Array BioPharma Inc (COLUMBUS)

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Corporate Speakers:

- Ron Squarer; Array BioPharma; CEO
- Keith Flaherty; Termeer Center for Targeted Therapy; Director

Participants:

- Stephen Willey; Stifel Nicolaus Research; Analyst
- Ted Tenthoff; Piper Jaffray & Co.; Analyst

PRESENTATION

Ron Squarer: Good morning and good afternoon on the East Coast. This is Ron Squarer, CEO of Array BioPharma. I'd like to thank everyone for joining this encore webcast of our ASCO COLUMBUS Presentation. I am joined today by our Chief Commercial Officer Andy Robbins and our Chief Medical Officer Dr. Victor Sandor.

But the main event today is really Dr. Keith Flaherty, Director of the Termeer Center for Targeted Therapy at Massachusetts General Hospital Cancer Center and Professor of Medicine at the Harvard Medical School, who will be presenting the additional overall survival results from our phase three COLUMBUS trial that was presented earlier this morning.

Now, we are going to be making forward-looking statements and I'd encourage all investors to take a look at our recent -Qs and -Ks for a full description of risk associated with the forecast and predictions that we will be making today.

And with that, I am very pleased to turn the call over to Dr. Flaherty.

Keith Flaherty: I'm going to go through the presentation as it was delivered just a short while ago in the melanoma oral session. However, I'm going to take the prerogative of this being a different venue presentation. And so I'm going to review the data, certainly highlight the same elements that we see as key in this updated analysis and first ever presentation of the overall survival data.

But I'm also going to highlight a few areas that I think are really key points to drive the discussion following the presentation. On behalf of a international set of investigators, [Raynor, Dimmer] presented this data just a couple of hours ago. A key point to emphasize going into this discussion that I want to pull of this slide or maybe two key points. One is that it is a long settled issue, now more than four years ago, that BRAF MAK combination therapy is superior to BRAF inhibitor monotherapy.

And that is true at the level of both efficacy and safety/tolerability. **W**e can revisit that point in later discussion if you like, but just to emphasize this point that it's with

dabrafenib and trametinib, vemurafenib cobimetinib. And as we'll review again today, with encorafenib binimetinib; that thesis is well established.

Also well established are that for the two currently FDA approved BRAF MEK combination regimens, there are two hallmark and regimen specific toxicities that are in fact typically considered to be the most problematic. Pyrexia, which can be a complicated syndrome, not only fever but some associated finding or symptomatic issues with that as well, which really are very common, three-quarters of patients having some element of that symptomatology and oftentimes does require management, dose interruption if not reduction.

Vemurafenib cobimetinib, has sensitivity that's unique to it because vemurafenib brings that into the regimen and vemurafenib monotherapy has essentially just as much, but given that patients are on BRAF MEK combination therapy for twice as long and that it can distribute over the entire course of treatment, it remains a major issue for that regimen.

There are other class [effect] toxicities, we'll touch on ENCO BINI toxicities later in the presentation that are shared across all of these regimens but reminding you of these two regimen-specific toxicities. A study design, just a couple of points to highlight. Again, this is updated data and first ever OS data, but the analysis that was planned from the beginning, as you can see, primary end point of regression free survival and of course key secondary endpoint of overall survival.

Preplanned, pre-specified hierarchical analysis in terms of allocating statistical power to it. Like other BRAF MEK combinations, this study was designed to have a common comparator of vemurafenib. Dabrafenib trametinib was evaluated in two phase three trials, just to remind you. One of which was vemurafenib controlled. And then of course vemurafenib cobimetinib versus vemurafenib.

That ends up being a major benefit to us in the field as we try to interpret these data in the context of those previously presented and published data sets. Of course it was critical within this study to understand with this regimen, the superiority of combination therapy over BRAF inhibitor monotherapy, so you see the combination versus encorafenib monotherapy.

And then a really powerful point of this study realized already with the progression free survival data but also with OS is we have for the first time ever a direct comparison of a next generation BRAF inhibitor to a first generation BRAF inhibitor. ENCO monotherapy versus vemurafenib monotherapy, which again is critical data, now looking at overall survival complementing the progression free survival data.

