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This filing relates to the proposed transaction between Revolution Medicines, Inc. a Delaware corporation ("Revolution Medicines"), and EQRx, Inc., a Delaware corporation ("EQRx"), pursuant to the terms of that certain Agreement and Plan of Merger, dated as of July 31, 2023 (the "Merger Agreement"), by and among Revolution Medicines, EQRx, Equinox Merger Sub I, Inc., a Delaware corporation and a wholly owned subsidiary of Revolution Medicines ("Merger Sub I"), and Equinox Merger Sub II LLC, a Delaware limited liability company and a wholly owned subsidiary of Revolution Medicines ("Merger Sub II" and, together with Merger Sub I, the "Merger Subs" and each a "Merger Sub").

On October 22, 2023, Revolution Medicines made available the following information during an investor call held by Revolution Medicines:

Operator:

Good morning, and welcome to Revolution Medicines Conference Call. At this time, all participants are in a listen-only mode. After the speaker's presentation, there will be a question-and-answer session. To ask a question during the session, you would need to press star one one on your telephone, you will then hear an automated message advising your hand is raised. To withdraw your question, please press star one one again. Please be advised that today's conference is being recorded.

I'd now like to hand the conference over to your first speaker to Erin Graves, senior director of corporate communications and investor relations. Please go ahead.

Erin Graves:

Thank you and welcome everyone to today's investor webcast. Joining me on today's call are Dr. Mark Goldsmith, Revolution Medicines' chairman and chief executive officer, Dr. Steve Kelsey, our president of R&D, and Dr. Wei Lin, our chief medical officer. Peg Horn, our chief operating officer and Jack Anders, our chief financial officer, will join us for the Q+A portion of today's call.

As we begin, I would like to note that our presentation will include statements regarding the current beliefs of Revolution Medicines with respect to our business and the proposed acquisition of EQRx, including statements regarding our development plans and timelines for our portfolio and pipeline and the expected timing and benefits of the proposed acquisition, all of which are intended to be covered by the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 for forward-looking statements.

These statements are subject to a number of assumptions, risks, and uncertainties. Actual results may differ materially from these statements, and except as required by law, the company undertakes no obligation to revise or update any forward-looking statements. I encourage you to review the legal disclaimer slide of our corporate presentation and all of our filings with the SEC concerning these and other matters.

During this call, we will be referring to slides from our corporate presentation, which was posted to our website prior to this call.

With that, I will turn the call over to Dr. Mark Goldsmith, Revolution Medicines' chairman and chief executive officer.

Mark A. Goldsmith:

[Slide 2]

On behalf of the employees of Revolution Medicines and our many collaborators and partners, it's my pleasure to welcome you to this R&D review following multiple exciting scientific presentations by our collaborating investigators at the Triple and ESMO meetings.

Our company's mission is to revolutionize treatment for patients with RAS-addicted cancers through the discovery, development and delivery of innovative, targeted medicines.

Today, I'll begin by briefly reviewing our pioneering class of drug candidates that target the oncogenic RAS(ON) drivers of common, life-threatening cancers.

Next, Dr. Steve Kelsey, our president of R&D, will recap the recent presentations on our unprecedented RAS^{MULTI} inhibitor (RMC-6236) and RAS^{G12C}-selective inhibitor (RMC-6291), our first two RAS(ON) inhibitors that have shown differentiated and promising initial clinical profiles.

And then Dr. Wei Lin, our Chief Medical Officer, will summarize our initial single agent and combination development strategies aiming to deliver durable clinical benefit broadly to patients with RAS-addicted cancers.

[Slide 4]

The fundamental biologic principle behind our work is that excessive RAS(ON) signaling caused by tumor RAS mutations drives malignant growth in many human cancers.

These oncogenic mutations can occur in any of the natural isoforms of RAS – KRAS, NRAS or HRAS – and most frequently occur at mutational hotspots at amino acids G12, G13 or Q61.

Such mutations are responsible for over 200,000 new cancer diagnoses in the US alone each year, and in particular, are frequent causes of lung, pancreatic and colorectal cancer.

[Slide 5]

Innovative work by Kevan Shokat and Jon Ostrem paved the way for first generation inhibitors that bind to the $KRAS^{G12C}$ mutant in the inactive, or OFF, form and prevent conversion into the active, or ON, form. We have taken a very different approach — developing oral compounds that bind to and inhibit the active, or ON, form of RAS. We built an industrial-strength product engine incorporating a vision and early work by Greg Verdine and colleagues at Warp Drive Bio, a company we acquired five years ago.

We call our compounds tri-complex inhibitors, since they are designed to bind selectively and with high affinity to a relatively flat surface on the disease target by forming tri-complex structures that contain the disease target, a highly abundant cellular chaperone protein, such as cyclophilin-A and the tri-complex inhibitor bound in a pocket between them. Drug candidates in our collection of more than 20,000 design-based RAS inhibitors directly and rapidly inhibit the intended oncogenic RAS(ON) cancer drivers in tumor cells, and induce deep and durable suppression of RAS cancer signaling by a mechanism of action that defies common ways that tumors can resist RAS(OFF) inhibitors.

The studies we will review today have provided compelling clinical validation of the first two RAS(ON) Inhibitors as single agents and, we believe, for this new class of inhibitors broadly.

[Slide 6]

Today we will touch on several of our six named development-stage RAS(ON) inhibitors that, as a group, were designed to treat nearly all patients with RAS cancers.

The first of these investigational drugs, RMC-6236, is clearly unique in that it potently binds to and inhibits every form of K, N or HRAS we've ever tested, including nearly all known oncogenic variants as well as the wild-type, or normal, RAS proteins. We call this bold compound a RAS^{MULTI}(ON) inhibitor.

The other RAS(ON) inhibitors in our pipeline are designed as mutant-selective compounds targeting individual oncogenic RAS variants.

[Slide 7]

These two distinct and complementary approaches – an inhibitor of the RAS family of proteins and specific inhibitors of individual RAS mutants – are intended to enable multiple monotherapy and combination strategies against RAS-addicted cancers. You will hear more about how we plan to implement these strategies later in this presentation.

[Slide 8]

I'll take a moment now to introduce the remarkable drug candidate RMC-6236 that is summarized here, and then Steve will take it from there into the clinical data.

[Slide 9]

As shown in this example of a preclinical RAS-dependent non-small cell lung cancer model, the oral, potent, tri-complex RAS family inhibitor RMC-6236 induces dose-dependent regressions in RAS-addicted cancers, even at low doses. Regressions representing partial or complete responses have been observed most frequently in the dose range of 10-25 mg per kg. Preclinically RMC-6236 is well tolerated in this active range and, as you'll see, plasma exposures in humans corresponding to this preclinical dose range are achieved doses of 80-120 mg per day with objective tumor responses.

[Slide 10]

As recapitulated here, we've shown examples of compelling response rates to RMC-6236 in xenograft tumor models carrying five different $KRAS^{G12}$ mutations and representing the three major epithelial RAS-addicted human cancers. Such responses to RMC-6236 were also characterized by impressive durability in most models, as indicated.

Earlier this year we disclosed a small, preliminary set of encouraging clinical findings from the RMC-6236-001 single agent dose escalation study that in many ways appeared to mirror the preclinical profile. I'm pleased to invite Dr. Steve Kelsey to review our significantly larger preliminary clinical data set that is consistent with, and substantially extends, the encouraging trends seen in those initial findings. Steve?

Stephen Kelsey:

[Slide 11]

Thanks, Mark. I am going to summarize the key data from the three presentations on RMC-6236 and RMC-6291 that were recently given at the Molecular Targets and Cancer Therapeutics, or 'triple meeting' and earlier today at the ESMO meeting.

Slide 11 is to remind you of the study design for the RMC-6236 Phase 1 dose-escalation study, which currently focuses on patients with advanced solid cancers that harbor KRAS mutations at position G12, currently excluding G12C mutations.

We have escalated the dose of RMC-6236 up to 400 mg daily. The color coding of the boxes is synchronized with the data slides that we will show shortly. Dose optimization is still ongoing, particularly for patients with non-small cell lung cancer and pancreatic ductal adenocarcinoma. We have not yet decided whether to test the 500 mg daily dose level as we are still evaluating 400 mg daily. Recall that doses below 80 mg daily were not expected to be associated with tumor regressions in patients, based on preclinical exposures and human PK modeling, which turned out to be reasonably concordant with clinical reality.

[Slide 12]

As of the 11th of September, 131 patients had been treated with RMC-6236, the majority with either pancreatic ductal adenocarcinoma or non-small cell lung cancer.

The spectrum and frequency of the G12 mutations in the study were consistent with the epidemiologic distribution.

Patients had received a median of two prior regimens for their RAS mutant cancer.

[Slide 13]

The pharmacokinetics of RMC-6236 as a single agent showed good oral bioavailability, kinetics consistent with once daily dosing, and dose-dependent increase in exposure.

Beginning at 160 mg daily, and more consistently at 200 mg daily or above, steady-state exposures were within the range of those observed in mice at 25 mg per kg daily, a dose that you've just heard delivered significant and broad activity in the tumor xenograft studies shown on slide 10.

I'd also like to note that dosing at 80 mg in patients provided exposures below but approaching that of the 10 mg per kg mouse exposure at which tumor regressions were observed in sensitive preclinical models. Dosing at 120 mg or above in patients achieved exposures more consistent with, and frequently exceeding, that of 10 mg per kg daily in mice.

[Slide 14]

As we have previously reported, RMC-6236, despite its ability to potently inhibit both mutant and Wild-Type RAS, was well-tolerated across dose levels and with drug exposures that were well within the range required for potent inhibition of mutant and Wild-Type RAS.

We have seen few Grade 3 or greater adverse events overall and have not yet defined a Maximum Tolerated Dose. Skin rash remains the most frequent treatment-related adverse event and the most common dose-limiting toxicity as defined by the protocol.

At higher dose levels, some gastrointestinal toxicity has been observed, although Grade 3 events were likewise uncommon.

Only one treatment-related Grade 4 event has been observed, a gastrointestinal perforation at 80 mg daily that has been previously described in some detail and is believed to be due to shrinkage of the full thickness bowel tumor.

The safety and tolerability profile of RMC-6236 compares favorably with that previously reported for some of the $KRAS^{G12C}$(OFF) inhibitors and with historical profiles for standard of care cytotoxic chemotherapy.

