Adenoid Cystic Carcinoma Research Foundation

A Guide to Systemic Therapy for Patients with Progressive Adenoid Cystic Carcinoma

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HOW TO USE THIS GUIDE

The purpose of this guide is to provide patients and their physicians context and information about treatment plans that may or may not include systemic therapy. The guide is fairly technical, so patients who are less familiar with this topic may wish to print out the document and review it with their physician. Physicians may prefer to skip past the background sections and focus on the past, current and pending clinical trials.

EXECUTIVE SUMMARY

- No chemotherapy or targeted drugs have been approved by regulatory authorities for ACC because none have been found to be effective across large groups of ACC patients.
- Accordingly, many patients with progressive disease undergo surgery or radiotherapy treatments to stop or slow the growing recurrences. However, there is little published evidence on the effectiveness of many of these approaches, and many patients eventually try systemic therapy in a clinical trial.
- Past ACC clinical trials have led to shrinking tumors in small subsets of patients and stable disease in large groups of patients. However, the normal course of ACC often involves long periods of stable disease, making it difficult to appraise the significance of stable disease in ACC clinical trials.
- Current Phase II clinical trials for ACC patients involve drugs developed for other cancers and have weak scientific rationales for why the drugs should be particularly effective in ACC.
- Studies into the basic biology of ACC are uncovering molecular targets of therapy that may be particularly relevant to ACC. Along with preclinical screening of targeted agents in new ACC mouse models, these developments are increasing the likelihood of success in forthcoming ACC clinical trials.
- The decision to enroll in a clinical trial is both very honorable and very personal. Patients should feel comfortable engaging in detailed discussions with their physicians to determine if and which clinical trials are appropriate.

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Natural History and Standard of Care

Physicians refer to the normal course of a disease as its "natural history" and the normal treatment patterns of a disease as its "standard of care". The natural history of ACC is peculiar and unpredictable. Typically, the growth of ACC tumors is slow within the first five years of diagnosis with approximately 80% of patients surviving that period. However, the cancer may have a relentless course with approximately half of all patients experiencing distant metastases, usually to the lungs, liver, bone or brain. Such metastases may occur many years or even decades after initial treatments leave no evident signs of disease in the patient. Overall survival rates fall to approximately 45% within 15 years of diagnosis.

The standard of care for treating ACC patients calls for surgery to remove the primary tumor, followed by radiation to minimize the likelihood of recurrence in the same site. ACC's high propensity for growing along nerves (perineural invasion) often results in the need to surgically remove parts of nerves and to increase the coverage area of radiation treatments. If a patient suffers a recurrence, the response often involves "watchful waiting" as the tumors may grow very slowly or stabilize for many months or years. Additional radiation or surgeries may be tried in cases of "progressive disease" – when there are new tumors, existing tumors that are clearly growing, or new symptoms such as pain. Radio-surgery, radio-frequency ablation, cryoablation, chemo-embolization and brachytherapy are some of the treatments used by ACC patients with significant or painful metastases; however, past studies are inadequate to establish the relative merits of these treatments. Patients rely upon their physicians (and often their own research) to determine which treatments are most appropriate given the size, number, location and growth rate of recurrences.

"Systemic therapy" refers to drugs that travel through the bloodstream to reach cancer cells throughout the body, and includes both chemotherapy and targeted agents. No systemic therapy has been approved for ACC because none has been effective across large groups of ACC patients. However, clearly-progressive ACC patients may have to resort to systemic therapy when dealing with tumors that are dispersed widely throughout the body, growing rapidly and/or located near vital organs that are not treatable with surgery or radiation. In such situations, clinical trials may represent a reasonable choice, although each patient (with the help of their physician) must come to their own assessment of the likelihood of success and the tolerability of side effects. Given the toxicity of chemotherapy, most patients prefer targeted agents.

Overview of Clinical Trials

A clinical trial is a medical research study in which people volunteer to test new methods of prevention, diagnosis, or treatment of a disease. Patients may benefit from access to new drugs before they become widely available; close monitoring from leading cancer researchers; an active role in managing their own care; and an opportunity to help others in contributing to cancer research. Of course, there are also the very real risks that the treatment is ineffective and/or the side effects are significant. And a clinical trial may require a lot of time for travel and treatments. The decision to enroll in a clinical trial depends on many factors that are individual to each patient.

