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European Journal of Cancer 40 (2004) 1474–1484

European Journal of Cancer

www.ejconline.com

Review

# Systemic therapy for advanced hepatocellular carcinoma: a review

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Received 12 February 2004; accepted 13 February 2004
Available online 19 May 2004

**Abstract**

Hepatocellular carcinoma (HCC) is a common cause of cancer mortality worldwide. Whilst local treatments are useful in selected patients, they are not suitable for many with advanced disease. Here, we review phase II and III trials for systemic therapy of advanced disease, finding no strong evidence that any chemotherapy, hormonal therapy, or immunotherapy regimen trialled to date benefits survival in this setting. Many trials were inadequately powered, single centre, and enrolled highly selected patients. From this review, we cannot recommend any therapeutic approach in these patients outside of a clinical trial setting. Including an untreated control arm in clinical trials in HCC is still justified. Every effort should be made to enroll these patients into adequately powered trials, and promising phase II results must be tested in a multicentre phase III setting, preferably against a placebo control arm. Prevention of hepatitis B and C remains vital to decrease deaths from HCC.


*Keywords:* Carcinoma; Hepatocellular; Liver neoplasms; Antineoplastic agents; Antineoplastic combined chemotherapy protocols; Immunotherapy; Drug therapy; Combination; Antineoplastic agents; Hormonal

## 1. Introduction

Hepatocellular carcinoma (HCC) is the third commonest cause of cancer mortality worldwide, being responsible for over 500000 deaths annually [1]. Mortality rates vary between 1/100000/year in Northern Europe to over 20/100000/year throughout the Asia-Pacific region [2]. In the Asia-Pacific region, HCC mortality rates closely parallel the prevalence of chronic hepatitis B (HBV) infection, with the highest rates found in patients with established HBV-cirrhosis [3]. In Europe, North America and Australia, the incidence of HCC has doubled since 1983 despite a falling prevalence of HBV infection, reflecting the impact of the Hepatitis C (HCV) epidemic [4–6]. The numbers of HCV-related HCC will more than double by 2010 [7].

The median survival of HCC is less than 12 months from diagnosis, reflecting both late presentation and lack of effective therapy. Only 10–20% of HCC are suitable for resection at presentation [8], with a 5-year recurrence-free survival of only 10–20% [7,9,10]. Hence, most patients presenting with HCC will eventually develop advanced disease. Treatments trialled for advanced disease include cryotherapy, selective internal radiotherapy with lipiodol $I^{131}$ or yttrium-90 microspheres, systemic and intra-arterial chemotherapy, hormonal therapy and immunotherapy. Arterial chemoembolisation is useful in selected patients with unresectable disease, and a meta-analysis favoured this treatment over conservative treatment or suboptimal therapies (Odds Ratio (OR) 0.53, 95% Confidence Interval (CI) 0.32–0.89) [11]. However, not all patients are suitable for chemoembolisation, nor is it universally available. This review is confined to systemic therapy of advanced disease, and does not include intra-arterial treatments. We comment on results of adjuvant post-operative treatment where relevant, but do not comprehensively address adjuvant therapy, which has been covered in two recent systematic reviews [12,13].

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doi:10.1016/j.ejca.2004.02.027

## 2. Review methods

A Medline search from 1966 to 2003 used the following strategy:

[Exp Carcinoma, Hepatocellular/ or hepatoma.mp or HCC.mp].

And [advanced.tw or locally advanced.tw or exp Neoplasm Metastasis/ or metastatic.tw or inoperable.tw or unresectable.tw].

And [exp Antineoplastic combined chemotherapy protocols/ or systemic treatment.tw or exp Antineoplastic Agents, Hormonal/].

This search was supplemented by targeted searches for each agent, and searching of the American Society of Clinical Oncologists (ASCO) online abstract database. References of review articles were also searched. Trials of intra-arterial treatments were excluded.

Phase II and III trials were included, as were some case series where no other information was available. Case reports and phase I trials were excluded. Over 120 trials were identified. Most were small phase II trials, and the mean number of patients on study was 47, falling to fewer than 40 patients when studies of tamoxifen were excluded. Only 26 randomised trials were identified, most being randomised phase II trials rather than adequately powered phase III trials.

The review findings are discussed as three major treatment modalities: cytotoxic chemotherapy, hormonal therapy and immunotherapy, but we have made no attempt at meta-analysis.

## 3. Review findings

### 3.1. Cytotoxic chemotherapy in HCC

The use of cytotoxic agents in advanced HCC has been disappointing, with few agents showing response rates (RRs) above 20%, and none demonstrating convincing survival benefits in the phase III setting. HCC has a high incidence of expression of the multi-drug resistance gene (MDR1) and consequent high levels of P-glycoprotein (P-gp) [14], which is associated with a poor response to chemotherapy in this disease [15]. Furthermore, many of these patients have underlying chronic liver disease and impaired hepatic function, increasing the toxicity of standard doses of many drugs and the difficulty of delivering combination chemotherapy.

#### 3.1.1. Single-agent and combination doxorubicin

Doxorubicin has been considered one of the most active agents in advanced HCC since the 1970s. Early phase II trials and case series reported RRs ranging from 25% to 100% with single-agent doxorubicin [16–19]. Subsequent randomised phase III studies supported a higher RR for doxorubicin than 5-fluorouracil (5-FU)-based regimens [20,21] and etoposide [22], but failed to show survival benefits. More recent phase II studies and case series have not shown RRs over 20% [23–26], and in a single randomised controlled trial of doxorubicin versus no antitumour treatment in 60 patients, doxorubicin did not show a superior RR or survival [27]. A meta-analysis showed no significant effect of doxorubicin on 1-year survival (Mean difference 3%, 95% CI – 4–11%) [28], but was confounded by the use of numerous differing regimens in the non-doxorubicin arms. Attempts to modify drug resistance using tamoxifen together with doxorubicin gave higher RRs in phase II testing [29], but no benefit over tamoxifen alone in a non-randomised comparison [30]. The use of pegylated liposomal formulations of doxorubicin and daunorubicin has not increased RRs in phase I/II studies, and reports of the toxicity profiles of these agents are variable [31–36].

Phase II trials of doxorubicin together with gemcitabine, lomustine (CCNU), streptozocin and clofazimine have not shown RRs or median survivals over those expected with doxorubicin alone [37–40].

#### 3.1.2. Single-agent and combination epirubicin

Phase II trials and retrospective case series of epirubicin in advanced HCC report tolerable toxicity profiles, but there are no reports of RRs superior to doxorubicin [41–43]. The concurrent use of tamoxifen did not increase the RR [44]. Higher RRs have been reported using epirubicin and etoposide together [45]. In this trial, most of the 36 patients were Okuda stage I–II, and patients with bilirubin >51.3 μmol/l were excluded. Objective responses were seen in 39% of patients, with decreases in α-fetoprotein (αFP) levels, and a median survival of 10 months. However, there was considerable haematological toxicity. The favourable results may be influenced by the exclusion of hyperbilirubinaemic patients. This combination has not yet been tested in the phase III setting. In the adjuvant setting, combination epirubicin and mitomycin C has shown a non-significant trend towards improved survival versus no adjuvant therapy [46]. However, in another adjuvant trial intravenous (i.v.) epirubicin plus transarterial chemotherapy with cisplatin was associated with a worse outcome [47].

#### 3.1.3. Other anthracyclines

RRs of 0–27% have been reported in small phase II studies of single-agent Mitoxantrone [48–50], and this agent has been widely used intra-arterially. A single randomised comparison between mitoxantrone and single-agent cisplatin in 69 patients gave a median survival of 3.5 months in both arms, and no objective responses to mitoxantrone. A randomised phase III comparison of the semi-synthetic anthracycline Menogaril versus

Interferonβ (IFNβ) resulted in no objective responses or survival differences (Median survival 5 vs. 2.5 months (nonsignificant difference (NSD))) [51]. Oral idarubicin gave objective responses in 17% of 45 patients in one study [52], but has not been tested further.

