Second-line treatment in advanced colon cancer: are multiple phase II trials informative enough to guide clinical practice?

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This article reviews the available data regarding the activity of second-line chemotherapy following 5-fluorouracil (5-FU), irinotecan (CPT-11) or oxaliplatin (OXA) alone or in combination. Studies undertaken in this setting, published both as full papers and in abstract form, were critically analyzed. The main conclusion is that clinical research for second and subsequent lines of treatment in advanced colon cancer (ACC) clearly needs to be optimized. A large number of small, non-randomized phase II trials have been reported without definitive conclusions. Efficient conduct of a limited number of high-quality randomized phase II trials with validation of promising regimens via phase III studies seems a preferable approach. This would not only accelerate the evaluation of new therapeutic options, but also, and more importantly, limit the number of patients receiving suboptimal treatments. The responsibility of this indispensable and urgent task lies with all researchers in this field and their partners in the pharmaceutical industry. One means to implement this approach is through strict selection of studies to be both presented and published, encouraging the spread of information provided by statistically well-designed and well-conducted trials that will eventually lead to the definition of the best standard of care for ACC patients. The conduct of repetitive phase II trials that test minor variations in dose and schedule, while commonplace, does little to advance the field. *Anti-Cancer Drugs* 14:703–713 © 2003 Lippincott Williams & Wilkins.

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Introduction

Colon cancer is the third most common cause of cancer mortality in both sexes, leading to approximately 400 000 deaths each year in the western world [1]. It is also the third most common malignancy in both women and men [2]. Eighty percent of colon cancer patients present with localized disease [3], for which surgery is the primary treatment modality, resulting in complete remission in approximately 50% of patients [4]. However, one half of the patients ultimately experience relapse. Patients with stage I disease have a favorable prognosis, with a 5-year survival of approximately 80–95%. For patients with Dukes C colon cancer the 5-year survival drops to 30–55% [4]. Adjuvant chemotherapy (CT), aiming to eliminate microscopic disease following surgical removal of primary tumor, is now the standard of care in this group of patients. The 5-year disease-free survival (DFS) after 6 months of adjuvant [5-fluorouracil (5-FU)/folinic acid (FA)] treatment is about 50–65% [3], providing a 10–15% absolute improvement in overall survival (OS) [5]. Thirty percent of colon cancer patients at presentation are not candidates for a surgical approach (i.e. locally advanced or metastatic disease) [2]. The prognosis of this group is generally poor, with a median survival of 4–6 months when untreated and less than 3% survive at 5 years [3]. However, a small subset, i.e. those with limited liver metastasis, lung metastasis or locally recurrent disease, may be amenable to surgical resection with the possibility of relatively long-term survival, when treated with combined local and/or systemic therapies.

With the available systemic treatment options, ACC remains incurable. The main goals of treatment for these patients are to alleviate disease-related symptoms, improve quality of life (QoL) and, if possible, prolong survival. CT has an established role in both improving survival and palliating symptoms in this setting. Since its synthesis by Heilderberger in 1957 [6], 5-FU has been the traditional mainstay agent in colon cancer for more than four decades. As a single agent, 5-FU provides responses in only 10–15% of patients [7]. 5-FU/FA combination enhances the response rate (RR) about 2-fold (up to 23%), but without significantly improving survival [8]. Protracted infusion leads to a further significant increase in RR (to around 30%), but once again without improvement in survival beyond 1 year [9]. The 5-FU-based regimens commonly used in Europe are the de Gramont, the AIO (Arbeitsgemeinschaft Internistische Onkologie) and the TTD (The Grupo Espanol para el Tratamiento de Tumores Digestivos) regimens. Bolus 5-FU/FA regimens remain the standard way of administration of 5-FU/FA in the US, although this is

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Table 1 Second-line phase II trials of OXA in 5-FU-resistant/refractory ACC patients