And just to remind you of the outcome analysis, primary endpoint per protocol progression free survival as presented and published here hazard ratio 0.54 best in class difference in terms of impact on progression free survival as reflected by the hazard ratio, again with this common comparator vemurafenib in this study.

Now with more time, and more follow up, here's the patient disposition. You see that now a large majority of the patients have discontinued treatment, and most of those due to disease progression. And you can see predictably that more patients on BRAF inhibitor monotherapy than combination therapy.

Adverse events in the low double digit percent rate being the basis of discontinuation. Very similar to previous reports of this data set, but also with other available BRAF MEK combination therapies. And then, at the bottom of this slide, importantly, just under a quarter of the patients still on ENCO BINI combination therapy at the time of this analysis.

Baseline characteristics of course haven't changed with the updated data, but just to highlight the real point that we tend to focus on in the melanoma field, the fraction of patients who have elevations in serum LDH here between 25% and 30%, typical of studies in this population. Some studies a little lower, some a little higher, but roughly comparable. [N1c] to remind you, contained serum LDH as a component of that assessment so these tend to track together. Having it roughly 2/3 of the patients being N1c again, quite comparable to previously conducted studies.

Previous immunotherapy was a relatively trivial element of this study although adjuvant interferon which would have been the therapy alluded to here was reflected in this study population. But checkpoint therapy with ipilimumab was really not an option yet based on having availability of data and regulatory filings.

It's post protocol therapy that of course is of relevance for this trial, for the BRAF MEK combination trials as well. And so not relevant for interpreting response rate and progression free survival outcomes, because those are of course intrinsic to the treatment regimen itself. But overall survival, certainly a feature we pay attention to.

You see here a range of 20% to 25% of patients receiving post protocol, PD-1, PD-L1 therapy. Again, more patients are progressing at an earlier time point on vemurafenib in particular, so you expect that number to be the highest amongst them. And then, just under 20% of patients receiving CTLA-4; relatively trial fraction receiving PD-1 CTLA-4 combination.

Just a brief comment about this point here of BRAF inhibitor monotherapy and BRAF MEK combination therapy. For these patients who discontinued either because of disease progression or even adverse events, you see that clinicians and patients were actually still gravitating to the same treatment regimen. This was actually an element that was contained within some of previously evaluated BRAF MEK combinations. Some of those studies went to great lengths to try to, essentially, keep patients in the study population and offer post progression therapy within that study.

Here you're seeing, because of the availability of those BRAF MEK regimens, a fraction of patients who even though they've had disease progression are going on to receive post progression therapy with either monotherapy or combination therapy.

And that's just a notable point because we've in this disease, as in other oncogene defined populations that there are patients who can do quite well even after having a progression event, if they have essentially what we call oligoprogressions, one site of disease in particular, if that lesion could be treated or if it's really minor radiographic change, enough to trigger a resist call progression.

But not enough to change the patients' clinical situation, we will oftentimes continue post progression targeted therapy which is just an important point to keep an eye on when thinking about overall survival. And here, you see details in terms of the timing of utilization of those therapies, whether PD-1 CTLA-4 were given as the immediate next therapy or even if patients might have gone to receive (technical difficulty) much to communicate on that point.

This is the primary outcome measure of this ASCO presentation, so yes, the secondary endpoint for pre-specified overall survival comparing the combination regimen to the vemurafenib control which as was the case for vemurafenib as the control arm for the PFS analysis, it's the primary point of comparison for the OS analysis as well.

And you can see here, two striking features, hazard ratio best observed in this area in terms of the lowest hazard ratio for BRAF MEK versus BRAF monotherapy. And couple other points to pull off this slide, the vemurafenib control arm performing very comparably by median as well as by landmarks, but certainly by median.

The vemurafenib control arm performs as expected from previously presented and published studies. And now, a combination result that is the best result we've seen in the field, median, overall survival, 33.5 months, comparing favorably to the just over two year, 24 month, roughly median overall survival for the previous regimens.