*3.1.4. Fluoropyrimidines*

5-Fluouracil and related drugs are the most widely used and active agents in many gastrointestinal malignancies, prompting extensive testing of fluoropyrimidines in HCC. Objective RRs with bolus 5-FU range from below 10% [20,53,54] to 28% [55]. The combination of 5-FU, levofolinic acid, and oral hydroxyurea did not the improve RRs (10%) [56].

However, the fluoropyrimidines are schedule-dependent drugs, with increased activity in other cancers when given as a continuous infusion rather than a bolus. Continuous i.v. infusions require permanent i.v. access and are cumbersome for patients. An alternative is inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme which degrades 5-FU. High levels of DPD are normally found in normal liver and HCC. Combinations of DPD inhibitors (eniluracil, uracil) and oral 5-FU or pro-drugs (tegafur) increase the bioavailability of oral 5-FU, achieving plasma levels similar to continuous i.v. infusion [57]. Despite the excellent pre-clinical rationale, three studies using eniluracil and oral 5-FU [58,59] or tegafur and uracil [60] have shown no objective responses. However, in a small randomised phase II study of tegafur and uracil versus supportive care, the treatment group had superior outcomes (RR 18%, median survival 12 months vs. 6 months $P < 0.01$) [61]. Furthermore, in a randomised trial, adjuvant oral 1-hexylcarbamoyl-5-fluorouracil (HCFU) improved recurrence-free survival in patients with stage I disease, although it was underpowered to detect an overall survival advantage, suggesting that this approach may have some activity [62].

Oral capecitabine has been trialled with the same rationale, producing a RR of 13% with minimal toxicity [63]. The combination of thalidomide and capecitabine is well tolerated, with responses in 2 of 11 patients [64]. These preliminary results suggest that capecitabine could be trialled in combination with other agents.

In an i.v. combination approach, a recent single-centre study reported a RR of 47% in 38 patients with advanced HCC using low-dose continuous infusion 5-FU with low dose cisplatin, with a time to progression of over 7 months [65]. Any benefits of this regimen should be confirmed in a phase III trial before it is more widely adopted.

*3.1.5. Anthracyclines plus 5-FU*

Results of multi-agent regimens including both anthracyclines and 5-FU, often with a third agent (CCNU, teniposide (VM-26), Mitomycin C; PIAF regimen (doxorubicin/5-FU/cisplatin/α-IFN)) have shown longer median survival times (7–10 months) than many single-agent studies [66–68]. However, the RRs are not superior to single agent anthracyclines [69,70], and there is likely to be selection bias for these more aggressive regimens. Furthermore, some of these trials included patients having surgery before or after chemotherapy. These combinations have not been trialled against best supportive care or single-agent treatment.

*3.1.6. Taxanes*

Despite pre-clinical evidence suggesting that the taxanes may be useful in HCC [71], they have been little studied clinically. Paclitaxel is extensively hepatically metabolised, and should be used cautiously in patients with hepatic impairment. Paclitaxel in a 3-weekly schedule caused two deaths in 20 patients with HCC, with no anti-tumour effect [72]. A phase I study of weekly paclitaxel was less toxic, giving one partial response in 16 patients [73]. Other studies using paclitaxel are ongoing. We could not identify any studies using single-agent docetaxel in HCC, although the North Central Cancer Treatment Group (NCCTG) is conducting a phase II trial of docetaxel and gemcitabine in this setting.

*3.1.7. Topoisomerase inhibitors*

Irinotecan is active in other gastrointestinal malignancies and *in vitro* against HCC cell lines [74]. It is metabolised to the active compound SN-38, which reaches high concentrations in the biliary system, and undergoes enterohepatic recycling [75]. One phase II trial of irinotecan in HCC suggests high toxicity and minimal anti-tumour activity [76], while a second suggests it is tolerable, but has not yet reported efficacy [77]. Topotecan and cisplatin in combination was inactive [78] and topotecan with oxaliplatin was toxic in cirrhotic patients, although less toxic and modestly active in non-cirrhotic patients [79].

Etoposide is a topoisomerase II inhibitor which has been extensively trialled in intrahepatic infusional therapy. However, no trials of systemic single agent etoposide have a RR over 10% [80–83]. Combining etoposide with tamoxifen as a putative multidrug resistance (MDR) modulator, objective responses were reported in 24% of 33 patients with manageable toxicities [84]. These findings have not been confirmed.

*3.1.8. Nucleoside analogues*

Gemcitabine and cladribine are highly active *in vitro* against human HCC cell lines [85]. Although an early trial of single-agent gemcitabine in HCC showed a RR of 18% [86], these promising results were not confirmed by subsequent trials [87–89]. Gemcitabine synergises with cisplatin and other drugs. However, in HCC, gemcitabine and doxorubicin did not increase the RR (12%) over that expected with doxorubicin alone [40].

Combination cisplatin and gemcitabine may be more promising, with objective responses of 17 and 21% being reported in two recent trials [90,91], and 17% of 35 patients in a retrospective analysis when amifostine was added to the combination [92].

#### 3.1.9. Cisplatin

Intravenous cisplatin alone has modest anti-tumour efficacy in HCC (15% RR [93]) but has been extensively used intra-arterially. Cisplatin-based combinations have been considered elsewhere in this review.

#### 3.1.10. Thymidylate synthase inhibitors

Raltitrexed and nolatrexed are active in other gastrointestinal malignancies, and nolatrexed has been tested in HCC, with a RR of less than 10% being reported in a phase II trial [94]. A subsequent randomised phase II trial comparing nolatrexed with doxorubicin did not produce any objective responses, but showed a small, non-significant survival benefit for nolatrexed [95]. A phase II study of nolatrexed in 48 patients gave a median survival of 24 weeks, despite a low 3% RR [96]. The survival "benefits" seen over historical control data may be due to patient selection; however, a phase III trial comparing nolatrexed with doxorubicin is underway and should help answer this question.

#### 3.1.11. Other cytotoxics

Numerous new cytotoxic compounds are undergoing early phase testing in HCC, including irofulven [97], pegylated arginine deaminase [98], and the epothilone B analogue BMS-247550 [99], with some early indications of anti-tumour activity.

In conclusion, despite some high reported response rates for combination chemotherapy, only one small randomised phase II trial has demonstrated any survival benefits, for tegafur and uracil [61]. This is countered by a small corresponding negative trial, and the results have not been confirmed in a multicentre setting. Rigorous patient selection for these trials and their single-centre populations suggest that the results are not generalisable. On the basis of this review, we cannot yet recommend any single-agent or combination chemotherapy approach outside the context of a clinical trial. The use of an untreated control arm in clinical trials of chemotherapy in HCC remains justifiable.

### 3.2. Hormonal therapies

#### 3.2.1. Somatostatin analogues

Somatostatin has direct and indirect effects on tumour growth, and can induce apoptosis, down-regulate epidermal growth factor (EGF) binding sites, inhibit insulin-like growth factor-1 (IGF-1) production, inhibit angiogenesis, and cause tumour hypoxia [100]. Over 40% of HCCs express somatostatin receptors [101], and octreotide scans are positive in some patients [102]. Thus, there is a good pre-clinical rationale for use of somatostatin analogues in HCC. In 1998, Kouroumalis et al. [103] published results of a randomised phase III trial of Octreotide versus no treatment in 58 patients with unresectable HCC without variceal bleeding or hepatic encephalopathy. The control group had more patients with larger tumours and advanced Okuda stage, although the groups were otherwise similar. Median survival was 13 months for treated patients and 4 months for controls. Octreotide was well tolerated and over 50% of patients had improved appetite and overall well-being. This trial generated intense interest in the use of somatostatin analogues in this disease.