The overall toxicity profile, including only infrequent and relatively modest increases in transaminases, increases our confidence that RMC-6236 will be tolerated in combination with standard of care treatments. Potential drug combinations include immune checkpoint inhibitors such as pembrolizumab and our own in-portfolio, mutant-selective, RAS(ON) inhibitors such as RMC-6291 and RMC-9805.

[Slide 15]

Recall that the RMC-6236-001 study is a first-in-human Phase 1 dose escalation study.

Necessarily, the first cohorts of patients were treated at doses below those that were expected to result in significant anti-tumor activity.

In fact, as discussed on slide 13, exposures in patients reached those at which tumor regressions could be anticipated at around 80 to 120 mg daily and above. This prediction was elegantly supported and exemplified by Dr. Spira in his recent presentation and poster on RMC-6236 at the Triple Meeting on the 13th of October. The case history of a patient with ovarian cancer was reported. This patient who had progressed on prior therapies had stable disease when started on RMC-6236 at 20 mg daily, but on escalation to 80 mg daily the tumor reduced in size and the patient achieved a partial and sustained response.

Therefore, we have reported anti-tumor activity for efficacy-evaluable patients with non-small cell lung cancer and pancreatic cancer who started treatment with RMC-6236 at a dose of 80 mg daily or greater at least eight weeks prior to the data cutoff for ESMO, which was October the 12th. The timing of this analysis ensures that all reported patients had received at least one follow-up CT scan reported to us at the time of the analysis.

You can see from the waterfall plot of 40 evaluable patients with $KRAS^{G12}$ mutant non-small cell lung cancer the overall response rate, including unconfirmed partial responses, was 38 percent. There was one confirmed complete response.

The overall response rate observed so far compares favorably with inhibitors of $KRAS^{G12C}$ that have been tested in $KRAS^{G12C}$ mutant non-small cell lung cancer and is above historical response rates for standard of care chemotherapy, exemplified by docetaxel.

The majority of unconfirmed partial responses in our non-small cell lung cancer cohort have been subsequently confirmed, and some RECIST responses were observed for the first time after the initial 6-week scan. Due to the relatively short follow-up for patients enrolled at the higher dose levels in this study, it is possible that the observed overall response rate for RMC-6236 in lung cancer is an under-estimate of the eventual outcome and we will continue to assess this.

As predicted by the preclinical work, multiple tumors with either $KRAS^{G12D}$ or $KRAS^{G12V}$ mutations were responsive to RMC-6236. To our knowledge, RMC-6236 is the first RAS inhibitor described with clinical activity against lung cancer with either of the two most common RAS mutations in human cancer. Furthermore, in lung cancer, the G12D and G12V genotypes together are about as common as the G12C genotype, or roughly 12.5 percent.

Although we haven't tested RMC-6236 in patients with the G12C mutation yet, preclinical data shows that RMC-6236 is highly active in tumors harboring the $KRAS^{G12C}$ mutation, and we'd expect it to be so in patients. We also expect tumors harboring other mutations to be sensitive as well, but none have been represented sufficiently in the lung cancer patient cohort so far to be able to assess this.

Furthermore, while the data set is too small and early to determine whether any differences exist in outcomes across the different G12 genotypes, overall RMC-6236 could well prove to be applicable in 25 to 30 percent of human non-small cell lung cancer patients.

[Slide 16]

Slide 16 shows more temporal information on each patient with non-small cell lung cancer. The median follow-up is relatively short at 3.1 months, and the majority of patients remain on study therapy.

[Slide 17]

To reinforce the anti-tumor activity of RMC-6236 in KRAS mutant lung cancer, I would like to highlight this case, presented by Dr. Arbour at ESMO earlier today, of an 83-year-old female with a heavy smoking history who was diagnosed with $KRAS^{G12V}$ mutant non-small cell lung cancer. Her prior treatment for non-small cell lung cancer included a checkpoint inhibitor doublet and subsequently chemotherapy but she progressed and presented with dyspnea at rest and cough before starting RMC-6236 at 300 mg daily.

Within one week, she noticed a marked decrease in both symptoms, and she started playing golf again. Her first CT scan showed a complete response, which was confirmed on her next scan, and she currently continues on treatment.

[Slide 18]

Slide 18 shows the waterfall plot of 46 patients with $KRAS^{G12}$ mutant pancreatic cancer, again only including patients at doses above 80 mg daily and who started treatment with RMC-6236 at least eight weeks prior to the data cutoff on October 12th so as to ensure that information from at least one follow-up CT scan was captured on each patient. The overall response rate, including unconfirmed partial responses, was 20 percent, although one of these patients did discontinue RMC-6236 prior to response confirmation. This overall response rate compares favorably with historical data for salvage chemotherapy in pancreatic cancer where response rates are typically around 10 percent.

The disease control rate was 87 percent meaning that only 13 percent of pancreatic cancer patients treated with RMC-6236 had progressed at their first response evaluation. Typically, around 30-40 percent of patients with advanced pancreatic cancer will have been found to have progressed at their first response assessment when receiving salvage chemotherapy after their initial chemotherapy has failed.

As with non-small cell lung cancer, pancreatic adenocarcinoma tumors with $KRAS^{G12D}$ and G12V mutations were responsive to 6236. In addition, two patients with pancreatic tumors harboring $KRAS^{G12R}$ mutations, a mutation almost exclusive to pancreatic cancer and the third most common RAS mutation in pancreatic cancer, also responded. With the three RAS mutations that are most commonly found in this tumor type showing sensitivity, we believe the breadth of activity is consistent with the preclinical experience and highly encouraging for our efforts to help patients.

[Slide 19]

The swimmer plot on slide 19 confirms the short follow-up for patients in this study. As with the lung cancer cohort, it is too early to calculate a median progression-free survival, but it is encouraging that only two patients with pancreatic cancer who had an initial response have progressed, after 18 and 25 weeks on treatment respectively. Median progression-free survival for these patients treated with chemotherapy has been reported to be in the range of 12 to 14 weeks. Durability of anti-tumor effect, irrespective of RECIST response, will be an important factor in determining the clinical impact of RMC-6236.

[Slide 20]

To confirm the anti-tumor activity of RMC-6236 we evaluated mutant KRAS allelic burden in circulating tumor DNA before and on treatment. Slide 20 shows that treatment with RMC-6236 was associated with a significant reduction in circulating mutant KRAS DNA. Consistent with previous reports, reduction in ctDNA tracked with clinical response by RECIST.

So to date, and while dose optimization is still ongoing, RMC-6236 has been well tolerated at active dose levels with significant antitumor activity in both non-small cell lung cancer and pancreatic cancer, and against at least three common RAS genotypes. The early overall response rate in both lung cancer and pancreatic cancer compares favorably with current standard of care for patients with advanced tumors who have failed prior systemic therapy.

[Slide 21]

Now let's turn to RMC-6291, our mutant-selective $KRAS^{G12C}$ inhibitor that binds covalently to the ON state of $KRAS^{G12C}$ and rapidly and irreversibly inhibits it.

[Slide 22]

This compound is highly potent, inducing tumor stasis in preclinical models at 3 mg per kg daily and regressions, including frequent complete responses, at 10 mg per kg daily or higher.

[Slide 23]

RMC-6291 has a number of distinguishing properties from RAS(OFF) inhibitors based on its unique binding and mechanism of action. For example, it is highly active in some preclinical tumor models that are resistant to first-generation RAS(OFF) inhibitors. Shown here are two examples of significant antitumor activity by RMC-6291 in tumors that are resistant to sotorasib (on the left) or adagrasib (on the right) carrying associated resistance mechanisms that are believed to be clinically relevant.

[Slide 24]

Further, in some preclinical models in which RMC-6236 or RMC-6291 as single agents were only partially active, the combination of these two compounds delivers significant and highly sustained antitumor benefit. This observation supports an important part of our overall strategy for the RAS(ON) inhibitors that will be discussed later.

[Slide 25]

Slide 25 shows the study design for the RMC-6291 single agent Phase 1 dose-escalation study.

As a reminder, the study focuses on patients with advanced solid cancers that harbor $KRAS^{G12C}$ mutations, the majority of which have either non-small cell lung cancer or colorectal cancer.

To date we have escalated the dose of RMC-6291 up to 400 mg twice daily. All of the doses tested were predicted to have some degree of anti-tumor activity based on preclinical model.

As with the RMC-6236 results shown earlier, the color coding of the boxes is synchronized with the dose levels on the data slides that we will show shortly.

Dose optimization for RMC-6291 is still ongoing and the data are preliminary, but we believe provide a meaningful early snapshot of the potential of our first mutant-selective tri-complex RAS(ON) inhibitor.

[Slide 26]

To date, 63 patients have been treated with RMC-6291; of which 23 have non-small cell lung cancer and 33 have colorectal cancer. The remaining seven have various tumor types including cholangiocarcinoma and gynecologic cancers.

Twenty-five, or 40 percent, of these patients had previously received a $KRAS^{G12C}$(OFF) inhibitor; most of these patients received their $KRAS^{G12C}$(OFF) inhibitor as their most recent prior therapy before being treated with RMC-6291. All of the patients previously treated with a $KRAS^{G12C}$(OFF) inhibitor had progressed on their prior KRAS(OFF) inhibitor, and the gap in the time between discontinuing RAS(OFF) inhibitor and starting RMC-6291 was a median of nine weeks, although with a wide range of two weeks to around two years.

As with many Phase 1 dose escalation studies in this space, patients had received a median of three prior therapies for their cancer.

With particular relevance to interpreting the safety and tolerability of RMC-6291 in the non-small cell lung cancer population, please note that one third of the lung cancer patients treated with RMC-6291 had received an immune checkpoint inhibitor within 12 weeks of starting RMC-6291. Prior immune checkpoint inhibitor therapy within the previous 12 weeks was reported by investigators at Memorial Sloan Kettering Cancer Center as a predictor of significant toxicity with $KRAS^{G12C}$(OFF) inhibitor therapy, particularly hepatotoxicity associated with sotorasib.

[Slide 27]

The pharmacokinetic profile of RMC-6291 shows that it is orally bioavailable, and exposures increase in a dose-dependent manner. The clearance of RMC-6291 from plasma is consistent with the twice daily dosing regimen which was initiated at the 200 mg dose level.

