KerrisdaleCapital

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Mirati Therapeutics, Inc. (MRTX)

Investors Ignoring KRASi Risks

We are short shares of Mirati Therapeutics, a $4.6bn clinical-stage biopharmaceutical company whose lead drug candidate, MRTX-849, is a small-molecule KRAS inhibitor (KRASi). The KRAS protein plays a critical role in cell proliferation and differentiation, and mutations of the gene that encode it are present in one of seven tumors, and in over 30 percent of lung adenocarcinomas. Cracking KRAS has long been one of the holy grails of cancer research, and in the last year, both Amgen and Mirati have suggested they're close.

Both companies have released Phase I data showing that their respective KRASi are capable of shrinking tumors in second-line treatment of patients with KRAS-mutated non-small-cell lung cancer (NSCLC). The compounds also seem to work as intended: by inhibiting the signaling activity of the specific KRAS mutant ($KRAS^{G12C}$) that accounts for ~12-14% of all NSCLC diagnoses. As the only pure KRAS proxy, Mirati's market value has soared. But lost in the euphoria is a realistic assessment of the data and its implications for Mirati. While Amgen's AMG-510 and Mirati's MRTX-849 have indeed induced responses in NSCLC patients, it's becoming clear that the response rate is low and the duration of these responses is incredibly short-lived. That makes approval of the drugs as single agent therapies *extremely unlikely*, even in second line treatment.

As the clinical futility of these KRASi as monotherapy is slowly recognized, the emphasis of the research – and anticipation – is shifting towards their use in a variety of combination therapies, both in first- and second-line treatment. But the data and research are not encouraging. Recent data on the efficacy of checkpoint inhibitors in KRAS-mutant NSCLC strongly suggests that combining them with KRAS inhibition would do nothing to enhance their already robust effect and *could even be detrimental*. Research has also recently revealed considerable heterogeneity in KRAS-mutant tumors, which utilize a wider range of molecular pathways to continue proliferating than had been previously assumed. The upshot is that successful combinations of '849 with other targeted therapies are unattainable because *it's impossible to know in which patients they will be effective*. If that weren't enough, combination attempts are also all but certain to encounter toxicity issues.

The KRAS space is also on the verge of an influx of competition, with several players – including Revolution Medicines and Boehringer-Ingelheim – taking differentiated approaches to targeting KRAS that bypass the resistance mechanisms that '849 has been shown to encounter. These compounds are already in the clinic, and even if Mirati can somehow identify a patient population in which '849 is effective, maintaining market share will be a constant battle. The last decade has shown that first-generation targeted therapies are quickly followed by more potent and effective second-generation compounds. For KRASi, these are already in the clinic recruiting patients for Phase 1 trials, but none are in Mirati's almost-empty pipeline.

Finally, while most of Mirati's value is tied up in the dream of '849, investors are still ascribing significant value to Mirati's other oncology compound, sitravatinib. But given sitravatinib's almost-complete failure as a single agent, we're confident the drug will fail the multiple combination trials Mirati is now conducting. Bolstering our confidence are the weak data, a barely believable mechanism of action, and a sloppy trial riddled with data discrepancies and irregularities that are easily identified in Mirati's sitravatinib presentations. With both '849 and Sitravatinib destined for futility, and its pipeline practically non-existent, Mirati investors will soon discover that the only thing the company can successfully inhibit is their performance.

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I. Investment Highlights

Mirati's KRAS inhibitor, MRTX-849, will probably not be approved as single-agent therapy in second-line non-small-cell lung cancer (NSCLC) Most of Mirati's value is tied to MRTX-849, which is a small-molecule KRAS inhibitor. Though KRAS's role as a "driver" mutation (i.e., *driving* tumor growth) has been known for decades, it's long been considered "undruggable," even as a host of other oncogenic proteins have been successfully targeted in recent years. In the race for a drug that could block the activity of mutant KRAS, the first two companies to come up with a candidate have been Amgen and Mirati.

Both drugs have identical mechanisms of action. They don't inhibit *all* KRAS activity, or even all kinds of *mutant* KRAS activity. Rather, they bind exclusively to $KRAS^{G12C}$ – a particular KRAS mutation found frequently in non-small cell lung adenocarcinoma – inhibiting the activity of the protein and, theoretically, the resultant cancerous tumor growth. The first indication for which approval of the two G12C inhibitors is being sought is second-line (and later) single-agent treatment of NSCLC patients with $KRAS^{G12C}$ mutations. Unfortunately, there are multiple data points that, taken together, suggest that these first generation KRAS inhibitors (KRASi) will come up short in the quest for FDA approval:

- **The trajectory of Amgen's data** – Amgen was the first to dose patients with its AMG-510 in late 2018, and first presented data on the compound's activity at the American Society of Clinical Oncology (ASCO) meeting in June of last year, with an update presented in September. In a bit of irony, much of the excitement around MRTX-849 has been spurred by data from the Amgen clinical trial, which includes many more patient data points and longer treatment periods. The underlying assumption is that, given the identical MOAs, the two drugs will have similar therapeutic efficacy in patients.

  Amgen's initial data release revealed that of 10 NSCLC patients who were treated with '510, 5 showed a partial response (defined as tumor shrinkage of more than 35%), 4 had stabilized, and 1 had progressed. Only 3 patients received the highest dose of '510, and all 3 of those showed a partial response. The initial results understandably generated enormous excitement about the new class of KRASi drugs: given the lack of second line treatment options in these patients, the FDA has a low bar for accelerated approval – a 30% objective response rate (ORR) with a median duration of response of about 6 months.

  But the data presented by Amgen in late September showed that in 2 of the 5 initial responders, the cancer had progressed, and in one case the patient died. Both patients were part of the highest-dosage treatment arm. In the small sample of 3 high-dose patients, the median duration of response was less than 3 months.

By late September, though, Amgen had data on 23 patients, including 13 treated at the highest dose. In the high-dose group (the only one that can even vaguely be described as successful), 7 of 13 patients – 54% – demonstrated a partial response. Again, while the headline ORR looked good, 3 of those 7 patients showed disease progression less than 15 weeks into treatment. Of the other 4 patients, 3 hadn't yet made it to 10 weeks, and the other one – at about 24 weeks – hadn't yet reached the 6 month threshold. If just one of those 3 less-seasoned patients shows disease progression before the 6 month-mark – and that seems likely based on the trajectory of the other patients – the drug will have failed to reach the benchmark 6 month median in an even larger sample than the initial 3 patients.

It's been over 6 months since Amgen's last data update and over 8 months from the last data cutoff. Presumably, Amgen has known for *over 4 months* whether the median duration of response of '510 successfully hit 6 months in more patients. If it did, we think Amgen would have let the market know by now. Further fueling our suspicion of failure, on February 25th, Amgen said that it would report data from the '510 trial by *mid-year*, as opposed to the "early 2020" timeframe that it had originally guided to in September, and noted that "in addition to response rate, it will be important to consider stable disease." That seems like an awfully strong admission that Amgen is trying to move the approval goalposts from ORR/DOR to mere stabilization. We believe the likelihood of succeeding in that is close to nil.

- **Mirati's Data** – compared to Amgen's data, Mirati's single data release for MRTX-849, which was greeted with a one-day boost in market capitalization of $750 million, was devoid of any real content. Though 10 NSCLC patients enrolled in the trial, only 6 were evaluated, with no word from Mirati on why at least one, and maybe two, of the patients went off treatment prior to the first evaluation scan. Of the 6 evaluated, 3 saw a partial response. As with Amgen's '510, while the 50% ORR looks impressive, or at least acceptable, the longest duration of response was a much less impressive 10 weeks. As with Amgen's '510, we expect that given some more time, at least some of those responses will deteriorate into disease progression, calling into question the efficacy of the drug. And as with Amgen's '510, Mirati has now known for about two months whether this initial cohort of patients has been able to achieve an adequate DOR, but has delayed its expected '849 data update from the first half of the current year (probably at ASCO) to the second half of the year (ESMO, World Lung, or the triple meeting). A good rule of thumb for clinical stage pharmaceutical companies is that they don't delay releasing data if the results are good.

- **Preclinical data** – the inability of G12C inhibitors to durably arrest tumor growth shouldn't be very surprising. Over the last few years, preclinical research has revealed two phenomena that speak to the ultimate efficacy of these first-gen KRASi. The first is that KRAS-mutant tumors have varying dependence on KRAS, which

means it's not always the KRAS mutation that's driving tumor growth. So in a significant proportion of KRAS mutant tumors, a KRAS inhibitor just won't impact tumor growth very much, if at all.

Another phenomenon, discussed in the preclinical literature only very recently, is the tendency for tumors to rapidly develop resistance to KRAS inhibitors like '510 and '849. Several resistance mechanisms have been discovered, suggesting that the precision targeting of mutant KRAS, even when *initially* successful, quickly turns ineffectual.

- **The KRAS research culture** – we've had many discussions with prominent research oncologists over the last few months, and the focus of KRAS research has very emphatically moved from KRASi research to combination therapy research, in which a KRASi would be combined with another targeted therapy to generate a deeper and/or longer response. As one investigator told us, "when everyone starts shifting the emphasis from monotherapy to combination therapy so quickly, it's not a good sign for monotherapy."

In sum, the overwhelming conclusion we draw from the data that Amgen has presented, the data that both Amgen and Mirati *haven't* presented, and the findings and direction of KRAS preclinical work, is that '510 – and by extension, MRTX-849 – will come up short in the quest for accelerated FDA approval for second-line treatment of KRAS-mutant NSCLC.

Even in combination with other targeted therapies or immune-checkpoint inhibitors, MRTX-849 is unlikely to prove efficacious or additive There are two kinds of combination strategies that have been suggested as being relevant to KRASi, and on which Mirati has already begun early stage clinical trials.

The first is a combination of a KRASi like '849 with other targeted therapies. The logic here is that knocking out the KRAS-mutant cell-signaling pathway *in combination* with another critical cell-signaling pathway would avert resistance and result in a more lethal tumor-killing effect. But the characteristic heterogeneity of KRAS-mutant tumors that limits the efficacy of single-agent KRASi is also likely to limit the efficacy of any one of these combinations.

The problem is that there are countless permutations of different nodes and pathways involved in promoting tumor growth in $KRAS^{G12C}$-mutant cancer. These can be upstream, downstream, or parallel to the KRAS node itself, *but there's no way to tell in advance which of them is responsible for the cancer, or which of them will be critical for the tumor's resistance mechanism*. If the wrong one is chosen, the only effect induced will be high levels of toxicity with no incremental therapeutic effect. It's possible that biomarkers will one day be found that could inform this kind of combinatorial strategy, but the field is currently a long way from that, and by

the time it gets there, Mirati's first generation KRASi will be a distant memory, with second and even third generation KRAS-targeting compounds having materialized by then.

The other contemplated combination is with immune checkpoint inhibition (ICI), which has revolutionized oncology over the last decade and, in the process, become the standard first-line therapy (sometimes in combination with chemotherapy) in NSCLC. There doesn't seem to be much of a rationale for combining '849 with an ICI in first-line therapy beyond "if it works, first line therapy is a huge market." In fact, the fig leaf of preclinical data upon which Mirati is basing its combination attempt shows no indication that KRAS inhibition can enhance the effect of checkpoint inhibition. What it *does* show is that in one carefully chosen mouse xenograft model, combining '849 with an ICI resulted in a slightly improved tumor response compared to '849 alone. But the tumor model used for these experiments showed no significant response to ICI therapy alone, and an overwhelming response to '849 alone. In other words, it bore zero meaningful resemblance to real-life KRAS-mutant NSCLC.