An exciting result and really the primary basis of this presentation and its enthusiastic receipt. Here is some of that landmark assessment, just to give a feel for, again, the performance of the vemurafenib control.

Helpful for cross trial comparison if one were to try to perform them is an emphasis on the vemurafenib control benchmarking across the studies to have confidence then that the combination arm is in fact performing as well as the median comparison would suggest. And I would say, across the data points shown here, certainly seems to be the case.

I would like to make a point which we can come back to in discussion that's really critical. And that is where the censoring really starts to pick up in this data set out towards three years and beyond, of course.

We have a lot of confidence in the estimate around 24 months and even out to 30 months, but this is where the data becomes a bit less reliable, and I just point towards future presentations and updates where it'll be critical for us to keep tracking this data set, particularly as we have longer follow up available already particularly from the dabrafenib trametinib studies. There have been fewer updated presentations of [Encorafenib].

Subset analysis, I think really very little here to highlight, and certainly nothing that appears to be very different compared to the progression free survival analysis in terms of subsets. No clear outliers, all of the confidence intervals around these estimates within the band as you can see here, says some intriguing small subpopulation findings, but nothing really that would suggest that this is a regimen that's really differentially effective for any one of these sub groups.

The combination versus Encorafenib itself, as you can see here, an important measure in terms of demonstrating superiority, this, as you know, is now further down the hierarchical testing strategy, in terms of statistical analysis. As noted here, nominal hazard ratio and P value clearly showing a trend that it's not statistically significant; the 0.05 level, again, was not -- this is not a primary end point of the study and certainly not a basis for suggesting that the combination is not better than monotherapy, as I highlighted earlier. That's a long settled issue in the field, that combination therapy is superior, in fact.

The other side of that, of course, though, is that Encorafenib, as supported by the progression of free survival data and now very clearly with the OS data as well, this is a BRAF inhibitor that is superior to our previous generation. We've always considered vemurafenib and dabrafenib to be effectively identical and really not worthy of a head to head comparison based on large data sets and cross trial comparisons of those.

But here, this study contained within it, this secondary end point of a direct comparison of novel BRAF versus previous BRAF. And I would just remind you that even pre-clinically, studies were done to demonstrate superiority of this BRAF inhibitor versus the emerging/available BRAF inhibitors at the time.

This very much validates that concept and reinforces then the efficacy data that we're seeing with the combination that appear to be best in class. Updated progression free survival data, just a little inching down of the hazard ratio compared to the previous analysis.

You wouldn't expect a lot of change up through the median of course, because that was already mature at the time of the first analysis, but with more updated data, you do see now that the curves remain separated and robustly so out through the periods of time that we have maturity of data, as I said before, about 24, 30 months.

I'll highlight that it is critical in judging the relative efficacy of this regimen compared to others, that mapping this out over even more time, three years and beyond, I think will be

a critical way of trying to reinforce the apparently unique efficacy of this regimen. Already looking very robust compared to other regimens at 24 and 30 months, but where the tail of the curve rides over longer periods of time, I think will really be a critical point to keep an eye on. And here's some of that landmark data just numerically.

Progression free survival for the other comparisons, not surprisingly not really changed, continue to see superiority of the combination over Encorafenib monotherapy, similarly the direct comparison as I just mentioned a moment ago for the novel RAF over conventional. Response rates surprisingly not different. Overall we are seeing a rise in complete response rate, which is expected based on the other BRAF/MEK regimens as those data sets matured over time.

We saw this happen as well, but now getting close to 20% complete response rate with this regimen based on local review and as is typical, complete responses are the hardest to hold up on [central review] but nonetheless comparing apples to apples across data sets, a very robust and best in class complete response rate.

And median duration also not very different than prior analyses as you might expect. Just work my way through the builds, sorry. Safety data, really not different, although patients are still on therapy as I highlighted before. You do expect as patients are on therapy, some adverse event reporting to continue, contributing to cumulative adverse event numbers, as described here.

A key point about this data though is that one needs to keep in mind that the longer a patient is on treatment, in this case the most efficacious regimen, the more opportunities there is to tick up these numbers over time. It's critical to do time adjusted comparisons across these regimens if you're to try to understand the relative weight of overall adverse events of severe adverse events highlighted here.