The exposure-to-target engagement relationship in preclinical studies predicts greater than 90 percent average cross-linking of total $KRAS^{G12C}$ in human subjects receiving 100 mg twice daily or higher. Please note that, distinct from $KRAS^{G12C}$(OFF) inhibitors, most or all cross-linked intra-tumoral $KRAS^{G12C}$ should represent direct inhibition of the active or 'ON' state of mutant $KRAS^{G12C}$.

[Slide 28]

RMC-6291 was generally well tolerated up to 400 mg twice daily. Grade 1 or 2 gastro-intestinal toxicities, predominantly nausea and/or diarrhea, were the most frequent treatment-related adverse events.

QTc prolongation has been observed, although only one case (representing two percent of patients overall) showed an increase in QTc to greater than 500 milliseconds, and there have been no cardiac toxicities associated with this electrocardiographic abnormality. Only one treatment-related AE, a Grade 3 QTc prolongation in a patient who was tolerating RMC-6291 well otherwise, required discontinuation of RMC-6291 per protocol.

Increases in liver enzymes were of low Grade and low frequency, supporting the potential for combination with immune checkpoint inhibitors.

[Slide 29]

Slide 29 shows the clinical activity of RMC-6291 in all patients with non-small cell lung cancer. 3 out of 7, or 43 percent, of lung cancer patients who had not previously received a $KRAS^{G12C}$(OFF) inhibitor responded.

Five out of 10, or 50 percent, of the lung cancer patients who had previously received a $KRAS^{G12C}$(OFF) inhibitor responded. The disease control rate for both sets of patients was 100 percent, with no early progression.

[Slide 30]

Efficacy also showed for the 20 patients with colorectal cancer who had not previously received a $KRAS^{G12C}$(OFF) inhibitor. Eight patients, or 40 percent, had partial response and the disease control rate was 80 percent.

We have not reported on the clinical activity of the eight patients with colorectal cancer who had previously received a $KRAS^{G12C}$(OFF) inhibition. The potential clinical activity of RMC-6291 was compromised by the detection of multiple additional pathogenic mutations in the circulating tumor DNA of these patients prior to starting RMC-6291, and it is likely that different approaches will be required for these tumors.

[Slide 31]

The swimmer plots on slide 31 provide additional temporal information about the patient populations that appear on the waterfall plots. Follow-up for most patients is short. Although it is too early to calculate a median progression-free survival, no patient with an initial unconfirmed objective response and a follow-up scan has subsequently failed to confirm, and no patient who has responded by RECIST has yet progressed or discontinued the treatment.

[Slide 32]

To confirm the anti-tumor activity of RMC-6291, we're also showing the reduction in circulating $KRAS^{G12C}$ mutant allelic frequency by dose and by response. With the caveat of small numbers, and considerable heterogeneity, molecular responses are, as expected, associated with tumor shrinkage. Molecular responses do not seem to increase in depth with dose levels greater than 200 mg twice daily.

Overall, the initial data show encouraging clinical activity for RMC-6291 in patients with $KRAS^{G12C}$ mutant non-small cell lung cancer and colorectal cancer.

In particular, the response rate in patients with non-small cell lung cancer that previously received a $KRAS^{G12C}$ (OFF) inhibitor compares very favorably with recently reported data on the experience with other $KRAS^{G12C}$ inhibitors. And the overall response rate for single agent RMC-6291 in colorectal cancer is similar to that reported for other KRAS inhibitors in combination with anti-EGFR antibodies.

While preliminary, these data are consistent with the differentiated mechanism of action for RMC-6291 that has previously been presented, and support the potential of RMC-6291 for further development.

I'll now turn back to Mark.

Mark A. Goldsmith:

[Slide 33]

Thank you, Steve, for that clear review of important data from the first two RAS(ON) Inhibitor investigational drugs in our pipeline with encouraging clinical activity across multiple, common $KRAS^{G12}$ tumor genotypes and tumor types, data that we believe provide clinical validation of this exciting and highly differentiated class of drug candidates.

I'd also like to remind everyone that a third investigational drug from this class is also undergoing initial clinical evaluation, although we don't have sufficient experience to report on it today. This compound, RMC-9805, is an unprecedented, oral inhibitor that selectively and covalently engages $KRAS^{G12D}$, the most common mutated driver of RAS-addicted cancers. It is highly active preclinically, and we look forward to reporting on its clinical profile at the appropriate time.

[Slide 34]

I'm also pleased to introduce formally RMC-5127, the newest, exciting mutant-selective compound from the RAS(ON) Inhibitor class to enter development at RevMed. This oral inhibitor is highly selective and potent against the second most common driver of RAS-addicted cancers, $KRAS^{G12V}$. This compound is in IND-enabling development and we look forward to bringing it into the clinic.

[Slide 35]

And, a reminder that previously we've described two other mutant-selective RAS(ON) Inhibitors in development, RMC-0708 targeting the $KRAS^{Q61H}$ variant, and RMC-8839 targeting the $KRAS^{G13C}$ variant.

[Slide 36]

We are proud of our extensive portfolio of R&D assets focused on RAS-addicted cancers, now dominated by this deep collection of RAS(ON) Inhibitors. We've reviewed the current status of our three clinical-stage compounds, including the first two for which we have initial safety, tolerability and clinical activity data, as well as three additional development candidates and a further pipeline of preclinical and discovery assets.

In a moment we'll bring on Dr. Lin to give us a preview of what's next for the exciting compound RMC-6236. Let me comment here that we also believe RMC-6291 is quite promising and we await additional monotherapy data to help guide prioritization of the multiple potential paths by which we can drive clinical impact and ultimately pursue commercial value from this compound. In the meantime, you'll see that we are already moving forward with a study of the combination of RMC-6291 and RMC-6236.

Let me now update you on two RAS Companion Inhibitors we have in clinical development.

First, RMC-4630 is a selective inhibitor of the RAS-regulator SHP2 that we envisioned as a potential combination drug with RAS inhibitors.

Despite encouraging early data from the CodeBreak 101 study, in the global Phase 2 RMC-4630-03 study, the combination of RMC-4630 (dosed at 200 mg Day 1 Day 2) with sotorasib (dosed at 960 mg QD) showed additive side effects compared to either agent alone.

A clinical benefit in response rate or durability was not observed, likely limited by dose interruptions and discontinuations due to intolerability.

Given the exciting clinical profile of RMC-6236, we have given this compound priority over RMC-4630 for evaluation in combination with our mutant-selective RAS(ON) inhibitors.

But RMC-4630 continues as an option for possible evaluation in other combinations in the future.

Second, RMC-5552, a first-in-class bisteric, selective mTORC1 Inhibitor, was designed to treat cancer patients with RAS mutant tumors bearing co-mutations that upregulate mTORC1 signaling

The ongoing RMC-5552-01 Study has provided objective evidence of single agent clinical activity in patients at tolerated doses (as recently updated at the Triple meeting), including partial responses

Consistent with our initial vision for this compound, future development will focus on combination treatment with RAS(ON) Inhibitors, particularly for patients with tumors carrying both a RAS mutation and markers of mTORC1 hyperactivation.

[Slide 37]

Let's now return to our headline asset, RMC-6236.

As Steve showed, this inhibitor has proven to be broadly active in patients with multiple common tumor types, and driven by multiple common RAS genotypes.

We plan to execute further development of RMC-6236 with both speed and breadth by making parallel investments in both late-stage monotherapy trial(s) and clinical studies of combination approaches.

As you'll see, we are committed to expanding the scope of development for RMC-6236 by evaluating the broadest possible range of RAS genotypes, of lines of treatment, and of tumor types.

Dr. Lin will provide this overview of our current thinking, which of course remains subject to data-driven decisions and consultation with investigators and regulatory authorities. Wei?

Wei Lin:

[Slide 38]

Thank you, Mark.

Our vision for the development of RMC-6236 is to bring the benefit of direct RAS(ON) inhibition to the greatest number of patients with RAS-addicted cancers. To achieve this vision, we will pursue in parallel the initial registration of RMC-6236 as monotherapy in multiple later-line indications with high unmet needs while exploring combinations that may significantly improve the standard of care in the first-line and adjuvant settings. To broaden the impact of RMC-6236 on the lives of patients with RAS-addicted cancers, we aim to build on the proof-of-concept emerging from our first-in-human study and expand the development of RMC-6236 in multiple dimensions. These plans include going beyond $KRAS^{G12}$ mutations, going into earlier lines of therapy, and going into all solid tumor types.

Let me describe in more detail these three dimensions. First, RAS mutations. In our first-in-human trial, the preliminary safety and antitumor activity of RMC-6236 have been established in patients with lung and pancreatic cancers specifically harboring $KRAS^{G12}$ mutations. However, preclinical data indicate that RMC-6236 is broadly active across all three canonical RAS isoforms, KRAS, NRAS, and HRAS, as well as against all three common mutation hotspots, G12, G13, and Q61. Therefore, in our potential future registration trials, we aim to broaden the biomarker selection to include all three RAS isoforms and all three mutation hotspots. As we expand from populations where we have established clinical proof-of-concept to populations where we are relying on preclinical proof-of-concept, we'll use nested designs and hierarchical testing to mitigate potential risks from including expanded populations. I will illustrate this approach in our proposed monotherapy randomized trial designs later in the presentation.

Second, lines of therapy. While the highest unmet needs are in previously treated patients, the untreated first-line and adjuvant patients represent the largest number: over 200,000 patients with RAS-mutated cancers newly diagnosed in the United States each year. Furthermore, adjuvant therapy presents the only setting where we may be able to offer cancer patients the potential for a cure. Our strategy in expanding into earlier lines of therapy involves a multi-pronged approach that include development of our RAS(ON) inhibitor doublets, as well as combinations of a RAS(ON) inhibitor with standard of care and other anti-cancer therapies.

Third, tumor types. While lung, pancreatic, and colorectal cancers are the most common RAS-addicted cancers, many other solid tumors, such as melanoma, ovarian, endometrial, and cholangiocarcinoma contain RAS mutations at a high frequency. The most efficient approach to expand the evaluation of RAS(ON) inhibition to these patients is a tissue agnostic registration strategy via a potential single-arm Phase 2 trial, and our current strategy is to explore initiating this type of trial.

