



Looking for Signposts: An Update on Progressive Adenoid Cystic Carcinoma

July 2011

The purpose of this document is to provide updated information about treatment options to ACC patients with progressive disease and their physicians. In particular, the following topics are discussed:

- [Stereotactic Body Radiation Therapy \(SBRT\)](#)
- [Personalized Medicine: Tumor Profiling to Guide Systemic Therapy](#)
- [Chemotherapy Sensitivity and Resistance Assays \(CSRAs\)](#)
- [Open and Pending Clinical Trials](#)
- [Appendix: Clinical Trials Contact Information](#)

Many of these topics relate to concepts introduced in ACCRF's recent "[Guide to Systemic Therapy](#)", which may be accessed at www.accrf.org. Please refer to that document for more extensive context.

Introduction

ACC survivors fall into one of three broad groups: (1) no evident disease, (2) stable disease, and (3) progressive disease. The first group with **no evident disease** usually has completed surgery and radiation treatments and is monitored indefinitely for potential recurrences. The second group with **stable disease** often follows a strategy of "watchful waiting" for clear signs of tumor growth, though some of these patients opt for surgery, stereotactic body radiation therapy (SBRT) or interventional radiology (such as radiofrequency ablation or brachytherapy). There is no clear consensus among physicians about a single standard treatment for this second group. Systemic therapy (chemotherapy and targeted drugs) usually is not chosen because no drugs have yet been found to be effective in a significant subset of ACC patients.

Patients with **progressive ACC** – with tumors that are clearly growing – face a journey with even more potential paths and few signposts. If the tumors are few, well-defined and don't encroach on vital organs, then the options of surgery, SBRT or interventional radiology may be appropriate. The treatments may not be curative, but they may lead to disease stabilization and gain valuable time. In many situations, physicians recommend to patients with multiple growing recurrences that systemic therapy is necessary to address the evident and as-yet-unidentified tumors. ACCRF's "[Guide to Systemic Therapy](#)" provides the history of ACC clinical trials and describes the trend toward molecularly-driven studies that have a higher likelihood of success than in the past. In all cases, it is prudent for patients to consult with a multi-disciplinary team of [ACC specialists](#) (surgeons, radiation oncologists and medical oncologists) before selecting the best course of action for their particular situation.



Stereotactic Body Radiation Therapy (SBRT)

After the resection of their primary tumors, most ACC patients receive [photon](#) radiation to kill any remaining microscopic ACC cells; local recurrence of tumors is avoided in over 90% of cases. Typically, post-operative photon radiation consists of daily treatments, five times per week for 6 weeks or so. Each of 30-35 treatments may involve 2 Grey (Gy) of radiation, resulting in total radiation exposure to the targeted tissues of 60-70 Gy. Relatively low radiation doses over an extended time period increase the chances that (1) tumor cells will be killed when they happen to be dividing and are most sensitive, and (2) normal cells will repair themselves from the radiation damage. In some cases where radiation doses must be limited, chemotherapy or targeted drugs may be administered to sensitize the cancer cells to radiation. For some unresectable or deep tumors, [neutron](#), [proton](#) or [carbon ion](#) radiation platforms may be more appropriate than photon radiation, and have different dosing and schedules.

Stereotactic body radiation therapy refers to a different approach to using radiation to treat cancer. Rather than using many low doses to deal with microscopic tumor cells as with photon radiotherapy, SBRT uses one or a few high doses of radiation to destroy tumor cells. Up to 100 Gy of radiation might be administered over the course of 5-6 treatments, or “fractions”. Multiple platforms are considered to be SBRT: Cyberknife, Novalis, TomoTherapy and Trilogy, among others. An excellent review of the options is “[Stereotactic body radiation therapy: 2007 update](#)”.

As with surgery, SBRT requires a close appraisal of the number, size, shape, location and growth rate of tumors to be treated. If there are too many tumors, they are not clearly circumscribed, or they encroach on vital organs, then neither surgery nor SBRT may be appropriate. Patients should consult with multiple physicians to gain the best perspective on the way forward.

The Agency for Healthcare Research and Quality (AHRQ) recently released a Technical Brief entitled “[Stereotactic Body Radiation Therapy](#)”. The conclusion is that there have not been sufficient studies to determine whether SBRT leads to better outcomes for patients, although there are clear theoretical advantages. Helpfully for patients, the report includes an Appendix with a [list of facilities performing SBRT on solid tumors](#). With approximately 400 sites across the country, most U.S. patients should have ready access to an SBRT facility. Given that many of the sites do not have familiarity with ACC, they should be consulted in conjunction with a patient’s other treating physicians.



