ASTRAZENECA ESMO ANALYST CALL

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5:30 p.m. ET

Mondher Mahjoubi: Good evening. Ladies and gentlemen, good evening. On behalf of AstraZeneca and the Cancer Enterprise Leadership Team, welcome to this investors meeting, and welcome to ESMO. My name is Mondher Mahjoubi. I'm the head of global product & portfolio strategy for oncology. I have the privilege and the pleasure this evening to chair the meeting and to kick off our session.

I will be handing over very quickly and shortly to my colleagues, Rachel Humphrey, who leads the late-stage development team for Immuno-oncology and Susan Galbraith, who is the head of the early-stage clinical development for AstraZeneca.

Before we start, I wanted to very quickly remind you where we're coming from. And remember that a year ago, at Amsterdam, we didn't have this – such opportunity to meet with you. We came to this meeting last year with very modest presence. We had a handful number of abstracts. And as a matter of example, we presented data for 11 patients on PD-L1 and 60 patients, I think, for 9291.

It was the start of the momentum that you've seen over the last couple of months, and actually four months ago in Chicago, at the ACSO meeting, we had the pleasure to meet with you and to update you on, first of all, our strategy, on how to get back to a leadership position in this field, but also share with you the progress of our pipeline, and in particular, the six NMEs that are in late-stage with 13 projects in Phase III.

Today, we are at ESMO again, and we are extremely excited, because as I said, the momentum keep growing. You will see from the presentation the progress was made in particular in developing AZD9291, which is our anti-EGFR inhibitor targeting the T790M

mutation positive in non-small-cell lung cancer, but also the progress we've made in developing our antibody against PD-L1, MEDI4736.

We decided to focus the session this evening on these two assets, so with no further delay, I will hand over to Rachel Humphrey, who will update us on the progress for PD-L1, and then Susan will share the update on 9291. We'll take questions at the end of the session. There will be questions here in the room, but also questions online.

I wanted also to let you know that the slides are already available on the – our Web site, the investor relation Web site, so you will find all the information available whenever you get online. Thank you.

Rachel Humphrey: Good evening. OK, I'm going to focus on the immuno-oncology program, specifically the PD-L1 project, and the combination with tremelimumab. First we'll start with the monotherapy PD-L1 project.

So just a reminder about the anti-PD-L1 antibody, MEDI4736, there are two key messages here. The first, that this PD-L1 inhibitor does not bind to PD-L2. It is strictly a PD-L1 inhibitor. And the second is immunogenicity. There isn't any to speak of. There were two patients out of 196 at the 10 mg/kg that showed transient drug antibodies, but they did not impact PK. And so, therefore, it's not an active issue at the 10 mg/kg dose.

Another important thing, you heard that last year at ESMO we presented 11 patients' worth of data. At this meeting, we're presenting 408 patients in the expansion of our Phase I, but as of this week, we've enrolled over 600 patients, and that number is climbing rapidly in both monotherapy and combination.

So study 1108 was a Phase I/II dose escalation study with expansion into multiple tumor types. There was a dose escalation portion that went up to 15 mg/kg Q3 weeks. The 10 mg/kg Q2 weeks was chosen as the dose for further exploration, because it hit the target extremely well and was 100-fold above the dose where we began to see activity.

The expansion program with over 500 patients treated as of September was conducted in the cancer types you see there. There are eight additional cancer types added to these eight. And we won't be talking more about that later. Suffice to say that the expansion into a greater number of cancer types has been initiated.

OK. Here's safety of 4736 monotherapy, a handful of messages here. No evidence of colitis of any sort. No high-grade pneumonitis. And no drug-related deaths.

I'll draw your attention down below to the pneumonitis. There were five pneumonitis events of all grades. Four of them were incidentally found on X-ray. The fifth was – and they were asymptomatic – the fifth was a symptomatic patient who was progressing in the lung. And otherwise, there are no other reported events of note.

This walks you through the safety profile in all the cancer types for which we have data at this time. And you can see that the pattern is the same across the cancer types. There's no meaningful difference.

OK. Let's talk now about the anti-PD-L1 monotherapy across all the tumor types. This is a classic spaghetti plot. The patients who have experienced any amount of shrinkage or stabilization is colored in green, and there are grey lines there – I hope you can see them – for those patients that have progressed. But you can see that the majority have experienced some level of benefit as defined by shrinkage or response.