[Slide 39]

Now I want to delve more deeply into our monotherapy development plan in non-small cell lung cancer. Each year approximately 200,000 people in the United States and 2,000,000 people worldwide are diagnosed with non-small cell lung cancer. The majority will die from their disease at some point, making it the most lethal of all cancers. RAS signaling plays a role in the majority of non-small cell lung cancer, and RAS is the most common oncogenic driver in non-small cell lung cancer, with approximately 30 percent of newly diagnosed non-small cell lung cancer patients having tumors that harbor a RAS mutation.

The current global standard of care for second-line patients who have been treated with immunotherapy and platinum-based chemotherapy is docetaxel. Docetaxel plus ramucirumab, while approved, is not widely used. Sotorasib and adagrasib are indicated for use only in patients with $KRAS^{G12C}$-mutated non-small cell lung cancer. Because they have not gained full approval, they are not formally considered standard of care by major health authorities. As the table on the right illustrates, while sotorasib had shown a higher response rate, the improvement in median progression-free survival was only 1.1 month (from 4.5 to 5.6 months), and there was no overall survival benefit. Therefore, the entire population of patients with RAS-mutated non-small cell lung cancer share a common global standard of care in docetaxel, and expect median survival of less than one year represents a major unmet need.

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To address this high unmet need, we are planning a global randomized Phase 3 trial comparing RMC-6236 against docetaxel in patients with RAS-mutated non-small cell lung cancer who have been treated with immunotherapy and platinum-containing chemotherapy. The biomarker selection will include KRAS, NRAS, and HRAS, will include G12C and non-G12C mutations, and will include G13 and Q61 mutations. The study endpoints are progression-free survival, overall survival, and patient reported outcomes.

In our currently contemplated trial design, we have taken into account the potential complexity associated with including patients with RAS mutations spanning positions G12, G13 and Q61. We expect that a package to support a broad approval will need to include sufficient data to demonstrate efficacy in each mutation subgroup. We have a number of approaches to serve this goal, including a nested design with hierarchical statistical testing that begins with a focus on the patient group with the highest probability of success and sequentially expands into additional groups. We will be discussing our proposed analysis plan with the FDA before finalizing our phase 3 design.

The design presented here is preliminary and has not been reviewed by health authorities. So the final design may change. What will not change are our beliefs that a high unmet need exists and our commitment to evaluate RMC-6236 broadly in patients with RAS-mutated non-small cell lung cancer as we try to improve the standard of care for these patients.

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Next let’s review a potential monotherapy development plan for RMC-6236 in pancreatic cancer. This disease is notorious for having the worst prognosis among all major cancers. Most of the approximately 50,000 patients in the United States and 500,000 patients worldwide who are newly diagnosed with pancreatic cancer each year will die from the disease. More than 90 percent of pancreatic cancer harbors a RAS mutation, making it the dominant oncogenic driver in this disease. Among the chemotherapy regimens commonly used in the second-line setting, the median progression-free survival is between three and three and a half months, and a median overall survival is between six and seven months, making this indication one of the highest unmet needs in oncology.

While the first generation KRAS^{G12C}(OFF) inhibitors have shown antitumor activity, KRAS^{G12C} mutation occurs in only one percent of pancreatic cancer, so these inhibitors are not relevant for most pancreatic cancer patients. However, their initial evidence of efficacy provides the first proof-of-concept that human pancreatic cancer is a RAS-addicted cancer and, together with the clinical data we presented at ESMO and the Triple meeting, strongly supports the continued evaluation of RMC-6236 in the broader population of RAS-mutated pancreatic cancer.

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To address this high unmet need, we are considering a potential global randomized Phase 3 trial comparing RMC-6236 against a physician's choice of chemotherapy regimens in patients with RAS-mutated pancreatic cancer. These are second-line patients whose tumors harbor a RAS mutation. The broad biomarker selection will include all RAS isoforms and G12, G13, and Q61 mutations. The study endpoints would include progression-free survival, overall survival, and patient reported outcomes.

Similar to our non-small cell lung cancer Phase 3 trial, this trial design has to account for the complexity associated with including multiple mutations. At the appropriate time, we will be discussing our proposed analysis plan, including a potential nested approach, with the FDA before finalizing our Phase 3 design. Therefore, the final design may change based on regulatory feedback. Our goal is to provide a robust dataset to support a broad approval in RAS-mutated pancreatic cancer.

The high prevalence of RAS mutations in pancreatic cancer is a strong indicator that this is a RAS-addicted cancer. Therefore, we are committed to evaluating the potential of RMC-6236 to improve the standard of care for these patients broadly.

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So far, you have heard how we are thinking about the development of RMC-6236 as a monotherapy, using non-small cell lung cancer and pancreatic ductal adenocarcinoma as priority examples. Of course, we believe that the potential clinical utility of RMC-6236 and our entire RAS(ON) inhibitor pipeline is much broader. Now, I want to share four strategies expanding RMC-6236 development from monotherapy to combinations. Combinations underlie our plan in the first-line setting where effective treatment options may exist, and we will consider combinations with standard of care as a development option. Combinations also underlie our plan in the adjuvant setting where we may have the opportunity to evaluate a potential cure for patients. And combinations underlie our plan to expand into multiple tumor types.

Our first strategy is RAS(ON) inhibitor doublets. We hypothesize that in RAS-addicted tumors, potent inhibition of RAS signaling drives efficacy, and a main resistance mechanism is the recovery of RAS signaling in tumor cells. This hypothesis is supported by data on resistance to the first generation KRAS inhibitors. Therefore, our first combination strategy is to develop RAS(ON) inhibitor doublets, which based on preclinical results we've presented may prevent or delay the emergence of resistance and may translate to longer durability of treatment benefit and longer survival for patients. Given our differentiated mechanism of action based on tri-complex inhibitor technology and our deep pipeline of RAS(ON) inhibitors, RevMed is uniquely positioned to execute on this strategy. In the RAS^{G12C} space, we have already initiated the development of RMC-6236 plus RMC-6291 in a Phase 1 trial and are actively recruiting patients.

Our second strategy is to replace chemotherapy with RAS(ON) inhibitors. First-line non-small cell lung cancer, where the standard of care is chemotherapy plus immunotherapy, is an ideal indication to explore this strategy. RAS(ON) inhibitors or RAS(ON) inhibitor doublets aim to deliver better outcomes for patients by targeting the oncogenic addiction with greater efficacy, improving on the safety profile of chemotherapy. The combination development of RMC-6236 plus anti-PD1 and RMC-6291 plus anti-PD1 is currently in the advanced planning stage.

Our third strategy is to combine with other targeted therapies. In colorectal cancer, receptor tyrosine kinase reactivation, especially EGFR, is a primary mechanism that appears to limit the efficacy of the first generation KRAS^{G12C}(OFF) inhibitors. Combination with anti-EGFR therapy has shown benefit in addressing this limitation. While KRAS^{G12C} mutation represents only approximately three to four percent of colorectal cancer, RAS mutations overall occur in approximately 50 percent of colorectal cancer. We therefore expect to evaluate the combination of RMC-6236 plus anti-EGFR antibody in this large patient population.

Our fourth strategy is to combine RMC-6236 plus standard of care. Pancreatic cancer is a good example for this strategy. For patients with RAS-mutated pancreatic cancer, neither immunotherapy nor targeted therapy is approved, and the standard of care remains chemotherapy in both first-line and the adjuvant settings. Combination with chemotherapy offer RMC-6236 an alternative development path, especially for patients with tumors harboring an additional mutation not addressed by RAS(ON) inhibitor doublets. The combinations of RMC-6236 plus chemotherapy are currently in the advanced planning stage.

Of course, these four strategies may evolve as we learn more about each of our RAS(ON) inhibitors, their combinability, their efficacy in different tumor types and lines of therapy. We believe that this multi-pronged approach will improve our chance to change the standard of care in RAS-addicted cancers. Back to you, Mark.

Mark A. Goldsmith:

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Thank you, Wei.

As you can see, we've made a great deal of progress with our rich portfolio of RAS(ON) Inhibitors, and we have exciting ongoing activities and development plans.

To put the clinical findings to date in perspective, together the first two of our investigational drugs from this class have already shown significant antitumor activity in patients against the four most common oncogenic RAS^{G12X} mutations, which we believe validates our ability to target the large RAS^{G12X} subset. Together these compounds have also shown significant activity across the three major types of RAS-addicted epithelial cancers.

Projecting the validated RAS^{G12X} subset onto the epidemiology of these common solid tumors, it can be inferred that these first two compounds in aggregate credibly may be able to serve a remarkable 3/4ths of the RAS-mutated forms of these three major cancers. This compelling scope of opportunity may become even more inclusive as we expand clinical evaluation of RMC-6236 to the G13- and Q61-mutated RAS genotypes and to other tumor types and continue advancing other assets in our pipeline.

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We are most grateful to the patients and their families who have participated in our trials so far or plan to, to our investigators and collaborators, to our employees, partners and advisors, and to our investors for helping us sustain our ambitious program in order to outsmart cancer.

Operator:

Thank you. As a reminder to ask a question, you will need to press star one one on your telephone. To withdraw your question, please press star one one again. Please stand by while we compile the Q&A roster.

And I show your first question comes from the line of Marc Frahm from TD-Cowen. Please go ahead.

Marc Frahm:

Hi, thanks for taking my question. Congrats on the data over the past week. Maybe to start off with one with the data today, it does look like there's maybe a bit more delayed responses sometimes in pancreatic cancer than maybe what you're seeing in lung cancer. They're biological rationale that based on your preclinical data you're seeing that might explain that?

Mark A. Goldsmith:

Thanks, Marc, for your question. I really appreciate it. I'm going to ask Steve Kelsey first to comment on that and we'll see where we go from there.

Stephen Kelsey:

It's not at all clear that the data to support the delayed response from pancreatic cancer comes from prefrontal models necessarily. I think it comes from a wealth of clinical experience with pancreatic cancer generally that it is a very different disease from non-small cell lung cancer both in terms of the way it's constituted with a lot of the bulk of the tumor often being not actually tumor tissue. So, that's the first thing. So, even if you eradicate all the tumor, you may still end up with a significant lump on a CT scan which takes a while to remodel because it's mainly fibrous tissue.