Personalized Medicine: Tumor Profiling to Guide Systemic Therapy

Historically, physicians prescribed systemic therapy (drugs) based on the location of the tumor (prostate, breast, lung, etc.) or the histology of the tumor (squamous cell carcinoma, adenoid cystic carcinoma, etc.). Chemotherapies that targeted all rapidly-dividing cells were the mainstay of treatment and were viewed as effective if 20% or more of each group of patients responded to a drug. Many patients didn't benefit, but some unpredictable subsets of patients did benefit. Over the past decade, physicians increasingly have been considering not only the location and histology of a patient's tumor in selecting a systemic therapy, but also the **tumor profile** (molecular analysis of DNA mutations and RNA expression). The intent is to "personalize" treatment by administering drugs that are matched with the aberrant molecules driving a particular tumor.

Targeted therapies, drugs that selectively interfere with particular molecules, have had great success in some tumor types. Up to 95% of some patient populations treated with targeted therapies have had objective responses (significant tumor shrinkage), often with fewer side effects than chemotherapy.

Most cancers do not have an effective targeted therapy at the moment, but there is a growing list of drugs and associated tumor types with success stories: Tamoxifen in estrogen-receptor-positive breast cancers, Trastuzumab (Herceptin) in HER2-positive breast and gastric cancers, Imatinib (Gleevec) in chronic myelogenous leukemia (CML) and Gefitinib (Iressa) in EGFR-positive lung cancers, among many others.

At the recent Annual Meeting of the American Society of Clinical Oncology (ASCO), M.D. Anderson researchers presented a scientific abstract that compared the response rate of Phase I clinical trial patients with and without treatment guided by tumor profiling. Among patients with one molecular aberration in their tumors, 29% of those matched to a targeted agent had a response (significant tumor shrinkage) compared to only 8% for those patients for whom there was no matched targeted drug. And patients matched to targeted therapy had a median survival that was 6 months longer than unmatched patients. Only about 40% of patients entering the Phase I clinical trials at M.D. Anderson had one of the molecular aberrations analyzed. And just less than a third of those had a response. But, clearly, the odds favored patients whose tumors were profiled.

Many patients with progressive ACC resort to systemic therapy. Unfortunately, as described in ACCRF's Guide to Systemic Therapy, no chemotherapy or targeted drugs have been found to be active in a large portion of ACC patients. Instead, there have been a few cases with responses spread across many different drugs. The fact that most ACCs have a similar genetic alteration (a rearrangement of the MYB gene) implies that one day there may be a targeted therapy that will be active across many ACC patients. However, aside from the MYB rearrangement, ACC tumors are like most other tumor types in that they have multiple additional genetic alterations that are different from person to person. For example, one patient's tumor may have a mutation in the PI3K pathway while another may have extra



copies of the the EGFR gene. Each patient may respond to a different drug based on the mix of genetic alterations driving their particular tumor.

A [recent news story](#) highlighted the promise of personalized medicine. An ACC patient with a particular genetic alteration visited [South Texas Accelerated Research Therapeutics](#)¹ (START) in San Antonio, TX. The START physician profiled the tumor, identified a genetic alteration and then matched it to a novel targeted therapy, leading to a significant response in the ACC patient. While this story demonstrates the power of tumor profiling, it should be accompanied with an important caveat. **Most ACC patients are unlikely to harbor the same genetic alteration as the patient in the news story, and therefore are unlikely to respond in the same manner to the same drug.**

For those patients with the inclination, insurance coverage or available funds, tumor profiling is a very reasonable choice. Dramatic advances in genomic sequencing are permitting forward-thinking physicians to provide meaningful guidance on targeted therapy to their patients. **Currently, the probability of finding a genetic alteration with a matched therapy may be low in any given patient. On the other hand, if one is found, the probability of a response with appropriate targeted drugs may be higher than that expected with traditional chemotherapies or unmatched targeted drugs.** Over time, scientists will identify more genetic alterations as well as the drug therapies that will treat them. Two examples of tumor profiling services are the [Multiplex Solid Tumor Panel](#) at the Oregon Health & Science University and the [Translational Research Lab](#) at the Massachusetts General Hospital. ACC patients should check with their insurance companies to learn whether tumor profiling services are covered; if not, costs may reach \$1,000 or more, depending on the service.

It is worth noting that, at the moment, the most helpful tumor profiling services look for somatic mutations (DNA misspellings) in 50 or so genes amongst the 400+ known cancer genes. Some services focus on gene expression (the amount of each RNA in the tumor), but the linkage to matched therapies is much weaker than with somatic mutations. For example, over-expression of the CKIT gene is common in ACC, but drugs that inhibit the c-kit protein (e.g. Imatinib) are not active in ACC; they are active only in gastrointestinal stromal tumors with somatic mutations in the CKIT gene. **Patients should understand that many genetic alterations do not have a matched, effective therapy.** No targeted therapies have been discovered yet that inhibit MYB (one of the presumed drivers of ACC tumors), though significant efforts are under way to identify such therapies.

