common abnormal laboratory findings in this trial were hyperglycemia, hypercholesterolemia, and anemia. The most common grade 3/4 adverse events observed with temsirolimus (regardless of causality) in this trial included anemia (20%), hyperglycemia (11%), asthenia (11%), and dyspnea (9%). Most adverse events were manageable with supportive care or dose reduction.

As with the other targeted therapies, there are ongoing clinical trials evaluating combination and sequencing therapies, as well as head to head studies (temsirolimus vs. sorafenib) and further, studies investigating possible biomarkers. There is currently a phase 2 study, non randomized, open label, of temsirolimus in subjects with advanced RCC with 80 subjects. Most of the studies with temsirolimus are focused on combination therapies, which will be discussed in a later chapter.

Table 15. SWOT Analysis of Temsirolimus

Strengths	Weaknesses	Opportunities	Threats
• mTOR inhibitor allows treatment for patients that don't respond to TKI's • Favored treatment for poor risk patients; improved OS over INF • Increase quality of life; fewer toxicities than TKIs • IV more easily reimbursed than oral medications	• Used 1L for treatment of poor prognosis patients as opposed to good or intermediate of which there are more patients • IV administration as compared to other mTOR inhibitor, which is oral.	• mTOR inhibitor pathway less common than TKIs • May see better response in patients with high LDH • May see improvement in combination treatment with an agent that targets a different pathway, such as Bevacizumab	• Drugs in pipeline with same MOA • Everolimus also approved for RCC • TKIs in the pipeline may compete for the low risk patients

Table 16. Projected Temsirolimus Sales, United States 2009 to 2013

PRODUCT NAME ($ MILLIONS)	2013	2012	2011	2010	2009
Temsirolimus	90.4	85	80	75	70.1

Temsirolimus is the favored therapy for RCC patients that are poor risk, which is between 10-15% of the clear cell population. Further, temsirolimus has more of the market share as opposed to everolimus; the other mTOR inhibitor approved for RCC treatment, because it is favored for 1L, but can also be an option as 2L in TKI refractory patients. Everolimus is not used as 1L since the clinical trial for approval was in refractory patients. However, it is an oral tablet as compared to temsirolimus. Also, the toxicity profile is less than TKIs and there are fewer mTOR inhibitors in the pipeline as compared to TKIs. These facts lend temsirolimus to possible combination therapies with TKIs or bevacizumab. Temsirolimus may face competition as new agents try to fit in the niche as 1L therapy for poor risk prognosis, however temsirolimus's market share will continue to grow steadily.

Very Early Phase (Investigational Clinical Trials)

In addition to early phase studies focusing on RCC specifically, there are also several agents exploring solid tumors; that include the kidney. Again, these drugs focus on novel MOA's, but also the VEGF receptor.

Table 30. Very Early Phase Pipeline Drugs, not yet specific to RCC

COMPOUND	MODE OF ACTION	TYPE	SPONSOR COMPANY	CLINICAL TRIALS
Motesanib (AMG706)	VEGFR Inhibitor	Small Molecule	Amgen	Solid Tumors (Phase 1)
Telatinib	VEGFR Inhibitor	Small Molecule	Bayer	Solid Tumors (Phase 1)
Brivanib	VEGFR Inhibitor	Small Molecule	BMS	Solid Tumors (Phase 1/2)
Angiocept (CT322)	VEGFR Inhibitor	Small Molecule	BMS	Cancer (Phase 1/2)
OSI-930	VEGFR Inhibitor	Small Molecule	OSI	Solid Tumors (Phase 1)
CEP-11981	VEGFR Inhibitor	Small Molecule	Cephalon	Relapsed/Refractor Solid Tumors (Phase 1)
XL820	VEGFR Inhibitor	Small Molecule	Exelixis	Solid Tumors (Phase 1)
XL647	VEGFR Inhibitor	Small Molecule	Exelixis	Solid Tumors (Phase 1)
CDP791	VEGFR Targeting	Antibody Fragment	UCB Group	Phase 2
PTC299	VEGF Targeting	Small Molecule	PTC Therapeutics	Advanced Tumors (Phase 1)
INGN 241	VEGF Targeting	Adenovirus	Introgen	Neoplasm Metastasis (Phase 2)
Cilengitide (EMD 121974)	Integrin Inhibitor	Small Molecule	Merck	Metastatic Solid Tumors (Phase 1/2)
E7820	Integrin Inhibitor	Small Molecule	Eisal	Malignancies (Phase 1)
CP-868,596 (PDGF)	PDGF Inhibitor	Small Molecule	Pfizer	Advanced Solid Tumors (Phase I)
XL184	c-Met Inhibitor	Small Molecule	Exelexis	Tumors (Phase 1)
ARQ-197	c-Met Inhibitor	Small Molecule	ArQule	Metastatic Tumors (Phase 1)
PF2341066	c-Met Inhibitor	Small Molecule	Pfizer	Not yet, early development
MP-470	c-Met Inhibitor	Small Molecule	SuperGen	Solid Malignancies (Phase 1)

