DISCUSSION – EGFR-TARGETED AGENTS

Dr. Lynch: For the dual kinase inhibitors, are you surprised that response rates aren’t higher or more activity hasn’t been seen, or do you think it’s just too early?

Dr. Engelman: I’m not surprised. I think, it is probably faulty to assume there is one mechanism of resistance in a patient and just going after a T790M mutation may fail.

Dr. Shepherd: Some of these “dual inhibitors” really aren’t dual inhibitors. Basically, I think lapatinib is mainly a HER2 inhibitor and a weak EGFR inhibitor. It is going forward in breast cancer where it appears to be very active as a HER2 inhibitor, but there were hardly any responses seen in the phase 2 lung cancer trial.

Dr. Janne: Lapatinib is a very good EGFR inhibitor; however it preferentially binds the inactive conformation of EGFR, which may be why it doesn’t work in lung cancer.

Dr. Lynch: Why do you need to block both MET and EGFR? Why wouldn’t just inhibiting MET be enough?

Dr. Engelman: It appears that ERB B3 can get activated either by EGFR or by MET. To kill these cancer cells, you have to turn off ERB B3 phosphorylation, so you really need to block both activators.

Dr. Espinoza-Delgado: Then is it correct to assume that if you block the PI3 kinase, which is a conversion of both pathways, you should be able to block it?

Dr. Engelman: ERB B3 is doing other things besides just activating PI3 kinase. If you look at these addicted models, when you inhibit EGFR, you not only down-regulate PI3 kinase, you also down-regulate ERK and down-regulate STAT. I don’t think inhibiting PI3 kinase as a single therapy will be nearly as effective as cutting it off at the head when you down-regulate all those pathways that branch off of EGFR.

Dr. Natale: Do you have a sense for the relative importance of ligand-dependent versus ligand-independent models across all of lung cancer?

Dr. Janne: In the presence of MET amplification, it’s ligand-independent. That’s true not only in the resistant situation; it’s also true in the very rare subsets. About one or two percent of lung cancers have de novo MET amplification, very analogous of the gastric cancer cell lines or gastric cancer models. There are probably ligand-depend processes, a MET and HGF/MET autocrine loop, that happen. I don’t know what percentage this is.

Dr. Shapiro: It’s worth noting that the small molecule MET TKIs can be divided into two classes: those that are cleaner and those that hit other kinases as well. The ARQ197 drug is one of the “clean” ones. One doesn’t worry too much about overlapping toxicity with an EGFR inhibitor and side effects associated with c-Met inhibition have overall been mild. XL880 is an example of a compound that not only inhibits c-Met, but is also a very potent VEGFR2 inhibitor. The majority of toxicities are probably related to VEGFR2 inhibition.

Dr. Lynch: If you think about where we’ve come in two years it’s really been pretty remarkable how quickly things have emerged in terms of our knowledge and understanding of EGFR biology and the potential of these new drugs.

Dr. Shepherd: In terms of first-line treatment of patients who have mutations, this may, indeed be an acceptable thing to do but I just want to remind everyone that achieving a median survival of 18 months with an EGFR inhibitor first-line may not be as good as we can do with chemotherapy. The median survival of patients with mutations treated with chemotherapy in the first-line erlotinib trials was longer than 2 years. I think we must wait for the randomized trials to answer the question for us. It may be the right thing to do but I don’t think we know this at this time and we need the randomized data.

Dr. Hanke: I think all this points to the importance of looking for resistance mechanisms up front by screening cell lines and other approaches, right up front in drug development, which we are starting to do routinely in industry. You have to remember that when you find these resistance mechanisms, you don’t yet have clinical experience to tell you if it’s going to be important in clinical disease. We often find mutations that don’t appear to be important in the biology of a particular target. It’s very complex to leverage this information before knowing the clinical significance of a particular mutation of amplification.

Dr. Hirsch: My impression is that we need to learn more about the scheduling of the drug combinations. But what predicts sensitivity to the drugs? How can we synergize the effect of the drugs? What about the combination of H-stack inhibitor and the EGFR TKIs? The preclinical data very clearly demonstrate synergy.

Dr. Sorensen: I think the big problem with developing these second generation EGFR TKIs is going to be identifying the right patient population. By developing them in the acquired resistance setting, you’re setting the bar awfully high if you’re just hitting EGFR as we’ve discussed. You’re missing MET and so these drugs may never make it to the point where one is FDA approved so that you can add it to a MET inhibitor. I’m concerned about how they’re going to make it through the process.