Typically, new drugs must go through 3 phases before applying for approval from regulatory authorities (the Food and Drug Administration, or FDA, in the United States). Phase I clinical trials are small (15-30 patients), accrue patients with multiple tumor types (e.g., all solid tumors), focus on safety and toxicity (adverse events), and escalate dosages to find the highest dose that can be taken safely. Phase II clinical trials are larger (25-100 patients) and test the effectiveness of a drug in patients with a particular tumor type (e.g., prostate cancer). Phase III trials are very large (100 to thousands of patients) and focus on whether the drug is more effective than the standard of care in patients with a particular tumor type. Given the rarity of ACC and the lack of a clear standard of care for progressive ACC patients, there is unlikely to be a Phase III clinical trial for ACC; rather, regulatory authorities are likely to review results from one or more Phase II clinical trials in deciding whether to approve a drug for ACC. Such an approval would make the drug generally available for the treatment of ACC patients and the costs would be covered by most health insurance plans.

How do researchers know whether a drug is effective? There are many metrics (or "endpoints") that are used, including overall survival, disease-free survival, and progression-free survival. Given that many patients may live a long time and that they may cycle through multiple drugs, researchers often look to tumor shrinkage or growth (rather than survival metrics) while a patient is in a trial to ascertain effectiveness in a timely manner. Since 2000, the standard for measuring a drug's effect on tumor volume has been the Response Evaluation Criteria in Solid Tumors (RECIST). In short, the RECIST criteria break down tumor measurements into 4 categories:

- Complete Response (CR) – Disappearance of tumors
- Partial Response (PR) – 30% or greater shrinkage in measurements of tumors
- Progressive Disease (PD) – 20% or greater growth of measurable tumors or the appearance of new tumors
- Stable Disease (SD) – Insufficient shrinkage or growth to qualify as Partial Response or Progressive Disease

Complete Response and Partial Response often are summed together to create Objective Response. Similarly, Objective Response and Stable Disease lasting more than 6 months are summed to create Clinical Benefit. Patients with Progressive Disease usually are taken off a clinical trial, while the rest continue to receive the drug. Historically, Phase II and Phase III clinical trials that demonstrated an Objective Response Rate of 20% or more were considered promising for chemotherapies.

This section on clinical trials provides a very general overview. Much more complete descriptions of clinical trial phases, protocols, regulatory approvals, inclusion/exclusion criteria, informed consent, randomization, placebos and other topics are available at the following websites:

- http://www.cancer.gov/clinicaltrials/learning (National Cancer Institute)
- http://www.cancer.net/patient/All+About+Cancer/Clinical+Trials (ASCO)
- http://www.clinicaltrials.gov/ct2/info/understand (ClinicalTrials.gov)

Chemotherapy, Targeted Agents and Personalized Medicine

Chemotherapy is the use of chemicals to kill rapidly dividing cells. However, cancer cells are not the only rapidly dividing cells in the human body. Normal cells in the body that are particularly sensitive to standard chemotherapy treatments are located in the blood, bone marrow, digestive tract and hair follicles. Depending on the particular drug, patients on chemotherapy may deal with a combination of fatigue, hair loss, depression of the immune system, nausea and other side effects. The heart, liver and kidneys of a patient may also be damaged by certain chemotherapies.

Despite the significant side effects of chemotherapy, there have been substantial successes in certain cancers. Nearly 90% of children with acute lymphoblastic leukemia (the most common pediatric cancer) are cured through treatment with chemotherapy. Likewise, men with testicular cancer are cured in over 90% of cases with chemotherapy. These cases represent true cures with no remaining cancer cells in the body and no recurrences following treatment.

Targeted agents are drugs whose activity is intended to interfere with specific molecules involved in cancer progression. They may block cell growth signals, boost the immune system, stop the growth of blood vessels supporting tumors, deliver toxic drugs to cancer cells or fix cell processes that would normally suppress tumors. Rather than targeting all rapidly dividing cells (as with chemotherapy), targeted agents rely upon specific molecular markers to distinguish between cancer cells and normal cells. The treatments may come in the form of a chemical (small molecule inhibitors) or biologics (antibodies, vaccines and other medicines created through biological processes). The names of small molecule inhibitors often end in “ib” (for “inhibitor”) while those of biologics often end in “ab” (for “antibody”).