OXA monotherapy

Reference	N[a]	Dose of OXA	ORR (%)	PFS*/TTP (months)	Median survival (months)	Statistical design for calculation of RR[φ]
Machover (trial 1)[14] ϕ	55/58	130 mg/m^2 q3wk	11	6	8.2	NR
Machover (trial 2)[14] ϕ	51	130 mg/m^2 q3wk	10	4.5+	NR	NR
Levi[15] ϕ	25/30	CM 30/mg/m^2/day for 5 days q3wk	10	5*	10	NR
Chacon[16]	32/41	130 mg/m^2 q3wk	9.8	NR	NR	NR

OXA + 5-FU/FA combination

Reference	N[a]	ORR (%)	PFS*/TTP (months)	Median survival (months)	Statistical design for calculation of RR[φ]
Levi (CM)[17] ϕ	42	57	10*	13	NR
Garufi[18] (CM)	25	29.2	5.8*	12	NR
Brienza[19] ϕ	98/111	25.5	4.1	9.6	NR
Berteault-Cvitkovic[20] (CM)ϕ	37	40	9.3*	16.9	NR
De Gramont[21] (FOLFOX 1,2,3)ϕ	67	26.9	NR	13	NR
De Gramont[22] (FOLFOX 2)ϕ	46	46	7*	17	NR
Andre[23] (FOLFOX 3)ϕ	30	20	6.5*	14.2	NR
Andre[24] (FOLFOX 3)ϕ	38/40	18.4	4.6*	10.6	NR
Andre[24] (FOLFOX 4)ϕ	51/57	23.5	5.1*	11.1	NR
Maindrault[25] (FOLFOX 6)ϕ	60	27	5.3*	10.8	NR
Mandrault[26] (FOLFOX 7)ϕ	48	42	6*	16.1	NR
Gerard[27] ϕ	36/37	28	10*	10	NR
Meyer[28]	38	36	5.5*	7.6	
Rougier[29] ϕ	33	21.2	4.7	11.5	A descriptive analysis of efficacy and safety was planned with a total of 30 patients/arm. No statistical hypothesis was tested.
Hsieh[30]	60	33.3	4.8	12.1	
Bleiberg[31]	79	24	4.0*	10	
Guerin-Meyer[32]	43/47	25	5	NR	
Brueckl[33]	26	15.3	NR	12	
Abad[34]	32/51	25	NR	NR	
Nobile[35]	41/52	31.7	NR	NR	
Mosconi[36] (FOLFOX 4)ϕ	22	18.2	6	7	p0: 10%, p1: 25% α: 5% β: 20% n: 43
(FOLFOX 2)	23	21.8	5	9	p0: 10%, p1: 25% α: 5% β: 20% n: 43
Janinis[37] ϕ	24	13	11	12	Two-stage Simon design; p0: 10%, p1: 30% α: 5% β: 10% n: 33

OXA and CPT-11 combination after 5-FU failure

Reference	N[a]	ORR (%)	PFS/TTP (months)	Median survival (months)	Statistical design for calculation of RR$^{\varphi}$
Calvo[38]	33	57.6	8	NR	
Scheithauer[39] ϕ	36	42	7.5	>11	Two-stage Gehan design. Probability of rejecting a RR $\geq$ 20% is <5%; CI for sample size calculation (n: 30) for second stage: NR
Wassermann[40]	24/34	44	7.5	NR	
Yves[41]	24/32 (CPT-11/5-FU/FA–OXA/5-FU/FA)	16	8	10	
	29/32 (OXA/CPT-11)	28	10	12	
Rougier[29] ϕ	33	15.2	4.2	11	A descriptive analysis of efficacy and safety was planned with a total of 30 patients/arm. No statistical hypothesis was tested
Kreztschemar[42]	32	37.5			
Becouarn[43] ϕ	30 (CPT-11/OXA)	23	8.5*	12.3	Two-stage Simon design; p0: 5%, p1: 10% α: 5% β: 10% n: 70
	32 (alternating CPT-11/5-FU and OXA/5-FU/FA)	6	8.2*	9.8	
Baretta[44]	37/47	49	9	NR	
Salud[45]	21/36	28.5	NR	NR	
Ballina[46]	14/21	28	NR	NR	
Lonardi[47]	30/31 (alternating CPT-11 and OXA)	41	NR	NR	