Both Mirati and Amgen have also touted tumor-level immune markers from their preclinical experiments, which purportedly show that KRAS inhibition makes tumor cells more immunogenic, or susceptible to the immune response that ICIs unleash. The problem is that recent data from Merck's KEYNOTE-042 trial shows that KRAS-mutant NSCLC is already *extremely* immunogenic, with ICIs demonstrating *superior* outcomes in KRAS-mutant patients compared to those with so-called "wild-type" KRAS (i.e., non-mutated KRAS). The implication is that the bar for '849 to improve upon the tumor-killing effectiveness of ICIs is so high, it's incredibly unlikely to be cleared.

The trial data also show that chemotherapy, which normally synergizes well with checkpoint inhibition by increasing the immunogenicity of the tumor, *doesn't do so in patients with KRAS-mutant tumors and may even be counterproductive*. So the exact mechanism being claimed by Mirati and Amgen as the rationale for their combination trials *fails in KRAS-mutant tumors in the clinic* because ICIs are already highly effective as *single agents* in these patients. This is exactly the fait that awaits '849 in combination with checkpoint inhibition.

Potential toxicity in combination with ICIs is another (not mutually exclusive) possibility, particularly considering the high dose of '849 that Mirati is pursuing, and the higher levels of adverse events and dose-limiting toxicities that '849 has reported compared to AMG-510. MRTX-849 will just be the latest compound in a long list of immunotherapy combination attempts that have failed.

MRTX-849 is a first-generation KRAS inhibitor that will quickly become obsolete even in the improbable scenario that it's approved A second generation of KRAS inhibitors, with different MOAs than the G12C inhibitors from Mirati and Amgen, is already in the clinic. The first is Boehringer-Ingelheim's BI-1701963, which takes a broader approach to the KRAS pathway by inhibiting the interaction of *all* KRAS proteins (not just mutant-KRAS) with SOS1, a protein

that helps transform KRAS from its dormant to its active state, thus fueling tumor growth. Targeting the SOS1 interaction with KRAS avoids at least some of the resistance mechanisms identified with '849/'510, potentially resulting in an increased DOR. Boehringer is also testing a combination of BI-1701963 with a MEK inhibitor (MEK being a molecular pathway adjacent to KRAS). Based on our discussions with Boehringer researchers, the logic of their clinical trial with a MEKi is to also address some of the challenges inherent in KRAS-mutant heterogeneity, which could potentially result in increased response rates.

A different approach is being taken by Revolution Medicines, which is targeting the KRAS pathway through the inhibition of KRAS in its active state, bypassing a key resistance mechanism observed in response to the G12C inhibitors, which can only bind to inactive KRAS proteins. Revolution's program is in not yet in the clinic, but the company has presented its preclinical data recently, and expects to nominate a development candidate shortly. Revolution has also worked on an approach similar to Boehringer's but hasn't yet released any data.

Beyond Boehringer's more robust MOA, and Revolution's multi-target approach to KRAS, Moderna Therapeutics is pioneering a vaccine approach (currently in Phase 1) that targets multiple KRAS-mutants, Bayer has a program that (like Boehringer) targets the SOS1-KRAS interaction, and both J&J and Lilly have G12C inhibitors similar to '510/'849 in Phase 1. The odds are just very low that Mirati – with its one flawed G12C-targeting compound – will be a significant player in KRAS.

Sitravatinib is Mirati's latest worthless TKI (tyrosine kinase inhibitor) that will quickly fade from memory Sitravatinib, the other compound in Mirati's pipeline, inhibits the activity of multiple receptor tyrosine kinases (RTKs). Irregular activity of these cell-surface receptors, which regulate various critical cellular processes, is associated with the development and progression of many types of cancer.

Sitravatinib is an interesting example of "thesis creep," which seems characteristic of Mirati's clinical programs. The compound was first advanced as a *single agent* therapy to inhibit the activity of RTKs that were dysregulated due to mutations in the genes that encode them. The first meaningful data, presented in a press release in early 2017, showed an ORR of 50% in a grand total of 4 NSCLC patients. In October of 2017, at the World Conference on Lung Cancer, instead of updating the data from the Phase 1 trial, Mirati presented a case study of a partial response in *one* patient with a rare mutation that had been heretofore untreatable. By this time, Mirati's filings had already relegated Sitravatinib's single-agent prospects to the backburner and began focusing on its potential in combination with an ICI.

Fast forward to 2018, and Mirati's single-agent data on Sitravatinib consisted of a 20% ORR in 20 *renal cell carcinoma* patients (the NSCLC data had disappeared). By this time, it had become apparent that Sitravatinib was a total failure as a single-agent in NSCLC patients with the RTK mutations the compound was supposed to target. At the current time, the only single

agent Sitravatinib trial still running is a Phase 1 in patients with the rare CBL mutation that Mirati discussed at World Lung 2017. Given the lack of any data updates in about *two years*, and the fact that the company's 2019 10-K has eliminated any mention of the drug's single agent prospects, we wouldn't expect much.

Faced with futility as a single agent, Mirati has changed the *entire rationale* for sitravatinib's utility. Instead of blocking mutation-stricken RTKs, sitravatinib now blocks RTKs that are responsible for immunosuppressive activity that generates resistance to ICIs. Of course, it's the same RTKs, but the mechanism of action being touted is retrospectively changed. With sitravatinib purportedly blocking this immunosuppressive activity, Mirati is repurposing it to treat NSCLC patients that have progressed on an ICI. The strategy is to *re*treat with an ICI, but this time in combination with Sitravatinib, which would enhance the immunogenic effect of the ICI.

It's hard to know just how badly this is going. The latest data we have from Mirati on Sitravatinib is from a Phase 2 study, with a data cutoff of August 27th, 2018 – *almost two years ago*. The data weren't very good back then: the ORR was 19.6% (11 of 56 patients); the Kaplan-Meier-estimated DOR of 9.2 months contradicts a DOR of 6 months that's easily calculable from the swimmer plot; and the median overall survival KM estimate of 15.1 months seems suspect considering that 45% (25/56) of the patients dropped out of the study before the 6 month mark. That doesn't even consider some bizarre features of the trial such as a "complete response" from a patient whose tumor shrank by only half, two patients whose disease progressed but who remained on the study, and other peculiarities we cover in further detail below.

Undeterred by all this, Mirati has doggedly pursued a Phase 3 trial in which the Sitravatinib/ICI combo will go up against docetaxel in NSCLC patients refractory to an ICI/chemo combination. Given docetaxel's reported response rates in ICI-refractory patients are actually higher than the 20% response rate elicited by sitravatinib, we expect the trial to end in failure. Apparently, so does Mirati – they recently dropped their 2020 Q4 interim analysis (of ORR, which could potentially have set them up for accelerated approval), leaving only the overall survival analysis that will have to wait until year-end 2021. By then, the focus will conveniently have shifted to KRAS combination strategies.

This wouldn't be the first time that a highly touted Mirati compound will fade just as excitement builds for the next one. Going back to Mirati's posters and presentations from years past, other targeted compounds like glesatinib and mocetinostat can be found, all now relegated to the dustbin of history after failing in the clinic. Sitravatinib is next. And we don't expect MRTX-849 to be too far behind.

II. Company Overview

Mirati: Capitalization and Financial Results

Capitalization	
Share price ($)	$95.38
Fully diluted shares (mm):	
Shares outstanding*	43.1
Dilutive impact of warrants	9.7
Dilutive impact of options/RSUs	2.8
Total	55.6
Fully diluted market cap (mm)	$5,302
Less: cash*	739
Enterprise value	$4,563

Financial Results	2017	2018	2019
Revenue	$-	$ 13	$ 3
Net Income	(70)	(98)	(213)

Source: company filings, Kerrisdale analysis
** Shares outstanding and cash balance are adjusted for Mirati's equity offering on 1/9/2020*

The RAS protein – RAS is short for "rat sarcoma," so called because the various RAS genes were first identified from studies of two cancer-causing viruses in rats – is a central node in some of the most critical cellular signaling pathways. These complex intracellular pathways are composed of chains of proteins that communicate signals from the surface of the cell membrane all the way to the DNA in the cell nucleus. The signals are responsible for managing critical cellular processes including proliferation, differentiation, adhesion, death, and migration. Mutations in the genes that encode the RAS proteins interrupt the normal functioning of these signals and drive cancerous tumor growth: about one in seven tumors (in *all* kinds of cancers) involves a mutation in the KRAS gene (one of the 3 different RAS genes). In the modern era of targeted cancer therapies, KRAS has thus been referred to as the "holy grail" of targeted therapy and the "beating heart" of cancer.

There have been a variety of attempts made to treat KRAS-driven cancers, including:

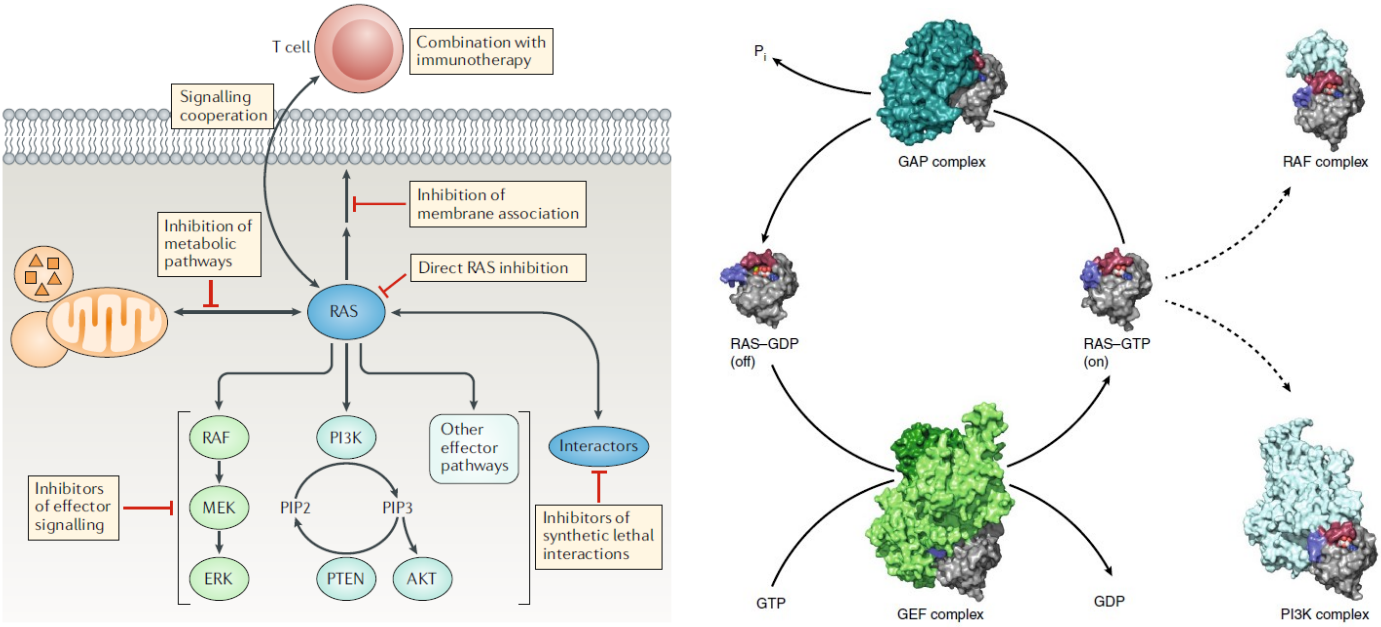
- Directly targeting KRAS by blocking the ability of the KRAS protein to physically situate itself near the cell's plasma membrane. This approach just hasn't worked in KRAS tumors because the tumors rapidly develop resistance to the blockage of the pathway targeted by the drug by using an alternative pathway that remained totally opened.[1]

- Indirectly targeting KRAS by targeting downstream effectors (see the graphic below), particularly the RAF-MEK-ERK pathway (RAS activates RAF, which activates MEK,

[1] Berndt, N et al. *Targeting protein prenylation for cancer therapy*

which activates ERK), also known as the mitogen-activated protein kinase (MAPK) pathway. RAF inhibitors, though, have paradoxically *accelerated* tumor growth in cancers that don't possess a RAF mutation, and ERK inhibitors are still very early in the process of preclinical development. MEK inhibitors, meanwhile, have shown limited efficacy in KRAS-mutant cancers – they clearly inhibit cell growth, but don't show any improvement in patient outcomes compared to the SOC treatment. As we discuss below, the MRTX-849 data is eerily reminiscent of the data from early MEK inhibitor trials, and the resistance mechanisms observed are also similar.[2]

RAS on/off and its associated pathways



Source: Ryan, MB, Corcoran, RB *Therapeutic strategies to target RAS-mutant cancers*, Mullard, A. *Cracking KRAS*

The KRAS protein itself, though, has generally been considered undruggable because of the physical structure of the protein. But in 2013, Kevin Shokat and his team at UCSF found a way to bind a small molecule to one mutant version of the KRAS protein in which the glycine (G) in the 12th codon of the gene is substituted with a cysteine (C) – hence the name $KRAS^{G12C}$. RAS proteins are molecular switches, cycling between the on-state, in which they are bound to GTP (guanosine triphosphate) molecules, and the off-state in which they are bound to GDP (guanosine diphosphate) molecules (see the diagram above, right). The G12C mutation occurs at a "hot spot" in the gene that interferes with the on/off switch, leading to a state in which RAS signaling is "stuck" in the "on" configuration. Shokat's molecule would bind to mutant-KRAS (via covalent bond with the mutated cysteine) in its *off* state, locking it in that configuration.