The goals of targeted agents are (1) to be more effective than other available treatments such as chemotherapy, surgery and radiation, and (2) to be less harmful to normal cells, thereby reducing side effects. These goals have been achieved in a growing number of tumor types with the most prominent examples including targeted agents such as Trastuzumab (Herceptin) for breast cancers driven by HER2 protein signaling, Imatinib (Gleevec) for chronic myelogeneous leukemia and gastrointestinal stromal tumors, and Gefitinib (Iressa) for lung cancers with a mutation of the EGFR gene. The concept has been proven that targeted agents may extend lifespans and even cure patients; the challenge is to increase the number of tumor types benefiting from targeted agents.

Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. Individuals are divided into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Treatments may then be provided to those who will benefit, sparing side effects (and expense) for those who will not. In short, personalized medicine is about getting the right drug to the right patient.

Cancer is not one disease. Historically, tumor types were defined by location (breast, colon, lung, salivary glands, etc.) or by histology (the size, shape and patterns of tumor cells). The presumption was that the cause and response to any given treatment would be the same for each defined tumor

group. However, the genomics revolution has shifted the framework, classifying tumors not only by location and histology, but also by the molecules that are altered, abundant and/or activated in a particular tumor. It turns out that there are many different ways in which tumors develop, even in the same location. Whereas all breast cancer patients used to cycle through the same chemotherapies, now they are divided into groups defined by how much estrogen, HER2 or other molecular targets are present in each tumor. Different targeted agents are prescribed according to the many different molecules that drive different cancers.

The rise of targeted agents and personalized medicine is changing the way drugs are developed and clinical trials are carried out. Traditionally, new cancer drugs were found primarily by trial and error. New compounds were identified, tested in labs, and then clinical trials cycled through various tumor types to see if they were active in any of them. A partial response in a Phase I trial might be sufficient justification to move forward with a Phase II trial in a particular tumor type. Increasingly, the process is becoming more rational. Drugs are being characterized by the molecular targets they inhibit and then matched to the tumor types that appear to be driven by those molecular targets. Unable to consistently produce cancer drugs with a significant impact on a large number of patients, drug companies are seeking to produce cancer drugs with a significant impact on smaller subsets of patients across multiple tumor types.

Despite the advances, developing effective new therapies of human cancers is not easy. An article in Nature Reviews Drug Development in 2009 reported that only 18% of anticancer agents entering clinical trials between 1995 and 2007 were approved by the FDA. In contrast, the class of targeted agents called “kinase inhibitors” enjoyed a much higher approval rate of 47%. Unsurprisingly, the success rate was much higher when researchers matched the right drugs to the right patients. While this paradigm shift may represent good news for some drug companies, it is great news for patients entering clinical trials with clear scientific rationales. The likelihood of success is rising.

Past Clinical Trials in ACC

Patients enrolling in clinical trials perform an incredibly honorable service for the entire patient community. Without them, it would not be possible to determine systematically whether a particular treatment is effective or safe. Even clinical trials that show that a drug is ineffective are incredibly valuable; future patients may be spared the unnecessary side effects and may try other drugs that might result in a response. Some physicians prescribe approved cancer drugs “off-label” (i.e., approved for tumor types different from the treated tumor) to their patients who cannot travel to or do not qualify for a clinical trial; but those results are not tabulated and shared with others as is the case with clinical trials. Without a doubt, current ACC patients owe a debt of gratitude to those who have helped guide our current understanding of how ACC responds to systemic therapies.

Over the past two decades, about 20 Phase II clinical trials were designed specifically for ACC patients or for salivary gland cancer patients with a large group of ACC patients. These trials are listed in the table below. It is not an exhaustive list as it excludes some smaller studies with fewer

than 9 ACC patients as well as some privately-funded studies that were not published. Chemical names are used for each compound with trade names included in parentheses. Hyperlinks to Wikipedia provide general descriptions of the drugs.