[a](−/−): number of patients evaluable for efficacy/total number of patients who failed 5-FU treatment; (−): number of evaluable patients for efficacy who failed 5-FU treatment; CM: chronomodulated; PFS: progression-free survival; TTP: time to progression; ORR: objective response rate; NR: not reported; ϕ: published as an article; p0: the largest response probability which, if true, implies that the therapeutic activity does not warrant further investigation of the study treatment; p1: the lowest response probability which, if true, implies that the therapeutic activity warrants further investigation and the second stage of the trial can start; φ: the statistical hypotheses are not usually stated in the abstracts due to size restrictions in the abstract books; therefore only the statistical information provided by published articles is examined.

evolving. The emergence of new drugs during the 1990s, such as irinotecan (CPT-11) and oxaliplatin (OXA) has widened the spectrum of therapeutic choices for ACC [10,11]. The present paper focuses on the activity of second-line CT following 5-FU, CPT-11 or OXA alone or in combination.

Methods

A systematic literature search was performed using two major sources: (i) the Medline search tool, applying the words 'metastatic or advanced colorectal cancer', 'second-line chemotherapy', '5-FU refractory', '5-FU resistantl', 'oxaliplatin' and 'CPT-11', and (ii) the proceedings books of the major international medical oncology meetings such as the American Society for Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and European Conference of Clinical Oncology (ECCO). The abstracts with preliminary results are excluded. The available data, whether published in a full paper or as an abstract, are critically analyzed.

Do patients benefit from second-line treatments? Evidence from phase III trials

The best and most remarkable evidence clarifying the impact of second-line treatment in ACC is provided by two landmark randomized phase III studies [12,13]. These two European trials evaluated the benefit of CPT-11 in patients failing treatment with 5-FU bolus regimens, when compared to the best supportive care (BSC) or to an intensive 5-FU-based infusional treatment. CPT-11 was administrated at a dose of 350 mg/m^2, i.v., every 3 weeks. In both trials, the primary endpoint was OS and QoL assessment was one of the secondary endpoints. In the Cunningham trial [11], 279 patients were randomized to either CPT-11 plus BSC or to BSC alone. The CPT-11 arm yielded superior results in terms of median survival (9.2 versus 6.5 months, $p = 0.0001$) and 1-year survival (35.2 versus 13.8%), but also median pain-free survival and other QoL measures. In the Rougier trial [13], 267 patients were randomized to receive either CPT-11 or infusional 5-FU. The median survival times were 10.8 and 8.5 months for the CPT-11 and the infusional 5-FU patient groups, respectively ($p = 0.035$). Since a modest benefit was expected from infusional 5-FU in patients who had previously failed bolus 5-FU treatment, the difference in OS between the two arms, although still statistically significant, was less striking than in the Cunningham trial. Nevertheless, both trials proved the survival benefit from second-line treatment in ACC and led to the approval of CPT-11 in this setting in 1998.

Do phase II trials provide further evidence for the activity of second-line treatments?

There are many phase II trials evaluating the activity of CPT-11, OXA or both, either as monotherapy or in combination with 5-FU/FA, as second-line therapy for patients who are refractory to a previous 5-FU/FA regimen. Unfortunately, the majority of these phase II trials are small, non-randomized and the regimens tested have never been moved forward to be evaluated in a phase III trial. Furthermore, the information provided is limited to response rate (RR) and, in some, also to either median progression-free survival (PFS) or median time to progression (TTP). Tumor RR, PFS and TTP may reflect the biological activity and the control of the disease, but are, nonetheless, only surrogate endpoints for overall survival. More importantly, they do not necessarily translate into direct patient benefit, as is the case for OS or QoL. Notwithstanding these limitations, one can argue that it might be rational in certain circumstances to use a treatment that improves these surrogate endpoints until definitive conclusions regarding OS are available for a particular regimen.