[2] For a review of the history of attempts at targeting KRAS, see Ryan, MB and Corcoran, RB *Therapeutic strategies to target RAS-mutant cancers*

Theoretically, turning mutant KRAS off would knock out the downstream signaling cascade responsible for tumor growth. Because the binding site for the molecule was at the mutated cysteine, KRAS activity outside the tumor would also remain theoretically untouched.

But the path from a molecule that inhibits $KRAS^{G12C}$ in a test tube to one that's chemically optimized to do so *in vivo* is a long one, and in early 2018, Amgen was the first to get an investigational new drug (IND) application approved. Mirati was close behind, getting IND status for MRTX-849 at the end of 2018. Meanwhile, Wellspring Biosciences – a subsidiary of Shokat co-founded Araxes – was granted IND status for ARS-3248, another G12C inhibitor in the mold of '849 and '510, in May of 2019. Eli Lilly also entered the fray in mid-2019 with G12C inhibitor LY-3499446. All four molecules are currently in Phase 1 and/or Phase 2, with AMG-510 farthest along. Given the prevalence of the G12C mutation in NSCLC – about 12-14% of all lung adenocarcinomas have a $KRAS^{G12C}$ mutation – most of the patients in these trials are second line NSCLC patients, with other G12C-mutant solid tumor patients also participating (primarily colorectal cancer).

KRAS heterogeneity introduces complications

While the race for a G12C inhibitor drug candidate was going on, parallel research on KRAS was revealing that the status of mutant KRAS was more complex than originally thought. The obvious assumption underlying the search for a KRAS inhibitor is that blocking mutant-KRAS will meaningfully impact tumor viability. But it's now understood that in KRAS-mutant cancers, the cancer is *almost never* exclusively dependent on the dysregulated KRAS signaling.

There's a long list of experiments and findings that have demonstrated this phenomenon.[3] The most striking, in our view, is an elegant set of experiments funded by the NIH and National Cancer Institute that were reported in early 2018.[4] Research oncologists analyzed 92 different cell lines from a variety of cancers, including 64 KRAS-mutant lines. They then selectively knocked out various nodes – individually and in combination – along the molecular pathways in which RAS plays a role (for a non-exhaustive list of these nodes, see the diagram above, left). They found, surprisingly, that over a third of KRAS-mutant cell lines *did not even register a response to a total shutdown of KRAS signaling*. In 6 G12C-mutant lung cancer lines, *only 1* responded to KRAS knock-down. Even in cell lines that did respond to KRAS-knockdown, the response wasn't uniform, and rarely did viability deteriorate to the point of cell death.[5]

It's true that findings like this seldom translate perfectly to the complexity of tumors in the clinical setting, but the findings are incredibly significant for what they say about KRAS-dependence. In

[3] For a review, see Yang H et al. *New Horizons in KRAS-Mutant Lung Cancer: Dawn After Darkness*
[4] Yuan, Tina L et al. *Differential Effector Engagement by Oncogenic KRAS*
[5] Ibid, "KRAS knockdown in dependent lines corresponds to a **striking loss of proliferation but rarely translates into appreciable cell death**." [emphasis added]

short, a significant proportion of KRAS-mutant tumors are totally independent of mutant-KRAS signaling, and even those that aren't can usually find an alternative path to viability. The heterogeneous nature of KRAS-mutant tumors means that there exist a host of different cellular signaling paths used by these tumors to proliferate. It's possible that even *within the same tumor*, there are various population subtypes, each with different pathway dependencies. Unfortunately, there's currently no good way to detect in advance whether a KRAS-mutant tumor is dependent on KRAS. And even in "KRAS-addicted" tumors, there's an array of different pathways used for oncogenic signaling, and there's no way to identify which particular molecular route is being hijacked by the cancer.

That's important because, as illustrated by the continued viability of KRAS-dependent cancer cells in the face of KRAS-blockage, and as we detail below in our discussion of resistance mechanisms, neutralizing KRAS is hardly sufficient. It needs to be accompanied by a simultaneous shut-down of the critical links up, down, or parallel to the relevant pathway. Without knowing which links or pathways are critical, a KRAS inhibitor – even one that completely shuts down KRAS signaling – is mostly impotent.

III. MRTX-849 is Extremely Unlikely to be Approved as Second-Line Monotherapy in NSCLC

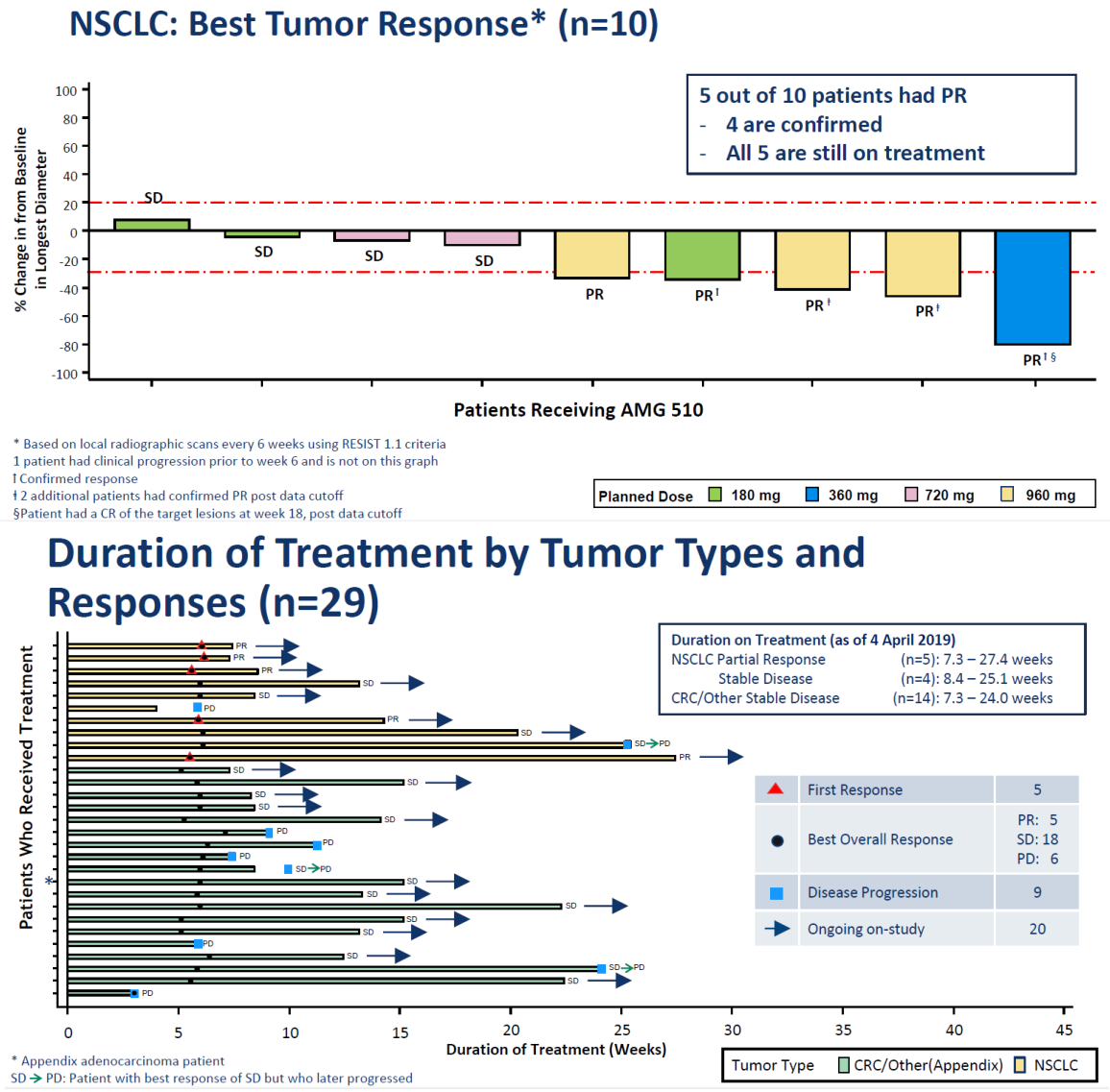
The clinical trial data from Amgen and Mirati are not very good

> *We also think that the pathway forward from a regulatory perspective is most clear [in NSCLC]…there is quite a long precedence of single-arm, single agent trials being used for registration in non-small cell lung cancer,* ***as long as the response rates are above 30%, and the durability of those responses [is] in the range of six months or longer****. We think that that's the fastest path towards initial registration.* [emphasis added]
>
> Mirati CEO Charles Braun at JPM Healthcare Conference – 1/14/2020

Both Amgen and Mirati, in their Phase 1/2 trials for AMG-510 and MRTX-849, respectively, are targeting a ~30% objective response rate (ORR) and a ~6-month duration of response (DOR). That's the goal that needs to be met in order to have a chance at FDA accelerated approval as second line treatment for $KRAS^{G12C}$-mutant NSCLC. Data on the G12C inhibitors is necessarily limited given the small scale of the trials thus far. Amgen's data is more extensive than Mirati's both because its trial began about half a year earlier and because Mirati has been reticent in updating its negligible data set. It has been assumed, justifiably though with some risk, that Mirati's data will be substantially equivalent to Amgen's.

