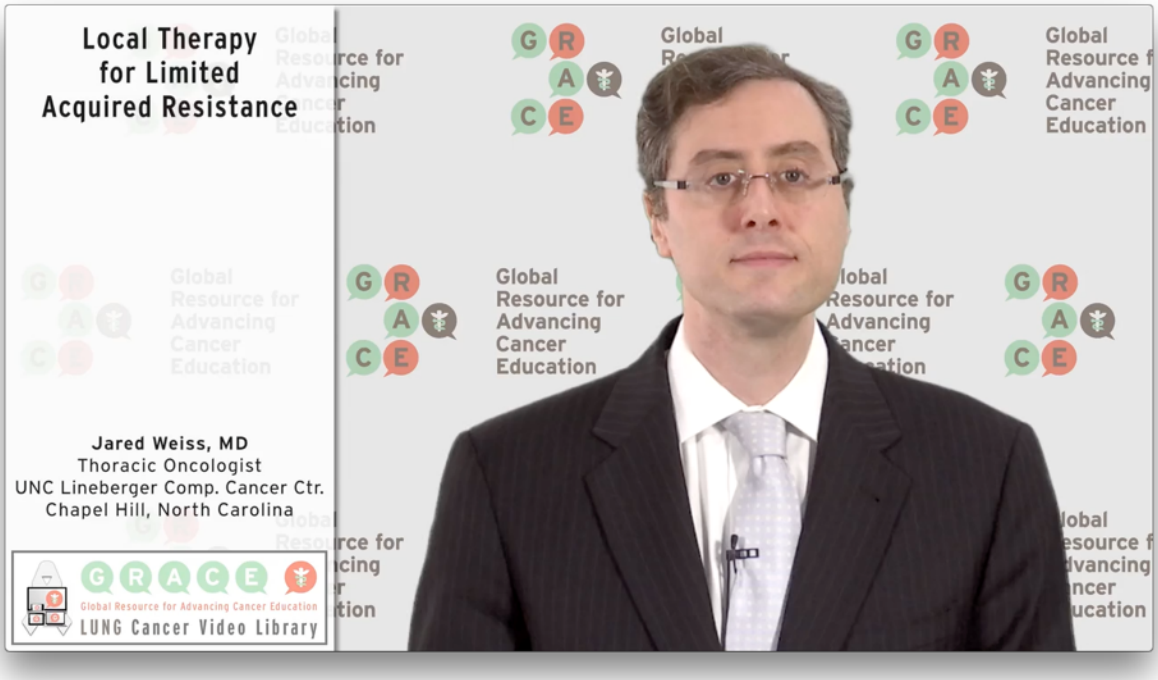
Global Resource for Advancing Cancer Education