Table 1 [14–47] summarizes data from phase II trials where OXA, either alone or in combination with 5-FU/FA or CPT-11, was evaluated as the second-line treatment for ACC, after failure on 5-FU-based chemotherapy ($N = 1672$). An objective RR (ORR) of approximately 10% was reported when OXA was administered alone ($N = 180$). Several different combinations of OXA and 5-FU/FA have been investigated (e.g. FOLFOX 1–4, 6 and 7) in order to determine the most effective combination regimen with optimal administration schedule and less toxicity [48]. The median ORRs in these phase II trails testing OXA and 5-FU/FA combination was 25.5% (range: 13–57%) ($N = 1063$). In all these trials, the median survival for the second-line treatment was in the range of 8–17 months (the median of the median survivals was 12 months). The median ORR of the listed phase II trials testing OXA and CPT-11 combination after failure on a 5-FU-based regimen was 28% (range 6–57%) ($N = 429$), which is similar to the one achieved with the combination of either agent with a 5-FU/FA regimen. Sequential or alternating regimens seem to yield lower RR [41,43] in randomized trials, although their role is still under investigation. The OXA, CPT-11 and 5-FU combination has also been evaluated in a small phase II trial in 5-FU-refractory ACC patients [49].

Table 2 [50–74] reports the data from phase II trials that evaluate the efficacy of CPT-11 as monotherapy and in combination with a 5-FU/FA regimen, following failure with a previous 5-FU-based chemotherapy. Two different administration schedules were studied: 350 mg/m^2 every 3 weeks and 125 mg once weekly for 4 weeks followed by a 2-week drug-free interval. These schedules yielded similar results; the median ORR of the CPT-11 monotherapy trials was 13% (range: 9-26%) and the median survival was in the range of 7–25 months (the median of the median survivals reported was 10.2 months) ($N = 2323$). Different CPT-11 and 5-FU/FA combinations with

Table 2 Second-line phase II trials of CPT-11 in 5-FU-resistant ACC patients

CPT-11 monotherapy (350 mg/m^2 q3wk)

Reference	*N*[a]	ORR (%)	PFS*/TTP (months)	Median survival (months)	Statistical design for calculation of RR$^{\varphi}$
Anton[50]	54/62	13	NR	NR	
Barcelo[51]	31	23	NR	10.5	
Hoeffken[52]	311/321	10	2.3+	NR	
Mendez[53]	99/115	21.2	4.8	25.6	
Rougier[54] ϕ	130	17.7	6*	10	A descriptive analysis of efficacy and safety was planned with a total of 30 patients/arm. No statistical hypothesis was tested
Salinas[55]	27	11	NR	8	
Schöffski[56]	93/108	12	4.2	10.4	
Van Custem[57] ϕ	95/107	13.7	3.9*	10.4	Single-stage Fleming design; p0: 6% p1: 16% $\propto$: NR, β: NR, n: 79
Schöffski[58]	102/111	11	4	9	
Van Custem[59] Ω	363/455	12.9	4.5	9.5	
Vincent[60]	28/35	10.7	3.7	7.4	
Santoro[61]	15	26	NR	13	
Frontini[62]	93/105	10.7	4.5*	>14	
Tsavaris[63]	33	18.1	NR	NR	
Navarro[64]	23/32	17.4	2.9	6.8	

CPT-11 monotherapy (once weekly for 4 weeks followed by a 2-week drug-free interval)

Reference	*N*[a]	Dose (mg/m^2)	ORR (%)	PFS*/TTP (months)	Median survival (months)	Statistical design for calculation of RR$^{\varphi}$
Casinello[65]	38	125	21	NR	NR	
Pitot[66] ϕ	90	125	13.3	7.7	8.3	Two-stage design p0: 10% p1: 30%; $\propto$: 7% β: 10%, N: 30 patients. Trial later expanded to include a total of 90 treated patients
Rothenberg[67] ϕ	64	125	14.1	5.1	10.6	NR
	102	100	8.8	3.3	9.3	NR
Pazdur[68]	175/183	125	11	NR	NR	
Shimoda[69] ϕ	46	100 qwk and 125 q2wk	22	NR	NR	NR
Rothenberg[70] ϕ	43/48	125–150	23	6	10.4	NR
Michael[71]	49/65	125	10	NR	NR	