The same group subsequently studied long-acting somatostatin analogues in a phase II trial in 28 patients [104]. The treated group had a median survival of 7 months, and were compared with a non-randomised "control" group, with a median survival of 3.5 months. Again, 60% of treated patients had an improved quality of life (QOL), as opposed to 23% of the non-randomised "controls". A further report compared patients treated with long-acting somatostatin analogues with historical controls, describing increased median survival from 8 months in "controls" to 15 months in the treated patients, with an improved performance status [105].

Other groups have not reproduced these results. A randomised phase III trial of 70 patients compared Sandostatin LAR with placebo, with a reported median survival of 2 months in both arms, and no improvement in performance status [106]. Of note, over half the patients on this study received no or one injection of study drug. Patients on this study had better Okuda and Child-Pugh scores than those studied by Kouroumalis and colleagues, making the short median survival somewhat surprising. However, participants in this Asian trial had more underlying HBV and portal vein thrombosis. Three further phase II trials have used long-acting somatostatin analogues, all reporting RRs under 5% and median survivals from 4 to 9 months ([107,108], personal communication, Dr J Cebon, Austin Repatriation Medical Centre, Melbourne Australia). Octreotide scan positivity was not associated with response. Somatostatin analogues have been unable to fulfil their early promise, and there is currently no evidence to support their use outside of clinical trials.

#### 3.2.2. Tamoxifen

The liver contains oestrogen receptors (ERs) with high affinity for oestradiol and can modulate protein synthesis in response to circulating sex hormones [109], and a proportion of HCCs express ERs [110–114]. The authors recently performed a Cochrane review of tamoxifen in advanced HCC, identifying 10 unconfounded, randomised trials (Cochrane collaboration, in

press). Many trials were small and had conflicting results [115–124]. However, two large, well-designed randomised phase III trials showed no evidence of a survival benefit for tamoxifen [110,125]. The Hazard Ratio (HR) for tamoxifen treatment was 1.05 (95% CI 0.94–1.16) on meta-analysis, arguing against the use of tamoxifen in advanced HCC or as a control arm in further trials (Cochrane collaboration, in press).

#### 3.2.3. Other hormonal interventions

HCC commonly expresses variant ERs (vERs), and whilst tamoxifen does not suppress proliferation in these patients, megestrol acetate (MA) blocks both wild-type and vERs [109]. Two small phase II studies of MA did not give any objective responses, although neither selected for vER expression [111,126]. Villa and colleagues proposed that MA may only benefit patients whose cancer expressed vERs, and enrolled 45 such patients into a randomised placebo-controlled trial, reporting longer median survival in the MA arm (18 months vs 7 months, $P = 0.009$) [127]. Treatment was well tolerated in all of the trials. MA also impacts positively on cancer-related cachexia and may enhance survival independent of tumour regression [128]. A multicentre randomised placebo controlled trial of MA is currently underway under the auspices of the Asia-Pacific Hepatocellular Carcinoma Trials Group, with a target accrual of 300 patients. This trial should clarify the role of MA in advanced HCC, and preliminary results are expected in mid-2005.

There is also evidence that HCCs express high concentrations of androgen receptors [129], can be induced by androgens [130], and that experimental tumours may respond to anti-androgen treatment [131]. Androgen blockade has been tested in two randomised placebo-controlled trials of a luteinising hormone-releasing hormone (LHRH) agonist/anti-androgen combination [132,133], and a phase II trial of flutamide [134], showing no effect on objective tumour response or survival. A single small phase II trial of cyproterone acetate in cirrhotic patients with unresectable HCC showed a RR of 20%, but a short median survival of 3.2 months [135]. These results have not been replicated, and cyproterone acetate has been implicated in the development of HCC in a small case series. In a single report, the aromatase inhibitor anastrozole did not give any objective responses, nor any indirect evidence of benefit [136].

In conclusion, despite the excellent pre-clinical rationale, there is no hormonal therapy in HCC which could be considered standard, or could form a control arm for a clinical trial. Any promising results must be tested in the phase III setting against placebo for evidence of survival benefits, and such a trial is ongoing with MA. These treatments should not be used in HCC outside of a clinical trial setting.

### 3.3. Immunotherapy

Interferons have multiple mechanisms of action, including direct antiviral effects, immunomodulatory actions, and direct and indirect antiproliferative effects [137]. IFNα is widely used as antiviral therapy for chronic HBV and HCV infections. Early phase II studies of IFNα [138], β [139] and γ [140] did not demonstrate any favourable treatment effects. However, a randomised phase III trial comparing IFNα with systemic doxorubicin in 75 patients suggested that IFNα had a superior RR and less systemic toxicity [141]. A subsequent randomised phase III trial of IFNα vs. no antitumour therapy in 71 patients reported a statistically significant doubling of survival (7.5–14.5 weeks) and RR of 31% in patients on IFNα [142]. However, these results were not replicated in a later randomised trial of IFNα vs. no treatment in 58 patients, with a lower RR (7%), no survival benefit, and problematic toxicity in the treatment arm [143]. Thus, there is no convincing evidence that single-agent interferons benefit patients with advanced HCC. In the adjuvant setting, two small randomised trials suggest that IFNα [144] and IFNβ [145] may decrease post-operative recurrence of HCC. These results must be confirmed in adequately powered, well-designed trials.

There have been numerous early phase studies of interferons with chemotherapy, most commonly anthracyclines [146–152], showing modest activity, with no evidence of improved survival, RRs or symptomatic benefits greater than that expected from chemotherapy alone. Similarly, studies of interferons with fluoropyrimidines or platinum-based chemotherapy are too small to draw conclusions about efficacy [153], or have not shown promising results [154,155]. Two exceptions include a phase III randomised trial of IFNα plus cisplatin versus no treatment, showing a survival advantage for the treatment arm (8 months vs. 3 months, $P = 0.001$) despite a low RR (13%) [156]; and a phase II trial in 29 patients with portal vein thrombosis given methotrexate, 5-FU, cisplatin and IFNα 2b, reporting an ORR of 45% [157]. However, these results remain to be confirmed. A recent phase II trial of IFNα 2b and continuous infusion 5-FU reported a RR of 25% and median survival of 19 months in 43 patients [158]. However, 33% of these patients had the more chemosensitive histology, fibrolamellar carcinoma, and some responders underwent liver transplantation or resection after chemotherapy. Amongst those with HCC, the RR was 14% and median survival was 15 months.

Other immunotherapy approaches trialled in small phase II and pilot studies include tumour lysate-pulsed autologous dendritic cells, tumour necrosis factor α (TNF α), and Keyhole Limpet Haemocyanin [159]; tumour-specific cytotoxic T lymphocytes (CTLs) or LAK cells [160]; subcutaneous granulocyte macrophage-

colony stimulating factor (GM-CSF) with IFNγ [161]; and subcutaneous IL-2 with Melatonin [162]. However, these approaches remain investigational.

In conclusion, there is no convincing evidence that immunotherapy (alone or in combination with chemotherapy) should be used in HCC, other than in clinical trials.

### 3.4. Other agents

Other agents and combinations trialled in advanced HCC, include β-all-*trans*-retinoic acid [163], thalidomide [164–167], celecoxib with thalidomide [168], and rofecoxib with octreotide [169]. None have reported RRs over 10%. However, several authors suggest that thalidomide may stabilise disease and provide palliation in some patients. This approach should be tested against placebo in a well-conducted randomised trial incorporating validated quality of life measures before it is widely used.

## 4. Conclusions

In reviewing this topic, there is a paucity of large, well-designed clinical trials in advanced HCC which can guide therapeutic decisions. The two largest studies reviewed did not show benefits for tamoxifen [110,125], a finding which, although disappointing, will hopefully prevent the futile prescription of tamoxifen to these patients. Of the remaining trials, only six were randomised controlled trials with over 100 patients. Simple statistics suggest that to detect an improvement in median survival from 6 to 8.5 months, (a HR of approximately 0.7), a two-arm trial would need to follow approximately 250 patients for 2 years. Thus, most of these trials are underpowered to detect such small survival benefits. Trials of fewer than 100 patients will only detect a significant difference if the experimental treatment nearly doubles median survival, and it remains possible that active agents have been discarded after testing in trials which were not designed to detect such modest, but realistic, benefits.