Table 1. Responses of ACC Patients to Systemic Therapies

Compound(s)	Molecular Targets	ACC Patients	Complete Response	Partial Response	Stable Disease	Pub. Year	Pub. Link
Cetuximab (Erbitux)	EGFR	23	0%	0%	87%	2009	View
Gemcitabine & Cisplatin	Chemo	10	0%	20%	NA	2009	View
Gemcitabine	Chemo	21	0%	0%	52%	2008	View
Sunitinib (Sutent)	Multiple	12	0%	0%	92%	2008	View
Lapatinib (Tykerb)	EGFR, HER2	19	0%	0%	79%	2007	View
Bortezomib (Velcade)	Proteasome	25	0%	0%	64%	2006	View
Gefitinib (Iressa)	EGFR	19	0%	0%	68%	2005	View
Imatinib (Gleevec) & Cisplatin	Multiple (KIT) & Chemo	28	0%	11%	68%	2010	View
Imatinib (Gleevec)	Multiple (KIT)	10	0%	0%	70%	2007	View
Imatinib (Gleevec)	Multiple (KIT)	15	0%	0%	60%	2005	View
Paclitaxel	Chemo	14	0%	0%	50%	2006	View
Paclitaxel & Carboplatin	Chemos	10	0%	20%	NA	2000	View
Vinorelbine & Cisplatin	Chemos	9	22%	22%	NA	2001	View
Vinorelbine	Chemo	13	0%	15%	NA	2001	View
Epirubicin	Chemo	20	0%	10%	50%	1993	View
Cisplatin & 5-FU	Chemos	11	0%	0%	55%	1997	View
Cisplatin & Doxorubicin & Cyclophosphamide	Chemos	12	0%	25%	42%	1996	View
Cisplatin & Doxorubicin & Bleomycin	Chemos	9	11%	22%	55%	1992	View
Cisplatin	Chemo	10	0%	0%	50%	1992	View
Cisplatin	Chemo	13	15%	0%	46%	1991	View
Mitoxanthrone	Chemo	32	0%	12%	69%	1996	View
Mitoxanthrone	Chemo	18	6%	0%	67%	1990	View

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The broad conclusion to be drawn from the history of clinical trials with ACC patients is that some standard chemotherapies produce objective responses or clinical benefit in small subsets of ACC patients, but none have been shown to have broad effectiveness, long durations of response or a meaningful impact on survival. The few complete responses with chemotherapy in the 1990s have not been replicated in later clinical trials and are presumed to have been the result of different (pre-RECIST) measurement criteria, incorrect diagnoses or other factors.

In the past several years, targeted therapies have resulted in high rates of stable disease in ACC patients. However, this metric must be interpreted carefully for the following reasons:

- Many ACC patients with recurrences have stable disease for long periods when not being treated, so stable disease may be the natural course of disease and not the result of the drug.

- Differences in inclusion criteria across clinical trials must be considered. For example, the Sunitinib and Lapatinib clinical trials enrolled only patients whose ACC was progressing, while the Imatinib and Cetuximab trials enrolled patients with recurrent and/or metastatic ACC that may not have been progressing. In that context, the rate of stable disease in Sunitinib (92%) and Lapatinib (79%) is more impressive than the rate of stable disease in Imatinib (60% and 70%) and Cetuximab (87%).

- ACC grows more slowly than many cancers. So growing disease in ACC may not meet the RECIST criteria of growing by 20% within 2 months to be classified as "progressive disease". Several months may pass with steadily growing metastases in an ACC patient before the 20% threshold is reached; in the meantime, the patient will be classified as having "stable disease". The more meaningful metric in ACC is stable disease for more than 6 months; that figure is not always reported but has been fairly good in three recent trials (52% for Cetuximab, 48% for Gemcitabine and 47% for Lapatinib).

Patients should keep in mind that objective responses and stable disease are measures of tumor volume, not overall survival. It is reasonable to assume that smaller tumors mean a longer lifespan, but that has not been the case in some other tumor types; once a treatment stops being effective, tumors may grow back more quickly. Patients must weigh the potential side effects of any treatment against the possibility of extended survival and reduced pain from tumor shrinkage.

Clinical trials provide patients with an opportunity to expand the entire ACC patient community's knowledge about how best to use systemic therapy. Similarly, ACC patients may support pivotal preclinical research by considering tumor donations prior to undergoing surgery. Information on donating tumor specimens is available by clicking here.

Current Clinical Trials in ACC

At the moment, thousands of Phase I clinical trials are open to patients with all tumor types, including ACC. However, only nine Phase II clinical trials are specifically designed for patients with ACC or salivary gland cancers (including ACC). They are listed below. Given the rarity of ACC, Phase III clinical trials for ACC are unlikely ever to take place; regulatory authorities may rely upon positive Phase II trials in deciding whether to approve new drugs for ACC.

