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Targeted therapies and the treatment of non-clear cell renal cell carcinoma

J. Bellmunt[1*†] & J. Dutcher[2]

[1]*Solid Tumor Oncology (GU & GI), Medical Oncology Service, University Hospital del Mar-IMIM, Barcelona, Spain;* [2]*St Luke's-Roosevelt Hospital Center, Beth Israel Medical Center, Continuum Cancer Centers, New York, USA*

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Background: Targeted therapies have shown profound effects on the outcome of patients with advanced renal cell carcinoma (RCC). However, the optimal treatment for RCC of non-clear cell histology (nccRCC)—typically excluded from trials of targeted agents—remains uncertain.
Materials and methods: By carrying out extensive searches of PubMed and ASCO databases, we identified and summarised research into the biological characteristics, clinical behaviour and treatment of different histological subtypes of nccRCC, focusing on targeted therapy.
Results: The available data suggest that treatments currently approved for RCC are active in ncc subtypes, although the overall clinical benefit may be less than for clear cell RCC. Temsirolimus has proven benefit over interferon-alfa (IFN-α) in patients with nccRCC, based on phase III data, while everolimus, sunitinib and sorafenib have all demonstrated some degree of activity in nccRCC in expanded-access trials. No clear picture has emerged of whether individual histological subtypes are particularly responsive to any individual treatment.
Conclusions: Further molecular studies into the pathogenesis of RCC histological subtypes will help direct the development of novel, appropriate targeted agents. Clinical trials specifically designed to evaluate the role of targeted agents in nccRCC are ongoing, and data from trials with sunitinib and everolimus will be reported soon.
Key words: chromophobe renal cell carcinoma, non-clear cell RCC, papillary RCC, sarcomatoid features, targeted therapies, Xp11 translocated RCC

**Correspondence to:* Dr Joaquim Bellmunt, Section Chief, Solid Tumor Oncology (GU & GI), Medical Oncology Service, University Hospital del Mar-IMIM, Paseo Maritimo 25-–29, Barcelona 08003, Spain. Tel: +34-93-2483137; Fax: +34-93-2483366; E-mail: jbellmunt@parcdesalutmar.cat
†Present address: Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA.

introduction

Renal cell carcinoma (RCC) is a heterogeneous disease with several different histological variants and associated molecular genetic changes [1]. Three major histological subtypes account for 85%–90% of all renal malignancies: clear cell RCC (75%–90% of tumours), papillary RCC (10%–15%) and chromophobe RCC (4%–5%) [1, 2]. The remaining renal malignancies (~10%–15%) include uncommon, sporadic and familial carcinomas, as well as unclassified carcinomas [1] and some newly defined translocated tumours [3]. Some tumours may display mixed histological types, i.e. mixed stromal and epithelial tumours, mixed papillary and clear cell carcinomas [2, 4–6].

In the last decade, targeted therapies that block angiogenic activity mediated by the vascular endothelial growth factor (VEGF) signalling pathway (sunitinib, sorafenib, pazopanib, axitinib and bevacizumab) or by the mammalian target of rapamycin (mTOR) signalling pathway (temsirolimus and everolimus) have shown profound effects on the clinical outcome of patients with advanced RCC [7–15]. However, because of the relatively high prevalence of clear cell RCC, clinical trials of targeted agents have typically focused on this population of patients while frequently excluding those with non-clear cell histology. The optimal treatment of patients with RCC of non-clear cell histology, including the role of targeted therapy, remains uncertain and is under investigation.

This review discusses the underlying biology of non-clear cell RCC variants, as well as available and emerging clinical data that may guide clinicians when selecting treatment for patients presenting with these relatively rare tumour types.

histological and morphological subtypes of non-clear cell RCC

Although clinical studies commonly group all forms of non-clear cell RCC together, there are distinct differences in the presentation, behaviour and response to treatment of the various histological subtypes (Table 1) [2, 16–21]. However, the prognostic significance of histological subtype (including clear cell) is unclear; although some studies show it to be relevant by univariate analysis, the prognostic information is lost by multivariate analysis [22–25].