CPT-11 + 5-FU/FA combination

Reference	*N*[a]	ORR (%)	TTP (months)	Median survival (months)	Statistical design for calculation of RR$^{\varphi}$
Seitz[72]	35/49	23	NR	NR	
Rougier[29] ϕ	35	11.4	3.2	12.2	
Durrani[73]	41	22*	NR	NR	
Rigatos[74]	31	25.8	NR	<12	

[a](–/–): number of patients evaluable for efficacy/total number of patients who failed 5-FU treatment; (–): number of evaluable patients for efficacy who failed 5-FU treatment; PFS: progression-free survival; TTP: time to progression; ORR: objective response rate; NR: not reported; ϕ: published as an article; p0: the largest response probability which, if true, implies that the therapeutic activity does not warrant further investigation of the study treatment; p1: the lowest response probability which, if true, implies that the therapeutic activity warrants further investigation and the second stage of the trial can start; φ: The statistical hypotheses are not usually stated in the abstracts due to size restrictions in the abstract books; therefore only the statistical information provided by published articles are examined; Ω: This trial includes the data from four phase II trials.

minor modifications in the dose and schedule have been tested in ACC patients and the median ORR of these trials was *22%* (range 11–*26%*). The median survival was reported in only two trials and was of 12 months in both (N = 156).

Two randomized phase II trials compared the efficacy of OXA to CPT-11 after failure on 5-FU-based chemotherapy (Table 3) [29,75]. Ulrich-Pur and colleagues evaluated the efficacy of either OXA or CPT-11 in combination with mitomycin C and found that both regimens had equivalent efficacy, but did not exceed the activity of either agent alone. Rougier *et al.* randomized 5-FU-resistant ACC patients to OXA/5FU/FA, CPT-11/5FU/FA or CPT-11/OXA and obtained similar results for the first two arms in terms of ORR and median survival. By involving an upfront randomization, these two trials evaluated different treatment options simultaneously and suggest that the efficacy of OXA is probably comparable to CPT-11 in this setting.

Table 3 OXA versus CPT-11 as second-line treatment of 5-FU-resistant ACC patients

Reference	N[a]	Treatment arms	ORR (%)	Median response duration (months)	Median survival (months)	Statistical design for calculation of RR
Ulrich-Pur[75]	27	OXA + MMC	18.5	NR	NR	
Ulrich-Pur[75]	30	IRI + MMC	23.3	NR	NR	
Rougier[29] ϕ	35	OXA	22.6	6.7	11.5	NR
Rougier[29] ϕ	33	IRI	12.1	8.1	12.0	NR

[a](−/−): number of patients evaluable for efficacy/total number of patients who failed 5-FU treatment; (−): number of evaluable patients for efficacy who failed 5-FU treatment; ORR: objective response rate; NR: not reported; ϕ: published as an article.

Other agents, either alone or in combination with OXA or CPT-11, have also been evaluated after the failure of 5-FU/FA. The efficacy of the thymidylate inhibitor raltitrexed has been evaluated in a phase II trial that included 40 ACC patients who had previously been treated with a 5-FU-based regimen [76]. The published results showed an ORR of 17.5% for those patients who failed 5-FU and a median survival of 11.6 months for the entire cohort of 43 patients. In a recently published phase II study, the combination of OXA and raltitrexed provided an ORR of 36% in 25 ACC patients who had previously failed 5-FU-based CT [77]. Van Custem *et al.* also evaluated this combination in 50 ACC patients with progression while on first-line 5-FU/FA ± CPT-11 and reported an ORR of 16%, with a median survival of 7.1 months [78]. A multicenter phase II Spanish trial studied the efficacy of the combination CPT-11/raltitrexed as second-line treatment in 21 5-FU-refractory ACC patients and obtained an ORR of 14% [79]. Another phase II trial reported a RR of 30%, with a median survival of 7.1 months, for the combination of OXA/CPT-11/mitomycin C as second-line therapy for ACC [80]. Finally, CPT-11 and mitomycin C combination provided a RR of 34% with a median TTP of 4.2 months in 41 ACC patients who failed 5-FU-based chemotherapy [81].