But Amgen's data is actually weak, and has been trending weaker over time. The initial Amgen waterfall and swimmer plots, released at ASCO 2019, looked like this:

AMG-510 Data in NSCLC, ASCO 2019 (data cutoff 4/4/2019)

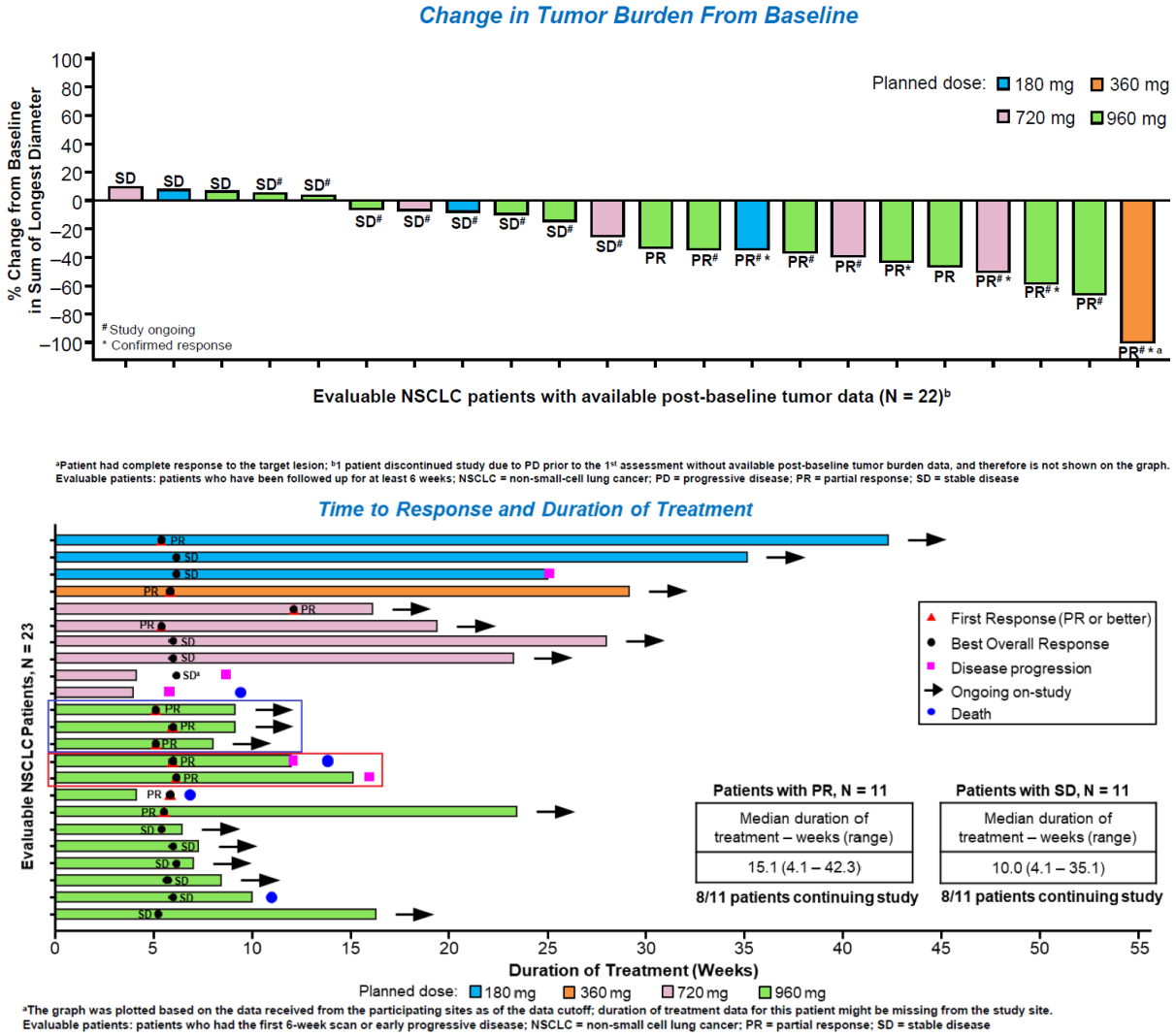


Source: Amgent presentation at ASCO 2019 (June 3rd, 2019), data cutoff is 4/4/2019

For reasons we elaborate upon below, we don't expect the KRAS inhibitors to really have much of an impact in colorectal cancer (CRC), so we'll focus on NSCLC, which is by far the larger market. It's important to note that Amgen's waterfall plot explicitly records the best overall response (BOR) rate in patients and it excludes the one patient that saw immediate disease progression after receiving treatment. Regardless, a partial response rate of 50% (5 of 10 patients), including 3 of 3 patients on the highest dose, was understandably seen as very promising, though only one partial response at that point hit the 6 month mark. The drug was also tolerated well with no serious safety events.

By the time Amgen updated the data at ESMO in late September, the data looked a bit worse:

AMG-510 Data in NSCLC, ESMO 2019 (data cutoff 7/17/2019)



Source: Amgen presentation at ESMO 2019 (September 28th, 2019, data cutoff is 7/17/2019), Kerrisdale analysis

The key inferences made from the above data, some of which Amgen directly addressed, include the following:

- Of the 3 patients on the highest dose that had seen partial responses back at the April cutoff, 2 unfortunately resumed disease progression and one had died (we marked these with a red box in the above swimmer plot).
- Of the 13 patients on the highest dose (in green on the swimmer plot), 7 patients exhibited a partial response for a 54% response rate. But some of those were unconfirmed and will not be confirmed due to disease progression. So the maximum confirmed ORR for the highest dosed arm of the study is about 38%, which is a far cry

from the 100% that was seen when Amgen presented the data at ASCO, and it could still go lower as 3 partial responses have yet to reach ten weeks of treatment and haven't yet been confirmed.

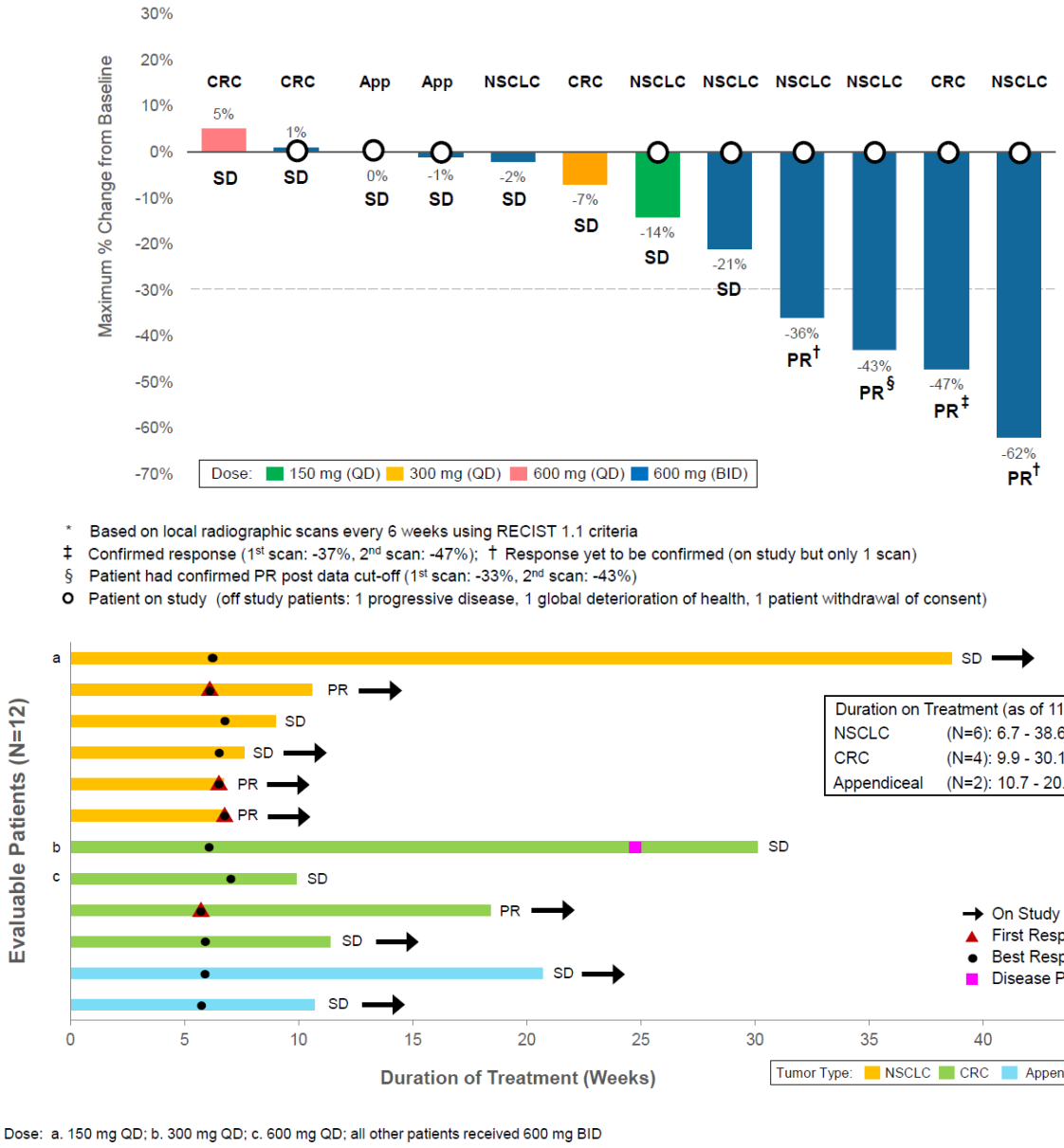
- Of the 7 patients that have responded to treatment on the highest dose, 3 suffered disease progression at various points before the 15-week mark. The simple math here is that if one of the 3 responding patients being treated for less than 10 weeks (we marked these with a blue box in the above swimmer plot) relapses before the ~26-week mark, the median duration of response will end up being less than 6 months. **In our view, this is the most probable outcome, and it means that from the data we have, we can infer that '510 has little chance of achieving accelerated approval**.

Since the July 2019 data that was presented about 6 months ago, Amgen has not given any meaningful update. In fact, while the company suggested at ESMO that they would provide updated data early in 2020, they recently pushed off the update. In a meeting with Goldman Sachs, on which the latter reported in a note dated February 25th, Amgen management said they would report data from the '510 trial in the middle of the year (potentially at ASCO), and also "noted that, in addition to response rate, it will be important to consider stable disease, and pointed to the prior history of BMY's Yervoy in melanoma as an example."[6] That's a damning admission by the company that they expect either the response rate or the duration of response (or both) to come up short of the accelerated approval benchmark communicated by the FDA. Additionally, it's unclear what the approval of Yervoy has to do with AMG-510. Yervoy's approval came after a randomized, double blind Phase 3 study completed in 676 patients, with a standard endpoint of median overall survival (OS). Amgen is running a single-arm Phase 2 treating 100 patients with AMG-510. It's true that Yervoy perhaps didn't elicit a very high response rate, but its efficacy was proven through a large RCT with a survival benchmark before approval. AMG-510 has undergone nothing of the sort.

Meanwhile, Mirati presented data from its '849 trial at the Triple meeting in October, but that data set is incredibly limited (6 NSCLC patients, with only one having taken '849 for longer than ~11 weeks). As a result, it's difficult to come to any strong conclusions from that data beyond the apparent similarities to Amgen's data. Of 6 NSCLC patients, 3 saw a partial response, including 3 of 5 on the highest dose, which is not very different than the original data that Amgen had released at ASCO. Also similar to Amgen's ASCO data, none of the patients that responded had yet made it past ten weeks of treatment (Amgen had 2 of 5 responding patients who were a bit more advanced in their treatment regiment, but neither of those was treated with the highest dose).

[6] Goldman Sachs Equity Research: "Amgen Inc: Management meeting takeaways" February 25th, 2020.

MRTX-849 Data in NSCLC, CRC, and Appendiceal Triple Meeting 2019 (data cutoff 10/11/2019)



Source: Mirati presentation at Triple Meeting 2019 (October 28th, 2019, data cutoff is 10/11/2019)

In colorectal cancer, one partial response was recorded out of the four patients treated. Considering Amgen's weak CRC data (one partial response in 27 patients), we don't believe a 25% response rate will be sustained over a larger number of patients. Moreover, the pathway characteristics of KRAS in colorectal cancer are different than in NSCLC as mutant-KRAS is rarely a central node of dependency in CRC.