Table 1. Clinicopathological features of the main RCC histological subtypes. Adapted from Lopez-Beltran et al. [2] and Atkins et al. [16]

RCC subtype	Incidence	Cell/tissue characteristics	Genetic features and characteristic hereditary alterations	Prognosis	Potential treatment
Clear cell	75%–90%	Clear cytoplasm, occasionally eosinophilic, hypervascular [17]	−3p, +5q22, −6q, −8p, −9p, −14q, *VHL* (3p25)	Aggressiveness according to grade, stage and sarcomatoid change	VEGF(R)- and mTOR-directed therapy
Papillary	10%–15%	Basophilic (type I) or eosinophilic (type II) cytoplasm, hypovascular [17, 18]	+3q, +7, +8, +12, +16, +17, +20, −Y, *c-MET* (type I), *Fumarate hydratase* (type II)	Aggressiveness according to grade, stage and sarcomatoid change	Activity reported with sunitinib, sorafenib, temsirolimus; possibly also everolimus and bevacizumab, MET-directed therapy (e.g. foretinib)? RET-directed therapy?
Chromophobe	4%–5%	Pale or eosinophilic granular cytoplasm, hypovascular [17, 18]	−1, −2, −6, −10, −13, −17, −21, hypodiploidy, *Birt–Hogg–Dube*	Tend to present with lower stage and grade than clear cell, with very low incidence of metastases. Overall prognosis may be no different to clear cell	Activity reported with sunitinib, sorafenib, temsirolimus, everolimus and pazopanib, KIT-directed therapy? RET-directed therapy?
Collecting ducts of Bellini	<1%	Eosinophilic cytoplasm, hypovascular [17, 19]	−1q, −6p, −8p, −13q, −21q, −3p (rare)	Aggressive: up to 40% of patients present with metastatic disease and a high proportion (~30%) have sarcomatoid features	Evidence to support the use of gemcitabine plus platinum-based therapy
Medullary	Rare	Eosinophilic cytoplasm, hypovascular [17, 20]	Rare loss of chromosome 22	Aggressive: mean survival of 15 weeks after diagnosis	
Xp11.2 translocation	Rare	Clear and eosinophilic cytoplasm, rich vasculature [21]	t(X;1)(p11.2;q21), t(X;17)(p11.2;q25), other	Some indolent, but aggressive particularly in adults	Activity reported with sunitinib, sorafenib and temsirolimus
Unclassified	4%–6%	Variable, sarcomatoid	Unknown	High mortality	For sarcomatoid: gemcitabine/doxorubicin; alternative: sunitinib ± gemcitabine, temsirolimus

mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptors.

papillary RCC

Papillary RCC, a malignant renal parenchymal tumour with a papillary or tubulopapillary architecture [26], is the second most common form of kidney cancer and occurs in ~10%–15% of affected patients [1]. It is histologically characterised by papillae containing a fibrovascular core with foamy macrophage aggregates, calcified concretions and frequent hemosiderin granules [27]. Necrosis and haemorrhage are frequently present [26]. Papillary RCC has been further divided into type I and type II subtypes [27–29]. Sarcomatoid dedifferentiation occurs in approximately 2%–5% of papillary RCC, of both type I and type II tumours [28, 30, 31]. Some papillary tumours contain clear cells, whose presence is associated with aggressive pathological characteristics and poorer prognosis [32].

Five-year overall survival (OS) rates of 78%–79% have been reported for patients with localised papillary RCC [23, 33], with cancer-specific 5-year survival rates ranging from ~86% to 94% [34–37]. Papillary malignancies tend to present as smaller tumours, at an earlier stage and with lower grade than clear cell tumours [27]. Although one large series ($N = 2,385$) reported a significantly better survival for papillary compared with clear cell RCC [34], a more recent, even larger multicentre study ($N = 4,063$) found a similar 5-year survival rate for patients with localised papillary and clear cell RCC (79.4% versus 73.3%), as well as for those with metastatic disease (10.3% versus 10.5%) [23]. Other studies have confirmed comparable prognoses for patients with localised disease of either histology [33, 35, 36], although a lower median survival of patients with metastatic papillary compared with clear cell RCC has been reported [35]. There are conflicting data on the differences/similarities in clinical behaviour between the two subtypes of papillary RCC (type I and type II), although type I papillary RCC appears to be associated with fewer aggressive features than type II, including a lower stage and grade, as well as with longer 5-year survival (~89%–94% versus 55%–74%) [27, 38, 39].

chromophobe RCC

Chromophobe RCC, the third most common form of kidney cancer, is histologically characterised by large polygonal cells with a transparent, slightly reticulated cytoplasm and a prominent cell membrane [26]. These cells are commonly mixed with smaller cells with granular, eosinophilic cytoplasm. Chromophobe RCC is characterised by extensive chromosomal loss (Table 1) [26].

Chromophobe RCC has been associated with a relatively high proportion of low stage and low grade tumours at presentation [23, 40–42]. The proportion of patients with metastatic chromophobe RCC at diagnosis is very low, ranging from 0% to 2.9% in multiple series [23, 40–44].