The study stops the dosing at 52 weeks. So you can see that the proportion of patients who've been followed out to as long as 90 weeks from the start of treatment have experienced post-discontinuation activity. There's one patient who had a clear progression at 60 weeks. This is a patient who was treated at one mg/kg and is being retreated now at higher doses, and a follow-up will be available in the coming months.

Moving over to the table on the right, of the total number of responders with a follow-up – a median follow-up of 29 weeks, 92 percent of those patients remain in remission. And this is the subset of patients who experienced a pure RECIST response. That is, they didn't have any new lesions. Their index lesions were dropping. Naturally, you can see from the spider plots that there are additional patients whose index lesions decreased and continue to decrease, and some of those have had new lesions and yet there – as you've seen before in this class, there continues to be tumor suppression.

As before, the enrichment of responses by PD-L1 status, that trend is continuing. Here the PD-L1 positive population with more patients treated over time, the objective response rate is 22 percent, and the response in the PD-L1 negatives – and this is across all tumor types – is 5 percent. And a disease control rate is also trending in the direction of improvement in the PD-L1 positive group, but suffice it to say these numbers are still small, but the continued trend is interesting and consistent with what others have seen.

So now we'll look at non-small-cell lung cancer specifically. Here you can see, again, evidence of encouraging activity and a trend in favor of separation by PD-L1 positivity. The majority of patients in the waterfall plot on the left in blue have some level of tumor shrinkage. And although it may not project, the vast majority of the patients, their index lesions are below the cutoff for progression. The PD-L1 negative trend shows a clear activity, but not as robust.

Moving over to the table, with a median follow-up of 24 weeks, the total number of true responders by RECIST that remain in remission as of the cutoff date in mid-August is 88 percent. And, again, the trend in favor of the PD-L1 positive holds up in the numbers, as well.

I'm going to point out that the objective response rate in lung cancer for the PD-L1 negative patients is 10 percent for the monotherapy. Hang on to that number, because we're going to refer to it again later.

OK. This puts the PD-L1 expression story in the context of other agents in the class. With more patients on, the pembrolizumab number of 23 percent in the PD-L1 positive population aligns with MEDI4736. The Nivo data presented at ASCO shows no apparent difference by PD-L1 status, and there's been no additional data from Roche than those presented at ASCO, where the denominator was 13 and the objective response rate observed in the PD-L1 positive population was 46 percent.

Now, there are a number of key features here I think are worth emphasizing. The first is that each company has its own assay. That's important, because the cutoffs are different, the proportion of patients who are positive may be different, and in the case of Roche, they're examining both the infiltrating lymphocytes, as well as the tumor, and so the nature of their result may be meaningfully different under those circumstances.

Of course, these aren't randomized study data with similar – or the same assay, so the absence of randomization makes it hard to interpret. Within the confidence intervals of these data, shown here as well as earlier at ASCO, these numbers are consistent and, as you put more patients on, you see changes in the numbers. But the basic message is the same, that PD-L1 positive patients appear to be doing better.

But we'd say that the most important message here is that MEDI4736 is clearly active in lung cancer, and putting it together with tremelimumab in combination offers us an opportunity potentially to increase the number of patients who are benefiting and really drive some value for patients.

OK. So here's the safety profile in head and neck cancer. It's consistent with what we saw in lung cancer. I'll highlight here the number of grade 3/4 events, although I went through that slide very quickly before, the story is the same in the lung cancer and the other tumor types. And as you can see, the number of grade 3/4 events is

one patient with fatigue, which is 2 percent out of the 61 that we treated in the Phase I study 1108. Once again, there are no evidence of colitis, no high-grade pneumonitis, and no drug-related deaths. It's a very nice safety profile.

OK. Here's the waterfall plot and the spider plot in head and neck cancer. The spider plot distinguishes PD-L1 positives from negatives. I think if we move over to the waterfall plot, you'll get a better feel for that. But just sticking with the spider plot for just a moment, there are patients who have experienced objective responses, stable diseased, the clinical benefit group, as measured by stability and shrinkage of the index lesions is in the majority of the patients here.