The second, obvious difference in pancreas between pancreatic cancer and cell lung cancer is the involvement of the immune system that a lot of non-small cell lung cancers have a lot of immune effective cells in there and those can significantly debulk the tumor whereas pancreatic cancer is notoriously difficult for the immune effect of cells to access. And so, it may just take a lot longer. And I think that's what we're seeing. I think that's what we're seeing, Marc, with the difference between how long it takes for a patient to achieve a partial response to 6236 in the pancreatic cancer versus the lung cancer patients.

Marc Frahm:

Thanks. That's really helpful. And then, maybe just on the idea of expanding out beyond G12X, you mentioned this frequently, if you see any meaningful differences in the level of activity against some of these other hotspots, but then also while your kind of finalizing these designs with regulators? Are there any plans to start enrolling some of those patients on a single-arm basis, just to kind of reconfirm clinical activity?

Mark A. Goldsmith:

Why don't I comment on the first question, and then Steve can hit on the second one. The first question, differences between G12 mutants, and G13, Q61. In the preclinical work you may recall, we studied a very large panel of cell lines, which is sort of the best way we have to get at this. And across many different genotypes, and many different tumor types, really, the only difference we could see in terms of response rates was between the G12 mutants and all the other mutants. They were all sensitive. As we've mentioned, we've not really found a mutant autogenic mutants or variants of RAS that isn't sensitive to some degree to RMC-6236, but there was a quantitative difference between the G12 and all the others. And that's why we prioritize G12 in this study, of course, as I mentioned, we're probably covering 3/4 or more of all of all RAS cancers, even just with the G12 mutations. But there just seems to be some difference in sensitivity. And I think Wei's comment about the nested design with hierarchical statistical testing is a really convenient and practical way for us to both focus on the highest probability subgroup representing 3/4ths of cancers and then also testing the others without taking a penalty for including them in the trial.

With regard to your second question, could you repeat the second part of the question?

Marc Frahm:

It was just… If there was going to be any plan to, at least in the interim while you're finalizing that design, enroll some of these patients with G13 or Q1 mutations?

Mark A. Goldsmith:

Oh sure. Maybe, Steve, do you want to comment on it?

Stephen Kelsey:

Yes, is the answer. We have been focused very much on pancreatic ductal adenocarcinoma or non-small cell lung cancer. Up to now, I think as we are moving… well, firstly, we're more confident that we have an active drug. And secondly, moving closer to dose optimization. We are planning to do a number of things and Wei describes some of those particularly the combinations that will allow us to move into earlier lines of therapy, but also its high priority for us to get some data in the other mutations beyond the G12 mutations. And also, in some of the other tumor types that have the G12 mutations as well, particularly colorectal cancer and some of the gynecologic malignancies. So, that's very much part of our plan for the next sort of six to 12 months.

Mark A. Goldsmith:

If I could add to that. Investigator and patient demand for RMC-6236 remains very high as we've talked about before and that continues to be the case based on feedback as recently as today from ESMO. Investigators are very interested, they have many ideas for other patients and the needs are quite deep and so we will certainly be making the compound available in a variety of expansion contexts, both to serve patients while we're still evaluating things, but also to collect the kinds of data you're talking about. So, I think we're about to hit sort of more of an inflection point in opening things up to a broader group of patients.

Wei, maybe he could comment also though on the tumor agnostic trial concept which you talked about briefly but is an important expansion tool. And something to move on relatively quickly, although you'd like to do that at a recommended Phase 2 dose, but to move relatively quickly on and to run in parallel with the more dedicated randomized Phase 3 trials. Wei, do you want to comment a little bit further on how that works and what the value of these?

Wei Lin:

Sure, happy to, Mark. Yes, as Mark mentioned and still Steve as well that we are going to be enrolling in the expansion cohort of our first human study, additional solid tumor that cover other histologies and other mutations through the expand on the pre-clinical observation that RMC-6236 is active much more broadly than in the patient population we've shown data so far. I think if the data continued to support that that could potentially lead to a discussion with [indiscernible] for potential tissue agnostic registration in both solid tumors. Thanks.

Marc Frahm:

Thank you. Congrats again.

Operator:

Thank you. And I show your next question comes from the line of Jonathan Chang from Leerink Partners.

Jonathan Chang:

Hi guys. Thanks for taking my questions. First question, given the early stage, still early-stage nature of the 6236 efficacy data, can you talk about whether you think the data could improve from here, whether it's a function of higher dose levels, longer follow up or otherwise?

And then the second question, if the data evolve over time in a way that's largely consistent with the data presented today, can you talk about your thoughts on whether the data are sufficiently compelling versus standard of care benchmarks? Thank you.

Mark A. Goldsmith:

Sure. Thanks. Maybe Steve can comment on both of those questions.

Stephen Kelsey:

Yes. So, the first question about what do we expect to happen to the data over time. I think our expectation is that the data will at least stay as is if not improved and there are a number of reasons for that. The first is that we've shown you data for all patients treated at 80 mg daily and above, and there's a big difference between 80 mg daily and 400 mg daily. So, the overall response rates right now don't forget are driven in large part by the patients that were enrolled at the lower dose levels and not so much by the patients who enrolled at the higher dose levels for whom we have less data.

The second reason is as you can see from those waterfall plots, there is a tendency for patients to the disease to continue to shrink and for some patients who have not achieved the criteria for partial response to move into the criteria for partial response. And actually, when we have done the analysis where we've actually looked at the response rates for patients that have been followed for longer than those that were included in this ESMO analysis, the response rates are actually higher than the response rates that were reported at ESMO. So, it is quite possible that the response rates will improve. Now, the thing that will really be telling, I think, and we'll have to wait some more months for the data is the durability, not just the durability of responses, but the durability of freedom from progression for patients who have had some degree of tumor shrinkage and have not progressed. And I think that will be probably more important and will be a bigger driver of the long-term impact of our RMC-6236 whether or not the response rate goes up or down by a few percentage points.

Mark A. Goldsmith:

Maybe I can add to that. I think a couple of things tend to get lost in that particular topic. One is the tolerability and safety profile is viewed by investigators and patients as very strong, and that has a real impact on so many things going forward. And so, do we need to improve in that regard? I don't think we need to improve in that regard.

Secondly, the breadth of genotype activity is unprecedented. And I don't think we need to improve in that regard.

And third, so far, the durability that we've measured is very strong. We just don't have enough observation period. So as Steve said, well, we'll just need to see, and we'll watch it but there's really no indication today that we have anything but a compound that will provide durability and ultimately that is really going to drive most of the approvals that Wei spoke about earlier. The only one I think in which the response rate matters is in that tumor agnostic study where that will be an important endpoint. So, we're pretty pleased with where we are today, and with the collection of data and patients' outcomes so far. We can't predict the future, but we're quite encouraged by it. And I'd also add that as I mentioned earlier, investigators are very excited about this. They're clamoring to be part of the studies of 6236 and they want to put their patients on the compound. So, I don't think that there is much for us to be concerned about from the point of view of the caregivers who are responsible for these patients recognize the deep unmet needs and frankly the very strong and highly differentiated outcomes that we described today for which there simply is no other comparator.

Stephen Kelsey:

Yes. So, you also asked specifically about benchmark comparisons. I think the easier one here is non-small cell lung cancer, I mean the comparators docetaxel the overall response rate than lung cancer is more tightly linked to the temporal endpoints of progression free survival and possibly even overall survival and soI think we have a fairly compelling case there and that's why we're intending to move forward. The difficulty with pancreatic cancer, I mean, look firstly the response rate is double that anything that's ever been seen in G12X mutant pancreatic cancer, right? I mean, there have been reports of G12C specific inhibitors being used in G12C and pancreatic cancer, which is an extremely small patient population. The outcomes are similar to what we've shown for RMC-6236 and our investigator basis, Mark said, is really excited about this. The challenge there is not so much whether the overall response rate is better than standard of care, it clearly is that the challenge is whether or not the durability, because overall response rate is not so tightly linked to progression free survival. We have to wait until we're confident that the progression free survival is of a nature there's going to be significantly impact patients by being significantly better than standard of care. And so, we're confident at the moment with the preliminary data that we have that the trajectory is in the right direction, but we've just don't have enough information right now, and particularly not at what ultimately be the recommended Phase 2 dose to be able to report out what we are like to have.

Jonathan Chang:

Understood. Thank you.

Operator:

Thank you. And I show our next question comes from the line of Eric Joseph from J.P. Morgan. Please go ahead.

Mr. Joseph, please go ahead with your questions.

Eric Joseph:

Great. Thanks for taking the questions. And Mark, Congrats on this data. I guess with dose selection in the plant Phase 3 is still pending, I'd be curious to know sort of what additional follow up you're seeking to arrive at those selection and sort of perhaps if there's a time frame that you might attach to that. And that Mark, you've previously talked about the possibility advancing tumor-specific dose regimens, 1 dose taken into lung cancer or another for pancreatic. I guess any additional thoughts on that potential strategy in light of the data that you're presenting here today? Thank you.

Mark A. Goldsmith:

Great. Thanks very much, Eric. Let me preface the first part of the answer to your first question. Let me provide a first part of the answer with regard to timeline, which is that we have indicated, and I think continue to believe that we have a very good shot at starting the first randomized Phase 3 global trial in at least one indication in 2024. We can't be more specific than that for the reasons that are kind of embedded in your question, but we're well on our way towards designing such a trial, and of course we need a little bit more information. Maybe, Wei can then fill in a little bit, not so much in terms of time, but just what are we doing to get to that dose selection for lung cancer and for pancreatic cancer as well. Which by the way, could end up being the same dose, I think I've earlier just said it is always possible that one would end up proceeding with a dose that's working very well in lung cancer while you're still evaluating higher doses in pancreatic cancer and that's sort of a TBD right now we're just being transparent about it, but maybe way can comment on that further and then we'll come back to the second part of your question.

Wei Lin:

Sure. Yes. As you know, the FDA has published guidance called Project Optimists on how to optimize dose and we're following that guidance very closely in expanding on patients who have non-small cell lung cancer and pancreatic cancer at more than one dose level to really optimize and identify the optimal dose to move forward and to discuss with FDA as the recommended Phase 2 dose. And I think, like Mark mentioned, it's possible that these two-tumor histology would arrive at the same dose or different. I think would be very data-driven in that regard. And so, that would be one of the key gatings identified RP2D for opening up our first of hopefully many registration trials in the coming year.