Overall 5-year survival rates for patients with chromophobe RCC were 81% and 87.9% in two different studies [23, 45], while cancer-specific 5-year survival rates ranged from 86.7% to 93% [34, 44, 46]. Whether or not patients with chromophobe RCC have a better survival outcome than those with other histological subtypes is unclear. Patard et al. [23] showed that patients with localised chromophobe RCC had a better outcome than patients with papillary or clear cell tumours (log-rank, $P = 0.03$), while Cheville et al. [34] found that patients with papillary or chromophobe RCC had a better prognosis than those with clear cell tumours ($P < 0.001$). However, Lee et al. [46] reported no significant difference in 5-year cancer-specific survival rates for patients with localised chromophobe or clear cell RCC ($P = 0.980$).

translocation RCC

Renal translocation carcinomas were first observed in children and young adults [47–49], forming a relatively large proportion of RCCs in these age groups [48, 49], but have also been reported in adults [50–52]. The majority have translocations at chromosome Xp11.2, resulting in gene fusions involving the *TFE3* transcription factor gene, and this translocation RCC is classified as a distinct entity [26].

At a gross level, Xp11.2 translocation RCC may resemble clear cell RCC [51]. Histologically, the tumours have clear or eosinophilic cells in nested, papillary or mixed growth patterns [26, 51, 53]. Nuclear immunoreactivity for TFE3 protein is highly sensitive and specific for Xp11.2 translocation RCC [26, 50, 51, 53]. In adults, Xp11.2 translocation RCC often presents at a relatively advanced stage [21, 50–53]. The clinical course is often aggressive, resulting in a survival rate that is significantly decreased compared with other types of RCC in both adults and children [21, 50, 52, 54], although older age may be associated with more advanced and aggressive disease [3].

other non-clear cell histological subtypes

Unclassified RCC is a diagnostic category for tumours that cannot be assigned to any other histological subtype [1]; based on surgical series, ~5% of RCC may fall into this category [2]. Two published series suggest that unclassified RCC is more likely to present with advanced clinicopathological features (higher grade, tumour necrosis, regional lymph node involvement and sarcomatoid differentiation) than clear cell RCC [55, 56].

More than 10 additional histological subtypes have been defined which occur rarely [1, 2]. These include (not exhaustively) Bellini duct carcinoma (or collecting duct carcinoma), medullary, multilocular cystic RCC, mucinous tubular and spindle cell carcinoma, and carcinoma associated with end-stage renal disease.

sarcomatoid change

Sarcomatoid components can occur in all histological subtypes of RCC, and do not in themselves represent a distinct histological entity [1, 31, 57]. In a large series ($N = 2,381$), 5% of patients overall had RCC with a sarcomatoid component [31]. Sarcomatoid elements are frequently observed in metastases of primary tumours with sarcomatoid features; it has been suggested that a cut-off of 30% sarcomatoid features in the primary tumour may be useful in predicting systemic sarcomatoid histology [58]. The aggressive characteristics of sarcomatoid RCC may be associated with increased malignant behaviour, reflected in an increased risk of death compared with tumours lacking a sarcomatoid component [1].

Conventional chemotherapy appears to be more effective for the treatment of RCC with sarcomatoid features than without, with some reports of long-term responders to doxorubicin plus gemcitabine [59] and a median OS of 8.8 months in a phase II study of this regimen [60]. Immunotherapy may also be of benefit to some patients with non-clear cell RCC; an early study reported a survival benefit in patients with sarcomatoid RCC who received high-dose interleukin-2 in combination with surgical resection, when compared with other forms of immunotherapy or surgery alone [61]. A report of a retrospective series of patients ($N = 43$), treated with tyrosine kinase inhibitors or bevacizumab, noted an association between the outcome and amount of sarcomatoid change in the primary tumour; those patients with limited sarcomatoid component (<20%) appeared to have a better outcome with anti-VEGF therapy [62].

molecular characteristics of non-clear cell RCC

A range of inherited syndromes are known to predispose to specific histological types of renal tumour; these include Von Hippel–Lindau (VHL) syndrome (associated with RCC of clear cell histology and mutations in the *VHL* gene), hereditary papillary RCC (associated with papillary RCC type I and alterations in the *c-MET* gene), hereditary leiomyoma RCC (associated with papillary RCC type II and mutations in the *fumarate hydratase* gene) and Birt–Hogg–Dube (BHD; associated with chromophobe RCC and alterations in the *BHD* gene) [2, 63].

It has been known for some years that genetic or epigenetic changes in the *VHL* tumour suppressor gene on chromosome 3p25.3 are present in up to ~90% of sporadic clear cell RCC tumours [64–66]. Although not generally thought to be characteristic of non-clear cell RCC histologies, *VHL* gene alterations were recently reported in ~16% of non-clear cell RCC cases from a large series of sporadic RCC [66].