Second-line therapy after OXA or CPT-11 failure

The treatment options, particularly after failure of CPT-11 and OXA, are scarce. Some phase II trials have suggested a modest benefit for the use of one of these agents after failure of the other (Tables 4 and 5) [82–90]. The reported RR is in the range of 7–17% for OXA in the case of CPT-11 failure and 4–20% for CPT-11 in the case of OXA failure. In the Tournigand study, ACC patients were randomized to receive either FOLFOX or FOLFIRI as first-line treatment and planned to crossover to the other arm upon progression. The RRs to FOLFIRI and FOLFOX after crossover were 7% (three of 42 patients) and 21% (10 of 46 patients), respectively. The median OS, including the first-line treatment, exceeded 20 months in both arms of the study.

The interim analysis of the EFC 4584 trial which recently led to the approval of OXA and 5-FU/FA combination for the second-line treatment of ACC in the US demonstrated not only the efficacy of this combination in ACC patients whose disease recurred or progressed during or within 6 months of completion of first-line therapy with the CPT-11and bolus 5-FU/FA combination, but also the superiority of OXA and infusional 5-FU/FA combination treatment over OXA monotherapy in terms of objective tumor response (9.9 versus 0 versus 1.2% for OXA + 5-FU/FA, infusional 5-FU/FA and OXA arms, respectively) and median time to radiographic progression (4.6 versus 2.7 versus 1.6 months for OXA + 5-FU/FA, infusional 5-FU/FA and OXA arms, respectively) [91]. This randomized, controlled, three-arm phase III trial completed its accrual with 821 enrolled patients and the interim analysis included 459 randomized patients. If these preliminary results are confirmed at the final analyses and validated in a similar well-conducted phase III trial, level I evidence for the second-line use of OXA and 5-FU/FA combination will be available.

A better understanding of the cellular processes for cancer growth and identification of numerous molecular targets led to investigation of a series of targeted biologic agents in early clinical trials. Cetuximab or C-225, a monoclonal antibody against the extracellular domain of the epidermal growth factor receptor (EGFR), was combined with CPT-11 and provided a RR of 17%, in patients with EGFR-expressing colorectal tumors, who had previously failed CPT-11 treatment in a phase II trial [92].

The impact of second-line treatments in first-line advanced colon cancer trials

Four large randomized phase III trials evaluated first-line CT in ACC [10,11,93,94]. In these trials, a significant proportion of patients (57 and 28% in OXA/5-FU/FA; 56 and 34% in CPT-11/5-FU/FA trials) in the control arm were allowed to crossover to the investigational treatment arm upon disease progression. One could speculate that the existence of such relatively high percentages of crossover, which mirrors current clinical practice, must have had an impact on the OS observed. Assuming that, at least in European studies, second-line therapy was offered to all patients fit to receive it, the observed results may represent a realistic estimation of the survival benefit in a non-selected patient population. Moreover, the surgical removal of metastases was possible in more

Table 4 OXA/5-FU/FA trials as second-line treatment after CPT-11 failure

Reference	N[a]	ORR (%)	TTP (months)	Median survival (months)
Ryan[82]	61	6.5	NR	NR
Patel[83]	55/66	21	NR	9.6
Kretzschmar[84]	34	12	3	NR
Kouroussis[85]	41	17	11	12
Tournigand[86] §	46	21	NR	NR
Zucali[87]	15/19	40	7	NR

[a](−/−): number of patients evaluable for efficacy/total number of patients who failed 5-FU treatment; (−): number of evaluable patients for efficacy who failed 5-FU treatment; TTP: time to progression; ORR: objective response rate; NR: not reported; §: an external review of responses was performed.