Dr. Wakelee: It does get harder as we move along. We’re doing lots of trials now looking at using the EGFR TKIs first-line and selecting the right population, but why? These patients are going to do better anyway. If the goal is to keep them alive as long as possible, why use a TKI up front unless we really believe that we’re going to somehow reduce their responses if we use it later?

Dr. Lynch: I think the advantage of using them up front when you have a responsive patient is that when a patient is on gefitinib or erlotinib for 1-4 years, which some of the patients on Dr. Sequist’s trial have been on, the quality of life during that time is pretty good compared to having chemotherapy. That’s one benefit. We need randomized trials to tell us whether it’s equivalent in terms of outcome. If it turns out...
that they are the same, I think starting with an EGFR TKI could have quality of life benefits. But we do have to make sure that we’re not impairing the outcome.

Dr. Wakelee: Also the resistance issue is a big one. We have all had clinical experiences with patients with good EGFR TKI responses. When they lose that response, they sometimes get very sick very fast and you can’t always treat them with chemotherapy. But if you give them a less toxic platinum doublet first-line, and their quality of life isn’t that bad, they get benefit for a while. Single agent bevacizumab is not too toxic either. Then we can come in with the EGFR TKI later.

Dr. Lynch: Right. The thing that you wrestle with is that the EGFR mutant patients are exactly the patient population that’s going to do well with carbo-tax-bevacizumab.

Dr. Sequist: We really need to do more biopsies, especially after sequential treatments. Pre- and post- therapy biopsies should be requirements for our trials. I know this is difficult but we can learn so much from just one biopsy. If you think about it, the discovery of T790 and the discovery of MET amplification were both in only a few patients. As a community, we all need to be committed to the biopsies.

Dr. Lynch: I agree completely but it’s hard to mandate. We actually had to change one of our trials to make biopsies optional because our major clinicians felt that they just couldn’t put patients on if it required a biopsy.

Dr. Janne: In the CALGB randomized phase two trial, which is erlotinib versus chemotherapy-erlotinib we actually mandate, as an eligibility criteria, at least a core needle biopsy to go on the trial. It has definitely slowed down the accrual. It’s feasible but it definitely is slower. I think in the relapse setting it’s that much harder. I think you need to do what you can.

Dr. Weitzman: I too have concerns about asking patients to subject themselves to subsequent biopsies. It would make it easier if we could show some kind of concordance between the first biopsy and subsequent biopsies. The other nice to have thing would be to try and correlate the subsequent biopsies with some more easily accessible peripheral marker.

Dr. Engelman: We don’t have to do necessarily do biopsies at the time of progression while the patient is alive. Autopsy series can be also useful. And autopsies are sometimes more palatable to the patients.

Dr. Lilenbaum: Clearly the science has revolutionized the way we understand lung cancer and the way we approach patients. We do have clinical features that are at the very least surrogates for the presence of some of these markers, and given that 99 percent of physicians in practice today do not have access to biomarkers, is it really true that if I use a combination of smoking status, gender, ethnicity, histology, etc. that its so much inferior to biomarkers in selecting patients? I don’t know.

Dr. Lynch: You might be right, but the BR21 study showed also very clearly that there were patients with squamous cell carcinomas, even males with squamous, who have benefited from the drug. Will you exclude, a male with squamous cell carcinoma?

Dr. Lilenbaum: No, not in that particular setting because the BR21 really applied to previously treated patients. I’m referring more to when you move it up front a little bit more, when you select your patients. We’re talking about selection of patients based on molecular markers versus clinical markers. Do they overlap? Do they not overlap?

Dr. Lynch: The best data I’ve seen looks at never smoking, which is probably the best marker.

Dr. Sequist: We’re just talking about EGFR and looking at non-smoking to pick a specific type of therapy but the ultimate goal is to be able to run a panel of genotype analyses on each patient to know what their status is for EGFR, MET, IGF etc and choose single agent or combination therapies based on that. Ideally, when we understand multiple different markers and how they affect therapy choices, trying to use clinical characteristics for each marker is going to be too complex.

Dr. Engelman: What we’re really looking at now is a snapshot. We have an opportunity to make a real dent in this type of cancer in five or ten years with continued research. That’s what’s exciting.