Although *VHL* mutations are uncommon in non-clear cell RCC, differences in the pattern of expression of VEGF and its receptors (VEGFR-1 and -2) between clear cell and papillary RCC have been observed, possibly reflecting the differences in the pathways regulating angiogenesis [67].

One of the underlying pathogenic features of papillary RCC may be dysregulation of the mesenchymal-epithelial transition factor (*MET*) signalling pathway, which is involved in cell motility, proliferation, angiogenesis and cell survival; overexpression of cytoplasmic c-met has been reported in ~80% of papillary tumours in two series [68, 69], and in one study correlated with higher stage tumours [69]. Evidence supporting the validity of the MET kinase as a therapeutic target comes from the results of a phase II study of foretinib, a multikinase inhibitor targeting MET, VEGF and other receptors, in sporadic and hereditary papillary RCC ($N = 74$) [70, 71]. In this study, the presence of germline *MET* mutations correlated strongly with foretinib activity; five partial responses (PRs) were observed in 10 patients (50% PR rate) with germline *MET* mutations, while 1 of 5 patients (20%) with somatic *MET* mutations achieved a PR. The overall objective response rate (ORR) was 13.5% [71].

Various components of the mTOR pathway have been found to be over-expressed (relative to normal kidney tissue) and possibly constitutively activated in clear cell RCC and also in other histological subtypes [72, 73]. Strong staining for cell membrane-bound KIT protein has consistently been shown in chromophobe RCC tumours, with one study also showing cytoplasmic reactivity [74–77].

Several research groups have studied the gene expression profile of RCC using DNA microarray analysis [78–80]. In each case, the different RCC histological subtypes were distinguished by unique expression profiles, suggesting that different tumourigenic pathways operate in each subtype, as reflected by their individual histological characteristics. While it is reassuring that molecular classification broadly supports classification based on histological features, gene expression profiling studies also allow identification of differentially expressed genes which may be used as specific molecular markers for diagnosis or prognosis, and which may in the future allow the development of novel targeted therapeutic agents [81, 82].

targeted therapies and non-clear cell RCC

A review of the available literature indicates that some of the targeted agents approved for the treatment of clear cell RCC may also be useful for the treatment of non-clear cell RCC.

phase III data

temsirolimus

Temsirolimus is an mTOR kinase inhibitor that acts by binding to the intracellular protein FKBP-12, forming a complex that inhibits the kinase activity of mTOR, ultimately leading to cell cycle arrest [83]. A phase III trial compared the efficacy and safety of temsirolimus alone with temsirolimus in combination with interferon-alfa (IFN-α) or IFN-α alone for the first-line treatment of poor-prognosis RCC [7]. Temsirolimus monotherapy significantly improved OS (median 10.9 versus 7.3 months; hazard ratio [HR] 0.73; 95% confidence interval [CI]: 0.58–0.92 months; $P = 0.008$ and progression-free survival (PFS; median 5.5 months [95% CI: 2.2–3.8 months] versus 3.1 months [95% CI: 3.9–7.0 months]) compared with IFN-α alone, although the ORR did not differ significantly between the two groups (8.6% versus 4.8%) [7]. The addition of IFN-α did not further improve the efficacy of temsirolimus.

This phase III study is of particular interest when considering the treatment of non-clear cell RCC, as it is the only phase III RCC trial to date with non-clear cell histology representation; of the 626 patients enrolled, 20% had RCC of non-clear cell histology (predominantly papillary RCC) [7, 84]. A retrospective exploratory analysis using data from the 416 patients randomly assigned to either temsirolimus or IFN-α monotherapy showed that the benefit of temsirolimus relative to IFN-α was significant in the subgroup of patients with non-clear cell histology [84]. In this population, the median OS was

11.6 months with temsirolimus and 4.3 months with IFN-α (HR 0.49; 95% CI: 0.29–0.85 months; Figure 1); median PFS, based on independent assessment, was 7.0 months with temsirolimus and 1.8 months with IFN-α (HR 0.38; 95% CI: 0.23–0.62 months). These outcomes are at least comparable with those for patients with clear cell RCC (Figure 1). The impact of temsirolimus on health-related quality of life also showed a trend for superiority over IFN-α in RCC of non-clear cell histology [85]. Taken together, these analyses strongly suggest that temsirolimus provides clinical benefit for the first-line treatment of RCC, irrespective of tumour histology.