CHAPTER 6:
SEQUENCING AND COMBINATION THERAPIES

Now that both the current therapies, as well as the pipeline therapies for RCC treatment have been explained, sequential and combination therapies and their role in the RCC market will now be discussed in detail.

Sequencing Therapies

Currently, targeted therapies are often sequenced naturally. For example, most patients with RCC that require systemic therapy, will be treated with sunitinib 1L followed by everolimus. However, there has not been a study to specifically test if this sequence is really effective or if a sequence of one TKI works better with a specific mTOR inhibitor. It may be the sequencing of agents that provides for the longer periods of remission, but it is not clear. Therefore, there are two studies using sequencing therapies where a patient is on one therapy for a certain period of time followed by a second therapy a certain period of time, with both therapies as 1L and 2L, depending on the arm of the study. It is thought that if a patient remains on an mTOR inhibitor or a TKI for a lengthy period of time that resistance may occur, since the treatment is effective for a certain period of time, but then is no longer effective.

Table 31. Possible Sequencing Therapy using Targeted Therapies Approved by the FDA

AGENTS	# OF PATIENTS	PHASE	PURPOSE
Sunitinib + Everolimus	390	2	Efficacy and safety of 1L Everolimus followed by 2L sunitinib vs. 1L sunitinib followed by 2L Everolimus
Sunitinib + Sorafenib	540	3	Efficacy and Safety of 1L sorafenib followed by 2L sunitinib vs. 1L sunitinib followed by 2L sorafenib in the treatment of 1L Advanced / Metastatic Renal Cell Carcinoma

Until now the existing data supporting sequential therapy in advanced RCC has been retrospective in nature. Additionally, a few small phase 2 trials evaluating sequential VEGF-R inhibitors (sunitinib after bevacizumab; axitinib after sorafenib) have been reported. Another small prospective phase 2 trial evaluating second-line sorafenib after either sunitinib-refractory disease or bevacizumab-refractory disease was also reported in abstract form. In this study, 56 patients who had failed either of these two therapies were treated with second-line sorafenib at the standard dose of 400mg twice daily. The median PFS was 3.8 months and although no responses were observed, 38% of patients on study had some degree of tumor volume reduction by RECIST criteria. Despite the lack of consensus regarding the definition and significance of 'refractory disease,' it is clear that cross-resistance among agents may not occur, and that having a prior response to a VEGF-R inhibitor does not predict for a subsequent response to a similar class of agents. Extensive research continues in an effort to elucidate the mechanisms of resistance to either VEGF-R or mTOR inhibitors.

Fig 9. Percentage Share of Market Comparing Classes of Targeted Therapies, US 2009