The future of Mirati's '849 has been foreshadowed by Amgen's '510 – the partial responses that have been seen will probably not be maintained for long enough to result in a 6 month duration

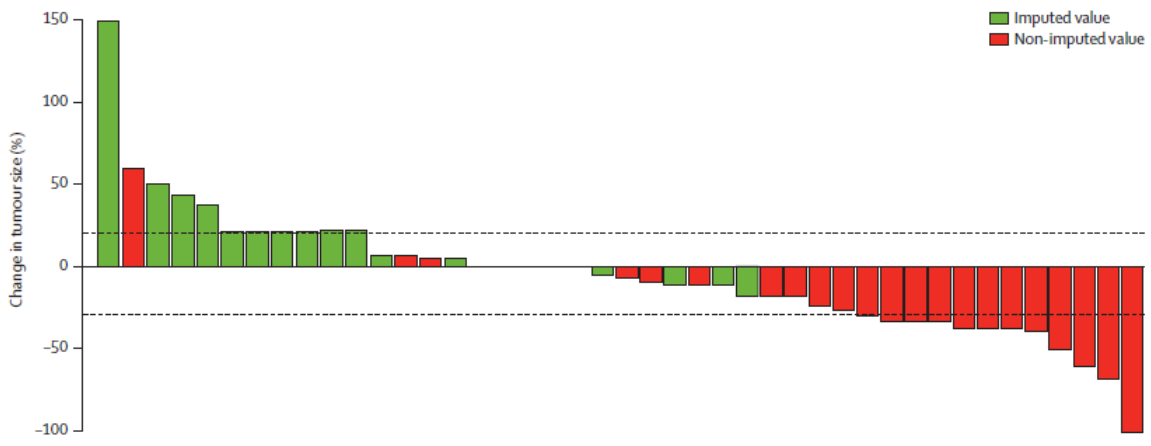
of response, and the response rate will fall as more patients are added to the trial. Indeed, Mirati surely has enough data to provide an update at ASCO, but has chosen to delay providing an update until the second half of this year (probably at ESMO, World Lung, or the Triple meeting). As with Amgen, we interpret a delayed data update as a tacit admission that the evolving data are more mixed than the initial release and will raise questions about the efficacy odds of approval of '849.

Selumetinib is a cautionary tale for G12C inhibitors

The trajectory of AMG-510 and MRTX-849, characterized by relatively promising initial response rates that fade quickly, should be familiar to anyone that's followed KRAS-mutant lung cancer for the last decade. The most promising drug candidate for these patients – before the recent data on immune checkpoint inhibitors – was MEK inhibitor selumetinib, which was invented by Array Biopharma. Array, now a subsidiary of Pfizer, is coincidentally the same company that originated MRTX-849 and subsequently licensed it to Mirati.

MEK is one of the downstream nodes from KRAS on the MAPK signaling pathway. Because KRAS was undruggable a decade ago, it was hypothesized that blocking the path downstream of KRAS might elicit a therapeutic response in patients with KRAS-mutant cancers. In a widely hailed Phase 2 result presented at ASCO in 2012, the combination of selumetinib and chemotherapy drug docetaxel showed extremely promising results. In a presentation given by Dr. Pasi Janne from the Dana Farber Cancer Institute – the same person, coincidentally, that presented the MRTX-849 data at the Triple meeting in October last year –the survival curves and waterfall plots for the combination in KRAS-mutant NSCLC were shown, and the waterfall plot was similar to the one for AMG-510:

Selumetinib + docetaxel for KRAS-mutant advanced NSCLC Phase 2 Study (2012)



Source: Janne, P et al. *Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study*

The plot for the selumetinib combination and the ones for '510/'849 are not perfectly comparable – the selumetinib trial measured the change in tumor-size at a predetermined interval of 12 weeks into treatment, while Amgen and Mirati are presenting "best overall responses" at *any* point between treatment initiation and data cutoff. The AMG-510 waterfall plot from ESMO indicates that in 22 out of 23 patients, the *best* response was the *first* response at the ~6-week mark, so the G12C inhibitors are being graded on a curve. In the Phase 2 of the selumetinib combination, the best overall responses were 37% of patients with a partial response, 44% with stable-disease, and the remaining 19% saw disease progression. That's slightly worse than the 39/56/4% splits from the entire Amgen data set and the 38/62/0% split in the highest-dosage group, but not profoundly different, particularly considering that the selumetinib trial was a true randomized placebo-controlled trial, whereas Amgen and Mirati are running single-arm proof-of-concept trials with far fewer patients (as of the latest data).

The fate of the selumetinib combination was a Phase 3 failure, which was detailed in JAMA in mid-2017.[7] While the Phase 3 trial design was identical to the Phase 2, the response rate to the combination therapy with selumetinib was only 20% compared to the 37% rate in the Phase 2, and progression-free survival was 3.9 months compared to 5.3 months in the Phase 2. The authors couldn't find any good reasons for the differences in results, but it wasn't the first time that a trial with a much larger sample size and better statistical power failed to confirm an optimistic result from a smaller sample set. The data from AMG-510, which deteriorates each time the sample set gets larger, seems to be following that pattern, and we expect the same for MRTX-849.

Adaptive resistance to first-generation KRAS inhibitors has been well documented and the field has already moved on

> *However, two decades of experience with targeted therapies for lung and other types of cancer have taught us that these therapies generally cannot eliminate all cells within a tumor. In almost all solid tumors responsive to targeted therapies, acquired drug resistance inevitably develops, which leads to clinical relapse.* ***An accumulating body of preclinical evidence suggests that cancers driven by mutant KRAS may be especially prone to activate adaptive resistance mechanisms that enable cell survival in the face of suppression of KRAS*** *or downstream mitogen-activated protein kinase (MAPK) signaling.* [emphasis added]
>
> Hata AN, Shaw AT *Resistance looms for KRAS^{G12C} inhibitors*
> Nature Medicine, 2/4/2020

[7] Pasi, J et al. *Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non–Small Cell Lung Cancer*

Preclinical evidence on KRASi resistance provides much-needed scientific context for the disappointing direction in which the data is headed. It shouldn't be surprising that the responses in AMG-510 patients seem to break down rather quickly. Tumors have long been known to possess an array of resistance mechanisms to combat the tumor-killing compounds that are used to treat them. With the G12C inhibitors, the mechanisms of resistance have been detailed in preclinical work that has been published recently, some of it in parallel to the clinical trials being run by Amgen and Mirati. Ironically, some of this research was published by Mirati scientists in their pursuit of potential combination therapies that involve MRTX-849.

One resistance mechanism that was characterized in detail last year by a team from Memorial Sloan Kettering is "adaptive feedback activation of RTKs (receptor tyrosine kinases)."[8] Normally, the mutant-KRAS protein cycles between the on/off states described above. The G12C inhibitor binds to the KRAS protein in its off-state, locking it in that configuration, and effectively shutting down the mutant signaling. But in a subgroup of cells, the growth-factor-receptors on the cell membrane respond to the "locked-down" KRAS by increasing their signaling activity and producing more KRAS protein. The snag is that the new KRAS that's produced in these cells is "manufactured" in the on mode, and KRAS in its on-state does not bind to the G12C inhibitor. This small group of cells is now resistant to the drug, and begins to proliferate, leading to the tumor growing again. At this point, the tumor is now substantially protected from the activity of the G12C inhibitor.

Another resistance mechanism, described recently by Dr. Meagan Ryan and her co-authors, is "RAS pathway feedback activation."[9] KRAS is one of three RAS proteins, HRAS and NRAS being the other two. The assumption is that in KRAS-mutant cancers, the mutant-KRAS is responsible for transmitting the "faulty" signals that result in cancerous tumor growth. Ryan and her co-authors found that when mutant-KRAS is blocked with a G12C inhibitor, the other forms of RAS – heretofore dormant in the tumors, and possessing no mutations – begin to activate, transmitting the tumorigenic signals from the receptors on the cell membrane downstream to RAF/MEK/ERK and eventually the cell nucleus. The detailed mechanics of this process in the clinical setting and how long it takes to play out there are yet to be explored. The authors suggest that combining the G12C inhibitor with a SHP2 inhibitor may hold off this resistance mechanism, though as we discuss at further length below, we think that it will take a while before any combination regiments can be effectively utilized.

The consequences of resistance in $KRAS^{G12C}$-mutant NSCLC are clearly manifested in relatively low overall response rates and short durations of response. These virtually ensure that accelerated approval for MRTX-849 will remain beyond Mirati's reach. But they also foreshadow that, like selumetinib, MRTX-849 is extremely unlikely to improve patient outcomes compared to second line docetaxel in a large randomized Phase 3 trial, which, regardless of the outcome, would still delay approval for years. That's especially the case given that immune checkpoint

[8] Xue, JY, Zhao, Y, *et al*. *Rapid non-uniform adaptation to conformation-specific KRAS(G12C) inhibition*
[9] Ryan, M et al. *Vertical pathway inhibition overcomes adaptive feedback resistance to $KRAS^{G12C}$ inhibition*

inhibition has become the standard of care in first line NSCLC, and docetaxel's response rates and DORs in the second line setting look to be comparable or better than what '510 and '849 are demonstrating in their Phase 2 trials.[10]

The research community apparently agrees. Our discussions with a large number of oncology researchers, as well as the subject matter focus of recent KRAS literature, indicate that the focus of the research community has rapidly moved from single-agent KRAS inhibition to combination therapies meant to address primary and adaptive resistance. Such a rapid shift is telling: the research consensus is concluding that the only way KRAS inhibitors will be useful is in combination. MRTX-849 is unlikely to emerge from the research frenzy intact.

IV. MRTX-849 will not Fare any Better in Combination than as a Single Agent

> *Our work reveals that* ***optimal targeting of KRAS-driven cancers will require coinhibition of both the driver oncogene and upstream, downstream, and parallel collateral dependencies****…the concept that a cancerous phenotype can be driven by a single oncogene* ***is being revised*** *given that…targeted therapies have fallen short on their promise of promoting durable responses and cures for patients.* [emphasis added]
>
> Lou, K et al.
> *KRAS^{G12C} inhibition produces a driver-limited state revealing collateral dependencies*
> Science Signaling, 5/28/2019

The Mirati/Amgen playbook for their G12C inhibitors seems to consist of *hoping* for good-enough data in their single-arm monotherapy Phase 2s to qualify for accelerated approval, while working on combination therapies that will give them longer staying power in the meantime. Mirati has planned four Phase 1 trials that will combine MRTX-849 with another drug. Three of these trials are combinations with other targeted therapies, and one is a combination with an immune checkpoint inhibitor (ICI).

Without good biomarkers, a targeted therapy combination with MRTX-849 is a shot in the dark

Resistance to KRAS inhibitors seems to manifest itself in two forms:

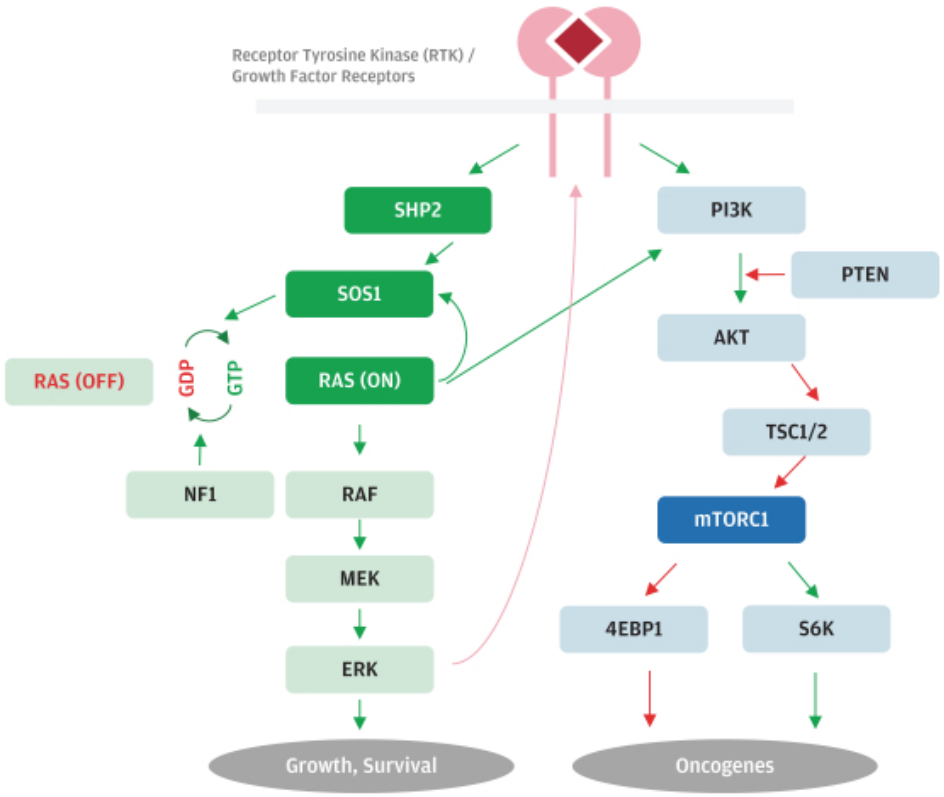
- Primary resistance, in which the tumor doesn't even respond to the treatment. This mode of resistance is related, by and large, to the KRAS heterogeneity discussed previously. A significant proportion of KRAS-mutants, and KRAS^{G12C}-mutants in

[10] We discuss this at further length in our discussion of sitravatinib below. See the references mentioned in footnote 24

particular, are not very dependent on KRAS signaling. Their response to the shut-down of that signaling is therefore negligible, if it even occurs.