expanded-access programmes

sunitinib

The sunitinib expanded-access programme included 588 patients with non-clear cell RCC, comprising 13% of the overall study population [86]. In this study, the overall median PFS was 10.9 months (95% CI: 10.3–11.2 months) and the median OS was 18.4 months (95% CI: 17.4–19.2 months); the corresponding survival times in the subgroup of patients with non-clear cell RCC were 7.8 months (95% CI: 6.8–8.3 months) and 13.4 months (95% CI: 10.7–14.9 months), respectively [86]. Although the sunitinib benefit in non-clear cell histologies appeared lower than in the overall study population, the median OS compares favourably with historical data [87].

sorafenib

Both the US and European sorafenib expanded-access studies enrolled patients with all RCC histologies [88, 89]. The 202 patients with non-clear cell RCC enrolled in the US study included 107 and 20 patients with papillary or chromophobe RCC, respectively [88]. The rate of clinical benefit (complete response [CR] + PR + stable disease for at least 8 weeks) was similar in patients with papillary RCC, chromophobe RCC, and in the entire population comprising 1891 assessable patients (84% versus 90% versus 84%). The median PFS in the overall population was 24 weeks (95% CI: 22–25 weeks), and was the same when patients with non-clear cell RCC were excluded. The median PFS in patients with papillary and chromophobe RCC (analysed together) was 21 weeks; the median OS in this cohort was 40 weeks compared with 50 weeks (95% CI: 46–52 weeks) in the overall study population.

An analysis of the 126 assessable patients enrolled at one Italian centre in the European expanded-access trial found that 29 had non-clear cell RCC histology (papillary, $n = 15$; chromophobe, $n = 3$; collecting duct, $n = 3$; sarcomatoid variants, $n = 3$; mixed or unknown, $n = 3$) [89]. Of these patients, 1 with papillary RCC achieved a PR with sorafenib (ORR 3.4%), compared with an ORR of 9.3% in patients with clear cell RCC. Two patients with papillary and one with chromophobe histology exhibited tumour shrinkage. No evidence of sorafenib activity was seen in collecting duct or sarcomatoid disease.

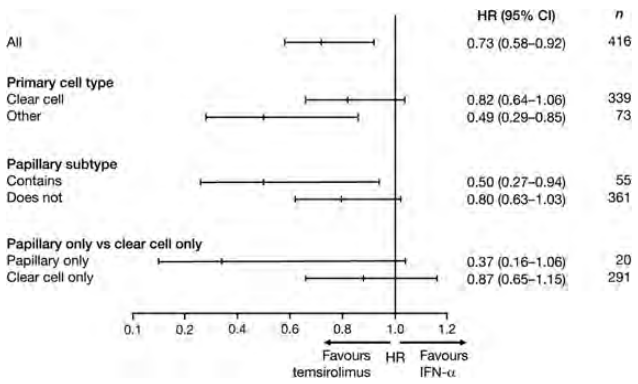

Figure 1. Overall survival (OS) with temsirolimus compared with interferon-alfa (IFN-α) in patients with RCC of clear cell and other histologies [84]. Adapted from Table 3 of Dutcher J.P. et al. [84]. With kind permission from Springer Science + Business Media.

everolimus

Data on the use of the mTOR inhibitor everolimus in non-clear cell RCC are limited, although a subgroup analysis of patients with non-clear cell RCC enrolled in the RAD1001 Expanded Access Clinical Trial in RCC (REACT) was presented at the ASCO 2012 Genitourinary Cancers Symposium [90]. REACT enrolled RCC patients of any histology who were intolerant to, or had progressed on, VEGFR inhibitors; of 1367 patients enrolled, 75 patients (5.5%) had non-clear cell RCC. Median treatment duration was similar in the non-clear cell subgroup and in the overall REACT population (12.14 weeks versus 14.0 weeks, respectively), as was the ORR (1.3% versus 1.7%) and rate of stable disease (49.3% versus 51.6%), suggesting that everolimus shows similar results in clear cell and non-clear cell RCC.

phase II data

sunitinib

Data from several prospective phase II studies of sunitinib in advanced non-clear cell RCC have been presented or published. For the most part, there was a low response rate to sunitinib (ORR 0%–7%), although the majority of patients typically experienced stable disease [91–94]. In two studies that enrolled papillary RCC only, respectively, none and 1 patient achieved a PR, and the rate of stable disease was 35% and 73%, respectively [92, 93]. However, a recently published phase II study of 31 patients with non-clear cell RCC (papillary, $n = 22$; chromophobe, $n = 3$; unclassified, $n = 5$; and Xp11.2 translocation, $n = 1$) reported an overall ORR of 36% (95% CI: 19% to 52%) and median PFS of 6.4 months (95% CI: 4.2–8.6 months) [95]. The median OS had not been reached, but the 1-year survival rate was 65%.

retrospective analysis

sunitinib and sorafenib

Sunitinib activity was also observed in a retrospective analysis of 53 patients with papillary or chromophobe RCC treated with sunitinib ($n = 20$) or sorafenib ($n = 33$) at five cancer centres in France and the United States [96]. Among the sunitinib-treated patients, 2 of 13 patients with papillary RCC achieved a PR (15%) and median PFS in this histological subtype was 11.9 months; 1 of 7 patients with chromophobe RCC achieved a PR and the median PFS was 8.9 months.