Mark A. Goldsmith:

And then, your second question really, I guess I've already commented on, and Wei did as well, which is do we end up with different doses, and I think that was sort of embedded a little bit in Jonathan's question about response rates. I think Steve gave you our very clear view that we're in a strong place today with the response rates, but it's also not the main thing that we're looking for, which is something I've talked about for the last number of months. As you know, the Disease Control rate is very high for both lung and pancreatic cancer, even at the doses that we've tested. And those we believe are more likely to be a predictor of durability, which is going to be the key to approvals rather than response rate per se. And I think Steve also mentioned that response rates, they're calculated at a moment in time, they're calculated to include patients who had only one scan and haven't even had the opportunity to convert and we've seen very high rates of conversion. So, I don't think we're too focused on those specific numbers, but there is a difference in the unmet needs between lung and pancreatic cancer and patients and their caregivers may be willing to take their time and tolerate higher doses. So, they may actually be justification for pushing dose sort of more aggressively in one population versus another. Again, I'm not advising that's what we will do, but that's the subject of ongoing discussion and we haven't reached an MTD yet in either population. So, there certainly is room to go and in general with RAS inhibitors once observed that more is better. The phrase I've used many times in the past. And so, that's something for us to keep on the table and we'll see whether things converge or diverge.

Eric Joseph:

Thanks. That's helpful. Maybe just a quick follow up if I could, I guess, is there anything in this 6236 data set that speaks to the potentiality for mutant KRAS heterogeneity, or a mix of KRAS mutations within the given patient's tumor. Were there any cases in this data set so far and,if so, could you speak to the activity of 6236 in that type of setting?

Mark A. Goldsmith:

I don't think we have, since for 6236 there are no patients in the study who have previously received a RAS inhibitor. So, there hasn't been any real selection pressure for the emergence of those rarer or second mutations that tend to become enriched over time in patients who had a RAS(OFF)inhibitor, but we haven't evaluated any patients like that simply because the protocol is designed. So, I don't think, to my knowledge, I don't think we've seen any second RAS mutations within the data set. Steve or Wei, if they want to add to that, I think we just don't know.

Stephen Kelsey:

Not in the 6236 data set. The 6291 data set, we've seen a number of patients with colorectal cancer who progressed on a care as digital self-inhibitors that have had multiple additional mutations and amplifications and that's I think one of the… I know we're talking about 6236 but we did mention that we hadn't reported outcomes for patients with colorectal cancer to retrieve the 6291, who had been previously treated with another G12C inhibitor and that's because the G12C inhibition with the G12 inhibitors frequently induces other mutations in colorectal cancer. But, in the 6236 data set, we have not seen that, and I think that's for the reasons of our mention is that because there are currently no other RAS inhibitors being used in these patients that selection pressure is very different, that these patients are undergoing selection pressure with cytotoxic chemotherapy. And so, the primary driver RAS mutation tends to still be the predominant driver in these patients.

Mark A. Goldsmith:

Which I think does set up, just to sort of close out that point it does set up the concept here that RMC-6236, which we continue to believe is going to be active against many different mutant forms and the preclinical evidence strongly supports that that it may in fact provide a much more robust and durable suppression of the RAS pathway because those clones that might be lurking as ultra rare, clones of heterogeneity in the background simply don't have the opportunity to emerge. And we'll take every day of benefit that might be able to provide. I think that could really serve patients, but that's a concept today based on the preclinical data, of course, we just don't have any clinical data yet to validate it.

Eric Joseph:

Okay. Great. Well, congrats again and thanks for taking the questions.

Mark A. Goldsmith:

Thank you.

Operator:

Thank you. And I show you the next question comes from the line of Chris Shibutani from Goldman Sachs. Your line is open.

Charlie Ferranti:

Hi everyone. This is Charlie on for Chris. Thanks so much for taking our questions and I'll add my congratulations as well, really exciting. So, first we were wondering just in terms of the ongoing work to pursue lung and registrational studies, whether you are considering the inclusion of active brain metastases, considering the preclinical evidence for activity within the CNS. And then as a follow up, I was just wondering with the lung complete responder, can you provide some clarity on when that patient had dosed down to 200 mgs? Thanks so much.

Mark A. Goldsmith:

Sure, active brain mets. Wei, you want to comment on what we're contemplating with regard to active brain mets in a registration study.

Wei Lin:

Yeah, sure. Happy to take. So, the current plan is actually followed, we plan to follow a very data-driven approach and so the current Phase 1 study has not included a patient with active brain mets. They all have included patients with treated brain mets. And so, since that's the data that's been generated and we'll follow that. So, the patient population plan for the Phase 3 would also include only patients with treated brain mets not active brain mets. However, in the future we do at the right moment plan to really possibly explore patients who have with active brain mets and then evaluate the activity of 6236 as well as 6291 in those populations.

Mark A. Goldsmith:

Yeah. And just to build on Wei's comments and as you sort of built into your question, we have shown preclinical data for all three of our clinical stage RAS(ON) inhibitors that showed activity in a model of brain metastases, RMC-6236 showed activity in an identical model to that used with, I think at aggressive and $KRAS^{G12C}$ tumors and 6236 was as good or superior to that. So, I think it is active on the other hand, the two mutant selective inhibitors showed even greater activity. In the preclinical model, we don't know exactly how well either of those predicts clinical behavior, but we're encouraged by them. And as Wei said, we will be in parallel, I think a key point to all of this is that we're going to study all of these different questions in parallel, while we're also driving towards the earliest possible and strongest possible approval. So, more to come, but I think parallel, parallel, parallel should be the theme of the day.

Your second question had to do with the patient who had a complete response, a pretty amazing response probably had a response faster than we measured it simply because based on her clinical behavior. But I think the first scan was done per protocol at six weeks. Wei, do you know? I think the question being asked here was whether, yeah, when did they dose reduce? And specifically, I refer from that that you're trying to relate that to the anti-tumor activity at 200 versus 300, but maybe Wei will clarify that.

Wei Lin:

Yeah. So, a patient who experienced a complete response was dose reduced in the middle of cycle 3.

Mark A. Goldsmith:

So, that would have been between the first CR scan and the confirmation?

Wei Lin:

That's right. Correct. Yeah. So, yeah, the first dose and then… So, which means that the confirmation was achieved at the lower dose.

Charlie Ferranti:

Great. That's so helpful. Thank you so much and congrats again.

Mark A. Goldsmith:

Thank you.

Operator:

Thank you. And as our next question comes from the line of Ami Fadia from Needham. Please go ahead.

Ami Fadia:

Hi, good afternoon. I'll add my congratulations on the data that's been presented over the last several days. My first question is just how do we think about where the response rates may be landing for lung and PDAC? And if you look at the responses by dose, your overall response rate across doses was about 38%, but if you look at the 160 mg dose in lung, that's at 56% and perhaps the higher doses don't have enough follow up yet. So, and then, for PDAC and sort of seeing about 20 to 25% for the 160 and 200 mg dose. So, my first question is would you expect that as data matures and as you close up response rates and lung could trend more towards that you know mid-50s range and is for PDAC, do you think that 20 to 25% is kind of where we will see the data as it matures? And then, I have one other question.

Mark A. Goldsmith:

Thanks, Ami. I appreciate the questions. I think I probably could just comment on this and then Steve if they want to add to it.

We can't predict the future. So, I think we're always very cautious about sort of guiding you to what we might see at some point when we have a different data set than we have today. But there's no question that in the course of the study,we have had data cut-offs that have shown significantly different response rates than those that you're seeing here. It's a moving target when you're dose-escalating and I think that was embedded in your preface, which is that we tried to get as late a data cut as we could practically provide for investigators and investors. The consequence of that is that it's loaded up with patients on higher doses but who have had very little follow up and that's just the reality of the calendar and it doesn't really have any particular significance.

So, while I don't think we want to stick a number out there, that is simply a speculation. I think Steve said it well that we expect at least to preserve the rates that we've seen, and we may well see increased rates over time, and I don't know about any particular number.

I think the second point about PDAC, I would just reiterate a really important underlying piece of science here, which is it's been known for decades that pancreatic cancers are predominantly non- tumor cells that result that drive the bulk of the tumor and remember CT scan really doesn't differentiate between tumor and non-tumor. And the non-tumor, Steve mentioned very briefly, is fibrosis. Desmoplasia is the term and it's a well-known and specific characteristic of pancreatic cancer. And so, when you're trying to shrink a tumor for a CT scanner, you get what you get, and it doesn't really tell you anything about what's going on in the tumor itself. It just tells you what the bulk white shadow is on the scan and there's linear dimensions. So, we don't know. There's never been a compound of this type to evaluate. So, we have nothing to compare it to and the hypothesis that's been in the literature for a long time focused on tumor versus stroma or fibrosis is now being tested with RMC-6236 for the first time in history.

So, we'll find out what it shows in the future, but we're not particularly anxious about it. I understand some other people might be particularly anxious about it, but not our investigators and not our patients and not us. It's just a fact of the complexity of these tumors. So, where we'll exactly land, I don't know. As Steve mentioned, we have seen the evidence, in fact, even one of the earlier questions was predicated on the idea that there are the time to response is longer in PDAC versus non-small cell lung cancer and that has some implications for sort of accumulating the evidence. So, we'll land where we land, and I'll stick by Steve's comment. Should be at least as good as where we are right now, ifnot better and in the end this will all be driven by durability response and not by whether we're at 21% or 26%. It makes zero difference to the regulatory authorities or to caregivers or to patients.

Ami Fadia:

Those are very helpful comments. I just have one other quick question. Can you comment on kind of where you're thinking as... is that currently with regards to the possibility of an accelerated approval pathway with the trial design you've discussed and sounds like you didn't highlight response rate as a key endpoint in those trials? Would you say that approval would be based on a PFS endpoint?

Mark A. Goldsmith:

Well, full approvals for both PDAC and lung for sure are going to be based on PFS and trends in overall survival, no question about that. But we know there's a lot of interest, particularly in the investor community, for what sort of so-called accelerated options we might have. And I think there are several that are already built into the trial design that might not have been called out explicitly, but Wei could comment on that. We've obviously had many internal discussions of it and maybe he can sort of draw out for you what are the ways in which accelerated approvals could be obtained.