Table 2. Current Systemic Therapy Clinical Trials for ACC or Salivary Gland Cancers

Compound	Molecular Targets	Phase	Open?	Sponsor	Site Locations	Link
Sorafenib (Nexavar)	RAF,PDGFR, VEGFR, KIT,RET	II	Yes	Istituto Nazionale dei Tumori	Milan (Italy)	NA
Sorafenib (Nexavar)	RAF,PDGFR, VEGFR, KIT,RET	II	Yes	The Christie Hospital	Manchester (UK)	NA
Vorinostat/ SAHA	HDAC	II	Yes	Karmanos Cancer Institute	Detroit (USA)	View
Dasatinib (Sprycel)	ABL,SRC,RAF, RET, VEGFR,KIT	II	Yes	University of Chicago/NCI	Multiple (USA & Canada)	View
Everolimus (Afinitor)	mTOR	II	Yes	Seoul National University	Seoul (Korea)	View
Nelfinavir (Viracept)	HIV Protease,AKT	II	Yes	University of Iowa	Iowa City (USA)	View
Imatinib (Gleevec)	KIT,ABL,PDGFR	II	Yes	Institut Gustave Roussy	Paris (France)	View
Panitumumab & Radiotherapy	EGFR as radio-sensitizer	II	No	University of Pittsburgh	Multiple (USA & Canada)	View
Cetuximab & Carbon Ion	EGFR as radio-sensitizer	II	No	University of Heidelberg	Heidelberg (Germany)	View

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Although all nine Phase II clinical trials have been approved by the relevant supervisory bodies, not all nine are currently recruiting ACC patients. The Dasatinib clinical trial is on hold while the results of the first stage are being evaluated to determine whether the second stage will proceed. The last two clinical trials are not yet recruiting patients, but should be recruiting soon. Updates for some of these – as well as potentially new – clinical trials for ACC may be accessed by clicking here.

ClinicalTrials.gov is a registry of nearly 100,000 clinical trials being carried out in over 170 countries; the listings include most publicly-funded and many privately-funded studies. Additional resources are available to assist patients in identifying clinical trials that may be appropriate for them:

- TrialCheck: http://www.cancertrialshelp.org/trialcheck/ or 877-277-8451
- National Cancer Institute: http://www.cancer.gov/clinicaltrials/search or 800-4-CANCER
- EmergingMed: http://www.emergingmed.com/ or 877-601-8601

Medical issues are not the only drivers of patient decisions about clinical trials. Financial, time and travel limitations may make it difficult to enroll in a trial that is medically appropriate. Fortunately, there are many organizations that will arrange for free lodging or free air transportation. The patient care coordinator for each clinical trial should provide information to patients on ways to make participating in the study easier and less expensive.

Clinical Trial Rationales and Levels of Evidence

Historically, clinical trials in cancer have relied upon random testing and encouraging anecdotes. A Phase II clinical trial in a particular tumor type may have been the result of an objective response in a patient who was enrolled in a Phase I clinical trial or who was prescribed an off-label drug. Or it may have been an attempt to document systematically the effectiveness of the next promising drug out of the pharmaceutical pipeline. Most clinical trials in ACC have grown out of this system and – given the state of knowledge on the disease – there were no better options than random testing. However, the scientific understanding of ACC's basic biology is advancing to the point where soon there may be more compelling clinical trials to pursue with higher likelihoods of success.

What are the attributes of a drug that make it promising in a particular tumor type? The attributes fall into three broad categories of rationales: (1) inhibition of a target that is involved in a disease's mechanisms of action, (2) preclinical studies of drugs that demonstrate effectiveness, and (3) anecdotes from case reports and Phase I trials. Patients should evaluate each clinical trial in light of these three categories of rationales, with the highest priority given to the first category.

(1) Mechanisms of Action – Does the drug target the drivers of the disease?

a. Abundance of a Molecular Target – Many research studies look for "over-expression" of a protein to indicate its importance to the disease process. Tumor tissue is compared to normal tissue and those proteins that are relatively abundant in the tumor are presumed to drive the cancer. However, there are thousands of over-expressed proteins in each tumor, the vast majority of which are not driving the disease. So this rationale represents a very low hurdle.

b. Activation of a Molecular Target – Many proteins are relatively abundant in tumor cells, but they may not be in an activated state to trigger tumor development. Beyond over-expression, phosphorylation of a protein provides an additional layer of certainty that a protein is activated and matters in a cancer.

c. DNA Alterations – Many tumors have DNA alterations that lead to over-expression of known cancer genes or inactivation of known tumor suppressor genes. Mutations, translocations and copy number variations are difficult to identify, but often explain the biology of a tumor and provide clues to potential targets for therapy.

d. Pathway Analysis – Researchers attempt to understand all the molecular pathways and networks that define how a tumor survives and progresses, tracking how cancer-causing DNA alterations turn into RNA and then proteins. Upstream and downstream targets along the molecular pathways are explored and explain how cells grow uncontrollably. Functional studies of pathways provide the most complete understanding of a disease, and they are under way in ACC.

