr 3 100%, mortality 4% (<1% in contemporary series)	No. Few long-term AEs	[17–20]	$14 000 ($7000) [20]	$5000–10 000 (durable responses)
Nivolumab (second line)	Everolimus	MSKCC 36% favourable	4.2 vs 4.5 mo	25% vs 5%	1% vs 0.5%	Yes (26/94 of responses on-going at 60 mo)	Yes mOS 25.8 vs 19 mo (26% vs 18% alive at 60 mo)	OS	19% (vs 37%)	Yes	[43]	$168 000 ($14 000) [75]	$95 000 (mOS)
Ipilimumab + nivolumab	Sunitinib	IMDC 23% favourable	11.6 vs 8.4 (9.7 vs 9.7 ITT)	42% vs 29% (41% vs 43% ITT)	11% vs 1% (11% vs 2% ITT)	Yes (88% on-going CRs; 59% on-going ORs)	Yes mOS 47.0 vs 26.6 mo (NR vs 38.4 mo ITT)	OS, ORR, PFS	47% (vs 64%)	Yes	[45,46,53]	$197 000 ($14 000–27 000) [75]	$50 000–100 000 (immature data)
Pembrolizumab + axitinib	Sunitinib	IMDC 31% favourable	15.1 vs 11.1	59% vs 36%	5.8% vs 1.9%	–	Yes 90% vs 78%, HR 0.53	OS, PFS	75.8% (vs 70.6%)	No	[73]	China $179 000 [76], USA $481 000 [77]	$100 000–500 000 (immature data)

AE = adverse event; CR = complete response; FDA = Food and Drug Administration; HR = hazard ratio; IMDC = International Metastatic RCC Database Consortium; ITT = intention to treat; mOS = median OS; mPFS = median PFS; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan Kettering Cancer Center; NR = not reported; OR = overall response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RCT = randomised controlled trial.

[a] Estimations reported might be biased, and specific objective cost analysis studies should be performed; please refer to the Supplementary material for details.

3. Evidence synthesis

3.1. Survival data with TT

Only two of the approved TTs (Table 2), sorafenib and temsirolimus, were tested in clinical trials with OS as their primary endpoint. The sorafenib trial was a placebo-controlled trial with 903 patients, in which sorafenib did not provide OS benefit, while PFS and ORR benefit was achieved. One patient (0.2%) from the sorafenib arm achieved CR and no durable responses were reported. Temsirolimus was compared with a "standard treatment" (interferon-alpha) in a trial including 626 patients with intermediate or high Memorial Sloan Kettering Cancer Center (MSKCC) risk. OS was the primary endpoint in this three-arm trial (temsirolimus, temsirolimus and interferon-alpha, and interferon-alpha). Temsirolimus alone demonstrated increased OS compared with interferon-alpha (mOS 10.9 vs 7.3 mo), but this benefit was not seen with the combination. However, patients in the temsirolimus arm were younger, and had better performance score and better MSKCC risk classification. The median interferon-alpha treatment lasted only for 8 wk (43 wk median use reported in a recent publication [28]), while for temsirolimus, the figure was 17 wk.

The remainder of clinical trials of FDA-approved TTs were not powered to detect an OS difference and did not demonstrate OS differences in secondary analyses (Table 2). Some trials suggested OS benefit in nonmature data and/or at post hoc analysis (eg, sunitinib [29] and axitinib [30]). Only cabozantinib showed OS benefit in the second line in a non-prespecified secondary endpoint, and adverse events were common (68% grade 3–4) [31,32]. Mature OS results for cabozantinib are not published. Pazopanib demonstrated noninferior OS (secondary outcome) to sunitinib, which itself has never demonstrated OS benefit [26]. The trials with three TTs, compared with placebo, did not produce any OS benefit (sorafenib [2–4], second-line everolimus [33,34], and pazopanib [35,36]).

Sunitinib versus interferon-alpha trial is pivotal since sunitinib became the standard treatment based on these data [5,6]. The endpoints of this trial were published at clinicaltrials.gov only after the trial had completed recruitment (NCT00083889). PFS was the primary and OS the secondary endpoint in a trial of 750 patients. Interestingly, the only OS data published to date are from 2009 (recruitment complete in August 2005) with a <2-yr median follow-up, reporting a nonsignificant median OS benefit (26.4 vs 21.8 mo). The journal publication results seem to indicate that interferon-alpha was less effective and more toxic, while the more complete results at the clinicaltrials.gov report the opposite. None of the participants completed the trial and the lack of efficacy associated with sunitinib was higher (240 vs 219). Some adverse events were reported in the publication [5], but the total number of these events was not calculated. These were added to the latest clinicaltrials.gov update (January 2010). Grade 3–4 adverse events were present in 45.3% of sunitinib patients, while the percentage was 25.8% with interferon-alpha. In addition, a clear imbalance, atypical in randomised trials, between prognostic groups (favourable MSKCC risk sunitinib 38% vs interferon-alpha 32%) was noted. No CRs or durable responses were reported. Considering favourable-risk patients only, more patients had died in the sunitinib than in the interferon-alpha group at 2 yr (76% vs 72%) [6].