Wei Lin:

Happy to do that, Mark. Yes, I think also recently FDA has published guidance about their new perspective on starter approval. And I think historically six-hour approval has been largely based on single-arm studies and response rate with durability of response. I think for some indications that still makes a lot of sense, I think for other indications, it actually you could run a randomized trial and have interim readout based on PFS to enable accelerate approval and then ultimately have a final readout based on overall survival or PFS depends on which indication to enable full approval. All within the same brand mice trial, and there are certain advantage to that because that ensures the timely approval and then it just enables a single trial rather than a single arm for accelerate approval and a separate Phase 3 randomized trial for confirmation. So, we're going to consider all these options and as we discussed with regulators on what's the fastest way to bring this medicine to patients. And after exploring those options, we'll take the ones that actually would really be able to enable us to really benefit patients the most.

Mark A. Goldsmith:

If I could just build on that a little bit, I think it's been made abundantly clear by the FDA that for accelerated approval they are going to require that you have enrolled your full approval trial anyway. And so, it's not at all clear that it's faster to run something separate as well and I think the term accelerated is an unfortunate term. We think of it as an interim approval. And I think the evidence of the last month has demonstrated that that's the better way to think about it rather than as an accelerated approval acceleration… accelerated approval and speedy approval are not nearly the same thing. But nonetheless, I think given the structure of these requirements for enrollment, again, we've said this for many, many months and I think everybody can see why, that designing the trial principally around the full approval, but then having opportunities for potential interim looks, if the FDA is interested in that, then of course we will do so and make sure that the power enables the statistical, the structure, and the power enables us to do that.

And then the second point. Wei, do you just want to comment about the tumor-agnostic trial looks? I think again that went by a little bit quickly earlier than just how we think about it as in some ways comparable to that even much more potentially powerful and broader than a dedicated accelerated single arm trial.

Wei Lin:

Absolutely. To expand on what's been discussed earlier, [indiscernible] because RMC-6236 is expected to be broadly active across histologies and across genotypes of RAS mutations has been demonstrated our by our preclinical data. I think we believe that sort of approval based on tissue agnostic approach could be a viable approach if there's alignment with the regulators. And then in there we can enable a single-arm study because across both histologies there will be no common standard of care to really compare against and these will be patients who have really been treated with previously standard of care therapies, and then hence offer them a treatment option that otherwise they would not have. And so that would allow us to really broadly, really enable this medicine for many patients whose natural prevalence may be fairly low in terms of patient number and so instead of being able to support a randomized Phase 3 trial in each individual tumor type, then we can potentially gain approval across multiple tumor types for all solid tumors potentially with this strategy.

Mark A. Goldsmith:

Yes. Thanks, Wei. And so, I would just reiterate, obviously, we need feedback from the FDA who will react to the data. We think we're excited to be able to have the chance to talk with them at the right time. But you know this compound is truly unprecedented. So there just simply aren't examples one can look toward to see the kinds of breadth of opportunities that we uniquely have because of its profile. And you'll see, you can tell we're very committed to maximizing both the speed and breadth and quality of those approvals.

Ami Fadia:

Thank you.

Operator:

Thank you. And I show our next question comes from the line of Alec Stranahan from Bank of America. Please go ahead.

Alec Stranahan:

Hey, guys. Congrats on the data both at ESMO and the Triple Meeting and thanks for taking our questions. One question I had, and this has sort of been touched on partially in different responses, but maybe not directly, but any color you can provide on why G12C experienced patients were excluded from the 6236 study, particularly in light of the responses seen with the 6291 in these patients? Do you think we could actually see activity for 6236 in this patient population as well? And I imagine this probably feeds back into the commentary from Wei on the rationale for the doublet combo approach as well.

Mark A. Goldsmith:

Oh, sure. We'll take the first one, the easy one, which is preclinically 6236. It's an extremely active inhibitor of RAS^{G12C} tumor models, and so we fully expect it to be highly active. I think it was excluded simply for practical reasons, which is… largely because getting those patients naive and not having previously see a G12C(OFF) inhibitor requires an extra effort. And it is potentially a distraction from getting to the breadth. We've showed activity just in the data sets that you've now seen across four different RAS genotypes with objective responses in three of those genotypes already (D, V, R). I think there's very little doubt that this compound is quite active in G12C, and we will evaluate that more explicitly, formally coming up not too long from now.

The second question I think was 6291 plus 6236 and maybe Wei if he wants to add anything to what I just said about G12C, please do and also then maybe you could address the combination.

Wei Lin:

Sure, happy to do that. I'm just adding to Mark's comment. I think because 6291 was developed continuously with 6236. And I think we believe that we can demonstrate the proof of concept of our activity 6236 in G12, mutated RAS tumors just by looking at non-G12C, and then leaving the patient potentially available for 6291 development which now we're able to show you the data for a non-small cell lung cancer and other tumor types. So that's one of the things.

Now we are certainly very enthused about the 6236 plus 6291. And I think Clay Gustafson's assumption at the Triple Meeting have presented some preclinical data and our research group has also done it previously as well. So that combination is extremely active. And so, we're really enthused about that dual inhibition of the target. And I think given just the data that emerged from the resistance mechanism for the first generation G12C(OFF) inhibitors, both sotorasib and adagrasib, I think one of the themes that really emerged is just by ctDNA analysis of a patient who progressed on either sotorasib and adagrasib. More than 80% of patients retain their G12Cmutation and many of the patients have secondary mutation on RAS as amechanism resistance to these G12 inhibitors. It just highlights for many of these patients the tumor is really heavily addicted RAS and in spite of exposure to G12C inhibitor, they continue to be addicted to RAS and try to overcome with the mechanism that we call RAS or rescuing the signaling in the RAS map kinase pathway either directly with the second mutation at RAS, or even some of them have activation at the RTK or upstream and continue to feed signal into RAS and also downstream as well. So that's why we believe that that combination could be potentially highly active, even more so than either agent alone. And through that combination, we'd be redressed probably many of the potential mutation that can emerge with either single agent or with G12C(OFF) inhibitors. So that trial, as I mentioned before, has really opened and we're actually recruiting patients. And then when the data is available, we're looking forward to sharing that.

Alec Stranahan:

Okay, got it. Thanks. That's very clear. And one more question if I may. I imagine we're getting towards the end of the Q&A, but any updates can provide on the EQRx transaction. What are the next landmarks we should be looking for over the next month or so? And how should we be thinking about the recent data updates as it relates to deal pricing and closing?

Margaret Horn:

Thanks for that question. This is Peg, chief operating officer. So, this data disclosures over the last couple of days and weeks was a critical element of EQRx transaction design, as you know, and so I'd say the next critical question is our next landmark is when we will be having the shareholder meetings which are scheduled November 8th. Short of that, I think there's no immediate steps other than continuing to see how our…

Mark A. Goldsmith:

Vote early, vote often.

Peg Horn:

… votes come in.

Mark A. Goldsmith:

I'd like to just build on that a little bit. It's pretty clear that this compound, RMC-6236 has extraordinary breadth of activity. It's the first ever compound of its type, targeted therapy against all forms of RAS. It deserves a lot of attention, and it will get a lot of attention. The tolerability and safety profile breaks the dogma that had been out there very clearly. Initial durability are encouraging. Their strong investigator and patient interest, so much so that we have wait lists at every one of our clinical sites, which also squeezed out any potential for G12C earlier but we need to broaden. And then we have, and we'll gain, additional financial strength that gives us from this EQRx transaction that gives us the capacity to pursue the breadth of studies and further development and hopefully registration approaches that this compound serves and that patients deserve with it. So, it's a very important transaction for us. We think it's a unique way to strengthen our balance sheet. We appreciate the support of the EQRx team, and their shareholders and we look forward to closing this out shortly.

Alec Stranahan:

Great and thanks again.

Operator:

Thank you. And I show our next question comes from the line of Jay Olson from Oppenheimer. Please go ahead.

Jay Olson:

Congrats on these results and thank you for the comprehensive update. For the circulating tumor DNA analysis, it seems like most patients achieved impressive levels of reduction. Can you talk about how this finding may be implemented in future clinical studies and or in clinical practice and I have a follow up if I could.

Mark A. Goldsmith:

Yeah, I was just actually looking at that earlier this morning. I mean it is quite supportive of the anti-tumor activity we've seen and if we're reducing circulating tumor DNA, we're clearly doing something to these tumors that's important. So, it's supportive information in the clinical trial context. Wei, do you want to comment about implications for either future trials or for clinical practice?

Wei Lin:

Yeah, absolutely. Yes. It's a great question. I think the implication may be different for crowd conduct and clinical practice and it may be different for different tumor types and histologies. So, if you look at the three major tumor types that we have data for which include lung cancer, colorectal cancer, and pancreatic cancer, the presence of ctDNA baseline, it actually varies quite a bit. Probably in order of colon being the highest, lung second and pancreatic probably third. So majority, if not all, colorectal cancer patients at baseline have detectable ctDNA. Lung, probably somewhere between 50 to 100%. So maybe in the 70% range or so and pancreatic cancer is a bit less than that. That's just based on historical numbers that may… those numbers may evolve as technology advances and sensitivity as says may actually change as well for detecting ctDNA.

But having said that, so as you can see, if you look at what happening in our trial for 6236 because in higher doses, we predominantly enrolled lung and pancreatic cancer patients and non-colorectal only a portion of the patients that we evaluate CLDN4 has ctDNA at baseline. So the ctDNA data you've seen that we presented is actually for a subset of patients who have ctDNA at baseline. And so that's the implication for conducting trial is I think it's useful for really supportive data to correlate with tumor response, which we have for every single patient. I think provides a really biological support and allow us to maybe establish our proof of concept more confidently and with smaller data sets than otherwise without the ctDNA and if we were just based entirely on radiographic data.