And if you move to the right, you can see again a trend in favor of response by PD-L1 status, where though there are fewer patients who are PD-L1 negative in this series, the proportion of patients whose index lesions had a best response below the line of shrinkage appears to be better. And I'll show you some numbers here.

So I'm going to draw your attention to the middle line, where the objective response rate was 24 percent out of a denominator of 17 patients we know are positive. And the disease control rate at 12 weeks was 35 percent. And I'm going to preempt any questions about the pembrolizumab data that you saw this morning to help you frame these data in the context of those.

So here we're looking at PD-L1 positive patients across the entire PD-L1 positive subset. It's not separated by high or low. It's the full group of patients. And so if we're going to be comparing or looking at one in the context of the other, we would say that putting all the PD-L1 positive patients together, the best apples-to-apples comparison would be the data presented at ASCO, where the overall response rate in PD-L1 positive patients only for pembrolizumab was 19 percent.

Now, we're examining additional opportunities to further enrich the population. We have a robust translational program. But at this point,

these are the data we're reporting with our PD-L1 assay. Again, you can see the objective response rate in PD-L1 negative patients is a single patient out of 33. So, again, there's a trend in favor of PD-L1 positivity.

Oh, and one other thing. The ongoing responses here – this is six out of six patients – followed – for a median follow of 31 weeks, or close to eight months, is all of the six patients remain in remission. And, again, this is pure RECIST response by – by RECIST.

OK. Now we'll focus on the combination. I'll show you an update of the data. These were presented also in a poster during this meeting. This is an update on the escalation pattern. A few messages here. Again, on the right we put the Nivo/IPI combination, where the maximum tolerated dose was 1 in 3. They were also using 3 in 1, and they were unable to escalate higher than that.

At this point, we are still escalating. We've been through dose levels that include dose level five, which is full dose of tremelimumab, the dose we're using in the Phase II/III studies. That's 10 mg/kg Q4 weeks. And we are currently dosing at 20 mg/kg Q4 weeks of the PD-L1, which is comparable to the dose intensity of the current monotherapy dose, which is 10 mg/kg Q2 weeks.

I'll show you the safety. These data are notable for the following. I'm going to turn your attention to the highlighted column, where there were three patients out of the 24 treated to date that experienced adverse events leading to discontinuation. In the 5A cohort, there is an asterisk next to that zero. That's a DLT that occurred after the data cutoff, so that's our first authentic DLT, and that cohort has been expanded and additional data are pending.

But taking the number of events within the timeframe as per the data cutoff, the rate of events leading to discontinuation is 13 percent. And if you look at the column right next to it, the drug-related grade 3/4 events is 6 out of 24, or 25 percent. We note, again, the grade 5 event

of patient who died from complications of myasthenia in one of the early dose levels, there have been no additional drug-related deaths.

OK. Here's an update of the spider plot and the waterfall plot. Again, this was in the poster, but let me walk you through some basic features of this. To date, there are 18 patients who are efficacy evaluable based upon how long they've been on study or how long it's been since they were entered onto the study. The efficacy picture on the left continues to show a population of patients who either have tumor regression with response by RECIST or tumor stability.

The waterfall on the right shows you a picture by dose level. And you can see there are objective responses or tumor shrinkage in patients at all but the lowest dose level, which is in red. The table at the bottom highlights the RECIST response, which is 5 out of 18 patients for an objective response rate of 28 percent, and this is in all dose levels. Recall that we're still escalating. And the patients who achieved stable disease by RECIST is 5 out of 18 patients for a total of 10 patients out of 18 who experienced RECIST-based objective responses or stable disease control.

So this picture helps to frame the subset of patients who are PD-L1 negative. And the reason to look at this population is because many groups, including our own, are looking at PD-L1 positive patients for the monotherapy, so the medical need in the PD-L1 negative population remains important.

And go back to that 10 percent I pointed out, which is the yellow column on the left. Out of the 74 patients treated with 4736 monotherapy, 7 of them achieved objective response by RECIST. And of the 10 patients that we know are PD-L1 negative, out of the 18 whose efficacy criteria we understand, that was 3 out of 10 responses or 30 percent.

Now the numbers are small, and definitive conclusions cannot be reached, so take these data with a grain of salt. But we would view this pattern as interesting and encouraging.