Another interesting trial includes axitinib as monotherapy in first line (NCT00920816) [37]. This TT is of special interest as axitinib, combined with IT, is recommended in the recent guidelines as first-line treatment [9–11]. This trial is still "active", although recruitment was completed in April 2011. The primary endpoint was PFS against sorafenib, which was not met (10.1 vs 6.5), but it favoured axitinib. Serious adverse events were reported more commonly in axitinib-treated patients (34% vs 25%) [37]. Six years later in 2017 (after axitinib was approved in second line), a new publication of this trial indicated similar mOS (21.7 vs 23.3 mo), actually favouring sorafenib [30]. A significant difference was seen only with ORR (32% vs 15%), favouring axitinib [30]. As previously discussed, sorafenib is the only approved TT that had OS as the primary endpoint and that was compared with placebo [4]. However, as sorafenib did not provide OS benefit compared with placebo, OS worse than that with sorafenib is a bit underwhelming.

Some studies suggest that cytoreductive nephrectomy may improve host immune responses by reducing the levels of immunosuppressive factors [38]. In the reviewed trials, generally four out of five patients had a prior nephrectomy (Table 2). Groups were mostly balanced; however, trials with axitinib, cabozantinib, and lenvatinib had a somewhat lower (difference of ≥5%) number of prior nephrectomies than the comparator arm.

To summarise data from TTs, many therapies result in significant PFS and ORR benefits, but no OS benefits have been reported versus placebo, and the OS results versus interferon-alpha are debatable. Statistically significant OS benefit in first line was seen only with temsirolimus, where the imbalanced prognostic groups might have explained the results [39]. In addition, durable responses and CRs are rare.

3.2. Survival data with IT

HD-IL2 was approved after a phase II trial in 1992 ($n = 255$), making it the first FDA-approved drug for mRCC. In a long-term follow-up, this trial reported 15% ORR and 7% CR with a noteworthy median duration of response of 54 mo (>80 mo for CR, 20 mo for PR). Of the patients, 10–20% were estimated to be alive 5–10 yr after HD-IL2 treatment [17,18]. No placebo-controlled trials exist, but similar or better results with multiyear follow-up have been published in several postapproval trials [40–42]. With rigorous patient selection, a prospective case series reported an ORR of 48.1% and a CR rate of 21.6%. Patients who had metastases only in one to two organs had a CR of 25–27%, while patients with metastasis in more than two organs had a CR rate of 9%. Most CRs were durable, the median OS was 58.1 mo, and no treatment-related mortality was reported [20].

In 2015, a checkpoint inhibitor (nivolumab) provided OS benefit as a primary endpoint in second line, when compared with everolimus [43]. Nivolumab resulted in fewer severe adverse events [43], and it was suggested that patients had better quality of life [44]. Long-term multiyear durable responses were reported in 26/94 of responding patients. A recent ASCO-GU abstract (JCO.2020.38.6_-suppl.617) reported that 26%, compared with 18% in the everolimus group, were still alive at 5 yr. These data support a long-lasting OS benefit with single-agent checkpoint inhibitor even in second line.

In 2018, a publication with the combination of two checkpoint inhibitors (ipilimumab and nivolumab) showed unprecedented efficacy compared with sunitinib. The trial met all primary endpoints (OS, ORR, and PFS) in intermediate and poor IMDC risk patients (77% of 1096 patients). The trial also met its secondary endpoints of OS and ORR in intention-to-treat (ITT) patients, while fewer grade 3–4 adverse events were reported compared with sunitinib (47% vs 64%) [45]. Quality of life was superior with the combination [46]. However, an ad hoc subgroup analysis suggested no OS difference with IMDC favourable (0 points) patients and led to FDA approval for intermediate- and poor-risk (1–6 points) patients only. Interestingly, in an ad hoc analysis, OS benefit was seen with 1 and 3 IMDC risk points, but not with 0, 2, or 4–6 points [47]. The CR rates were 10% in intermediate- and poor-risk patients and 11% in the ITT group, while with sunitinib these were 1% and 2%, respectively. Most responses with the combination treatment group seemed to be durable, as reported in a subsequent publication with a median follow-up of 32 months [48].