This is just a reminder of the common toxicities that one sees with either the individual [rad] agents or a combination, very little difference compared to prior reports, so I won't belabor the point, but the distribution as noted.

We could, perhaps, have some discussion about pyrexia. Certainly it's lower for encorafenib monotherapy than the combination, but I would suggest that, in fact, this is not something that we see as a treatment related effect in the same way that we clearly see it with dabrafenib and tametinib, which, of course, is not shown here. In that case about three quarters of patients have pyrexia with that regimen. Photosensitivity, as you can see here, shined through with dabrafenib and a monotherapy and not a feature of encorafenib or binimetinib.

In conclusion, the numbers I will not repeat, but we have now the first presentation of the overall survival data. Very robust. Best we've seen in this class of therapies very clearly, and the difference also best observed to date to vemurafenib control therapy. Again, the common comparator across the BRAF MEK regimens.

Progression free survival with updating hasn't changed the median, but we are getting more of a sense now of the fraction of patients who maintain very long lasting progression free survival through 24 and 30 months, but I think important to continue to track that over more time. And we can discuss in detail, but as I said, post protocol therapy, in fact, quite similar, especially when one considers the most updated data that we have available for the other BRAF MEK regimens. Not at the time of initial reports or publication, but where we have comparable follow up time post protocol therapy as a feature of all.

And with that, happy to take questions.

QUESTIONS AND ANSWERS

Operator: (Operator Instructions)

Stephen Willey with Stifel.

Stephen Willey: Apologies for the background noise.

I guess in the discussants overview of the data when he was making the cross trial comparisons, specifically of the AE front, I guess I was a little surprised to see that the rate of Grade 3 for AEs across the different trials were similar.

I know some of the prior studies didn't start looking for some of the MEK specific adverse events of the outset, some of the retinopathies and also some of the lab abnormalities. I guess, can you maybe just provide a little bit of a correction there with respect to if you kind of back out those kind of MEK specific adverse events that weren't the focal point AE searches in the prior studies? What the trial comparison might actually look like in terms of safety?

Keith Flaherty: Yes, you've highlighted a couple of key points in terms of the admittedly relatively short era in which these regimens were evaluated, the various BRAF MEK regimens. But an important point in terms of how the protocols were written and, frankly, how the FDA weighed in on requirements for monitoring as well.

Ocular toxicity monitoring has varied significantly in this relatively short period of time in terms of how different MEK inhibitors as monotherapy or in combination, were advised to be monitored, again, by FDA influencing protocol design. And that's a very key point. You can pull this from manuscripts at least from all of the data sets to understand what the monitoring strategy was and then that, obviously, helps you to weight apparent differences.

I'll just make the subjective statement or the editorial statement that I have looked across the MEK inhibitors that we have, and certainly their single-agent evaluation, and I have yet to see a difference that's compelling when you control for monitoring strategy in laboratory alterations, retinal events as well.

As I've performed that exercise, I come out with the notion that the TPK elevations, for example, which are the laboratory alteration that we pay very little attention to in clinical practice, but if you look for it you can find it. And retinal events, of course, we used to think were potentially quite a serious concern years ago with MEK inhibitors, but we've, in fact, published a paper with binimetinib showing, in fact, that not only is it reversible while still on therapy, it can be reversible within the same day in which sub retinal edema is first detected.

It appears to be, yes, reversible on therapy and even transient in patients as well. We've never seen a really serious progression of that to a clinically significant event, so not to dismiss every toxicity one-by-one, but just to say that these kind of hallmark toxicities and MEK inhibitors are, A, not different across the class, and B, they are while detectible, not particularly clinically impactful.

There are symptomatic toxicities, of course, that are clinically impactful, and I've made the point in prior presentations and discussions that have been an investigator with this regimen from Phase 1 through to Phase 3, this is the best tolerated BRAF MEK combination of the bunch on the class effect toxicities.