Adding the objective response to the stable disease, we have 7 out of 10 of the patients who are PD-L1 negative achieving a pure RECIST objective response or stable disease, compared to 42 percent for the monotherapy picture. So I would say we're exactly where we want to be, given the number of patients that we've treated to date in the combination with a good safety profile, a competitive safety profile, with escalation continuing, and evidence of synergy that's consistent with a trend in favor of synergy that's consistent with preclinical models, as well as data presented by others who have a combination in this class.

OK. So we'd say that the anti-PD-L1 antibody 4736 has an encouraging safety profile consistent across the cancer types, active in multiple tumor types, although I'm not showing any of this data here at a poster here at ESMO. There were data presented for gastric and pancreas and HCC, again, encouraging signals.

These are consistent response rates, consistent array of signals with the rest of the PD class, and as you saw, ongoing responses in greater than 90 percent of patients with a median follow up of at least six months across the board.

The combination has a manageable safety profile, generally manageable with dose escalation continuing, although we didn't talk about it at any length. The patients who experienced AEs leading to discontinuation were generally reversible with steroids or discontinuation. There are early signs of tumor activity that we'd call promising, and the subset in PD-L1 negative patients where the monotherapy doesn't look to be very active, helps to reinforce the potential for additivity or synergy.

Now, I'm going to show you in the last few slides the pivotal studies that were – either have already started or about to start in lung cancer

and head and neck cancer. It's worth noting that we have a robust registrational program that's underway in these two cancer types.

So, first, we'll talk about the plan for speed. The anti-PD-L1 monotherapy is being tested in two clinical studies we've talked about already at ASCO. The first is the Atlantic study. It's a two-cohort, single-arm, uncontrolled Phase II study with the monotherapy divided into two cohorts by EGFR or ALK status. Patients are treated to PD, and overall response rate is the primary end point. We've been enrolling since the early part of the year, and we expect to show data next year, with the potential filing in 2016.

The second is the ARCTIC study, which asks two questions. One is PD-L1 positive monotherapy in the – monotherapy in the PD-L1 positive subset and the combination in the PD-L1 negative subset. This study is ready to start and will be initiated once the final refined dose for the combination is identified, which we expect to happen sometime by the end of this year or early next year at the latest. This is a study with dual primary endpoints of PFS and overall survival, and we expect our primary data readout in '17.

We're also looking for differentiated indications where you have the potential for first-mover advantage, and there are two worth noting. The one on the bottom we reported at ASCO. It's in stage III on unresectable patients and we recently announced that we are going to conduct a study in the adjuvant space. This is with PD-L1 4736 monotherapy in unselected patients.

No, it's PD-L1 – it's all comers with a primary endpoint in PD-L1 positive patients, stage IB to IIIA. We are conducting with the National Cancer Institute of Canada.

The head and neck program has a single-arm Phase II study, as well. That study has initiated enrollment already. And, again, here we think we'll have a data to report in 2015. There's a study in the middle there that offers opportunity for contribution of components. Though I didn't

say so specifically, the ARCTIC study in lung cancer also offers contribution of component opportunity, and therefore, we're essentially testing the combination of 4736 plus tremelimumab, both in lung cancer and in head and neck cancer, with the potential of understanding how the efficacy and safety compares to that of each of the components.

Phase III randomized study is also set to open as soon as the dose is available, and this is a study that looks at the monotherapy agent in PD-L1 positives, negative as well for additional contribution data. The combination in all-comers against the standard of care.

So we have three studies, one in lung cancer and two in head and neck cancer that is examining the combination. All three are set to start and will be initiated either at the end of this year or early next year when the dose is available.

Two slides on OX40. As you may have heard, we have two OX40 molecules in the clinic. The first has been there for quite a while, and I'll tell you about that in a moment, and the other, a fusion protein, initiated Phase I a few weeks ago. But, first, a word about the mechanism of action. This is a target that has multiple impacts on the immune system, inducing T cell activation and migration, and a variety of things that I won't read on the slide, but it's an important pathway. OX40 antibody is an agonist.

And in preclinical models, which I won't show you today, combinations with both CTLA-4 and PD-L1 look extremely promising and certainly merit additional combination work, as well as the monotherapy work.