(2) Preclinical Screening – What is the drug's effectiveness in non-human models of the disease?

a. In Vitro Studies – Tumor cells may be grown in plastic dishes and then screened with drugs to determine effectiveness. Such "in vitro" cell line models are not very predictive of how drugs will do in clinical trials but they are relatively inexpensive and allow the study of thousands of drugs. The lack of valid ACC cell lines has limited the usefulness of this approach thus far.

b. In Vivo Studies – Tumor cells from humans may be implanted into mice and then screened with drugs to see if the molecular targets are hit and whether the tumors shrink. Such "in vivo" xenograft models are thought to be more predictive of how drugs will do in clinical trials than cell line models, but they are relatively expensive, limiting the number of drugs that may be studied. Forthcoming data on ACC xenografts will inform future clinical trials.

(3) Anecdotal Clinical Evidence – Has the drug been effective in humans with the disease?

a. Case Reports – In the absence of any approved therapies for advanced ACC patients, some medical oncologists prescribe off-label usage of approved anticancer agents in the hope that the drugs will work on a particular patient. Successful cases may be published in scholarly journals to encourage further study of the drug in the tumor type. For example, one case report (Alcedo et al, 2004) claimed objective responses in 2 ACC patients treated with Imatinib (Gleevec). However, two subsequent Phase II trials reported no objective responses among 25 patients.

b. Phase I Clinical Trials – Many ACC patients with progressive disease have entered Phase I clinical trials open to patients with many tumor types. The Appendix includes a table with Phase I studies that mentioned a partial response or stable disease for at least one ACC patient. Clinical benefit in such trials may encourage the development of a Phase II trial, as was the case with Vorinostat. Most signals from Phase I clinical trials, however, are much less clear and will generate concepts for ACC infrequently and randomly.

Within each category of rationale (Mechanism of Action, Preclinical Screening and Anecdotal Clinical Evidence), the level of evidence for the promise of a drug rises as you go down the list. Pathway analysis that identifies validated targets matters more than DNA alterations, which in turn matter more than phosphorylation or over-expression. Likewise, in vivo studies are more convincing than in vitro studies. And Phase I experience is more pertinent than individual case reports.

Promising Molecular Targets and Agents for ACC

The ideal clinical trial for ACC patients would include support from all the possible rationales listed above: mechanisms of action, preclinical screening and anecdotal clinical evidence. In the past, the justifications for most Phase II clinical trials have relied most heavily upon anecdotal clinical evidence or the random willingness of a drug company to try a new drug on a new tumor type. In the future, ACC patients should take comfort in the fact that researchers are identifying targets that are particularly relevant to ACC and that have been screened in ACC animal models.

Unfortunately, the scientific literature is full of research papers that combine over-expression (1a) and in vitro studies (2a) as justifications for exploring drugs in ACC. A molecular target is found to be abundant in ACC tumors (as are thousands of proteins) and then an inhibitor of that target is shown to kill "ACC" cell lines in vitro. As described in a recent article, the available "ACC" cell lines have been found to be misidentified, undermining the conclusions of many of these research papers. Many scholarly articles continue to be published referencing the misidentified cell lines despite their invalidation as ACC models.

Looking at the current clinical trials, there is a wide range of supporting rationales:

- Imatinib (Gleevec) – The drug is very effective in treating patients with gastrointestinal stromal tumors (GIST) which, like ACC, over-express the KIT protein (which is encoded by the c-kit gene). However, specific c-kit mutations in GIST are found in those patients that respond to Imatinib, and those mutations are not found in ACC. Two trials of the drug in ACC have had disappointing results. Mere over-expression of KIT provided the best available scientific rationale several years ago, but it was a weak rationale (1a) in the absence of other mechanistic or preclinical evidence.
- Nelfinavir (Viracept) – Investigators at the University of Iowa published an article with a clear rationale for the Nelfinavir trial. They identified AKT as over-expressed (1a) and phosphorylated (1b) in many ACC tumors. They screened cell lines with an AKT inhibitor (2a) before it became known that the cell lines were misidentified. Without any preclinical screening data, the rationale for Nelfinavir is only slightly stronger than that for Imatinib
- Vorinostat/SAHA – At this juncture, there is no clear understanding of why HDAC inhibition should matter in ACC and no preclinical screening data supporting its effectiveness. However, anecdotal clinical evidence from a Phase I clinical trial (3b) led to further investigation in a Phase II clinical trial.
- Dasatinib (Sprycel) – Leaving aside KIT over-expression (1a), there is no mechanistic or preclinical rationale for why this drug should be particularly effective in ACC. The clinical trial is on hold pending review of first stage results; it would be more promising if the study proceeded to the second stage due to at least one partial response.
- Sorafenib (Nexavar) – The drug shares many of the same targets as Dasatinib as well as a lack of mechanistic rationales (only 1a). However, in vivo studies (2b) do provide some support for the concept.