None of the 28 patients with papillary RCC treated with sorafenib achieved an objective response [96]. The median PFS in this cohort was 5.1 months, significantly less than the 11.9 months achieved with sunitinib in patients with papillary RCC ($P < 0.001$). Two of the five patients with chromophobe RCC treated with sorafenib had a PR, with a median PFS in this group of 27.5 months.

Additional retrospective data for sunitinib and sorafenib are discussed in the Supplementary Material (A), available at *Annals of Oncology* online.

other targeted therapies in non-clear cell RCC

Foretinib is an oral, multikinase inhibitor targeting VEGFR-2, MET and other receptors (see the section on 'Molecular characteristics of non-clear cell RCC' above). Preliminary data from a phase I trial of advanced papillary RCC [97] suggested that the agent may have activity in this setting. In a recently reported multicentre phase II study of patients with sporadic and hereditary papillary RCC ($N = 74$), foretinib was associated with an ORR of 13.5% (while tumour shrinkage was reported in 50 out of 68 patients), a disease stabilisation rate (ORR + stable disease) of 88%, median PFS of 9.6 months and 1-year OS of 70% (median OS not reached) [71]. Toxic effects were manageable and typical of anti-VEGF therapy.

At present, there are no data supporting a role for bevacizumab plus IFN-α for the treatment of non-clear cell RCC, although preliminary data from a phase II study of bevacizumab monotherapy in metastatic papillary RCC were published in conjunction with ASCO 2011 [98]. This phase II study closed because of slow accrual after only five patients had been recruited; PFS in these patients was 25, 15, 11, 10 and 6 months, respectively. Bevacizumab was given as first-line treatment to four patients and following prior temsirolimus in one patient.

additional data on the activity of targeted therapies in non-clear cell RCC

Table 2 [27, 99–107] (and Supplementary Material [A], available at *Annals of Oncology* online) provides additional details from case studies and anecdotal evidence of the activity of targeted therapies in RCC with non-clear cell histology, including Xp11.2 translocation RCC and RCC with sarcomatoid features.

Table 3 (and Supplementary Material [B], available at *Annals of Oncology* online) lists details of ongoing and planned trials of targeted therapies in non-clear cell RCC.

overview of clinical management guidelines for patients with non-clear cell RCC

While prospective randomised data are not currently available, several systemic therapies are recommended for

Table 2. Summary of data from published case studies and anecdotal findings on the activity of targeted therapies in advanced/metastatic non-clear cell RCC

Patient age, years (sex)	RCC subtype	Line of therapy	Response	Duration of response	Reference
Temsirolimus					
55 (M)	Papillary RCC	Second	PR	10 months	Albiges et al. [99]
27 (F)	Chromophobe RCC	Third	PR	14+ months	Zardavas et al. [100]
57 (M)	Chromophobe RCC	Third	SD	26 months	Paule et al. [101]
51 (M)	Sarcomatoid features (90%)	First	Died within 2 months	–	Areses et al. [102]
64 (M)	Sarcomatoid features (95%)	First	PR	14 months	Areses et al. [102]
54 (M)	Sarcomatoid features (50%)	First	SD	7+ months	Areses et al. [102]
Sunitinib					
74 (F)	Papillary RCC	Second	PR	8.5 months	Ronnen et al. [27]
26 (F)	Papillary RCC	Second	PR	>2 years	Tuthill et al. [103]
43 (F)	Xp11.2 translocation RCC	First	PR	>3 years	Numakura et al. [104]
Unknown	CDC of Bellini	Second	Disease control OS	10 months 49 months[a]	Procopio et al. [105]
Unknown	CDC of Bellini	Second	Disease control OS	9 months 19 months[b]	Procopio et al. [105]
Sorafenib					
18 (M)	Xp11.2 translocation RCC	First	OS	15 months	Hou et al. [106]
Everolimus					
53 (M)	Chromophobe RCC	Second	PR	>2 years	Larkin et al. [107]
Bevacizumab + IFN-α					
55 (M)	Papillary RCC	Second	SD	8 years[c] >2 years	J. Dutcher, personal communication