- Adaptive resistance, described above, in which the KRAS inhibition initially impacts tumor growth, but the tumor rapidly adapts, in this case by exploiting other nodes in the relevant molecular pathways (see diagram below) to continue proliferating.

Molecular Pathways related to RAS



Source: This diagram is found in the recent IPO registration of Revolution Medicines

It's worth noting that it's difficult to perfectly correlate the phenomena of tumor shrinkage, partial response, stable disease, or disease progression with the various kinds of resistance. A partial response that fades into disease progression, for example, could be a manifestation of different subpopulations within the tumor (one that responds and one that exhibits primary resistance), or it could be an instance of adaptive resistance in which the tumor cells seize on a different molecular pathway to continue growing. Or it could be a combination of these phenomena. Even with a biopsy, it's not easy to tell. These are just different models of resistance to consider, and they're not necessarily mutually exclusive.

The different molecular pathways that KRAS-mutant tumors use to proliferate are delineated in the above diagram:

- KRAS-mutant tumors that are dependent on KRAS use the RAS/RAF/MEK/ERK (MAP-kinase) pathway, which starts with growth factor signaling from the receptors on the cell

membrane and continues, through a process of binding other molecules, to RAS and the rest. Tumors using the adaptive resistance mechanisms delineated above continue to use this pathway to survive and/or thrive, either bypassing KRAS and using the other parallel RAS proteins, or by having the RTKs (the receptors on the cell membrane) signal for the production of KRAS in the "on" state (labeled RAS(ON) above), which are totally immune to the activity of the G12C inhibitors.

- In tumor cells that are essentially independent of KRAS-signaling, it's generally the PI3K pathway through which oncogenic signaling occurs.[11] That's not to say that the RAS/RAF/MEK/ERK pathway is dormant in these cells, just that the critically dysregulated signals are not dependent on that path.

That's a bit of an oversimplification. There are other pathways through which oncogenic signaling can occur, though they are seemingly rare. The RAS and PI3K pathway are also not so neatly separated – ERK has been shown to interact with S6K, and RAS has been shown to interact with PI3K, and there are other arcane interactions that don't seem to figure prominently into the discussion on KRAS inhibition at the current time.[12] Tumor cells can also potentially use both pathways simultaneously, evading the knockdown of any single pathway, even in its entirety.[13]

Additionally, the centrality of the different pathway nodes varies. MEK inhibitors, like selumetinib, have been around for a long time, and have generally been ineffective in KRAS-mutant cancer patients (at least partly because of the same resistance mechanisms that have been found to operate on the G12C inhibitors). But one of the underlying assumptions (yet to be validated) of the race for a KRAS inhibitor is that blocking KRAS would be inherently more effective than blocking MEK, even though MEK is right downstream of KRAS. Similarly, research has shown PI3K may not be the best target for the PI3K pathway, and perhaps AKT or mTOR knock-down would be more effective.

With this in mind, Mirati has set up the following attempts at targeted therapy combinations with MRTX-849 for NSCLC:

- '849+afatinib: Afatinib is an EGFR inhibitor, and EGFR is an RTK that has been shown to be implicated in the resistance to G12C inhibition by signaling for the production of more RAS in the "on" state. The logic here is that if EGFR is shut down, then the concentration of RAS(ON) can be kept low enough that the G12C inhibition can properly target the RAS(OFF) protein.
- '849+CDK4/6 inhibition: CDK4 and CDK6 are proteins that are downstream of both the RAS and PI3K pathways, and are involved in cell division. Overactivity of CDK4/6 has been implicated in cancerous growth. The logic of inhibiting both $KRAS^{G12C}$ and CDK4/6

[11] PI3K is short for "phosphatidylinositol 3-kinase"

[12] See Asati, V et al. *PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives*

[13] Jaiswal, BS et al. *Combined Targeting of BRAF and CRAF or BRAF and PI3K Effector Pathways Is Required for Efficacy in NRAS Mutant Tumors*

is that oncogenic signaling from KRAS and/or PI3K may be manifested in CDK4/6 overactivation, so shutting down CDK4/6 would be lethal for cancer cells.

- '849+SHP2 inhibition: SHP2 is a protein that regulates the signaling from the RTKs to the RAS pathway. The logic of inhibiting SHP2 in combination with $KRAS^{G12C}$ is that some of the observed resistance mechanisms to G12C have involved feedback-driven RTK signaling, and inhibiting SHP2 could interfere with that oncogenic signaling.

In our view, these trials are a desperate shotgun approach to making MRTX-849 relevant in the absence of substantial single-agent efficacy. The inhibition of EGFR, CDK4/6, and SHP2 have all been tried as single agents in KRAS-mutant cancers, and all have failed.[14] There's some logic in all of the above combinations, but successful combinations in oncology almost always involve drugs that have shown efficacy on their own. Combining two drugs that each result in low response rates of short duration is the triumph of hope over experience.

Additionally, all the above candidates to be combined with '849 have demonstrated toxicity in patients as single agents because they don't just target mutant-signaling, they target *all* the EGFR/CDK/SHP2 activity, including in non-tumor tissue. '849 has not shown very high levels of toxicity because it only targets mutant KRAS, but other mutant-targeting therapies – including the blockbuster osimertinib, an incredibly effective EGFR inhibitor that targets only mutant EGFR – have shown significant toxicities in combination. That could potentially be a function of high dosages used by patients on these therapies, which is a feature of '849 treatment as well. In this context, the higher rate of adverse safety events in the '849 trial compared to the '510 trial could put Mirati at a structural disadvantage relative to Amgen in the KRAS inhibitor race.

But the most significant problem with all of the above combinations goes back to the heterogeneity of KRAS-mutant tumors and the complexity of the varying pathway combinations used for oncogenic signaling. The Shokat lab – the same group that discovered the binding mechanism employed by the multiple G12C inhibitors currently being trialed – conducted a set of experiments upon which many of the above combination strategies are based. They found that

> *Together, our experiments nominate two classes of combination therapies that either enhance $KRAS^{G12C}$ target engagement (namely, **EGFR**, FGFR, or **SHP2** inhibitors) or independently suppress persistent survival pathways (namely, AXL, PI3K, or **CDK4/6** inhibitors)…Our experiments revealed collateral dependencies* [i.e., alternative pathway nodes on which KRAS-mutant cancers are dependent] ***upstream** of $KRAS^{G12C}$ in NSCLC…We reveal that the relevant receptors in these signaling networks **are cell-type-specific**…We also identified collateral dependencies **downstream and parallel** to*

[14] For a review that covers EGFR and CDK4/6 inhibition, see Ferrer, I et al. *KRAS-Mutant non-small cell lung cancer: From biology to therapy*. SHP2 inhibition has not been tested in the clinic, but its most strident proponent, Revolution Medicines, has presented data on preclinical activity in several forms, and has positioned its own SHP2 inhibitor as a combination candidate rather than a single agent candidate. See Revolution's IPO prospectus and the poster and slides recently presented, including a waterfall plot with a response rate of 5.5% (1 of 18 patients).

> *$KRAS^{G12C}$ that were incompletely suppressed by driver oncogene inhibition.* [emphasis added][15]

In other words, they found that there are lots of other nodes and pathways involved in promoting tumor growth in $KRAS^{G12C}$-mutant cancer, and that these can be found upstream, downstream, and parallel to the KRAS node. ***But there's no way to tell in advance which pathway will be used or is being used, or which resistance mechanism is likely to be employed by the tumor***.[16] It's even possible that tumors are "fluid" in the sense that they can change which pathways they depend on to continue proliferating.[17] A combination with an EGFR inhibitor won't work for a tumor that develops resistance through other RTKs; a SHP2 inhibitor won't work for a tumor that develops resistance through the PI3K pathway; and a CDK4/6 inhibitor won't work if the RAS or PI3K pathways are operating through the myriad other downstream effectors.

There are no biomarkers that are currently known to reveal any of this critical information. Our conversations with various prominent research oncologists suggest that there is a lot of research that is ongoing in this area, including using new computational methods with ctDNA data, but the field is very early in this process. Until molecular or genetic biomarkers can reveal the specific pathways and mechanisms that are active in a patient's tumor, combination therapy will remain a proverbial roll of the dice.

The attempt to combine MRTX-849 with immune checkpoint inhibition will fail

Immunotherapy has revolutionized the oncology landscape in the last decade. In many kinds of cancer, tumor cells successfully neutralize the body's immune response through the expression of PD-L1 (programmed cell death-ligand 1) ligands on the tumor-cell surface. These ligands bind to the PD-1 proteins on the surface of T-cells, acting as a brake on their immune activity (hence the label "immune checkpoints"). Immune checkpoint inhibitors (ICIs) bind to either the PD-L1 on the tumor-cell surface or the PD-1 on the T-cell-surface, inhibiting the immune checkpoint, and unleashing the body's immune system against the tumor. No cancer treatment is perfect, and while ICIs are incredibly effective in what seems to be a continuously expanding list of tumor-types, not everyone responds to immune checkpoint inhibition, and many patients

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[15] Lou, K et al. *$KRAS^{G12C}$ inhibition produces a driver-limited state revealing collateral dependencies*

[16] There are other flaws in the study that have been pointed out to us in our conversations with research oncologists. For example, the set of experiments was conducted on only two standard lab models of G12C-mutant tumors – one in NSCLC and one in pancreatic cancer – among the tens of available G12C-mutant models, and both models used are significantly more susceptible to G12C-targeting than real-life G12C-mutant tumors in patients. So the suggested combinations will not be as effective in real tumors and, as the authors admit, the pathways identified are almost certainly not the only relevant pathways.

[17] In Yuan et al. (see the reference in footnote 3 above), the authors conclude "If the transition from the KRAS to the RSK [PI3K/S6K] state is fluid or reversible, a tumor might be able to escape therapies that target either state alone."

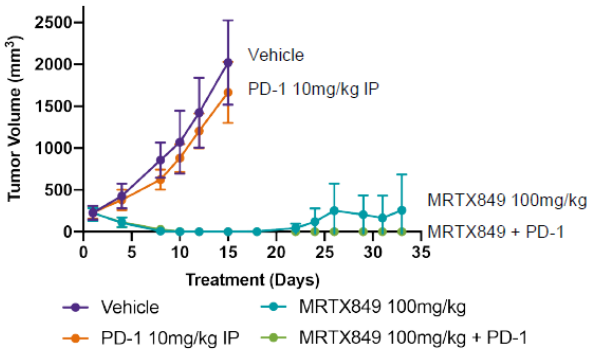
that respond still end up developing resistance (though the durations of responses tend to be relatively long). ICIs are also unsurprisingly associated with autoimmune-like toxicities.