- Cetuximab (Erbitux) and Panitumumab – EGFR, the target of these drugs, is not clearly over-expressed in most ACC tumors, so the mechanistic rationale for treating with the drugs alone is weak. Completed Phase II clinical trials for Cetuximab, Gefitinib and Lapatinib (all EGFR inhibitors) did not result in any objective responses. However, these current clinical trials are focused on improving the effectiveness of radiation therapy, using EGFR inhibitors as "radio-sensitizers". These studies may be more appropriate for patients dealing with primary tumors that cannot be taken out fully by surgery, so patients should discuss such factors with their physicians.
- Everolimus (Afinitor) – Currently, there is no mechanistic rationale for the importance of mTOR in ACC. In addition, the evidence supporting activity in ACC from preclinical screening and clinical anecdotes is unclear.

Overall, the level of evidence for current Phase II clinical trials in ACC is fairly weak (although individual physicians may have patient-specific information that would warrant greater confidence in a particular trial). This lack of evidence is primarily a reflection of the historical ignorance about the basic biology of the disease. But given the increasing knowledge base on ACC, the level of evidence for new clinical trials ought to rise substantially. Specifically, upcoming studies should look beyond merely the over-expression of particular targets, and address the following developments:

- Fusion Gene: Last year's article describing a recurrent translocation in ACC has identified the gene MYB as a likely culprit in tumor development. This finding has been confirmed by another article showing the significance of MYB in most ACC tumors, even those without the translocation. Unfortunately, MYB has not been drugged and it may be very difficult to do so. However, the following genes are known downstream targets of MYB that are over-expressed in most ACC tumors: API5, BCL2, BIRC3, CCNB1, CDC2, CD34, CD53, KIT, FGF2, HSPA8, MAD1L1, MYC, SET and VEGFA. Functional studies will identify additional rational targets, but these molecules – and the molecules with which they interact – may represent a good starting point.
- Phosphorylation – Certain molecular targets may be abundant, but not activated in tumor cells. Forthcoming data indicates that such may be the case with KIT, which may explain why inhibition of KIT by Imatinib (Gleevec) has not been effective in ACC. The molecular targets of proposed drugs should be demonstrated to be activated in ACC.
- In Vivo Studies – Over the past few years, xenograft mouse models of ACC have been established and molecularly profiled. Although the drug responses of these models may not mirror exactly the drug responses in humans, they should provide better signals than from in vitro studies. Designers of future clinical trials for ACC patients should avail themselves of these resources.

Patients should not presume that a Phase II clinical trial for ACC patients will have a more compelling scientific rationale than a Phase I clinical trial. There may well be Phase I studies that involve inhibitors of targets most relevant to ACC. Patients should discuss with a trusted physician the clinical trial most appropriate for a particular tumor profile, regardless of the phase.

A forthcoming clinical trial for ACC patients demonstrates the improved levels of evidence that are likely to characterize future studies. A clinical trial of Dovitinib will open in the coming months in Seoul, South Korea, and another trial in the United States is being planned. Dovitinib (also named TKI258) is a novel compound designed to inhibit FGFR, VEGFR, PDGFR and KIT. The following factors support the study's rationale:

- FGFR1 is over-expressed (1a) and phosphorylated (1b) in the preponderance of ACC tumors.
- FGF2, a molecule that binds to FGFR1, is a known downstream target of MYB that is rearranged and/or over-expressed in almost all ACC tumors (1c).
- Dovitinib has been screened in several xenograft mouse models of ACC and demonstrated activity (2b).

If it proceeds, the Dovitinib clinical trial would represent the first study in ACC with a clear mechanistic rationale supported by preclinical screening data. By no means does that ensure that ACC patients on the study would receive any clinical benefit. But, the chances are improved with additional levels of evidence.