This is the last slide coming up. We have murine OX40 that's been in the clinic for quite a while, has single agent activity, and we are – we are initiating a study that – or have initiated a study that combines this agent with both PD-L1, CTLA-4, and rituximab respectively. The PD-L1 arm has already begun enrolling, so we have patients who are

receiving that combination now, and the others will enroll as time goes on. Those cohorts are open.

The humanized anti-OX40 is a multimeric – the study is a monotherapy dose escalation study, and, again, that study is initiated dosing. There's a second humanized OX40 molecule with different features that allow us with all three constructs to ask meaningful questions about how they may differ. They're all OX40-targeted molecules, but what we would say is we have a robust pipeline that enables us to get at the right ones and pick the best of the three in order to proceed. The first study – first patient is expected to be enrolled into that last Phase I sometime in the next few months.

So, in fact, this is the last slide, which you don't have to read. It's small. But it highlights the fact that we have 21 combination studies underway or about to start, and about to start in the very near term. And this – there are 20 cancer types represented by these studies. Additional combination studies are also in the planning works, but these are the ones that are either ongoing or very shortly to start and worth attention now.

So our commitment to immuno-oncology is clearly very robust. Since last ESMO, we've initiated registration of programs in two cancers and have a wide variety of both combination studies, as well as multiple cancer types we are exploring.

So with that, I turn the podium over to Susan Galbraith, who will tell you more about 9291.

Susan Galbraith: Thank you, Rachel.

Welcome, everybody. So I'm happy to talk to you about the updates that we've got on our new selective EGFR inhibitor, AZD9291. Let me just start by reminding you about the design of this molecule. Based on the understanding that we've developed of the mechanisms that develop for resistance, the currently available EGFR inhibitors, we know that about 60 percent of them develop a second mutation, the

T790M mutation. And with the addition of that mutation, it changes the binding affinity for ATP, so it means that drugs – reversible EGFR inhibitors like Iressa get displaced from the binding pocket.

So what we've done is designed a molecule that binds irreversibly – and so overcomes that change in ATP binding affinity, and it binds personally to the sensitizing – to receptors that have the sensitizing mutation and also have the double mutant with a sensitizing mutation and the T790M. And it also does so with a 30-fold margin to the wild-type or normal receptor, and that's important, because clinically other irreversible inhibitors – drugs like afatinib and dacomitinib – are limited by the incidence of high-grade rash and diarrhea that's seen. And so they're not able to achieve exposures in the clinic that enable them to inhibit T790M.

Another important feature of the design of the molecule that I mentioned when I spoke to you at ASCO is that we designed it specifically to have a chemical scaffold that did not inhibit the insulin receptor on it, insulin-like growth factor receptor, which some scaffolds do, because we did not want those escalation to be limited by observing high blood glucose or (hyperglycemia).

OK, so those were the key design features. Since ASCO, we can now update you again – like Rachel, I'm happy to announce we've got over 600 patients now treated on the 9291 program, a program that only dosed its first patient in human in March of 2013 – so the rapidity of accrual really speaks to the unmet need in these patients that have T790M mutations.

The data that I'll go into in a bit more detail shows that in those patients, we've got a confirmed overall response rate of 70 percent now in patients treated at the dose we're taking forward into pivotal trials, the 80 milligram once-daily dose.

We're also able to update you on the progression-free survival. So the median response to those patients is now 8.2 months, and it leaves us

to give an initial estimate based on immature progression-free survival data of 9.6 months. And I say it's immature, and I'll go into that in a bit more detail when I show you the PFS plot. The data is only based on 30 percent of patients having had a progression event, which means that 70 percent of patients fortunately have not yet progressed. So we expect that that data and that estimate of median progression-free survival will continue to mature.

We're also presented data in the initial cohort of patients treated in the first line. Remember, I said that this drug was designed to also hit the sensitizing mutations. And I'll go through some of those data. So we're seeing response rate in line with expectations, as 63 percent in the first-line EGFR mutant patients. The preclinical data that we have – I'll talk about a little bit – shows that we've got potential to have sustained efficacy beyond what you see with the currently available EGFR inhibitors that are used in first-line. And again, the data that we've got confirms in a very large number of patients now the reduced wild-type toxicity based on that design element that I described.