Despite these drawbacks, ICIs have become the de-facto standard first-line therapy in advanced NSCLC. In patients with high levels of PD-L1 expression in their tumors, checkpoint inhibition is used as monotherapy, while in patients with low PD-L1 expression, a combination of ICIs and chemotherapy is the standard. The combination with chemotherapy came about because as monotherapy, ICIs have lower response rates than chemotherapy in advanced NSCLC patients with low PD-L1 expression. But in combination with chemotherapy, ICIs result in approximately *double* the overall response rate as chemotherapy.[18] Conventional chemotherapy significantly enhances the immune response triggered by ICIs, with multiple molecular processes identified as the basis for this immune-stimulating activity.[19]

Researchers have raced to find other compounds that could synergize with ICIs and potentiate their activity ("turning a cold tumor hot") or even enhance their efficacy in indications where they're already effective. The attempt to combine '849 with pembrolizumab, Merck's blockbuster PD-1 inhibitor, is just the latest in a long line of ICI combination efforts. Mirati and Amgen laid out the scientific rationale for the G12C-inhibitor/ICI combination in a series of preclinical experiments in which their respective compounds were combined with an ICI. The combination resulted in deeper and more durable tumor responses than either agent alone, as shown below:

MRTX-849 Combination with Checkpoint Inhibitor

KRAS G12C Inhibition Combined with Checkpoint Inhibitor Therapy Demonstrates Durable Complete Regressions *In-Vivo*[1]



Source: Mirati Corporate Presentation, January 2020

[18] Langer, CJ et al. *Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous NSCLC: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study*

[19] For a review and detailed examples, see Leonetti, A et al. *Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer*

The catch is that the mouse tumor model used by both Mirati and Amgen bears zero resemblance to $KRAS^{G12C}$-mutant tumors in real human beings. First, note how the mouse tumors respond almost completely to MRTX-849. Within 10 days, these tumors seem to completely shrink down to close to zero. The human tumors treated with MRTX-849, by contrast, have exhibited zero complete responses. It's also not at all clear, based on Mirati's presentation of the preclinical data, that a checkpoint inhibitor results in any additive or synergistic effect compared to '849 on its own – there's little difference between the tumor size trajectories of the mice treated with '849 and the mice treated with the combination.

But the most unrealistic element of the preclinical data is strongly related to why a G12C inhibitor is extremely unlikely to demonstrate *any* synergy with an ICI in the clinic. In the above diagram, the checkpoint inhibitor basically exhibits no efficacy: the tumor growth in the control group is almost indistinguishable from the growth in the mice treated with a checkpoint inhibitor (the orange line labeled PD-1 10mg/kg). But in KRAS-mutant NSCLC, checkpoint inhibition is *exceptionally* effective, and perhaps *especially* in the G12C-mutant variant. The efficacy of ICIs in KRAS-mutant NSCLC has been demonstrated repeatedly in retrospective analyses of the many trials involving ICIs, and several molecular mechanisms have been hypothesized.[20] KRAS-mutant tumors have also been associated with high levels of PD-L1, which could partly explain why they seem so susceptible to ICI therapy.[21] In mid-December, Merck disclosed the following exploratory data from its KEYNOTE-042 trial, in which advanced-NSCLC patients with medium and high levels of PD-L1 expression were treated with pembrolizumab:

Phase 3 KEYNOTE-042 Data

	With Any KRAS Mutation		With KRAS G12C Mutation		Without Any KRAS Mutation	
	KEYTRUDA Monotherapy	Chemotherapy	KEYTRUDA Monotherapy	Chemotherapy	KEYTRUDA Monotherapy	Chemotherapy
	(N = 30)	(N = 39)	(N = 12)	(N = 17)	(N = 127)	(N = 105)
OS, median, months (95% CI)	28 (23-NR)	11 (7-25)	NR (23-NR)	8 (5-NR)	15 (12-24)	12 (11-18)
OS, Hazard Ratio (95% CI)	0.42 (0.22-0.81)		0.28 (0.09-0.86)		0.86 (0.63-1.18)	
ORR, % (95% CI)	56.7%	18.0%	66.7%	23.5%	29.1%	21.0%
PFS, median, months (95% CI)	12 (8-NR)	6 (4-9)	15 (10-NR)	6 (4-8)	6 (4-7)	6 (6-8)
PFS, HR (95% CI)	0.51 (0.29-0.87)		0.27 (0.10-0.71)		1.00 (0.75-1.34)	

Source: Merck Press Release, December 12, 2019

[20] For a review of these trials, see Adderly, H et al. *KRAS-mutant non-small cell lung cancer: Converging small molecules and immune checkpoint inhibition*.

[21] See, e.g., Skoulidis, F et al. *Co-occurring Genomic Alterations Define Major Subsets of KRAS-Mutant Lung Adenocarcinoma with Distinct Biology, Immune Profiles, and Therapeutic Vulnerabilities* and Liu, C et al. *The superior efficacy of anti-PD-1/PD-L1 immunotherapy in KRAS-mutant NSCLC that correlates with an inflammatory phenotype and increased immunogenicity*, and the references therein. In the original Merck clinical trial for pembrolizumab in NSCLC – KEYNOTE-001 – about 80% of patients with identifiable KRAS mutations had medium or high levels of PD-L1.

Pembrolizumab monotherapy resulted in longer overall survival and progression-free survival, lower hazard ratios, and higher response rates in patients with KRAS-mutant tumors than in patients with no KRAS mutations. The results for patients with tumors that harbored specifically the G12C-variant of KRAS were even better than for patients with other KRAS mutations (though this difference was not statistically significant). Even more jarring, and damaging for the prospect of an '849/ICI combination, Merck also released data from its KEYNOTE-189 trial with splits for KRAS mutational status. Comparing the results of the two trials, it's apparent that in KRAS-mutant NSCLC, *chemotherapy is not synergistic with pembrolizumab*. So even though chemotherapy is clearly immuno-stimulating in non-KRAS-mutant tumors in the sense that it makes the tumor more vulnerable to ICIs, in KRAS-mutant tumors that's quite clearly not the case. It might even be counterproductive.

Based on conversations with research oncologists and molecular biologists, the simple explanation for this is that KRAS-mutants are already quite immunogenic. ICIs allow for the immune system to kill tumor cells so effectively in KRAS-mutants, that the immune-stimulating effects of chemotherapy are irrelevant. That's *exactly* what we expect with the '849/ICI combination. The Mirati and Amgen preclinical experiments show that '849 and '510m respectively, altered the tumor-microenvironment in ways that made it susceptible to an ICI, but real-life KRAS-mutant tumors are *already* susceptible to ICIs. A G12C inhibitor is not going to change that by much. The preclinical results were an artifact of "turning a cold tumor hot" but real KRAS-mutant NSCLC tumors are already scorching.

Beyond the underlying cancer-killing mechanisms, there's another good reason to expect that the G12C inhibitors will fail to synergize with ICIs: the only examples of ICI combinations that have shown effective synergy have been in situations where the second drug is already effective as a single agent. Chemotherapy is the obvious example, but there are several others, including triplet therapy in BRAF-mutant melanoma, the combination of pembrolizumab and RTK-inhibitor axitinib in metastatic renal cell carcinoma, and even combinations of ICI modalities.[22] In every single case, the drug that's successfully combined with the ICI has impressive single-agent efficacy on its own, which is not the case for '849 or '510. The rationale for combining '849 with pembrolizumab basically comes down to the ability to shrink a homogeneous tumor model in a mouse. It's a tenuous proposition at best.

[22] For data on triplet therapy in melanoma, including the activity of the combination of dabrafenib and trametinib in the absence of pembrolizumab, see Ascierto PA et al. *Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma*. For data on the combination of axitinib and pembrolizumab, see Rassy, E et al *Tyrosine kinase inhibitors and immunotherapy combinations in renal cell carcinoma*. For data on the combination of Nivolumab, an ICI that targets PD-1, and ipilimumab, an ICI that targets CTLA-4, see Larkin, J et al. *Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma*.

V. Sitravatinib is a Monotherapy Failure being Repurposed into a Combination Failure

Sitravatinib is a "dirty TKI" (tyrosine kinase inhibitor) in the parlance of the oncology field. In other words, it doesn't target one particular RTK, but rather, it targets a few receptor tyrosine kinases at once. RTKs are cell-surface receptors for all manner of different molecules that need to make their way through the cell membrane and into the cell. As with KRAS inhibition, the goal of inhibiting these RTKs is to stop oncogenic signaling at the root of tumor growth. At least that was Mirati's original rationale for sitravatinib.

From the start, though, the data on sitravatinib as a single-agent treatment in advanced cancer patients was weak and even contradictory. In a Phase 1 trial in which 52 patients enrolled, treatment was discontinued in 31 (60%) of them, 23 of which discontinued due to disease progression. Of 32 evaluable patients, Mirati only registered 2 partial responses. It seems like those responses were from patients in the 150mg-dose arm of the trial, but the poster that Mirati presented at ASCO in 2016 leaves the reader confused as to whether there were 4 or 10 patients in that arm of the trial. That was the last waterfall plot Mirati ever showed for sitravatinib as monotherapy in NSCLC. The only significant data update was through a press release in early January, 2017, in which Mirati announced that of 4 evaluable NSCLC patients in its sitravatinib Phase 1b trial, 2 demonstrated a partial response (1 confirmed) and the other two demonstrated stable disease. Mirati announced an equity offering simultaneously. That was the last meaningful data update on single-agent sitravatinib in NSCLC.

Single-agent Phase 1/1b data on sitravatinib in renal cell carcinoma patients was presented by Mirati at ASCO in 2018. Of 29 enrolled patients, only 20 "had sufficient time on…assessments for inclusion," which, based on the swimmer curve was somewhere on the order of 4 weeks. Of those 20 patients, 4 partial responses were recorded, and the majority of patients were off the study before the 6-month mark. The clinical trial is no longer listed on Mirati's website, so we assume that Mirati just gave up.