Table 5 CPT-11/5-FU/FA trials as second-line treatment after OXA failure

Reference	N[a]	ORR (%)	PFS (months)	Median survival (months)
Vardakis[88]	23	8.6	9.5	NR
Andre[89]	34	6	4.2	11.1
Tournigand[86] §	42	3	NR	NR
Maindrault[90]	20/22	20	6.7	NR

[a](−/−): number of patients evaluable for efficacy/total number of patients who failed 5-FU treatment; (−): number of evaluable patients for efficacy who failed 5-FU treatment; PFS: progression-free survival; ORR: objective response rate; NR: not reported; §: an external review of responses was performed.

than 20% of patients in the Giacchetti trial [94] and a 2-fold increase in the proportion of patients who had metastasectomy was observed in the OXA/5-FU/FA arm of the de Gramont trial [93]. The possibility of surgical removal with curative intent in a substantial percentage of patients, including those who received second-line treatments, further strengthens the notion that second-line therapy has an important role in the OS of ACC patients.

Discussion

For the present article, the data from not only published papers but also abstracts were reviewed. Although unusual, incorporation and analysis of data presented in abstract form appears important since currently the data from such brief interim reports can impact on current clinical practice. A total of 76 trials, including second-line raltitrexed trials and the trials reported in Tables 1–5, were analyzed. With the exception of the trials reported in Tables 4 and 5, all studies evaluated the activity of second-line treatments in 5-FU-resistant or -refractory patients. In the studies from Tables 4 and 5 the population was composed of patients pretreated either with OXA or CPT-11 as first-line chemotherapy for ACC. In total, 4461 patients who failed prior 5-FU-based chemotherapy were enrolled in second-line phase II trials investigating the efficacy of CPT-11 (as monotherapy or in combination with 5-FU/FA), OXA (as monotherapy or in combination with 5-FU/FA), CPT-11 + OXA combination and other agents either alone or in combination with CPT-11 or OXA. When the patients who are enrolled in the second-line CT trials after failure on first-line CT with OXA or CPT-11 are added, the sum becomes almost five thousand patients.

Only 25 of the trials discussed above were published as peer-reviewed articles in oncology journals. All others were published as abstracts at oncology meetings and therefore provide neither a full description of the statistical hypothesis nor mature final results.

Only six of the published trials provided a description of the statistical design used for the calculation of RR [29,36–37,39,43,57,66]. Phase II trials are used to screen the activity of a drug or combination of drugs in a given tumor type by measuring tumor shrinkage. The conduct of a well-designed single-agent or a feasibility combination phase II trial requires determination of the trial objective(s), the targeted patient population and a proper statistical design. It should address clinically relevant endpoints such as ORR, toxicity, and additionally it may provide an opportunity to make pharmacodynamic and pharmacokinetic evaluations. Most often the primary objective will be ORR and the required sample size should be calculated based on the expected RR. An ideal statistical design must minimize the number of patients treated with an inactive treatment and the risk of missing a truly active treatment. If the minimum level of activity to warrant further evaluation is achieved, only one or two phase II confirmatory trials need to be conducted before undertaking a phase III trial. In the light of these principles, we calculated the sample size of a hypothetical phase II trial that intended to investigate the activity of drug X as second-line treatment in ACC, using a Simon two-stage optimal design. The ORR reported for CPT-11 monotherapy ranges between 11 and 23% in multiple phase II trials and the FDA approved OXA + 5-FU/FA combination as a second-line treatment in ACC after failure to bolus 5-FU/FA + CPT-11 combination regimen based on an objective RR of 10%. In the light of these figures, it appears logical then to consider 5% as an unacceptably low ORR (i.e. treatment should be rejected at the end of a phase II trial if ORR is less than 5%). On the other hand, a treatment that has a true ORR greater than 15% should be selected for further investigation. Using the classical values of $\alpha = 5\%$ and $\beta = 10\%$ for the respective probabilities of falsely rejecting an active treatment and failing to select an active treatment and a Simon design, 37 patients are needed in the first step of the trial. If fewer than three patients achieve a response the trial must be stopped. Otherwise, accrual should continue until a total of 84 patients, with treatment rejection occurring in case there are fewer than eight observed responses. Unfortunately, these statistical details are not provided in most of the second-line ACC trials reported, which calls for caution in the interpreta-

tion of their results. Only 12 of the above-mentioned phase II trials have a sample size approximately similar to the one calculated in our example [19,52–54,56–59,62,66–68].