Whilst survival benefits are important, if these cannot be demonstrated, other measures of patient benefit must be incorporated into clinical trials. Again, these trials should be randomised, using validated measures of patient benefit and prospectively defined outcome measures. The development of a tool assessing "clinical benefit response", similar to that used in pancreatic cancer [170], may be useful. Few trials in HCC have incorporated quality of life tools; however, it is important that such tools are thoughtfully applied by investigators with expertise in this area, to avoid generating meaningless results.

Another problem in interpreting these trials is the heterogeneity of the patient populations studied. Entry criteria differed in each trial, with patients with poor prognostic factors (large tumours, portal vein thrombosis or cirrhosis) commonly being excluded. This makes it impossible to compare RRs and survival duration between trials, and more difficult to extrapolate the reported results to a general patient population. Furthermore, results from South-East Asian populations may not be generalisable to European and North American populations, due to differences in aetiology (HBV vs. HCV) and genetic polymorphisms in drug metabolism.

From this review, it is clear that there is no systemic therapy that can be considered standard for patients with advanced HCC. Every effort should be made to enrol these patients onto well-designed clinical trials. Promising results from single-centre phase II trials must be tested in a multicentre setting, and if the results are still interesting, in adequately powered multicentre phase III trials, preferably against a placebo control arm. There are large numbers of patients worldwide who could participate in such trials. It is particularly important that co-operative groups coordinate such trials in regions where HCC is highly prevalent. Without rigorous standards in the design and conduct of clinical trials in HCC, patients will continue to receive ineffective and potentially toxic therapies on the basis of unconfirmed results from early phase studies.

Without effective systemic therapies, prevention and early detection of HCC is paramount. The increasing availability of HBV vaccination for infants and children in Africa and South East Asia could prevent up to a million cases of HCC annually [171,172]. Without an effective HCV vaccine, prevention of blood-borne, vertical, and sexual transmission is still necessary [173]. The efficacy of screening high-risk patients with α-FP levels and ultrasound remains unclear [174], although it may no longer be possible to test this in a randomised trial. However, until systemic therapy for advanced HCC improves, these approaches will do more to prevent premature death from this disease than chemotherapy, hormonal therapy or immunotherapy.

## Acknowledgements

A.K.N. was supported by a Medical Oncology Group of Australia/Novartis fellowship.

## References

1. Ferlay J, Bray F, Pisani P, Parkin DM. In: *GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide*. Version 1.0 ed. IARC Cancer Base No. 5. Lyon: IARC Press; 2001.

2. Bosch F. Global epidemiology of hepatocellular carcinoma. In *Liver cancer*. New York, Churchill Livingstone, 1997, pp 13–28.
3. Yang HI, Lu SN, Liaw YF, *et al*. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *NEJM* 2002, **347**(3), 168–174.
4. Tsukuma H, Hiyama T, Tanaka S, *et al*. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *NEJM* 1993, **328**(25), 1797–1801.
5. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *NEJM* 1999, **340**(10), 745–750.
6. Colombo M, Kuo G, Choo QL, *et al*. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* 1989, **2**(8670), 1006–1008.
7. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999, **229**(6), 790–799 [discussion 799–800].
8. Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome. *Gut* 2002, **51**(4), 459–462.
9. Groupe d'Etude et de Traitment du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. NEJM 1995;**332**(19):1256–61.
10. Balsells J, Charco R, Lazaro JL, *et al*. Resection of hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 1996, **83**(6), 758–761.
11. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003, **37**(2), 429–442.
12. Chan ES-Y, Chow PK-H, Tai B-C, Machin D, Soo K-C. Neoadjuvant and adjuvant therapy for operable hepatocellular carcinoma (Cochrane Review). In *The Cochrane Library*. Chichester, UK, John Wiley & Sons, Ltd., 2003.
13. Mathurin P, Raynard B, Dharancy S, *et al*. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003, **17**(10), 1247–1261.
14. Huang CC, Wu MC, Xu GW, *et al*. Overexpression of the MDR1 gene and P-glycoprotein in human hepatocellular carcinoma. *J Natl Cancer Inst* 1992, **84**(4), 262–264.
15. Chou YY, Cheng AL, Hsu HC. Expression of P-glycoprotein and p53 in advanced hepatocellular carcinoma treated by single agent chemotherapy: clinical correlation. *J Gastroeterol Hepatol* 1997, **12**(8), 569–575.
16. Olweny CL, Toya T, Katongole-Mbidde E, Mugerwa J, Kyalwazi SK, Cohen H. Treatment of hepatocellular carcinoma with adriamycin. Preliminary communication. *Cancer* 1975, **36**(4), 1250–1257.
17. Vogel CL, Bayley AC, Brooker RJ, Anthony PP, Ziegler JL. A phase II study of adriamycin (NSC 123127) in patients with hepatocellular carcinoma from Zambia and the United States. *Cancer* 1977, **39**(5), 1923–1929.
18. Johnson PJ, Williams R, Thomas H, Sherlock S, Murray-Lyon IM. Induction of remission in hepatocellular carcinoma with doxorubicin. *Lancet* 1978, **1**(8072), 1006–1009.
19. Oon CJ, Chua EJ, Foong WC, *et al*. Adriamycin in the treatment of resectible and irresectible primary hepatocellular carcinoma. *Ann Acad Med Singapore* 1980, **9**(2), 256–259.
20. Falkson G, Moertel CG, Lavin P, Pretorius FJ, Carbone PP. Chemotherapy studies in primary liver cancer: a prospective randomized clinical trial. *Cancer* 1978, **42**(5), 2149–2156.
21. Choi TK, Lee NW, Wong J. Chemotherapy for advanced hepatocellular carcinoma. Adriamycin versus quadruple chemotherapy. *Cancer* 1984, **53**(3), 401–405.
22. Melia WM, Johnson PJ, Williams R. Induction of remission in hepatocellular carcinoma. A comparison of VP 16 with adriamycin. *Cancer* 1983, **51**(2), 206–210.
23. Chlebowski RT, Brzechwa-Adjukiewicz A, Cowden A, Block JB, Tong M, Chan KK. Doxorubicin (75 mg/m$^2$) for hepatocellular carcinoma: clinical and pharmacokinetic results. *Cancer Treat Rep* 1984, **68**(3), 487–491.
24. Sciarrino E, Simonetti RG, Le Moli S, Pagliaro L. Adriamycin treatment for hepatocellular carcinoma Experience with 109 patients. *Cancer* 1985, **56**(12), 2751–2755.
25. Johnson PJ, Dobbs N, Kalayci C, *et al*. Clinical efficacy and toxicity of standard dose adriamycin in hyperbilirubinaemic patients with hepatocellular carcinoma: relation to liver tests and pharmacokinetic parameters. *Br J Cancer* 1992, **65**(5), 751–755.
26. Colombo M, Tommasini MA, Del Ninno E, Rumi MG, De Fazio C, Dioguardi ML. Hepatocellular carcinoma in Italy: report of a clinical trial with intravenous doxorubicin. *Liver* 1985, **5**(6), 336–341.
27. Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer* 1988, **62**(3), 479–483.
28. Mathurin P, Rixe O, Carbonell N, *et al*. Review article: overview of medical treatments in unresectable hepatocellular carcinoma – an impossible meta-analysis. *Aliment Pharmacol Ther* 1998, **12**(2), 111–126.
29. Cheng AL, Yeh KH, Fine RL, *et al*. Biochemical modulation of doxorubicin by high-dose tamoxifen in the treatment of advanced hepatocellular carcinoma. *Hepatogastroenterology* 1998, **45**(24), 1955–1960.
30. Schachschal G, Lochs H, Plauth M. Controlled clinical trial of doxorubicin and tamoxifen versus tamoxifen monotherapy in hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2000, **12**(3), 281–284.
31. Hong RL, Tseng YL. A phase II and pharmacokinetic study of pegylated liposomal doxorubicin in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2003, **51**(5), 433–438.
32. Daniele B, De Vivo R, Perrone F, *et al*. Phase I clinical trial of liposomal daunorubicin in hepatocellular carcinoma complicating liver cirrhosis. *Anticancer Res* 2000, **20**(2B), 1249–1251.
33. Halm U, Etzrodt G, Schiefke I, *et al*. A phase II study of pegylated liposomal doxorubicin for treatment of advanced hepatocellular carcinoma. *Ann Oncol* 2000, **11**(1), 113–114.
34. Schmidinger M, Wenzel C, Locker GJ, *et al*. Pilot study with pegylated liposomal doxorubicin for advanced or unresectable hepatocellular carcinoma. *Br J Cancer* 2001, **85**(12), 1850–1852.
35. Yeo W, Chan KK, Mukwaya G, *et al*. Phase II studies with DaunoXome in patients with nonresectable hepatocellular carcinoma: clinical and pharmacokinetic outcomes. *Cancer Chemother Pharmacol* 1999, **44**(2), 124–130.
36. Ruff P, Moodley SD, Rapoport BL, Vorobiof DA, Maart K, Chasen MR. Long term follow-up of pegylated liposomal doxorubicin (Caelyx): a well tolerated and effective agent in advanced hepatocellular carcinoma (HCC. *Proc Annu Meet Am Soc Clin Oncol* 2001, **20** [Abstract 667].
37. Morstyn G, Ihde DC, Eddy JL, Bunn PA, Cohen MH, Minna JD. Combination chemotherapy of hepatocellular carcinoma with doxorubicin and streptozotocin. *Am J Clin Oncol* 1983, **6**(5), 547–551.
38. Chlebowski RT, Chan KK, Tong MJ, Weiner JM, Ryden VM, Bateman JR. Adriamycin and methyl-CCNU combination therapy in hepatocellular carcinoma: clinical and pharmacokinetic aspects. *Cancer* 1981, **48**(5), 1088–1095.
39. Falkson CI, Falkson G. A phase II evaluation of clofazimine plus doxorubicin in advanced, unresectable primary hepatocellular carcinoma. *Oncology* 1999, **57**(3), 232–235.
40. Yang TS, Wang CH, Hsieh RK, Chen JS, Fung MC. Gemcitabine and doxorubicin for the treatment of patients with advanced hepatocellular carcinoma: a phase I–II trial. *Ann Oncol* 2002, **13**(11), 1771–1778.