3.3. Survival data with TT combined with IT

Three FDA-approved options for combining TT with IT (Table 2) are currently available. Bevacizumab with interferon-alpha was approved in 2009 after completion of two trials, where the combination was compared with interferon-alpha alone. The primary endpoint was OS in both trials, and no difference was seen. Approval was based on secondary ORR and PFS endpoints. In 2019, two phase III trials were published, which combined axitinib with two different checkpoint inhibitors, pembrolizumab or avelumab (Table 2). The results are quite similar, indicating that both combinations resulted in more CRs (pembrolizumab 5.8% and avelumab 4.4%) than what has been reported previously with TT (0–2%). The pembrolizumab combination was able to meet its primary endpoint of OS, while the primary endpoint for the avelumab and axitinib combination was PFS, and OS follow-up was shorter at publication. Overall, the data were similarly in support of the IT combination group, leading to FDA approval of both combinations. However, as no OS benefit has previously been shown for axitinib, and in some data sets survival seems inferior to that with sorafenib [30], it is not clear how much axitinib contributes to efficacy when combined with IT.

3.4. Adverse events

With cytokine therapy, both responses and adverse events seem to be dose dependent [16,40–42]. In TT trials where interferon-alpha was used as a comparator, grade 3–4 adverse events for interferon-alpha varied from 26% in the sunitinib, 63% in the bevacizumab, to 78% in the temsirolimus trial (Table 2). HD-IL2 treatment, on the contrary, is intensive and all patients experience grade 1–3 hypotension, tachycardia, and fever, secondary to vascular leak and cytokine release syndrome [20]. In the trial that led to FDA approval, 4% of patients died due to adverse events judged to be possibly or probably treatment related [17]. In more contemporary series, treatment-related mortality has been lower (<1%) [20,50]. However, HD-IL2 is recommended only for patients in good health [19].

With TT, the frequency of grade 3–4 adverse events has varied from 34% to 71% (Table 2). A trial comparing pazopanib with sunitinib is interesting, as here similar efficacy with fewer adverse events was suggested for pazopanib [51]. Safety and quality of life favoured pazopanib [26]. The most interesting finding in this trial was, however, that grade 3–4 toxicities were common in both groups, and the mean time with these toxicities was 68 days with pazopanib and 98 days with sunitinib, indicating that patients were suffering from serious adverse events for almost half of the treatment period (3 out of the 8 months) [52].

Grade 3–4 adverse events in mRCC with checkpoint inhibitor monotherapy appears to be low (19% with nivolumab [43] or 29% with pembrolizumab, NCT02853344). Even with the combination checkpoint therapy (ipilimumab + nivolumab), fewer grade 3–4 adverse events were seen than with sunitinib (47% vs 64%) [53]. Interestingly, with the IT combination grade 3–4 adverse events peak during the first months, while with TT the adverse events continue throughout the treatment [48]. The highest grade 3–4 adverse event rates is seen when IT is combined with TT (71%, 76%, and 80%; Table 2).

Although some oncologists suggest that TTs are “well tolerated” [51], a comparison of adverse event rates in randomised trials does not support this view. In fact, the frequency of grade 3–4 adverse events favours IT (Table 2), even in the case of nivolumab + ipilimumab, the adverse event profile of which has caused concern. In particular, treatment-associated deaths were reported in early trials [45,46,53]. Fortunately, their frequency has decreased with improved management of immune-related adverse events [54].

3.5. Cost-benefit analysis

Table 3 describes treatments for mRCC that have showed survival benefit and an arbitrarily chosen >5% frequency of CRs and/or durable multiyear responses. These criteria might be a way to recognise treatments that are most likely to provide meaningful benefits to the patient. These treatments also offer a possibility of long-term remission.

Table 4 – Suggested reconsiderations in mRCC treatments (according to this review).

Suggested reconsiderations in mRCC treatments
1. Reconsider using treatments with no survival benefit in mRCC (including combinations with TTs due to AE and costs)
2. Reconsider new standard of care. The following treatments (in order) might be proposed:
(a) Ipilimumab + nivolumab (checkpoint inhibitors) or high-dose IL-2 treatment for eligible patients
(b) Interferon alpha/clinical trials/palliative care/TTs
Classification to subgroups (such as IMDC) might not be needed for treatment selection. However, IMDC favourable-risk patients seem to be those with less aggressive tumours, and the need for any systemic therapy should be evaluated on individual basis as systemic treatments lead to adverse events. In this subgroup, oligometastatic patients could even be considered for other treatments (eg, radiation or surgery) and this needs to be further evaluated in trials.
3. Survival, CR, and durable responses might be considered for trial endpoints
First-line trials might be compared against the new standard of care (HD-IL2 or ipilimumab + nivolumab). The role of ORR/PFS is limited with immunological treatments; iRECIST criteria might help future evaluations.