Now in colorectal cancer because we expect much more higher prevalence of ctDNA that utility is probably a lot more powerful. And even in a clinical trial design, I think currently for instance, in the action setting, patient who has had surgical resection out their primary colorectal cancer who have earlier stage colorectal cancer, if they have microscopic disease, there's a high likelihood there they would have ctDNA. And if that ctDNA the risk of recurrence is extremely high so in trial design you can actually use this as a way to select patients to randomize into a trial so you can imagine conducting an accurate study in colorectal cancer, enrolling only patients who have had surgery and still have presence of ctDNA in their blood. Highlighting these are the patients who are most likely recur because they have presence of microscopic metastasis not visible on CT scan. And so, if you enroll those patients, given their high risk of recurrence, that demonstrate ability, to demonstrate benefit for patients is actually higher then if you enroll in all-comer population mixed in with patients who would never recur because their disease, they actually basically disease free. So colorectal cancer I think you can probably use that both in clinical trial design as well as eventually in clinical practice because that would translate to then if the drug were approved, you would pick out those patients to receive the drug in home practice based on the present ctDNA after surgery. I think in other tumor types where the abundance of ctDNA at baseline is lower, it'll probably more… remains in use, more supportively in the design of clinical trials, especially in that concept. And since not everyone has ctDNA, it's harder to use that in clinical practice. I hope that helps.

Jay Olson:

Super helpful. Thank you for the detailed explanation. Separately, can you talk about any initial clues of resistance mechanisms you've seen with 6236?

Mark A. Goldsmith:

No, we can't. We just don't have much information on that at this point. It's too early and we just don't, we just don't have any data to speak from.

Jay Olson:

Okay, fair enough. Thanks for taking the questions.

Mark A. Goldsmith:

Thank you.

Operator:

Thank you. As a reminder to ask a question, you would need to press star one one on your telephone. And I show our next question comes from the line of Ben Burnett from Stifel. Please go ahead.

Ben Burnett:

Thank you very much and congrats on the updates. I just want to ask a clarification question on the ORR data and I can really appreciate that there a lot of eyes on how the PFS signal unfolds, but just want to make sure that we understand the ORR signals. I think there's the deck shows three unconfirmed responses that are no longer ongoing. Is that right? And what are the reasons for those patients not continuing therapy?

Mark A. Goldsmith:

Steve, do you want to comment on those?

Stephen Kelsey:

Yes. That, you are correct. We have a total of three patients that had an initial resist response and have discontinued treatment. One with pancreatic cancer and two with non-small cell lung cancer. And my understanding is that two of those patients had a progression between the first scan and the follow up scan and one of those. And then one more patient, I think, withdrew from the study for reasons that were not fully explained to us but were clearly that they were not related to a drug-related adverse event or an obvious and measurable clinical progression.

Ben Burnett:

Okay. That's very helpful. And if I could just also ask another question just around the strategy of pursuing a tumor-agnostic study, which I think is really interesting. But it looks like that this tumor-agnostic study would include some of the tumor types that you're also pursuing, I guess more directly and separately. Could you talk about how do you prosecute all of these and a capital efficient manner and I guess what I'm asking is, are there any go/no go decisions that would refine your strategy that we should be looking out for?

Mark A. Goldsmith:

Yes. Well, one of the reasons to include the tumor types for which there are dedicated studies is that you really have to anchor the tumor-agnostic study across one or more tumor types because… and then you end up collecting more data from those simply because they tend to be well-represented, they're the more common tumor type. So that just has to do with the sort of typical design of those. There's very high demand for RMC-6236. So, there's really not going to be any issue of sort of competition or difficulty finding patients. Sadly, and I think it's just the reality of all of these clinical indications that the needs are very deep and we have not been able to serve everybody during the conduct of the trial so far because of the sort of regimented way that we have to dose escalate and do expansions and so on.

So, there's lots of opportunity to do these studies. I think from a capital efficiency point of view, I think let's differentiate between spending less money and being capital efficient, which is also includes maximizing value creation and given that there are tumor types that simply won't be represented in the core of Phase 3 trials which necessarily are dedicated to specific indications, the opportunity to try to capture those in other ways which creates potential clinical benefit and opportunity, but also commercial implications associated with that is there and that sort of pure agnostic trials not a gigantic study anyway. So, we get to serve more patients at the same time that we're collecting more data at the same time that we're generating more potentially registrational data across tumor types, lines of therapy, genotypes, et cetera. So, we think that the point now is to maximize value creation and we will. That is our strategy. Will be an aggressive strategy to do so, especially in a competitive environment. And was there second part to that question?

Ben Burnett:

That was basically if there's maybe a go/no go decision between these…

Mark A. Goldsmith:

Yes, well, of course there are. Sure. Not going to allow you to ask me the follow-up question of what those are. Those are internal, but obviously and I think we said it many times here and we're very transparent about this. We'll continue to be driven by the data and make data-driven decisions. But we're giving you our best projections, genuine data-driven projections for where things are going to go and also reflects the activities that we're currently doing to support those projected plans. These are not theoretical. This is very high quality; important hard work being done by our development organization to prepare for everything we've mentioned here, there is in some stage of significant planning to do. But of course, the data will ultimately drive each of these decisions and I didn't see how we could do it otherwise.

Ben Burnett:

Okay, that's great. I appreciate it and congrats again.

Mark A. Goldsmith:

Thank you.

Operator:

Thank you. I'm showing up with no more questions in the queue. At this time, I'd like to turn the call back to Dr. Mark Goldsmith for closing remarks.

Mark A. Goldsmith:

Thank you, operator, and thank you to everyone for participating and actively acquiring us about this large, complex and very exciting program. And we very much appreciate your continued support of Revolution Medicines.

Operator:

This concludes today's conference call. Thank you for participating. You may now disconnect.

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Merger Agreement; the issuance of common stock of Revolution Medicines contemplated by the Merger Agreement; the expected timing of the closing of the proposed transaction; the ability of the parties to complete the proposed transaction considering the various closing conditions; the expected benefits of the proposed transaction; the competitive ability and position of the combined company; Revolution Medicines' development plans and timelines and its ability to advance its portfolio and research and development pipeline; progression of clinical studies and findings from these studies, including the tolerability and potential efficacy of Revolution Medicines' candidates being studied; the potential advantages and effectiveness of Revolution Medicines' clinical and preclinical candidates, including its RAS(ON) Inhibitors; the potential clinical utility of RMC-6236 in patients with non-small cell lung cancer and pancreatic cancer; the timing and completion of a clinical trial for the combination of RMC-6236 and RMC-6291; whether additional near-term and longer-term investments will strengthen the clinical advancement of Revolution Medicines' RAS(ON) Inhibitors; Revolution Medicines' ability to enable seamless program progression; Revolution Medicines' ability to advance its oncology assets and its intention to concentrate development resources on its three priority RAS-focused assets (RMC-6236, RMC-6291 and RMC-9805) following the proposed transaction; Revolution Medicines' expectation to not advance EQRx's research and development portfolio following closing of the proposed transaction; EQRx's expectation to wind down its programs; and any assumptions underlying any of the foregoing, are forward-looking statements. 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with therapies and procedures that are rapidly growing and evolving; (xxi) uncertainties in contractual relationships, including collaborations, partnerships, licensing or other arrangements and the performance of third-party suppliers and manufacturers; (xxii) the ability of each of Revolution Medicines and EQRx to establish and maintain intellectual property protection for products or avoid or defend claims of infringement; (xxiii) exposure to inflation, currency rate and interest rate fluctuations and risks associated with doing business locally and internationally, as well as fluctuations in the market price of each of Revolution Medicines' and EQRx's traded securities; (xxiv) risks relating to competition within the industry in which each of Revolution Medicines and EQRx operate; (xxv) the unpredictability and severity of catastrophic events, including, but not limited to, acts of terrorism or outbreak of war or hostilities; (xxvi) whether the termination of EQRx's license agreements and/or discovery collaboration agreements may impact its or Revolution Medicines' ability to license in additional programs in the future and the risk of delays or unforeseen costs in terminating such arrangements; (xxvii) risks that restructuring costs and charges may be greater than anticipated or incurred in different periods than anticipated; (xxviii) the risk that EQRx's restructuring efforts may adversely affect its programs and its ability to recruit and retain skilled and motivated personnel, and may be distracting to employees and management; and (xxix) the risk that EQRx's restructuring or wind-down efforts may negatively impact its business operations and reputation with or ability to serve counterparties or may take longer to realize than expected, as well as each of Revolution Medicines' and EQRx's response to any of the aforementioned factors. Additional factors that may affect the future results of Revolution Medicines and EQRx are set forth in their respective filings with the SEC, including each of Revolution Medicines' and EQRx's most recently filed Annual Reports on Form 10-K, subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the SEC, which are available on the SEC's website at www.sec.gov. See in particular Item 1A of Revolution Medicines' Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2023 under the heading "Risk Factors," and Item 1A of each of EQRx's Annual Report on Form 10-K for the fiscal year ended December 31, 2022 and Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2023 and June 30, 2023 under the headings "Risk Factors." The risks and uncertainties described above and in the SEC filings cited above are not exclusive and further information concerning Revolution Medicines and EQRx and their respective businesses, including factors that potentially could materially affect their respective businesses, financial conditions or operating results, may emerge from time to time. Readers are urged to consider these factors carefully in evaluating these forward-looking statements, and not to place undue reliance on any forward-looking statements, which speak only as of the date hereof. Readers should also carefully review the risk factors described in other documents that Revolution Medicines and EQRx file from time to time with the SEC. Except as required by law, each of Revolution Medicines and EQRx assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

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In connection with the proposed transaction, Revolution Medicines and EQRx filed with the SEC and mailed or otherwise provided to their respective security holders a joint proxy statement/prospectus regarding the proposed transaction (as amended or supplemented from time to time, the "Joint Proxy Statement/Prospectus"). INVESTORS AND REVOLUTION MEDICINES' AND EQRX'S RESPECTIVE SECURITY HOLDERS ARE URGED TO CAREFULLY READ THE JOINT PROXY STATEMENT/PROSPECTUS IN ITS ENTIRETY AND ANY OTHER DOCUMENTS FILED BY EACH OF REVOLUTION MEDICINES AND EQRX WITH THE SEC IN CONNECTION WITH THE PROPOSED TRANSACTION OR INCORPORATED BY REFERENCE THEREIN BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION ABOUT THE PROPOSED TRANSACTION AND THE PARTIES TO THE PROPOSED TRANSACTION.

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EQRx's investors and security holders may obtain a free copy of the Joint Proxy Statement/Prospectus and other documents that EQRx files with the SEC (when available) from the SEC's website at www.sec.gov and EQRx's website at investors.eqrx.com. In addition, the Joint Proxy Statement/Prospectus and other documents filed by EQRx with the SEC (when available) may be obtained from EQRx free of charge by directing a request to EQRx's Investor Relations at investors@eqrx.com.

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