So let me take you through the data in a little bit more detail. OK. First of all, let me just show you the patient population that are enrolled in the expansion cohorts of the (OR) study, a data set of 222 patients, and, again, you can see that it's split 60 percent Asian, 37 percent Caucasian, and there's a good distribution of patients that have had either one, two, or three or more prior EGFR inhibitors, which, again, 62 percent of patients having immediate prior EGFR tyrosine kinase inhibitor, 38 percent having had some intervening therapy, typically chemotherapy.

What we feel this represents is that you know we've got experience across multiple (sensors) in multiple countries and a distribution of patient demographics that will enable us to have generalization of the benefit risk profile across the patient populations that we intend to seek for initial indication.

This slide shows you the updated waterfall plot showing the best percentage change from baseline in the target lesions. Again, I'll draw your attention to the 70 percent confirmed overall response rate in the patients of the 80 milligram cohort and also the fact we're seeing efficacy at the lowest-dose cohort dose – which was 20 milligrams – and up to the 240 milligram dose cohort, which is the highest dose that we tested in this study. The longest response is now ongoing for over 11 months. And as I said, the median duration of response so far is 8.2 months.

So this slide shows you the progression-free survival curve, again, with the confidence intervals, which I hope you can see labeled around it. So as I said, the estimate currently of the median progression-free survival is 9.6 months. And I'll make the point that I made at ASCO that you really need a reasonable number of patients at risk at each of the points along a progression-free survival curve to be confident about the data. That's why we've projected the confidence intervals. And I really think that point is up to around 8 months in this plot, so we expect it to further mature.

Again, if you look at the 95 confidence interval around that median PFS, you can see that the lower limits of that 95 percent confidence interval is 8.3 months, and the upper limit is not yet reached. So we expect with increased maturity of data that this number may change and could further increase.

And I just want to talk about the safety data. Again, what we're presenting here is safety data across all the dose cohorts from 20 milligrams to 240 milligrams, and I've split it out for the – the patients with an adverse event. This is not just drug-related adverse events. These are all adverse events. And it's split out by grade with those at grade three highlighted in the right-hand column under each dose level.

So the first point to take away is that the incidence of grade three adverse events is low across all dose levels. If you look at the 80

milligram dose cohort, which his highlighted in the middle there, you can see, again, that we have zero or 1 percent grade three adverse events at that dose level. So let's go through the adverse events of particular interest.

For diarrhea and rash, we've got 30 patients and 29 patients that have had any grade of those particular events. I'd just point out that of the 29 patients with rash, 28 of them were grade one, and grade one rash can be as minimal as a couple of acneiform spots. That would still count as a grade one rash.

Again, I'll point out that all of the patients on this study have had prior experience of EGFR inhibitors and are well familiar with the adverse events that they get from those. What we're hearing – put together with this quantitative data – the qualitative assessment from the investigators, it's a burden that patients feel from these adverse events is substantially different, both qualitatively and quantitatively, from what currently available EGFR inhibitors provide.

We turn to the adverse events of interest at the bottom. Again, I pointed out that we have not seen grade three hypoglycemia, and that was based on the design element of the molecule. We also do not see a concern with QT prolongation.

In the 620 patients that formed the denominator of all the patients treated so far, we have seen 13 pneumonitis-like events, for an overall rate of around 2 percent. The majority of those events are sort of low-grade, but we have had one grade five pneumonitis event in a Japanese patient. So this is an event that is seen as a background rate in patients with lung cancer. It's seen with all EGFR inhibitors that have been described. And the rates that we are seeing are in line with expectations about EGFR inhibitors and this disease.

And I'm going to turn to some of the data that I've referred to in the first line. On the left-hand side of this slide is the waterfall plot from the first line patient cohort. And, again, I remind you that the current estimate

of the overall response rate in the patient population is 63 percent, which is in line with expectations, and the overall disease control rate is 95 percent. There were some patients in this cohort treated at 80 milligrams in blue and others at 160 milligrams in yellow.

So, again, I think just to remind you, the preclinical data that we have for the first-line models that mimic the first-line setting, you will see regression with both drugs like Iressa and drugs like 9291. Where 9291 differs from Iressa in those preclinical models is in the depth and durability of response that you see, and to get a sense of whether that is translated through to the clinic in terms of durability of these responsive and prolonged progression-free survival in the first-line, we're going to need more patients and more data, and we'll happily update you on that at ASCO next year.