AE = adverse event; CR = complete response; HD-IL2 = high-dose interleukin-2; IL-2 = interleukin-2; IMDC = International Metastatic RCC Database Consortium; mRCC = metastatic renal cell carcinoma; ORR = overall response rate; PFS = progression-free survival; TT = targeted therapy.

The data are most solid with ipilimumab + nivolumab (in the short term), as long term (>5 yr) survival data have been reported only with interferon-alpha, HD-IL2, and nivolumab monotherapy.

The calculated approximate costs of a saved life year vary considerably (Table 3). For cytokines, the cost seems to be lower ($36 000 for interferon-alpha and $10 000 for HD-IL2), while checkpoint inhibitors seem to result in a cost of $100 000 and the checkpoint inhibitor with TT combination doubles the cost per saved life year. For TT monotherapy, similar calculations cannot be performed as no reliable OS benefit or durable responses have been reported. However, if we use the best ever reported OS benefit of 4.6 mo with sunitinib [6], the cost of a saved life year would be $189 000–960 000 (treatment cost ranging from $72 675 [25] to $369 347 [55]). Even with this optimistic approximation, the cost is 14–69 times higher than the cost of a saved life year with HD-IL2.

Although only a proportion of patients respond to IT treatments, responses can be long lasting and as such their cumulative benefit is substantial. A durable response in a patient who lives 30 years might give more quality-adjusted life years than dozens of patients receiving TT. The costs of TT and checkpoint inhibitors are significant. However, IT offers a possibility of long-term responses and therefore high cost could perhaps be justified.

4. Conclusions

In this review, we have discussed more than a dozen phase III randomised TT trials on mRCC. Interestingly, very few TT trials provided OS benefit, although OS was designated as a primary or secondary endpoint in all trials. In contrast, most trials with IT provided a survival benefit. Our analysis of the data presented here leads to two important questions: is mRCC really so unique that OS benefit is not needed for regulatory approval and is PFS benefit a reliable surrogate marker for TT in mRCC? Accordingly, a re-evaluation might be useful if a short-term imaging response necessarily translates into a longer life for the patient. Maybe TT selects more aggressive tumour clones that outweigh the anticipated benefits [49,56,57]. TTs are not inexpensive, but even if cost would not be an issue, their serious adverse event profile would merit consideration, as several IT treatments have now shown survival benefit with less severe toxicity.

It has been proposed that ORR and PFS are acceptable surrogate endpoints, as OS differences can be diluted when patients are able to access other drugs, including the investigational agent, upon progression (“crossover”). While this is an important consideration, the original trials of TT, which were performed in an era without access to multiple treatments, are useful in demonstrating “unpolluted” treatment effects. In the original trials of sorafenib and sunitinib, no OS advantage was demonstrated. However, as multiple checkpoint inhibitors have provided OS benefit, it is likely that true OS benefit can still be noted when it exists.

Limited and immature available data indicate that when TT is combined with IT, OS or CR rates do not seem much improved over what would be expected with IT alone (nonrandomised comparison), while the adverse events and costs seem to be additive. On the contrary, with a pure IT combination (ipilimumab with nivolumab), OS and CR rates seem to be additive, while grade 3–4 adverse events are on the same level with TT monotherapy (Table 2). All systemic treatments, however, result in some adverse events, and a subset of favourable IMDC patients might not need immediate systemic treatment. Future trials could evaluate whether this subset would benefit from surgical or stereotactic radiotherapy approaches in an oligometastatic setting [58].

The postapproval data with HD-IL2 were found to be surprisingly good, and the use of these data in eligible patients might merit further consideration. However, no phase III trial data evaluating HD-IL2 against the current standard of care are available. Similarly, even the use of interferon-alpha might still be a valid, safe, and moderately priced option in mRCC. Future perspectives for mRCC look exciting and multiple interesting trials are on-going. Especially, phase II trials combining HD-IL2 treatment with checkpoint inhibitors (nivolumab NCT03991130 and pembrolizumab NCT02964078) seem to be promising given the data reviewed above.

To conclude, the major problem with the current situation is that the landscape is filled with multiple approved therapies, most of which have not shown survival

benefit. Approvals continue to be granted based on ORR and PFS responses without OS benefit (avelumab + axitinib, 2019 [59,60]). Reasons that might have contributed to the current situation are discussed in the Supplementary material. As advocated 12 yr ago in the *Lancet* [61], it appears sound to prioritise treatments that have shown OS benefit (Table 4). In mRCC, this would imply using IT as early as possible. The utility of combining immunotherapy with TTs will depend on trial results demonstrating the added benefit of the latter, none of which are available at present.

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Appendix A. Supplementary data

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