Meaning, you can call them constitutional, if you like, as a cluster cutaneous as well, but arthralgia, myalgia, and cutaneous toxicities shared across the class. This fares favorably compared to other in terms of patients' ability to tolerate the starting dose, maintain dose intensity. We presented this data, [SMR] last year I think was the last dose intensity presentation. But I'd point you to that as a way of powerfully describing that benefit.

The last point I would make is just to reiterate the one I indicated. Which is it's absolutely critical that if one's to do the analysis of adverse events across these trials they have to be time adjusted. By that I mean for follow up. Let's say 21 month follow up of each data set to the extent that we have that for each; that's a reasonable time point to look. But just to point you back to an obvious fact here. We're reporting longer progression free survival of regimen of several months. The median as you know, but at each relevant percentile.

And that means more time on therapy. More time to have at least laboratory if not symptomatic toxicities. The longer a patient's on therapy the longer they're going to have a likelihood of having reported adverse event. I used to say this about BRAF MEK combination therapy versus BRAF inhibitor monotherapy that it looked like it was comparable between the two treatments.

Roughly the same rates BRAF MEK versus BRAF mono. And I had to remind people, but they're on treatment for twice as long in the combination versus monotherapy. That's in fact half the toxicity per unit time. And again it's really a critical piece in doing these. This type of comparison you're eluding to.

Stephen Wiley: And then just a quick flow up on the LDH subgroup, I guess the diminished activity you tend to see here looks to be in line with other BRAF MEKs; I know this is kind of poor prognostic subgroup of patients. But I guess in your clinical practice are you treating these LDH high patients with BRAF mutations with IO as a frontline agent? And does the proportion of LDH high patients in this trial, I guess it's probably somewhere around 30 percent, is that pretty exemplary of what you typically see in terms clinical presentation?

Keith Flaherty: I'll answer that part first; yes. This is fairly representative of routine clinical practice. Interesting question. I'll come to it, but just to remind you of an obvious point. Here we're talking about a comparison of BRAF MEK versus BRAF.

We've never had a comparison of BRAF MEK versus PD-1, which is as you say the practice relevant issue in terms of thinking about patient selection. To walk you back to 2011 FDA approval of vemurafenib ipilimumab, up to the present day, clinicians generally look at the higher and higher level of serum LDH as being a stronger and stronger push towards BRAF inhibitor base therapy over immune checkpoint therapy.

And that's been in the field for years and continues to be the case. Really when you consider the PD-1 monotherapy suffers in terms of response rates and progression free survival in higher LDH subgroups versus lower, as is true across all classes of therapy, it doesn't change that tug of war very much. There are some clinicians that who think that PD-1 CTLA-4 combination therapy certainly BRAF wild type patients who would be perhaps reserved for these particularly poor prognosis patients.

But really I think in general the field wide consensus has always been the more adverse the patient features at baseline, if they have a BRAF mutation the more draw to be to BRAF MEK combination therapy. And again just to highlight this subgroup analysis, which I'm looking at again but perhaps you can't, is a comparison of a BRAF inhibitor based therapy versus BRAF inhibitor based therapy.

The last point I would make actually which is I think continues to be an intriguing trend in this class of treatments is how robust the efficacy is in the normal LDH group. A low disease burden, less aggressive subgroup of patients, which is as you can see the dominant subgroup. We've seen this across other data sets. It reinforces that the combination versus monotherapy which is again what's being compared here.

You get particular bang for your buck with the combination strategy in these low [disease burden] patients. I presented to dabrafenib trametinib long term follow up data before highlighting that of those patients who were three years and beyond ongoing disease control. A large faction of those patients were these good prognosis patients at baseline, just reinforcing that this is a regimen that can produce really quite remarkable outcomes in that group.

Operator: Mara Goldstein with Canter Fitzgerald.

Keith Flaherty: And it seems like were having some technical difficulty there. But we do have time for one more question if there's another participant who'd like to pose one?

Operator: Ted Tenthoff with Piper Jaffray.

Ted Tenthoff: I wanted to take this back just a half of step and maybe walk us through how you would go about trading patients? Clearly this is reserved for BRAF mutant patients but where does IO fit in, picking up on Steve's question? And is there any reason to use the other BRAF combos? Why would someone actually use those therapies still?