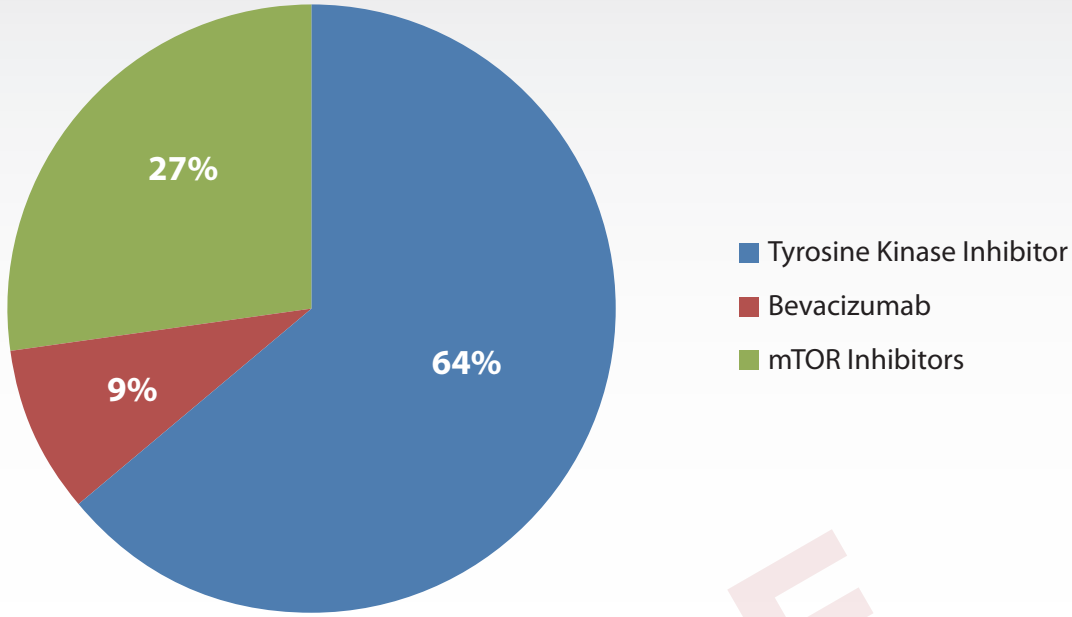
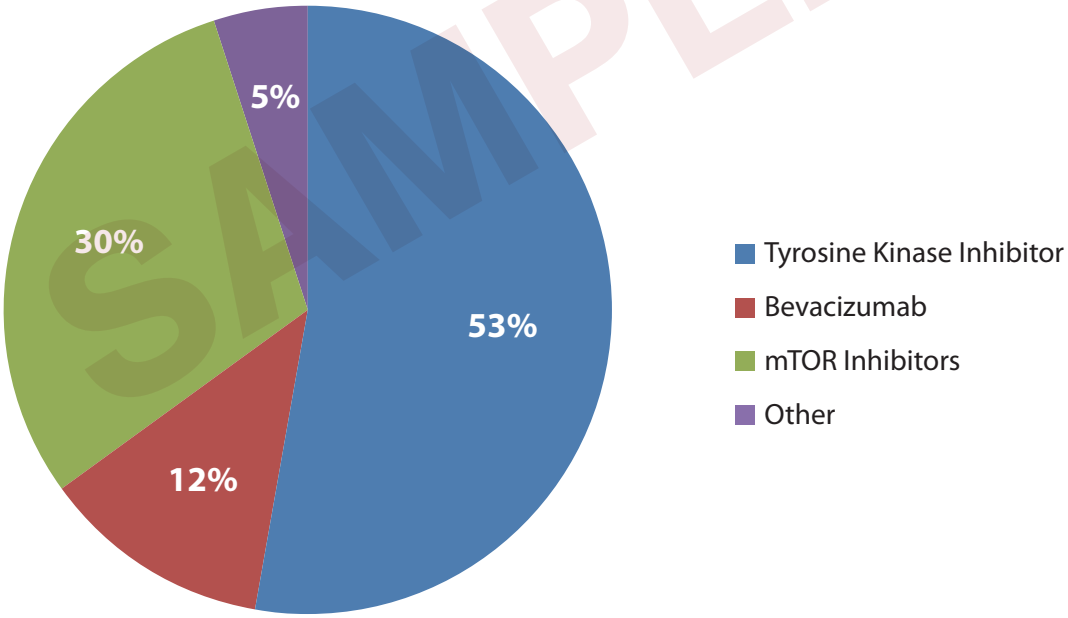


Fig 10. Percentage Share of Market Comparing Classes of Targeted Therapies, US 2013



When comparing mTOR inhibitors and TKIs, TKIs have a larger market share because they are the 1L treatment for good/intermediate risk patients and will also be used 2L when an mTOR is used 1L. However, as RSS patients live longer, the mTOR inhibitors will be used more often accounting for their increased percent of the total market in 2013. The TKI market share will decrease between 2009 and 2013 not because of mTOR competition, but more because of novel mechanisms of action, such as c-met inhibitors, as well as increased utility of bevacizumab.