[a]Patient previously received first-line sorafenib, with 33-month disease control.
[b]Patient previously received first-line temsirolimus, with 6-month disease control.
[c]Patient previously received first-line interleukin-2 with 8-year stable disease/slow progression; stable since bevacizumab alone.
CDC, collecting duct carcinoma; IFN-α, interferon-alfa; OS, overall survival; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

Table 3. Summary of ongoing and planned phase II trials of targeted therapies in non-clear cell RCC

Therapy	Type of RCC	Study description	Study status	ClinicalTrials.gov identifier
Temsirolimus versus sunitinib	Advanced non-clear cell RCC	Randomised, open-label trial comparing first-line temsirolimus with sunitinib	Completed (July 2012)	NCT00979966
Everolimus	Papillary RCC	'RAPTOR' study Safety and efficacy of everolimus monotherapy as first-line treatment	Recruiting Estimated primary completion date: August 2013	NCT00688753
Everolimus	Any type of non-clear cell RCC	Single arm. No restrictions on the number of previous treatments	Ongoing Estimated study completion date: October 2012	NCT00830895
Everolimus versus sunitinib	Papillary and chromophobe histologies	'ASPEN' study Randomised trial comparing first-line everolimus with sunitinib Excludes patients with collecting duct, medullary, small cell and oncocytoma pathology	Recruiting Estimated primary completion date: September 2013	NCT01108445
Everolimus versus sunitinib	Advanced non-clear cell RCC	Randomised trial comparing first-line everolimus with sunitinib	Recruiting Estimated primary completion date: August 2014	NCT01185366
Everolimus + bevacizumab	Advanced non-clear cell RCC	Patients previously untreated with any VEGFR or mTOR inhibitors	Recruiting Estimated primary completion date: July 2013	NCT01399918
Sunitinib	Advanced non-clear cell RCC	Single-arm study in patients who have received up to two prior systemic therapies for advanced RCC	Ongoing Estimated primary completion date: March 2014	NCT00465179
Sunitinib	Advanced non-clear cell RCC	Single-arm, first-line study	Recruiting Estimated primary completion date: NA	NCT01034878
Bevacizumab + gemcitabine + capecitabine	Sarcomatoid RCC	Investigational study	Ongoing Estimated primary completion date: August 2013	NCT00496587
Sunitinib versus sunitinib + gemcitabine	Sarcomatoid RCC	Eastern Cooperative Oncology Group, E 1808	Ongoing Estimated primary completion date: June 2021	NCT01164228
Pazopanib	Locally advanced or metastatic non-clear cell RCC	Planned study	Not yet recruiting Estimated primary completion date: February 2014	NCT01538238

NA, not available; RCC, renal cell carcinoma; mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor receptors.

the first-line treatment of stage IV, relapsed or recurrent non-clear cell RCC based on data from phase III trial subgroup analyses, expanded-access programmes and small retrospective studies. Both the ESMO Clinical Practice guidelines [108] and National Comprehensive Cancer Network (NCCN) guidelines [109] recommend enrolment in an appropriately designed clinical trial as the preferred treatment option. The NCCN then recommends temsirolimus (category 1 for poor-risk patients, category 2A for other risk groups), or sorafenib (category 2A) or sunitinib (category 2A). Pazopanib, erlotinib or axitinib are alternative options (category 3). Chemotherapy with gemcitabine + doxorubicin or gemcitabine + capecitabine is also given a category 3 rating for clear cell or non-clear cell RCC with predominantly sarcomatoid features [109]. The ESMO guidelines recommend temsirolimus, sunitinib or sorafenib, all with level IIIB evidence, for the treatment of metastatic non-clear cell disease [108].

other therapeutic modalities: local therapy

While targeted therapy is the focus of this review, many non-clear cell RCC tumours are relatively slow growing and therapy for localised disease is therefore frequently part of patient management. Surgical resection (partial or radical nephrectomy or nephron-sparing surgery) is the preferred treatment for localised and locally advanced RCC [110]. Cryotherapy and radiofrequency ablation are alternative approaches (particularly for elderly patients with small cortical tumours, hereditary RCC and multiple bilateral tumours) [108]

and have been associated with disease-free survival rates that are comparable with conventional surgery [111–113].

future directions

Research into the molecular characteristics of RCC has identified different gene expression profiles associated with the different histological and gross morphological profiles of the many subgroups of this tumour, most of which are regularly collected together under the umbrella term 'non-clear cell' RCC. Given these differences, it cannot be assumed that the efficacy and safety observed with targeted agents in the treatment of clear cell tumours will be paralleled in the non-clear cell setting. Nonetheless, the available data suggest that targeted agents currently approved for RCC are active to some degree in non-clear cell histologies. Temsirolimus has proven benefit over IFN-α in patients with non-clear cell RCC, based on phase III data, and expanded-access studies for everolimus, sunitinib and sorafenib have all confirmed the activity of these agents in RCC of non-clear cell histology.