Table 3. Rationales for Current and Pending ACC Clinical Trials

	Mechanisms of Action				Preclinical Screening		Clinical Anecdotes	
Compound	**Over-Expression**	**Activation**	**DNA Alterations**	**Pathway Analysis**	**In Vitro**	**In Vivo**	**Case Studies**	**Phase I**
Currently Open:								
Sorafenib (Nexavar)	x					x		
Vorinostat/SAHA								x
Dasatinib (Sprycel)	x							
Everolimus (Afinitor)								
Nelfinavir (Viracept)	x	x						
Imatinib (Gleevec)	x						x	
Panitumumab & Radiotherapy								
Cetuximab (Erbitux) & Carbon Ion Radiation								
Pending :								
Dovitinib/TKI258	x	x	x			x		

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Patient Discussions with Physicians

The decision to enter a clinical trial is very personal. Many patients with advanced but stable disease choose to remain untreated because ACC tumors may have extended periods without growth; the effectiveness, risks and side effects of currently available treatments may point those patients to "watchful waiting". Other patients prefer more aggressive treatments even if there is little or no growth in their tumors. In most cases, patients with growing tumors that are numerous, near vital organs and not clearly-defined will seriously consider systemic therapy and clinical trials. Each situation is unique and should be discussed with a knowledgeable physician.

When a medical oncologist does recommend a clinical trial to a patient, the following questions may help guide patients to the best decision for their situation:

- What factors have changed to prompt the recommendation of a clinical trial? Such factors may include new metastases, faster tumor growth and encroachment on vital organs.
- Would surgery, radio-surgery, radio-frequency ablation, cryoablation, chemoembolization or brachytherapy manage the disease adequately? How would the effectiveness and side effects of these treatment options compare to the recommended clinical trial?
- Why should the drug be particularly effective in ACC patients? What levels of evidence support the recommended clinical trial? Responses should relate to the drug's mechanisms of action, preclinical studies or anecdotal clinical evidence.
- What other clinical trials are available? How do their rationales compare to the recommended clinical trial? The patient may not need to understand fully the competing rationales, but should have confidence that the physician is weighing them.
- Are there any genomic tests that may indicate if my particular tumor is more likely to respond to the drug in the recommended clinical trial?

The final decision to proceed with any treatment will be based on a blend of the disease's progression, the treatment's anticipated effectiveness, the patient's tolerance of side effects, financial constraints and travel limitations. Patients may wish to refer their physician to this document to provide background information and context for the discussions. Lastly, if a physician recommends off-label usage of a drug that is being studied in a clinical trial for ACC, patients should consider joining the clinical trial; documenting and disseminating the results of such trials is of immense value to the entire ACC patient community.

In conclusion, ACC patients have relied primarily upon surgery and radiation in managing their disease. Progressive disease that could not be handled by those treatments has been resistant to systemic therapies – both chemotherapy and targeted drugs. The level of evidence supporting past clinical trials has been weak. As researchers learn more about the mechanisms of action that drive ACC, patients and researchers should have greater confidence in the likelihood of success in clinical trials.

Appendix

Table 3. Phase 1 Trials with Reports of ACC Clinical Benefit

	Molecular Targets	Year	Total/Evaluable Patients	Patient Evaluations	Link
Vorinostat/ SAHA	HDAC	2010	57/NA	Of 5 patients with ACC, 1 had PR and 4 had SD.	View
Sonepcizumab	S1P	2010	28/21	Of 8 patients with SD >2 months, 1 with ACC had SD>8 months.	View
PX-478	HIF1A	2010	40/36	14 had SD, 1 of which was ACC with SD>6 months.	View
PX-866	PI3K	2010	52/31	31 had SD>4 months, 1 of which ACC.	View
PF-00562271	FAK, PYK2	2010	99/NA	1 ACC had SD for 1 year.	View
Regorafenib (BAY73-4506)	VEGFR, FGFR, TIE2, PDGFR, RET, KIT, RAF	2010	38/36	5 had ACC, none with partial response, unknown with SD.	View
PF-00299804 & Figitumumab	EGFR, HER2/4 & IGF-1R	2010	47/42	8 had clinical benefit, with 2 PR including 1 salivary carcinoma.	View
XL147 & Erlotinib	PI3K & EGFR	2010	23/NA	1 ACC had less FDG uptake by PET & smaller lung nodule by CT.	View
XL647	EGFR, HER2, EPHB4	2006	37/NA	1 PR. 7 with SD>3 months, 1 of which was ACC.	View
Axitinib (AG-013736)	VEGFR, PDGFR, KIT	2005	36/NA	3 PR, 1 of which was ACC.	View

PR partial response. SD stable disease.

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