¹ ACCRF has an extensive relationship with START in preclinical research. START maintains and screens drugs in ACCRF's xenograft mouse models of ACC.



Chemotherapy Sensitivity and Resistance Assays (CSRAs)

Tumor profiling should not be confused with chemotherapy sensitivity and resistance assays. Tumor profiling involves analysis of tumor DNA to identify druggable molecular targets. CSRAs involve the procurement of fresh tumor samples (through biopsies or operations) and their exposure to drugs *in vitro* (in plastic dishes). The reaction of those samples is purported to predict the activity of the drugs in patients. ASCO published a [Technology Assessment of CSRAs](#) in 2004 and will be updating it in 2011 (with a similar conclusion). The document found that **there is insufficient evidence that patients benefit from CSRAs and ASCO does not recommend their use for the selection of chemotherapies.**

Open and Pending Clinical Trials

ACC patients with progressive disease should speak with their treating physicians about systemic therapy and clinical trials. Given that few ACC patients have responded to drugs approved for other tumor types, they should seriously consider participating in clinical trials. The advantage is that the clinical research studies provide patients with access to promising new treatments and close medical supervision. The disadvantage is that the drugs being tested have not yet been proven to be effective and all of the side effects may not be known. In addition, to participate in clinical trials, patients must meet specific qualifications and, in some cases, be willing to travel to receive treatments.

The table below lists all the Phase II clinical trials that are currently recruiting patients with ACC or salivary gland cancers. The Appendix includes contact information for patients seeking to learn more about the studies. Accrual has gone well in most of the clinical trials, providing comfort to study sponsors about the viability of future clinical research in ACC.

Table 1. Recruiting Phase II Clinical Trials for Patients with ACC or Salivary Gland

Compound	Molecular Targets	Info Link	Sponsor	Sites	Notes
Vorinostat/ SAHA	HDAC	View	Karmanos Cancer Institute	Detroit, MI Cleveland, OH, Bethesda, MD (USA)	Accruing well; expanding to second stage; activity in liver metastasis study
Dasatinib (Sprycel)	ABL, SRC, RAF, RET, VEGFR, KIT	View	University of Chicago/NCI	Multiple (USA & Canada)	Accruing well; expanded to second stage
Sorafenib (Nexavar)	RAF, PDGFR, VEGFR, KIT, RET	NA	Istituto Nazionale dei Tumori	Milan (Italy)	Accruing well
Sorafenib (Nexavar)	RAF, PDGFR, VEGFR, KIT, RET	NA	The Christie Hospital	Manchester (UK)	Accruing well
Nelfinavir (Viracept)	HIV Protease, AKT	View	University of Iowa	Iowa City, IA (USA)	Unknown accrual

Updated through June 2011.

On pages 10-14 of the [Guide to Systemic Therapy](#), a framework is presented for appraising the scientific rationales of each clinical trial. In short, the case is made that the studies with the greatest chance of success combine (1) targeting of known biological mechanisms of action in ACC, (2) preclinical drug activity in ACC models, and (3) anecdotal clinical evidence of responses. None of the current Phase II clinical trials has a compelling scientific rationale in all three categories, though each has some strengths. As soon as any promising results are published from the currently open studies, ACCRF will update the ACC community.

A forthcoming Phase II clinical trial of Dovitinib in ACC patients includes all the favorable components of a promising study. One of Dovitinib's molecular targets, FGFR1, is over-expressed and phosphorylated in most ACC tumors; FGF2, a ligand of FGFR1, is a known downstream target of MYB, which is rearranged in most ACCs; preclinical drug screens in ACC xenograft mouse models have shown good activity; and there is a report of a patient response. The table below lists the ACC clinical trials expected to open in the coming months.

Table 2. Pending Phase II Clinical Trials for Patients with ACC

Compound	Molecular Targets	Sponsor	Sites	Notes
Dovitinib	FGFR, VEGFR	University of Virginia	Charlottesville, VA (USA)	Likely to open by 4 th quarter
Dovitinib	FGFR, VEGFR	Seoul National University	Seoul (Korea)	Likely to open by 4 th quarter
MK-2206	AKT	Memorial Sloan-Kettering	New York, NY (USA)	Sponsored by NCI/CTEP; unknown opening
Axitinib	VEGFR, PDGFR, KIT	Memorial Sloan-Kettering	New York, NY Houston, TX Rochester, MN (USA)	Sponsored by NCCN ; unknown opening

Updated through June 2011.