I also want to draw attention to some anecdotal examples of activity that we've seen in patients that have brain metastases. Relapsed through brain metastases is an increasing problem for patients with EGFR mutated lung cancer. And many of the drugs that are currently available don't have good penetrants across the blood brain barrier.

9291, based on our preclinical assessment, does penetrate brain. And the estimates from those preclinical experiments is that we model the 80 milligram dose, we expect to get good exposure in the brain. So we have anecdotes at the moment of activity in patients with brain metastases, which is encouraging, and we'll continue to expand our experience in this group of patients that represent an area of high unmet medical need.

So on the basis of the preclinical data, the robust confirmed response rates in second-line, and the excellent tolerability profile that we have seen, we are planning to initiate a Phase III trial in the first-line setting of patients with EGFR mutant non-small-cell lung cancer, randomizing 9291 at the 80 milligram dose level to the first-generation tyrosine kinase inhibitor dealer's choice of (erlotinib or gafitinib).

So the primary end point for this study is progression-free survival. There are secondary end points of overall survival, response rate, quality of life. We anticipate enrolling the first patients into this study later this year and on the primary data readout in 2017.

I spoke at ASCO also about understanding how this drug may be combined. The excellent safety profile that we're seeing so far in activity we believe forms you know a great backbone on which to look for combinations with a range of other agents that might help to overcome resistance mechanisms.

And we did publish data at the (AACR) earlier this year showing that we have looked for mechanisms of resistance that occur to 9291 and seeing that we get MEK pathway activation in some preclinical models. On the basis of these data, we have now initiated enrollment into a study which is looking at the combination of 9291 plus our MEK inhibitor, selumetinib, 9291 plus our MET inhibitor, volitinib, which has shown activity in MET-amplified patients, and, of course, with PD-L1 in this study.

So first subjects was dosed in the third quarter in all three combinations. And, again, I look forward to updating you with data, potentially ASCO next year, on the results of these studies.

Now I want just to turn to innovation that's happening in the diagnostic area, as well. And I want to draw attention to data that we released as a press release late last week, where we announced that the CHMP European regulatory authority provided a positive opinion for the inclusion of testing by circulating tumor DNA in the Iressa label.

This is important, because not every patient is able to have a tumor biopsy, which is the current means of diagnosing and detecting the – sensitizing mutations in EGFR. So what that means is some patients don't know that they've got an EGFR mutation and wouldn't necessarily get the optimal therapy for their tumor.

The (ISOM data), which is shown on the left-hand side of this slide, show that the response rate for patients that have EGFR mutation detected by the circulating tumor DNA test is numerically very similar to the response rate that you see based on the tumor-based biopsy. And this provides an option for those patients who can't have an initial tumor biopsy.

The availability of circulating tumor DNA tests and the improved technology around those tests is also leading us to examine this technology in the 9291 program, and there was a poster presented earlier at this meeting detailing the activity that we've seen in 192 patients in the (ORA) program that I've got circulating tumor DNA data.

And, again, you see a similar pattern, which is that the response rate for patients that have T790M mutation detected by circulating tumor DNA appears very similar to the response rate of those patients that have that mutation detected by the tumor biopsy. So we'll continue to look at this, not just as a potential predictive marker, but also as a tool for monitoring response over time and quantitating that response.

So just to summarize, we've continued to have very rapid progress with extremely rapid accrual to the programs with 9291. We've seen an unprecedented confirmed response rate of 70 percent and disease control rate of 95 percent in patients with the T790M mutations treated at the 80 milligram dose level.

The progression-free survival we've seen in those patients we believe is encouraging, but it still immature and will continue to mature. We've seen activity in patients that have brain metastases, and we've seen encouraging activity in the first-line treatment of patients with sensitizing mutations in the epidermal growth factor receptor with preclinical data that supports the decision to move forward into a pivotal trial here.

The tolerability profile we've seen overall is consistent with what we reported at ASCO and remains encouraging. And we continue to push

forward in terms of the speed of the development of the program, initiating that first-line trial later this year.

So with that, I'm going to close here. We'll be happy to take any questions that you may have. Thank you very much.

Mondher Mahjoubi Thank you, Susan. Thank you, Rachel. So we'll open the floor for questions. We'll start with questions in the room here and from time to time I will look at the screen for the online questions.