TABLE 111-7 TARGETED THERAPIES IN HEPATOCELLULAR CARCINOMA: TRIALS

Phase III	Target	Survival (mo)
Sorafenib vs placebo	Raf, VEGFR, PDGFR	10.7 vs 7.9
Sorafenib vs placebo (Asians)	Raf, VEGFR, PDGFR	6.5 vs 4.2

Abbreviations: PDGFR, platelet-derived growth factor receptor; Raf, rapidly accelerated fibrosarcoma; VEGFR vascular endothelial growth factor receptor.

erlotinib, the data from a phase III trial were disappointing. Several forms of *radiation therapy* have been used in the treatment of HCC, including external-beam radiation and conformal radiation therapy. Radiation hepatitis remains a dose-limiting problem. The pure beta emitter ^{90}Yttrium attached to either glass (TheraSphere) or resin (SIR-Spheres) microspheres injected into a major branch hepatic artery has been assessed in phase II trials of HCC and has encouraging tumor control and survival effects with minimal toxicities. Randomized phase III trials comparing it to TACE have yet to be completed. The main attractiveness of ^{90}Yttrium therapy is its safety in the presence of major branch portal vein thrombosis, where TACE is dangerous or contraindicated. Furthermore, external-beam radiation has been reported to be safe and useful in the control of major branch portal or hepatic vein invasion (thrombosis) by tumors. The studies have all been small. Vitamin K has been assessed in clinical trials at high dosage for its HCC-inhibitory actions. This idea is based on the characteristic biochemical defect in HCC of elevated plasma levels of immature prothrombin (DCP or PIVKA-2), due to a defect in the activity of prothrombin carboxylase, a vitamin K–dependent enzyme. Two vitamin K randomized controlled trials from Japan show decreased tumor occurrence, but a major phase III trial aimed at limiting postresection recurrence was not successful.

CURRENT DIRECTIONS A number of new kinase inhibitors are being evaluated for HCC **(Tables 111-9 and 111-10)**. These include the biologicals, such as Raf kinase and vascular endothelial growth factor (VEGF) inhibitors, and agents that target various steps of the cell growth pathway. Current hopes focus particularly on the Met pathway inhibitors such as tivantinib and several IGF receptor antagonists. ^{90}Yttrium looks promising and without chemotherapy toxicities. It is particularly attractive because, unlike TACE, it seems safe in the presence of portal vein thrombosis, a pathognomonic feature of HCC aggressiveness. The bottleneck of liver donors for OLTX is at last widening with increasing use of living donors, and criteria for OLTX for larger HCCs are slowly expanding. Patient participation in clinical trials assessing new therapies is encouraged (*www.clinicaltrials.gov*).

The main effort now is the evaluation of combinations of the compounds listed in Tables 111-7 to 111-9 that target different pathways, as well as the combination of any of these targeted therapies, but especially sorafenib, with TACE or ^{90}Yttrium radioembolization. Combining TACE with sorafenib appears to be safe in phase II studies with promising survival data, but randomized studies are still in progress. The same is true for intra-arterial ^{90}Yttrium plus sorafenib as therapy for HCC and as bridge to transplant therapy.

TABLE 111-8 PROMISING TARGETED THERAPIES THAT FAILED THEIR CLINICAL TRIAL GOALS

Sunitinib
Brivanib
Linifanib
Everolimus
Erlotinib
ThermaDox
Oncolytic virus JX-594
Bevacizumab
Bevacizumab plus erlotinib vs sorafenib
Sorafenib plus erlotinib vs sorafenib

TABLE 111-9 NEW TARGETED AGENTS AND THEIR TARGETS IN CURRENT CLINICAL TRIALS

Targets	Inhibitors
EGF receptor	Erlotinib
	Gefitinib
	Cetuximab
	Panitumumab
cMET	Tivantinib (ARQ197)
	EMD1204831
	Cabozantinib
VEGF receptor	Bevacizumab
	Regorafenib
	Brivanib
	Cediranib
	Sunitinib
FGF1 receptor	AEW54
	R1507 (MAb)
	Linsitinib (OSI-906)
	Brivanib
TRAIL-R1 (proapoptosis)	Mapatumumab
PDGF receptor	Sorafenib
	Dovitinib
	Linifanib
IGF-I receptor	IMC-A12
	B11B022
	Cixutumumab
Ubiquitin-proteasome	Bortezomib

Abbreviations: EGF, epidermal growth factor; FGF1, fibroblast growth factor 1; IGF-I, insulin-like growth factor I; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

SIGNIFICANCE AND EVALUATION OF RESPONSES TO NONSURGICAL THERAPIES

Tumor growth or spread is considered a poor prognostic sign and evidence of treatment failure. By contrast, patients receiving chemotherapy are judged to have a response if there is shrinkage of tumor size. Lack of response/size decrease has been thought of as treatment failure. Three considerations in HCC management have completely changed the views concerning nonshrinkage after therapy. First, the correlation between response to chemotherapy and survival is poor in various tumors; in some tumors, such as ovarian cancer and small-cell lung cancer, substantial tumor shrinkage on chemotherapy is followed by rapid

TABLE 111-10 SOME NOVEL MEDICAL TREATMENTS FOR HEPATOCELLULAR CARCINOMA

EGF receptor antagonists: erlotinib, gefitinib, lapatinib, cetuximab, brivanib
Multikinase antagonists: sorafenib, sunitinib
VEGF antagonist: bevacizumab
VEGFR antagonist: ABT-869 (linifanib)
mTOR antagonists: sirolimus, temsirolimus, everolimus
Proteasome inhibitors: bortezomib
Vitamin K
^{131}I–Ethiodol (lipiodol)
^{131}I–Ferritin
^{90}Yttrium microspheres (TheraSphere, SIR-Spheres)
^{166}Holmium, ^{188}Rhenium
Three-dimensional conformal radiation
Proton beam high-dose radiotherapy
Gamma knife, CyberKnife
New targets: inhibitors of cyclin dependent kinases (Cdk), TRAIL induction caspases, and stem cells

Abbreviations: EGF, epidermal growth factor; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.