Dr. Keith Flaherty: Sure, but I gather you'd like me to start first with the full [matrices] of therapies--

Ted Tenthoff: Please.

Dr. Keith Flaherty: --available?

Ted Tenthoff: Yes.

Dr. Keith Flaherty: Yes, I'll tell you it continues to be a very unsatisfying discussion at least academically. Clinically we have to make decisions, which is to say we have to have discussions with our individual patients and walk them through what we know. For year by year as we get more aggregate data for PD-1 monotherapy, PD-1 CTLA-4 combination therapy and BRAF MEK, my discussion with patients hasn't really evolved very much, which is again frustrating in some ways as we have landmark data, one year, two year, three years.

We continue to take those patients with BRAF mutation based on these trial sets which really featured treatment naive patients in the vast majority of data.

Ted Tenthoff: Yes.

Dr. Keith Flaherty: As a starting therapy, these therapies seemed to produce very comparable outcomes. As much as people thought or predicted that they wouldn't, that targeted therapy would have more of a short-term benefit, and immunotherapy a greater long-term benefit. Again these are cross trial comparisons, but if you especially control for prognostic features and just look at the normal LDH group, we just don't have data that supports a difference of substantial magnitude.

As you know there's two modestly sized randomized trials still ongoing slowly accruing BRAF MEK combination therapy versus PD-1 CLTA-4 combination in one study, PD-1 monotherapy in the European trial. I don't know that those are really going to answer the question frankly. Because they're modestly sized; you probably need a very large study to be able to unpack a real difference if there were one and then some population differences if those existed.

We're stuck with what we've got in terms of cross trial comparison, differences in toxicity profile of course. In the field in general, because of the modest impact to PD-1 CLTA-4 over PD-1, we generally start the discussion with most patients as a discussion of BRAF MEK versus PD-1 monotherapy.

That's an apples to apples type comparison in terms of in truly serious toxicities. We feel even though they're quite different toxicities obviously and for patients who are uncomfortable or more comfortable or less comfortable with certain types of toxicities as we walk them through it, that oftentimes settles the discussion.

We tell them that efficacy is equal, toxicities are again different in nature as we talk them through them, that oftentimes settles it. But as an oncologist I would much prefer to be able to tell my patients well, here's the thing that's most likely to produce the efficacy outcome you want. And genetic and other molecularly defined subsetting studies that we and others are deeply involved in may be the thing that ultimately breaks this quote-unquote tie.

That's I guess my 2018 summary of the current landscape to go to your second part about well amongst the BRAF MEK regimens. The way I summarize this data in a couple of phrases is not so different than how I summarized it in many more phrases a moment ago. This is the best efficacy data we've ever seen. Response rate tracks the highest; admittedly the delta there is not very large but numerically highest we've seen.

Progression free survival at the median obviously which is the easiest number to quote, but at other landmarks as well, the highest we've seen, and that with a bit more of a margin. And we were waiting I would say was somewhat bated breath to see well which way was the overall survival data fall, would it make the progression free survival apparent difference look like a data outlier or would it reinforce it? And as I interpret this data, it reinforces it. The efficacy data just tracks in every instance to the Encorafenib component truly delivering more efficacy in this combination as the head to head monotherapy data would suggest.

And then on the adverse event side, as I said classified toxicities are a throughline through these regimens as in the constitutional toxicities and most cutaneous toxicities, dropping pyrexia and complicated pyrexia, dropping photosensitivity. Those are real benefits. These are real issues that actually drive switching amongst those therapies in routine clinical practice. If a physician has a preference for one, they'll go to the other.

If a patient hits a wall with those toxicities, so not having those is a benefit. I think it's both sides of this efficacy and safety that I think make this really quite a obvious and compelling regimen to consider.

Ron Squarer: And really thank you to Dr. Flaherty for taking the time in what is of course a very busy ASCO and schedule.

I'd also like to thank the investigators involved with this study, the patients who participated, then the Array employees who support the study, all towards improving patient care. And with that, we will close the call today. Thank you all very much.

Operator: And ladies and gentlemen, thank you for participating in today's conference. This concludes the program and you my all disconnect.