41. Tan YO, Lim F. 4′-Epidoxorubicin (Epirubicin) as a single agent in advanced primary hepatocellular carcinoma – a preliminary experience. *Ann Acad Med Singapore* 1986, **15**(2), 169–171.
42. Hochster HS, Green MD, Speyer J, Fazzini E, Blum R, Muggia FM. 4′-Epidoxorubicin (epirubicin): activity in hepatocellular carcinoma. *J Clin Oncol* 1985, **3**(11), 1535–1540.
43. Pohl J, Zuna I, Stremmel W, Rudi J. Systemic chemotherapy with epirubicin for treatment of advanced or multifocal hepatocellular carcinoma. *Chemotherapy* 2001, **47**(5), 359–365.
44. Raderer M, Pidlich J, Muller C, *et al*. A phase I/II trial of epirubicin and high dose tamoxifen as a potential modulator of multidrug resistance in advanced hepatocellular carcinoma. *Eur J Cancer* 1996, **32A**(13), 2366–2368.
45. Bobbio-Pallavicini E, Porta C, Moroni M, *et al*. Epirubicin and etoposide combination chemotherapy to treat hepatocellular carcinoma patients: a phase II study. *Eur J Cancer* 1997, **33**(11), 1784–1788.
46. Huang YH, Wu JC, Lui WY, *et al*. Prospective case-controlled trial of adjuvant chemotherapy after resection of hepatocellular carcinoma. *World J Surg* 2000, **24**(5), 551–555.
47. Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. *Arch Surg* 1998, **133**(2), 183–188.
48. Dunk AA, Scott SC, Johnson PJ, Melia W, Lok AS, Murray-Lyon I, *et al*. Mitozantrone as single agent therapy in hepatocellular carcinoma. A phase II study. *J Hepatol* 1985, **1**(4), 395–404.
49. Colleoni M, Nole F, Di Bartolomeo M, de Braud F, Bajetta E. Mitoxantrone in patients affected by hepatocellular carcinoma with unfavorable prognostic factors. *Oncology* 1992, **49**(2), 139–142.
50. Lai KH, Tsai YT, Lee SD, *et al*. Phase II study of mitoxantrone in unresectable primary hepatocellular carcinoma following hepatitis B infection. *Cancer Chemother Pharmacol* 1989, **23**(1), 54–56.
51. Falkson G, Lipsitz S, Borden E, Simson I, Haller D. Hepatocellular carcinoma: an ECOG randomized phase II study of beta-interferon and menagoril. *Am J Clin Oncol: Cancer Clin Trials* 1995, **18**(4), 287–292.
52. Tumolo S, Toffoli G, Bearz A, *et al*. Oral idarubicin for the treatment of hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2002 [Abstract 635].
53. Tetef M, Doroshow J, Akman S, *et al*. 5-Fluorouracil and high-dose calcium leucovorin for hepatocellular carcinoma: a phase II trial. *Cancer Invest* 1995, **13**(5), 460–463.
54. Link JS, Bateman JR, Paroly WS, Durkin WJ, Peters RL. 5-Flourouracil in hepatocellular carcinoma: report of twenty-one cases. *Cancer* 1977, **39**(5), 1936–1939.
55. Porta C, Moroni M, Nastasi G, Arcangeli G. 5-Fluorouracil and d,l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. *Oncology* 1995, **52**(6), 487–491.
56. Gebbia V, Maiello E, Serravezza G, *et al*. 5-Fluorouracil plus high dose levofolinic acid and oral hydroxyurea for the treatment of primary hepatocellular carcinomas: results of a phase II multicenter study of the Southern Italy Oncology Group (G.O.I.M). *Anticancer Res* 1999, **19**(2B), 1407–1410.
57. Baker SD, Diasio RB, O'Reilly S, *et al*. Phase I and pharmacologic study of oral fluorouracil on a chronic daily schedule in combination with the dihydropyrimidine dehydrogenase inactivator eniluracil. *J Clin Oncol* 2000, **18**(4), 915–926.
58. Benson III AB, Mitchell E, Abramson N, *et al*. Oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. *Ann Oncol* 2002, **13**(4), 576–581.
59. Llovet JM, Ruff P, Tassopoulos N, *et al*. A phase II trial of oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. *Eur J Cancer* 2001, **37**(11), 1352–1358.
60. Mani S, Schiano T, Garcia JC, *et al*. Phase II trial of uracil/tegafur (UFT) plus leucovorin in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 1998, **16**(3), 279–283.
61. Ishikawa T, Ichida T, Sugitani S, *et al*. Improved survival with oral administration of enteric-coated tegafur/uracil for advanced stage IV-A hepatocellular carcinoma. *J Gastroenterol Hepatol* 2001, **16**(4), 452–459.
62. Yamamoto M, Arii S, Sugahara K, Tobe T. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. *Br J Surg* 1996, **83**(3), 336–340.
63. Lozano RD, Patt YZ, Hassan MM, *et al*. Oral capecitabine (Xeloda) for the treatment of hepatobiliary cancers (hepatocellular carcinoma, cholangiocarcinoma, and gallbladder cancer. *Proc Annu Meet Am Soc Clin Oncol* 2000 [Abstract 1025].
64. Chun HG, Waheed F, Iqbal DC, Wolf Z, Li S, Kempin SJ. A combination of capecitabine and thalidomide in patients with unresectable, recurrent or metastatic hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1407].
65. Tanioka H, Tsuji A, Morita S, *et al*. Combination chemotherapy with continuous 5-fluorouracil and low-dose cisplatin infusion for advanced hepatocellular carcinoma. *Anticancer Res* 2003, **23**(2C), 1891–1897.
66. Ellis PA, Norman A, Hill A, *et al*. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. *Eur J Cancer* 1995, **31A**(10), 1594–1598.
67. Boucher E, Corbinais S, Brissot P, Boudjema K, Raoul JL. Treatment of hepatocellular carcinoma (HCC) with systemic chemotherapy combining epirubicin, cisplatinum and infusional 5-fluorouracil (ECF regimen). *Cancer Chemother Pharmacol* 2002, **50**(4), 305–308.
68. Leung TW, Tang AM, Zee B, *et al*. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and5-fluorouracil chemotherapy. *Cancer* 2002, **94**(2), 421–427.
69. Kajanti MJ, Pyrhonen SO. Phase II intravenous study of epirubicin with 5-fluorouracil in patients with advanced hepatocellular carcinoma. *Eur J Cancer* 1991, **27**(12), 1620–1622.
70. Al-Idrissi HY, Ibrahim EM, Abdel Satir A, Satti MB, Al-Kasem S, Al-Qurain A. Primary hepatocellular carcinoma in the eastern province of Saudi Arabia: treatment with combination chemotherapy using 5-fluorouracil, Adriamycin and mitomycin-C. *Hepatogastroenterology* 1985, **32**(1), 8–10.
71. Lin HL, Liu TY, Chau GY, Lui WY, Chi CW. Comparison of 2-methoxyestradiol-induced, docetaxel-induced, and paclitaxel-induced apoptosis in hepatoma cells and its correlation with reactive oxygen species. *Cancer* 2000, **89**(5), 983–994.
72. Chao Y, Chan WK, Birkhofer MJ, *et al*. Phase II and pharmacokinetic study of paclitaxel therapy for unresectable hepatocellular carcinoma patients. *Br J Cancer* 1998, **78**(1), 34–39.
73. Strumberg D, Erhard J, Harstrick A, *et al*. Phase I study of a weekly 1 h infusion of paclitaxel in patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 1998, **34**(8), 1290–1292.
74. Matsuoka H, Yano K, Seo Y, *et al*. Cytotoxicity of CPT-11 for gastrointestinal cancer cells cultured on fixed-contact-sensitive plates. *Anticancer Drugs* 1995, **6**(3), 413–418.
75. Chu XY, Kato Y, Ueda K, *et al*. Biliary excretion mechanism of CPT-11 and its metabolites in humans: involvement of primary active transporters. *Cancer Res* 1998, **58**(22), 5137–5143.
76. O'Reilly EM, Stuart KE, Sanz-Altamira PM, *et al*. A phase II study of irinotecan in patients with advanced hepatocellular carcinoma. *Cancer* 2001, **91**(1), 101–105.
77. Boige V, Taieb J, Hebbar M, *et al*. A multicenter phase II study of irinotecan (CPT-11) in patients with advanced hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2002 [Abstract 607].