Overall, however, our understanding of the role of targeted therapies in non-clear cell RCC is limited and needs to be developed in two ways. First, further molecular research into the similarities and differences between RCC subtypes would be instructive and may improve our understanding of why some patients with non-clear cell RCC have extremely good responses to currently available targeted therapy. For example, are those patients with non-clear cell RCC who respond to sunitinib also patients with tumours bearing *VHL* gene alterations? This research will also serve to guide the development of novel, more relevant targeted agents for the various non-clear cell subgroups.

Second, more clinical trials specifically designed to evaluate current targeted agents in non-clear cell RCCs are needed. A number of phase II trials are now ongoing or planned for patients with non-clear cell RCC, and these should provide interesting preliminary insights into the anti-tumour efficacy of particular agents in these tumours. Future phase III trials should include patients with RCCs of non-clear cell histology as well as clear cell RCC, with appropriate stratification to ensure balance between the treatment arms. Greater collaboration between centres and cooperative group studies should help to boost the numbers of patients with rare histological RCC subtypes, and patients should be encouraged to participate in clinical trials. These approaches will ultimately lead to improvements in the management of non-clear cell RCC that may yet equal those advances already achieved with the more common clear cell tumours.

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Active immunotherapy in HER2 overexpressing breast cancer: current status and future perspectives

A. Milani[1,2,†], D. Sangiolo[1,2,†], F. Montemurro[1,3], M. Aglietta[1,2] & G. Valabrega[1,2*]

[1]*Medical Oncology I, Institute for Cancer Research and Treatment (IRCC) Candiolo FPO (Fondazione del Piemonte per l'Oncologia);* [2]*Department of Oncology, University of Torino Medical School, Candiolo;* [3]*Investigative Clinical Oncology Unit (INCO), Candiolo, Italy*

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Background: The use of anti-HER2 monoclonal antibodies (mAbs) has improved the clinical outcome of HER2-overexpressing breast cancers (BCs). Unfortunately, often these tumors tend to relapse and, when metastatic, the duration of clinical benefit is limited over time and almost invariably followed by tumor progression. Alternative approaches to this essentially passive immunotherapy are therefore needed in HER2-overexpressing BC patients. As HER2 is one of the most suitable targets for active immunotherapy in BC, manipulating the immune system is a highly attractive approach.
Material and methods: A computer-based literature search was carried out using PubMed (keywords: breast neoplasm, HER2 vaccine, immunology); data reported at international meetings were included.
Results: This review provides a focus on the following active vaccinal approaches under clinical investigation against HER2-overexpressing BC: (i) peptide and protein based; (ii) DNA based; (iii) whole tumor cell based; (iv) dendritic cell based. Moreover, the review discuss future challenges in the field, trying to define the best setting for the development of this innovative strategy, considering both immunological and clinical aspects of HER2 targeting.
Conclusions: Development of effective vaccines for BC remains a distinct challenge but is likely to become a substantial advance for patients with HER2-overexpressing BCs.
Key words: active immunotherapy, breast cancer, HER2, vaccine

introduction

In the last decades, several attempts have been made to develop strategies that could effectively induce potent immune responses against various tumor types.

Manipulating the immune system to recognize and eradicate breast tumor cells is a highly attractive possibility in the treatment of epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC).

HER2 is a suitable target for immunotherapy as selectively expressed or overexpressed (HER2 positive) in a subpopulation of BCs [1–3].

At least two different approaches fall into the definition of immunotherapy.

The first one is passive immunotherapy, consisting in the adoptive transfer of antigen-specific T lymphocytes expanded *ex vivo* or the infusion of monoclonal antibodies (mAbs) specific for a given tumor antigen.

Passive immunotherapy with anti-HER2 mAbs such as trastuzumab, pertuzumab and Trastuzumab-DM1 (TDM1) is the current mainstay in the treatment of HER2-positive BC.

The addition of these antibodies was shown to significantly improve survival as first-line treatment of HER2-positive metastatic BC (MBC) [4–6]. Moreover, TDM1 showed its superiority to the current standard Capecitabine and Lapatinib

Correspondence to: Dr Giorgio Valabrega, Department of Oncology, University of Torino Medical School at the Institute for Cancer Research at Candiolo (IRCC); FPO (Fondazione del Piemonte per l'Oncologia) SP 142, Km. 3.95 10060 Candiolo (Torino), Italy. Tel: +390119933283; Fax: +39-0119933299; E-mail: giorgio.valabrega@ircc.it

†These two authors equally contributed to this work.