MK-2206 targets the same molecule, AKT, as the currently open Nelfinavir clinical trial. Axitinib inhibits many of the same targets as the currently open Sorafenib and Dasatinib studies as well as the completed Sunitinib study.

For patients with travel limitations or who cannot wait until the Phase II clinical trial of Dovitinib opens in the fourth quarter of this year, there are other options to begin treatment with FGFR inhibitors. However, they involve Phase I clinical trials that may have more stringent eligibility criteria, may have fewer slots available and may not be covered by insurance.



Table 3. Recruiting Phase I Clinical Trials of FGFR Inhibitors

Compound	Molecular Targets	Info Link	Sponsor	Sites	Notes
Dovitinib	FGFR, VEGFR	View	Novartis	Scottsdale, AZ Durham, NC Nashville, TN Salt Lake City, UT (USA)	
Brivanib	FGFR, VEGFR	View	Bristol-Myers Squibb	Los Angeles, CA Boston, MA Detroit, MI (USA) Edmonton & Toronto (Canada)	Arm D (Docetaxel combination) has preclinical support

Updated through June 2011.

For many patients, a diagnosis with ACC marks the beginning of a journey through an unknown and forbidding landscape with difficult decisions about surgery, radiation and systemic therapy. There had been very few signposts in that landscape for a long time. Fortunately, the combined efforts of ACC patients and researchers over the past few years have built some clear pathways and signposts to guide travelers. Better understanding of the molecular drivers of ACC and better preclinical models are reinvigorating researchers and improving the prospects for successful clinical trials. At ACCRF, our hope and expectation is that in the coming years ACC patients will enjoy longer and more peaceful journeys.

ACCRF is a non-profit organization whose mission is to accelerate the development of improved treatments and a cure for ACC. A description of the foundation's strategy and leadership is available at <http://www.accrf.org/html/about.php>.



Appendix: Clinical Trials Contact Information

Vorinostat (Recruiting Phase II)

Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA

Patricia LoRusso, MD 313-576-8716 or 313-576-8765

phase1@karmanos.org

University Hospitals Seidman Cancer Center, Cleveland, OH, USA

Kristi Beatty, BSN, RN 216-844-5546

Kristi.Beatty@UHHospitals.org

National Institutes of Health Clinical Center, Bethesda, MD, USA

Janelle Bingham, RN 301-435-2715

jbingham@mail.nih.gov

Memorial Sloan-Kettering, New York, NY, USA (pending)

Alan Ho, MD 212-639-3311

Nelfinavir (Recruiting Phase II)

University of Iowa, Iowa City, IA, USA

Jane M. Hershberger, RN, BSN 319-384-7912

jane-hershberger@uiowa.edu

Kellie L Bodeker, CCRC, MSHS 319-384-9425

kellie-bodeker@uiowa.edu

Sorafenib (Recruiting Phase II)

Istituto Nazionale Tumori, Milan, Italy

Lisa Licitra, MD

Lisa.Licitra@istitutotumori.mi.it

Sorafenib (Recruiting Phase II)

Christie Hospital NHS Trust, Manchester, United Kingdom

Nick Slevin, MD

Nick.Slevin@christie.nhs.uk

Dasatinib (Recruiting Phase II) – Partial list; full list at <http://clinicaltrials.gov/ct2/show/NCT00859937>

University of South Florida, Tampa, FL, USA

Clinical Trials Office 800-456-7121

canceranswers@moffitt.org

Emory University, Atlanta, GA, USA

Nabil Saba, MD 404-686-3496

University of Chicago, Chicago, IL, USA

Clinical Trials Office 773-834-7424

University of Maryland, Baltimore, MD, USA

Clinical Trials Office 800-888-8823

University of Michigan, Ann Arbor, MI, USA

Clinical Trials Office 800-865-1125



APPENDIX: Clinical Trials Contact Information (Continued)

Dovitinib (Pending Phase II)

University of Virginia, Charlottesville, VA, USA

Christopher Thomas, MD 434-243-6356

cyt@virginia.edu

Seoul National University Hospital, Seoul, Republic of Korea

Yung-Jue Bang, MD, PhD 82-2-2072-2390

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Dovitinib (Recruiting Phase I)

TGen Clinical Research Service, Scottsdale, AZ, USA

Ramesh Ramanathan 480-323-1350

Duke University, Durham, NC, USA

Daniel George, MD 919-668-8108 ext 3

Sarah Cannon Research Institute, Nashville, TN, USA

Jeffrey Infante, MD 615-329-7274

Huntsman Cancer Institute, Salt Lake City, UT, USA

Sunil Sharma, MD 801-587-5597

Brivanib (Recruiting Phase I)

USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA

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Dana-Farber Cancer Institute, Boston, MA, USA

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[Link](#)

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