78. Lee GY, Kim BS, Seo YT, *et al*. Phase II study to topotecan and cisplatin in advanced hepatocellular carcinoma. *Korean J Intern Med* 2003, **18**(2), 104–108.
79. Alexandre J, Tigaud JM, Gross-Goupil M, *et al*. Combination of topotecan and oxaliplatin in inoperable hepatocellular cancer patients. *Am J Clin Oncol* 2002, **25**(2), 198–203.
80. Cavalli F, Rozencweig M, Renard J, Goldhirsch A, Hansen HH. Phase II study of oral VP-16-213 in hepatocellular carcinoma. *Eur J Cancer Clin Oncol* 1981, **17**(10), 1079–1082.
81. Wierzbicki R, Ezzat A, Abdel-Warith A, *et al*. Phase II trial of chronic daily VP-16 administration in unresectable hepatocellular carcinoma (HCC. *Ann Oncol* 1994, **5**(5), 466–467.
82. Shiu W, Mok SD, Leung N, *et al*. Phase 2 study of high dose etoposide (VP16-213) in hepatocellular carcinoma. *Jpn J Clin Oncol* 1987, **17**(2), 113–115.
83. Yoshino M, Okazaki N, Yoshida T, *et al*. A phase II study of etoposide in patients with hepatocellular carcinoma by the Tokyo Liver Cancer Chemotherapy Study Group. *Jpn J Clin Oncol* 1989, **19**(2), 120–122.
84. Cheng AL, Chen YC, Yeh KH, Chuang SE, Chen BR, Chen DS. Chronic oral etoposide and tamoxifen in the treatment of far-advanced hepatocellular carcinoma. *Cancer* 1996, **77**(5), 872–877.
85. Graziadei I, Kelly T, Schirmer M, Geisen FH, Vogel W, Konwalinka G. Antitumor effect of the nucleoside analogs 2-chlorodeoxyadenosine and 2′,2′-difluorodeoxycytidine on human hepatoma HepG2 cells. *J Hepatol* 1998, **28**(3), 504–509.
86. Yang TS, Lin YC, Chen JS, Wang HM, Wang CH. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2000, **89**(4), 750–756.
87. Ulrich-Pur H, Kornek GV, Fiebiger W, Schull B, Raderer M, Scheithauer W. Treatment of advanced hepatocellular carcinoma with biweekly high-dose gemcitabine. *Oncology* 2001, **60**(4), 313–315.
88. Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. *Hepatogastroenterology* 2001, **48**(39), 783–789.
89. Fuchs CS, Clark JW, Ryan DP, *et al*. A phase II trial of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2002, **94**(12), 3186–3191.
90. Yang TS, Chang WC, Lin YC, Chen JS, Liau CT, Yeh KY. A phase II study of gemcitabine and cisplatin for patients with advanced hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1351].
91. Fuloria J, Parikh P, Prabhakaran P, *et al*. A multicentre, phase II trial of gemcitabine and cisplatin in unresectable hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2000 [Abstract 1143].
92. Lozano RD, Ellis LM, Hassan MM, Nooka A, Brown TD, Patt YZ. Gemcitabine, amifostine and cisplatin, (GAP) for treatment of hepato-biliary cancer: a retrospective analysis in 50 patients. *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1498].
93. Okada S, Okazaki N, Nose H, Shimada Y, Yoshimori M, Aoki K. A phase 2 study of cisplatin in patients with hepatocellular carcinoma. *Oncology* 1993, **50**(1), 22–26.
94. Stuart K, Tessitore J, Rudy J, Clendennin N, Johnston A. A Phase II trial of nolatrexed dihydrochloride in patients with advanced hepatocellular carcinoma. *Cancer* 1999, **86**(3), 410–414.
95. Mok TS, Leung TW, Lee SD, *et al*. A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999, **44**(4), 307–311.
96. Hamburg S, Miller W, Garcia-Vargas J, Joseph JL, Gundaker LF, Horan J. Survival benefit of nolatrexed in advanced hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1157].
97. Stuart K, Eder JP, Proper J, *et al*. Phase II trial of irofulven in patients with unresectable hepatocellular carcinoma (HCC). *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1107].
98. Izzo F, Marra P, Beneduce G, *et al*. Phase I/II testing of pegylated arginine deaminase in subjects with hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2003 [Abstract 1474].
99. Singh DA, Kindler HL, Eng C, *et al*. Phase II trial of the epothilone B analog BMS-247550 in patients with hepatobiliary cancer. *Proc Annu Meet Am Soc Clin Oncol* 2003, **22**, 281 [Abstract 1127].
100. Reubi JC, Laissue JA. Multiple actions of somatostatin in neoplastic disease. *Trends Pharmacol Sci* 1995, **16**(3), 110–115.
101. Reubi JC, Zimmermann A, Jonas S, *et al*. Regulatory peptide receptors in human hepatocellular carcinomas. *Gut* 1999, **45**(5), 766–774.
102. Rabinowitz I, Telepak R, Lee FC. Octreotide scans are positive in a subset of patients with hepatocellular carcinoma. *Clin Nuc Med* 2002, **27**(7), 499–502.
103. Kouroumalis E, Skordilis P, Thermos K, Vasilaki A, Moschandrea J, Manousos ON. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998, **42**(3), 442–447.
104. Dimitroulopoulos D, Xinopoulos D, Tsamakidis K, *et al*. The role of sandostatin LAR in treating patients with advanced hepatocellular cancer. *Hepatogastroenterology* 2002, **49**(47), 1245–1250.
105. Samonakis DN, Moschandreas J, Arnaoutis T, *et al*. Treatment of hepatocellular carcinoma with long acting somatostatin analogues. *Oncol Rep* 2002, **9**(4), 903–907.
106. Yuen MF, Poon RT, Lai CL, *et al*. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002, **36**(3), 687–691.
107. Rabe C, Pilz T, Allgaier HP, *et al*. Clinical outcome of a cohort of 63 patients with hepatocellular carcinoma treated with octreotide. *Z Gastroenterol* 2002, **40**(6), 395–400.
108. Raderer M, Hejna MH, Muller C, *et al*. Treatment of hepatocellular cancer with the long acting somatostatin analog lanreotide in vitro and in vivo. *Int J Oncol* 2000, **16**(6), 1197–1201.
109. Villa E, Colantoni A, Grottola A, *et al*. Variant estrogen receptors and their role in liver disease. *Mol Cell Endocrinol* 2002, **193**(1–2), 65–69.
110. Chow PK, Tai BC, Tan CK, *et al*. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: a multicenter randomized controlled trial. *Hepatology* 2002, **36**(5), 1221–1226.
111. Chao Y, Chan WK, Wang SS, *et al*. Phase II study of megestrol acetate in the treatment of hepatocellular carcinoma. *J Gastroeterol Hepatol* 1997, **12**(4), 277–281.
112. Colombo M, de Franchis R, Del Ninno E, *et al*. Hepatocellular carcinoma in Italian patients with cirrhosis. *NEJM* 1991, **325**(10), 675–680.
113. Jonas S, Bechstein WO, Heinze T, *et al*. Female sex hormone receptor status in advanced hepatocellular carcinoma and outcome after surgical resection. *Surgery* 1997, **121**(4), 456–461.
114. Nagasue N, Kohno H, Chang Y, Hayashi T, Nakamura T. Specificity of androgen receptors of hepatocellular carcinoma and liver in humans. *Hepatogastroenterology* 1990, **37**(5), 474–479.
115. Martinez Cerezo FJ, Tomas A, Donoso L, *et al*. Controlled trial of tamoxifen in patients with advanced hepatocellular carcinoma. *J Hepatol* 1994, **20**(6), 702–706.
116. Melia WM, Johnson PJ, Williams R. Controlled clinical trial of doxorubicin and tamoxifen versus doxorubicin alone in hepatocellular carcinoma. *Cancer Treat Rep* 1987, **71**(12), 1213–1216.
117. Farinati F, De Maria N, Fornasiero A, *et al*. Prospective controlled trial with antiestrogen drug tamoxifen in patients with unresectable hepatocellular carcinoma. *Dig Dis Sci* 1992, **37**(5), 659–662.