The absence of an external review of responses further weakens the accuracy of these phase II data, since RR is a subjective measure, highly dependent on the investigator.

Additionally, only four of these studies were randomized [29,41,43,75]. Integration of randomization, especially in a phase II feasibility study that evaluates the therapeutic benefit of a new agent or new combination, offers advantages. In contrast to phase III trials, the purpose of randomization is not to undertake a formal comparison, but instead to facilitate the extension to a randomized phase III trial if encouraging results are obtained. Nevertheless, it may help to detect whether one of the arms is inactive or too toxic. Moreover, the existence of a randomization could draw the investigator's attention to potential selection bias. It is critical to confirm that the RR of the control group is within the expected range, to avoid misinterpretation of the activity of the investigational treatment. The results of a randomized phase II trial may also prevent the conduct of an unrealistic phase III trial, with an inappropriately small sample size, based on misleading 'highly encouraging' RR obtained from several non-randomized small phase II trials. The drawbacks of an upfront randomization in phase II trials include the higher cost, the longer time needed to complete the trial and the larger sample size required. However, when the possibility of further extension to a phase III trial is considered, the trial becomes more cost-effective in terms of time, human resources and overall costs of drug development.

Conclusions and future perspectives

Despite the problems identified above, some conclusions can be made based on these studies. Second-line therapy is indeed effective in ACC, not only in terms of RR but also, and more importantly, in terms of survival and QoL. In the case of CPT-11 there is even level I evidence based on two well-designed randomized phase III trials. Additionally, as discussed previously, the results from the first-line randomized phase III trials, by allowing a high percentage of crossover, also provide some indirect evidence that second-line therapy has a positive impact in survival. Oxaliplatin seems to have similar efficacy, although this evidence is provided by only two small randomized phase II trials and a definitive conclusion awaits the results of a recently completed US trial. The role of 5-FU/FA in combined treatments is not yet clear. The combination of OXA and CPT-11 has not been proven superior to the combination of either drug with a 5-FU/FA regimen. The issue of combination versus sequential administration of drugs is still debated and under evaluation. Both OXA and CPT-11, one given after the failure of the other, have only modest efficacy. The role of other cytotoxic drugs, such as raltitrexed and capecitabine, is currently being investigated in phase II–III trials.

Future advances in the treatment of ACC will depend on more selective use of the available drugs, using predictive markers and possibly 'molecular signatures', and on the development of new, target-based molecules [95]. Preliminary data suggest that high levels of thymidylate synthase (TS), an enzyme normally inhibited by fluorouracil, may predict for a poor response to a fluorouracil-based regimen [96], particularly when associated with low levels of two other molecules also implicated in the 5-FU metabolic pathway, thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) [97]. These results are provocative and deserve further validation in large series and, particularly, in prospective trials.

In summary, level I evidence now exists supporting the use of CPT-11 after 5-FU/FA failure and the Rothenberg trial provides level II evidence that supports the use of OXA/5-FU/FA after CPT-11/5-FU/FA failure. For all other situations, i.e. after failure of any other regimen, current clinical practice of second-line treatment for ACC is based only on level III evidence obtained from non-randomized uncontrolled phase II studies. The performance of repetitive phase II trials not only creates misleading literature but also delays the further testing of truly effective second-line treatment strategies for ACC through definitive phase III trials. Therefore, the conduct of multicentric randomized phase III clinical trials with adequate power and proper endpoints must be a priority for research in this area. The emergence of several new potentially active agents in this setting further strengthens this need, and the enrollment of patients in many small non-informative trials testing similar combinations with minor variations in dose and schedule must be strongly discouraged.

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