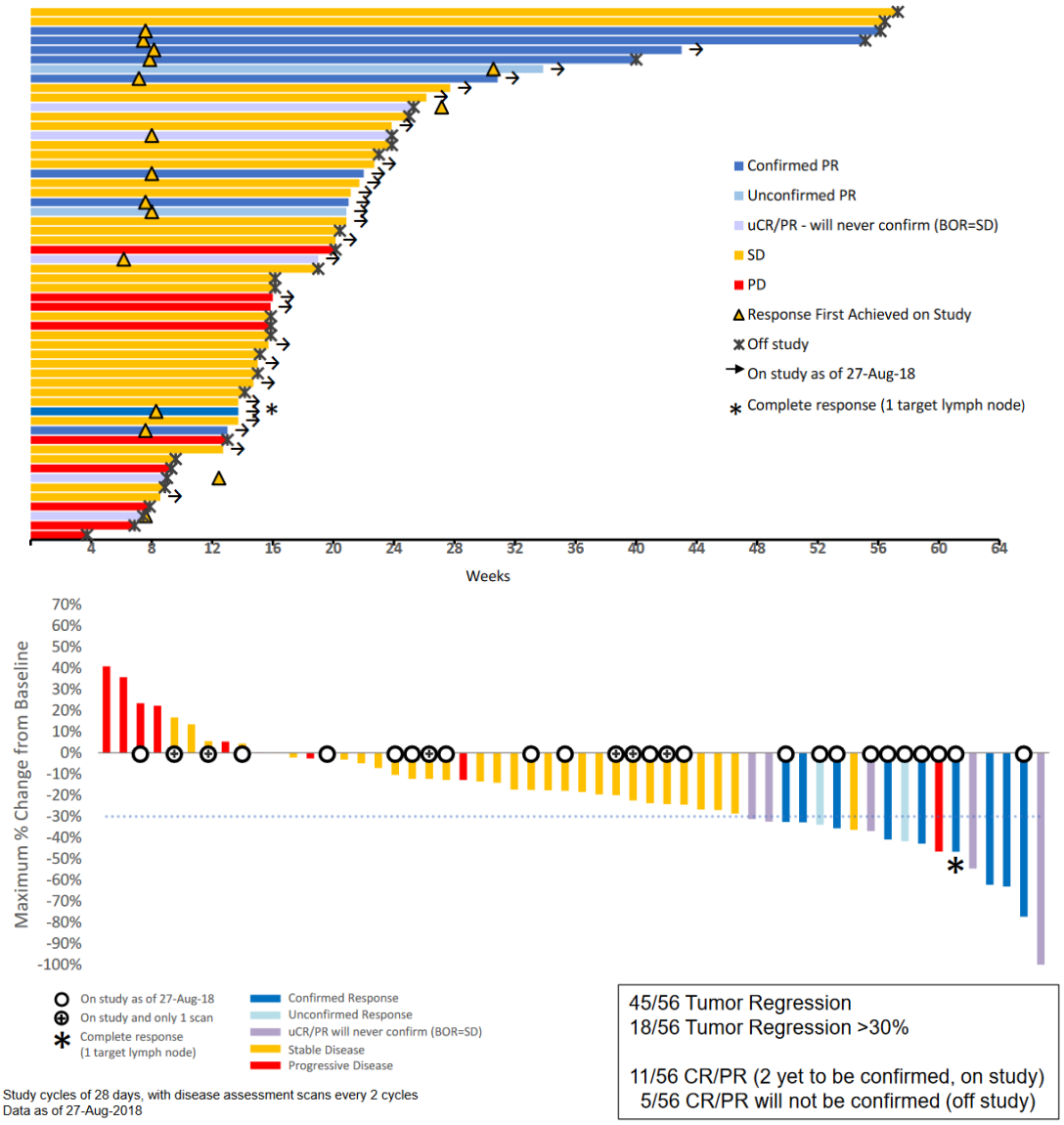
The only other single-agent data that Mirati has released for sitravatinib is for patients with a rare CBL mutation that has been theorized as a cause of solid-tumor cancers. At ESMO in 2018, Mirati showed a partial response in 2 of 8 evaluable patients, but most patients demonstrated relatively rapid disease progression, and only 1 patient had remained on the study at data cutoff. In Mirati's recently released 10-K for 2019, all mention of sitravatinib as a single agent drug candidate was dropped.

In mid-2017, with single-agent trials not going anywhere, Mirati began to repurpose sitravatinib as an "immuno-oncology agent." Instead of inhibiting faulty RTK signaling responsible for driving tumor growth (which failed), sitravatinib would inhibit the *same exact RTKs*, but for a different reason: these same RTKs – coincidentally – happen to suppress immune activity that could

otherwise be harnessed by ICIs to work against the tumor. Blocking these RTKs in patients that have progressed on immune checkpoint inhibitors could potentially restore the efficacy of checkpoint inhibition.

To test this hypothesis, Mirati began a Phase 2 trial enrolling patients "whose most recent treatment must have included a checkpoint inhibitor with the result of progression of disease on or after treatment." These patients would be treated with a combination of sitravatinib and nivolumab, an immune checkpoint inhibitor sold by Bristol-Myers Squibb. The latest swimmer and waterfall plots disclosed by Mirati are displayed below:

Sitravatinib data in 2L NSCLC ESMO 2018 (data cutoff 8/27/2018)



Source: Mirati presentation at ESMO 2018 (September 21st, 2018, data cutoff is 8/27/2018)

It's hard to know where to begin with this data:

- The confirmed response rate was a very weak 20% (11 of 56 patients). This is an important data point because in the current Phase 3 that Mirati is running, the sitravatinib and nivolumab combination is going up against docetaxel in ICI-refractory patients. Mirati's contention is that while a 20% response rate isn't great, it's better than the response rate seen in second-line patients treated with docetaxel, which Mirati pegs at either 7-11% or 9-13% (Mirati uses different ranges in different investor presentations). Remarkably, the sources Mirati draws upon for this data are a) other biotech companies' corporate presentations[23] or b) clinical literature that measures docetaxel responses in *patients who were previously treated with platinum doublet chemotherapy*. The latter is deeply misleading, as it's widely understood that docetaxel in ICI-refractory patients results in significantly higher response rates than in chemo-refractory patients. These studies surveying this are retrospective, but they peg the response rate to docetaxel in ICI-refractory patients in the 25-40% range, which is significantly better than what Mirati is claiming for sitravatinib.[24] The comparisons made by Mirati are useless at best and disingenuous at worst.

- In the corporate presentations Mirati has published since the 2018 presentation of the above plots, the company has claimed that based on this data, the Kaplan-Meier estimate for median duration of response was 9.2 months, the estimate for progression-free survival (PFS) was 6.8 months, and the estimate for overall survival (OS) was 15.1 months. It's difficult to take these estimates seriously. The KM-estimated DOR of 9.2 months comes from data in 11 patients that demonstrated partial responses, including 7 patients that were on the study for 3 months or less. The "estimate" has such a wide degree of error, that Mirati didn't bother attaching a confidence interval to it. Similarly, the OS estimate of 15.1 months is hardly believable: 84% (47/56 patients) of evaluable patients hadn't yet made it to 6 months, and 53% of those (25/47) were no longer on the study at all. Mirati also failed to explain *why* over half of patients dropped out: clearly, some suffered disease progression, but it looks like 23 patients that had responded or had stable disease also dropped out, and some of them quite early on.

[23] In an investor presentation that's dated "November, 2018" and no longer on Mirati's website, the company suggests that the ORR for Docetaxel in "checkpoint refractory patients" is 7-11%, and references a "Syndax corporate presentation" in the footnotes.

[24] See, e.g., Leger, PD et al. *Response to salvage chemotherapy following exposure to immune checkpoint inhibitors in patients with non-small cell lung cancer* or Schvartsman, G et al. *Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced NSCLC*. For a discussion of the underlying mechanism of this phenomenon, see Hadash-Bengad, R et al. *Immunotherapy Potentiates the Effect of Chemotherapy in Metastatic Melanoma—A Retrospective Study*

Besides the non-credible end-point estimates – none of which have been updated in about two years – and the completely misinformative comparisons to docetaxel, the swimmer and waterfall plots seem to point to a very sloppy trial:

- Two patients with disease progression remained on the trial, contrary to oncologic practice.
- One patient saw an unconfirmed response at 12 weeks even though they dropped out of the trial at about 8 weeks. Another unconfirmed response, labeled as "will not be confirmed" was still on the study as of data cutoff. Generally, an inability to confirm a response is a function of disease progression, which should be labeled as such.
- Per the trial protocol, disease assessment scans were to be made every 8 weeks, but at least two responders – significant given the low response rate – weren't scanned until 28-30 weeks.
- 30 of 56 patients were no longer on the study, but of those, only 6 demonstrated disease progression. There's no word on what happened to the other 24 patients. Mirati does disclose that 12 patients discontinued study treatment due to toxicity, but that's from the pool of 70 enrolled patients rather than the 56 patients plotted on the graphs. Mirati also disclosed that there were 65 evaluable patients so it's not clear only 56 patients were plotted.

Potentially even more suspicious than any of the above is the fact that Mirati has never updated this information since the 2018 ESMO conference. If those fragile Kaplan-Meier estimates could have been updated with solid data, we expect that Mirati would have released that by now. Instead, the company has diverted investor attention to a Phase 3 trial in which ICI-refractory patients will be given either docetaxel or the sitravatinib+nivolumab combination. We think the only thing to come out of this trial will be quality prospective data on the efficacy of docetaxel in ICI-refractory patients. Mirati, too, doesn't seem very confident. The company initially designed the trial to report an interim analysis at the end of 2020 in which superior outcomes on an ORR endpoint would serve as the basis for accelerated approval. In January, the company dropped that interim target and renamed its year-end 2021 "primary analysis" of overall survival as an "interim analysis with potential for full approval." We believe that's just posturing – any accelerated approval would anyway have been contingent on the development of the data. The reason they dropped the interim data readout is probably because they didn't think it would be very flattering. Finally, in a recent meeting with analysts from Oppenheimer, Mirati suggested that sitravatinib may be impacted by a COVID-19-related reduced patient enrollment in its Phase 3 trial.[25] Somehow, Mirati also announced that they mitigated that risk with the '849 trial.

We think that the combination of sitravatinib with an ICI is a charade, an attempt to salvage a drug that's proven mostly worthless as a single agent. The ex-post rationalization of the immuno-restorative effect of a multi-kinase inhibitor is a valiant effort, but sitravatinib is the latest in a long list of multi-kinase inhibitors, and if the logic of resuscitating the response to ICIs –

[25] March 30th note from Oppenheimer: "Key Takeaways from Discussion with Management"

literally *reversing resistance* to immune checkpoint inhibition – was even remotely compelling, it would have gained traction long ago. We expect that sitravatinib will soon join glesatinib and mocetinostat – two other compounds that Mirati has touted over the years but which, "in light of superior investment opportunities," were quietly dropped. In the context of all the noise being made in the KRAS space, sitravatinib looks like it will soon follow.

VI. Conclusion

Mirati first catapulted to the status of a billion-dollar biotech on the back of excitement over sitravatinib, which has largely turned out to be a mirage: almost all prospect of its single agent potential has evaporated, and the combination with checkpoint inhibition in checkpoint-refractory patients is an attempt that looks more like a diversion than a legitimate therapeutic candidate with a scientific rationale.

Most of Mirati's $4.6bn valuation now is tied to MRTX-849, a $KRAS^{G12C}$ inhibitor with a "$7 billion market opportunity" according to the company. But the total addressable market (TAM) numbers that Mirati is throwing around are laughable. For one, they assume a patient population that includes first line treatment. The only way '849 will come close to first line treatment is if it somehow gets approved in combination with checkpoint inhibition, and as we've explained in detail, the odds of that happening are close to zero. Mirati's absurd TAM proclamation also assumes a duration of treatment that's about 9 months, which is delusional considering that even in patients that respond to '849 treatment, the duration of response is just a few months. The TAM for second line treatment in $KRAS^{G12C}$-mutant NSCLC and CRC is, at best, $600-800 million.

Even if MRTX-849 gets approved for this indication in the far future (after a real Phase 3 trial), its market share is unlikely to be very high. AMG-510 will be first to market and have Amgen's marketing muscle behind it, while J&J and Lily also have their own G12C inhibitors in the clinic. Meanwhile, KRAS inhibitors with more carefully considered MOAs have also entered the clinic. These include Boehringer-Ingelheim's BI-1701963, which blocks the activation of KRAS by RTKs, thus accounting for some of the adaptive resistance mechanisms that challenge G12C inhibitors like '849. In the unlikely event that KRAS inhibitors are found to durably improve patient outcomes, approaches like BI's, and Revolution's RAS(ON) compounds, are likely to win out over those of Mirati's, as their activity encompasses multiple nodes in the KRAS-mutant molecular pathways in a single compound. Because of their more extensive activity, these approaches also lend themselves to more effective combination with other targeted therapies. As one research oncologist told us, the more broadly a drug can attack the oncogenic pathways, the more likely it is to succeed, and '849 is as narrowly targeted as can be.

Beyond '849, there's not much else in Mirati's pipeline. The company claims that they have a program that addresses a different KRAS mutation, G12D. But they also said that they'd have a

lead candidate molecule identified in the fourth quarter of 2019, and all we've heard from them since is that they just started IND-enabling studies. Considering that the clinical and preclinical literature have been utterly devoid of a G12D inhibition mechanism, and that it took seven years to get from a G12C inhibition mechanism to an actual drug candidate, we're skeptical.

Mirati's opportunity set is therefore best described as an extremely low-percentage chance of attaining a low-percentage share of a $600-800 million market circa 2025. What's that worth right now? A small fraction of $4.6 billion. Investors who have gambled on the M&A prospects of what amounts to a single dead-end compound will soon find out they're on the wrong path.

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