118. Farinati F, Salvagnini M, de Maria N, *et al*. Unresectable hepatocellular carcinoma: a prospective controlled trial with tamoxifen. *J Hepatol* 1990, **11**(3), 297–301.
119. Elba S, Giannuzzi V, Misciagna G, Manghisi OG. Randomized controlled trial of tamoxifen versus placebo in inoperable hepatocellular carcinoma. *Ital J Gastroenterol* 1994, **26**(2), 66–68.
120. Coll S, Sola R, Vila M, *et al*. Treatment with tamoxifen in patients with advanced hepatocellular carcinoma. Results of a randomized placebo controlled trial. *Hepatology* 1995, **4**(2), 404A.
121. Castells A, Bruix J, Bru C, *et al*. Treatment of hepatocellular carcinoma with tamoxifen: a double-blind placebo-controlled trial in 120 patients. *Gastroenterology* 1995, **109**(3), 917–922.
122. Liu CL, Fan ST, Ng IO, Lo CM, Poon RT, Wong J. Treatment of advanced hepatocellular carcinoma with tamoxifen and the correlation with expression of hormone receptors: a prospective randomized study. *Am J Gastroenterol* 2000, **95**(1), 218–222.
123. Barbare J-C, Milan C, Bouché O, et al. Treatment of advanced hepatocellular carcinoma (HCC) with tamoxifen: a phase III trial in 420 patients. In: Proc ASCO 21;2002 2002 [Abstract 551].
124. Riestra S, Rodriguez M, Delgado M, *et al*. Tamoxifen does not improve survival of patients with advanced hepatocellular carcinoma. *J Clin Gastroenterol* 1998, **26**(3), 200–203.
125. Perrone F, Gallo C, Daniele B, *et al*. Tamoxifen in the treatment of hepatocellular carcinoma: 5-year results of the CLIP-1 multicentre randomised controlled trial. *Curr Pharm Des* 2002, **8**(11), 1013–1019.
126. Colleoni M, Nelli P, Vicario G, Mastropasqua G, Manente P. Megestrol acetate in unresectable hepatocellular carcinoma. *Tumori* 1995, **81**(5), 351–353.
127. Villa E, Ferretti I, Grottola A, *et al*. Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. *Br J Cancer* 2001, **84**(7), 881–885.
128. Mantovani G, Maccio A, Lai P, Massa E, Ghiani M, Santona MC. Cytokine activity in cancer-related anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate. *Semin Oncol* 1998, **25**(2 Suppl 6), 45–52.
129. Negro F, Papotti M, Pacchioni D, Galimi F, Bonino F, Bussolati G. Detection of human androgen receptor mRNA in hepatocellular carcinoma by in situ hybridisation. *Liver* 1994, **14**(4), 213–219.
130. Guy JT, Auslander MO. Androgenic steroids and hepatocellular carcinoma. *Lancet* 1973, **1**(7795), 148.
131. Nagasue N, Yu L, Yamaguchi M, Kohno H, Tachibana M, Kubota H. Inhibition of growth and induction of TGF-beta 1 in human hepatocellular carcinoma with androgen receptor by cyproterone acetate in male nude mice. *J Hepatol* 1996, **25**(4), 554–562.
132. Grimaldi C, Bleiberg H, Gay F, *et al*. Evaluation of antiandrogen therapy in unresectable hepatocellular carcinoma: results of a European Organization for Research and Treatment of Cancer multicentric double-blind trial. *J Clin Oncol* 1998, **16**(2), 411–417.
133. Manesis EK, Giannoulis G, Zoumboulis P, Vafiadou I, Hadziyannis SJ. Treatment of hepatocellular carcinoma with combined suppression and inhibition of sex hormones: a randomized, controlled trial. *Hepatology* 1995, **21**(6), 1535–1542.
134. Chao Y, Chan WK, Huang YS, *et al*. Phase II study of flutamide in the treatment of hepatocellular carcinoma. *Cancer* 1996, **77**(4), 635–639.
135. Forbes A, Wilkinson ML, Iqbal MJ, Johnson PJ, Williams R. Response to cyproterone acetate treatment in primary hepatocellular carcinoma is related to fall in free 5 alpha-dihydrotestosterone. *Eur J Cancer Clin Oncol* 1987, **23**(11), 1659–1664.
136. Grosh W, Mueller S, Alexander BF, Caldwell S, Cohen R. Anastrozole (A) treament of patients IPTS) with advanced unresectable hepatocellular carcinoma (HCC). *Proc Annu Meet Am Soc Clin Oncol* [Abstract 1096].
137. Radaeva S, Jaruga B, Hong F, *et al*. Interferon-alpha activates multiple STAT signals and down-regulates c-Met in primary human hepatocytes. *Gastroenterology* 2002, **122**(4), 1020–1034.
138. Sachs E, Di Bisceglie AM, Dusheiko GM, *et al*. Treatment of hepatocellular carcinoma with recombinant leucocyte interferon: a pilot study. *Br J Cancer* 1985, **52**(1), 105–109.
139. The Gastrointestinal Tumor Study Group. A prospective trial of recombinant human interferon alpha2B in previously untreated patients with hepatocellular carcinoma. *Cancer* 1990;**66**(1):135–9.
140. Yoshida T, Okazaki N, Yoshino M, Okhura H, Shimada Y. Phase II trial of high dose recombinant gamma-interferon in advanced hepatocellular carcinoma. *Eur J Cancer* 1990, **26**(4), 545–546.
141. Lai CL, Wu PC, Lok AS, *et al*. Recombinant alpha 2 interferon is superior to doxorubicin for inoperable hepatocellular carcinoma: a prospective randomised trial. *Br J Cancer* 1989, **60**(6), 928–933.
142. Lai CL, Lau JY, Wu PC, *et al*. Recombinant interferon-alpha in inoperable hepatocellular carcinoma: a randomized controlled trial. *Hepatology* 1993, **17**(3), 389–394.
143. Llovet JM, Sala M, Castells L, *et al*. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology* 2000, **31**(1), 54–58.
144. Kubo S, Nishiguchi S, Hirohashi K, *et al*. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Int Med* 2001, **134**(10), 963–967.
145. Ikeda K, Arase Y, Saitoh S, *et al*. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000, **32**(2), 228–232.
146. Feun LG, Savaraj N, Hung S, *et al*. A phase II trial of recombinant leukocyte interferon plus doxorubicin in patients with hepatocellular carcinoma. *Am J Clin Oncol* 1994, **17**(5), 393–395.
147. Kardinal CG, Moertel CG, Wieand HS, *et al*. Combined doxorubicin and alpha-interferon therapy of advanced hepatocellular carcinoma. *Cancer* 1993, **71**(7), 2187–2190.
148. Bokemeyer C, Kynast B, Harstrick A, *et al*. No synergistic activity of epirubicin and interferon-alpha 2b in the treatment of hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1995, **35**(4), 334–338.
149. Lotz JP, Grange JD, Hannoun L, *et al*. Treatment of unresectable hepatocellular carcinoma with a combination of human recombinant alpha-2b interferon and doxorubicin: results of a pilot study. *Eur J Cancer* 1994, **30A**(9), 1319–1325.
150. Kountouras J, Boura P, Karolides A, Zaharioudaki E, Tsapas G. Recombinant a2 interferon (a-IFN) with chemo-hormonal therapy in patients with hepatocellular carcinoma (HCC. *Hepatogastroenterology* 1995, **42**(1), 31–36.
151. Brook MG, Dunk AA, McDonald JA, Lever AM, Goh C, Thomas HC. Human lymphoblastoid interferon does not increase survival when added to mitozantrone in the treatment of hepatocellular carcinomas. *Aliment Pharmacol Ther* 1987, **1**(4), 315–320.
152. Colleoni M, Buzzoni R, Bajetta E, *et al*. A phase II study of mitoxantrone combined with beta-interferon in unresectable hepatocellular carcinoma. *Cancer* 1993, **72**(11), 3196–3201.
153. Komorizono Y, Kohara K, Oketani M, *et al*. Systemic combined chemotherapy with low dose of 5-fluorouracil, cisplatin, and interferon-alpha for advanced hepatocellular carcinoma: a pilot study. *Dig Dis Sci* 2003, **48**(5), 877–881.
154. Feun LG, O'Brien C, Molina E, *et al*. Recombinant leukocyte interferon, doxorubicin, and 5-FUDR in patients with hepatocellular carcinoma-A phase II trial. *J Cancer Res Clin Oncol* 2003, **129**(1), 17–20.

155. Stuart K, Tessitore J, Huberman M. 5-Fluorouracil and alpha-interferon in hepatocellular carcinoma. *Am J Clin Oncol* 1996, **19**(2), 136–139.
156. Ji SK, Park NH, Choi HM, *et al*. Combined cis-platinum and alpha interferon therapy of advanced hepatocellular carcinoma. *Korean J Intern Med* 1996, **11**(1), 58–68.
157. Kaneko S, Urabe T, Kobayashi K. Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. *Oncology* 2002, **62**(Suppl 1), 69–73.
158. Patt YZ, Hassan MM, Lozano RD, *et al*. Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon Alfa-2b for treatment of hepatocellular carcinoma. *J Clin Oncol* 2003, **21**(3), 421–427.
159. Iwashita Y, Tahara K, Goto S, *et al*. A phase I study of autologous dendritic cell-based immunotherapy for patients with unresectable primary liver cancer. *Cancer Immunol Immunother* 2003, **52**(3), 155–161.
160. Haruta I, Yamauchi K, Aruga A, *et al*. Analytical study of the clinical response to two distinct adoptive immunotherapies for advanced hepatocellular carcinoma: comparison between LAK cell and CTL therapy. *J Immunother Emphasis Tumor Immunol* 1996, **19**(3), 218–223.
161. Reinisch W, Holub M, Katz A, *et al*. Prospective pilot study of recombinant granulocyte-macrophage colony-stimulating factor and interferon-gamma in patients with inoperable hepatocellular carcinoma. *J Immunother* 2002, **25**(6), 489–499.
162. Aldeghi R, Lissoni P, Barni S, *et al*. Low-dose interleukin-2 subcutaneous immunotherapy in association with the pineal hormone melatonin as a first-line therapy in locally advanced or metastatic hepatocellular carcinoma. *Eur J Cancer* 1994, **30A**(2), 167–170.
163. Meyskens Jr FL, Jacobson J, Nguyen B, Weiss GR, Gandara DR, MacDonald JS. Phase II trial of oral beta-all trans-retinoic acid in hepatocellular carcinoma (SWOG 9157). *Invest New Drugs* 1998, **16**(2), 171–173.
164. Feun LG, Marini A, Molina E, *et al*. Thalidomide as palliative care for patients with unresectable hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2003, **22** [Abstract 865].
165. Lin A, Brophy N, Fisher GA, et al. Phase II study of thalidomide in patients with unresectable hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* [Abstract 2202].
166. Kong HL, Boyer MJ, Lim R, Clarke S, Millward MJ, Wong JEL. Phase II trial of thalidomide in unresectable hepatocellular carcinoma: a Cancer Therapeutics Research Group study. *Proc Annu Meet Am Soc Clin Oncol* [Abstract 2282].
167. Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of Thalidomid for treatment of non-resectable hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* [Abstract 1035].
168. Chen C-S, Hillebrand D, Hill K, Lilly M. A pilot study of celecoxib combined with escalating doses of thalidomide for treatment of unresectable hepatocellular carcinoma. *Proc Annu Meet Am Soc Clin Oncol* 2002 [Abstract 2350].
169. Treiber G, Heinrich U, Fostitch P, Roecken C, Malfertheiner P. Palliative treatment of hepatocellular carcinoma (HCC) using octreotide, rofecoxib, or both. *Proc Annu Meet Am Soc Clin Oncol* 2003, **22**, 319 [Abstract 1281].
170. Burris H, Storniolo AM. Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil. *Eur J Cancer* 1997, **33**(Suppl 1), S18–S22.
171. Kane MA, Brooks A. New immunization initiatives and progress toward the global control of hepatitis B. *Curr Opin Inf Dis* 2002, **15**(5), 465–469.
172. Lin HH, Wang LY, Hu CT, *et al*. Decline of hepatitis B carrier rate in vaccinated and unvaccinated subjects: sixteen years after newborn vaccination program in Taiwan. *J Med Virol* 2003, **69**(4), 471–474.
173. Koff RS. Hepatitis vaccines: recent advances. *Int J Parasitol* 2003, **33**(5–6), 517–523.
174. Wun YT, Dickinson JA. Alpha-fetoprotein and/or liver ultrasonography for liver cancer screening in patients with chronic hepatitis B. *Cochrane Database Syst Rev* 2003, **3**, 3.