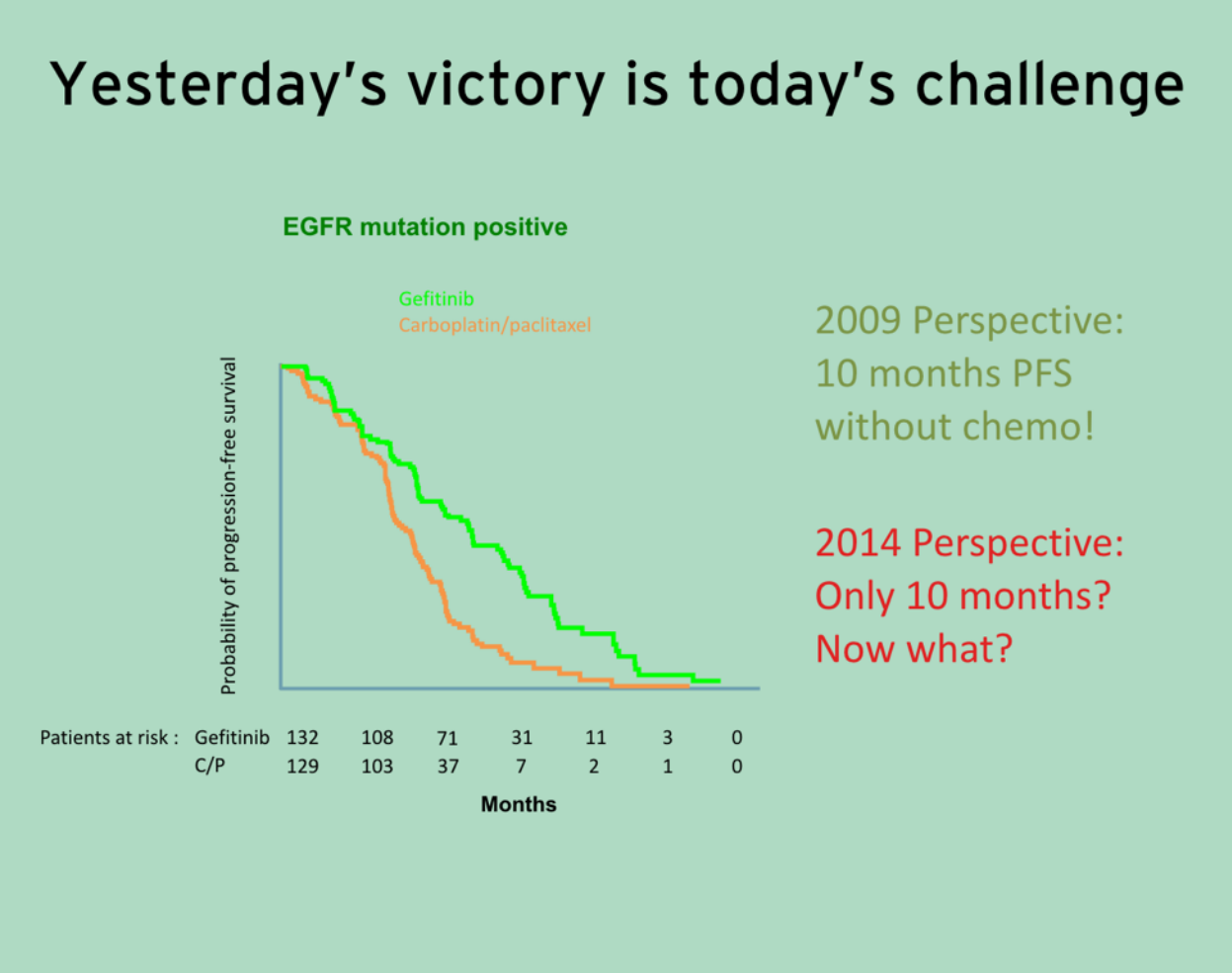
LUNG Cancer Video Library

Local Therapy for Limited Acquired Resistance



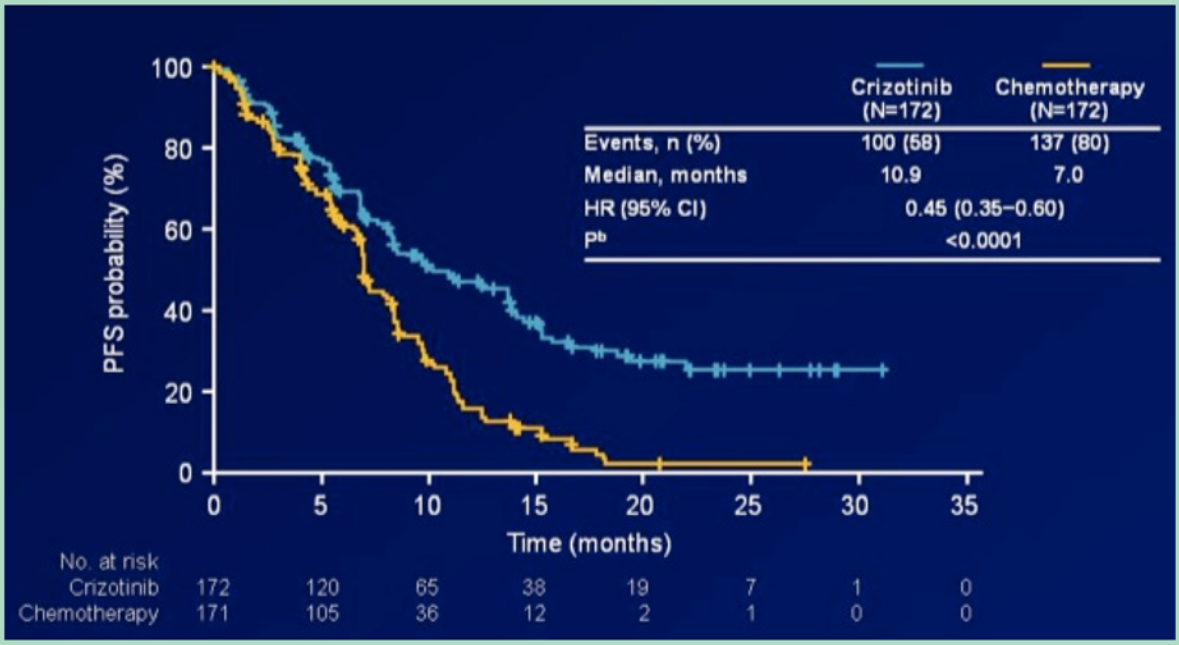
TRANSCRIPT & FIGURES

It's my privilege to speak to you today about a favorite topic of mine, local therapy for limited acquired resistance.



So just five years ago, we were celebrating the curves that I'm showing you here. This is great — we have a targeted therapy, it works better than chemotherapy, it's less toxic, it's more convenient, demedicalizes the patient's life, and this is a legitimate victory and I don't want to take that celebration away, but I think only five years later, I guess now six years later, I think the perspective is a little bit different as our drugs get more effective and the bar goes up.

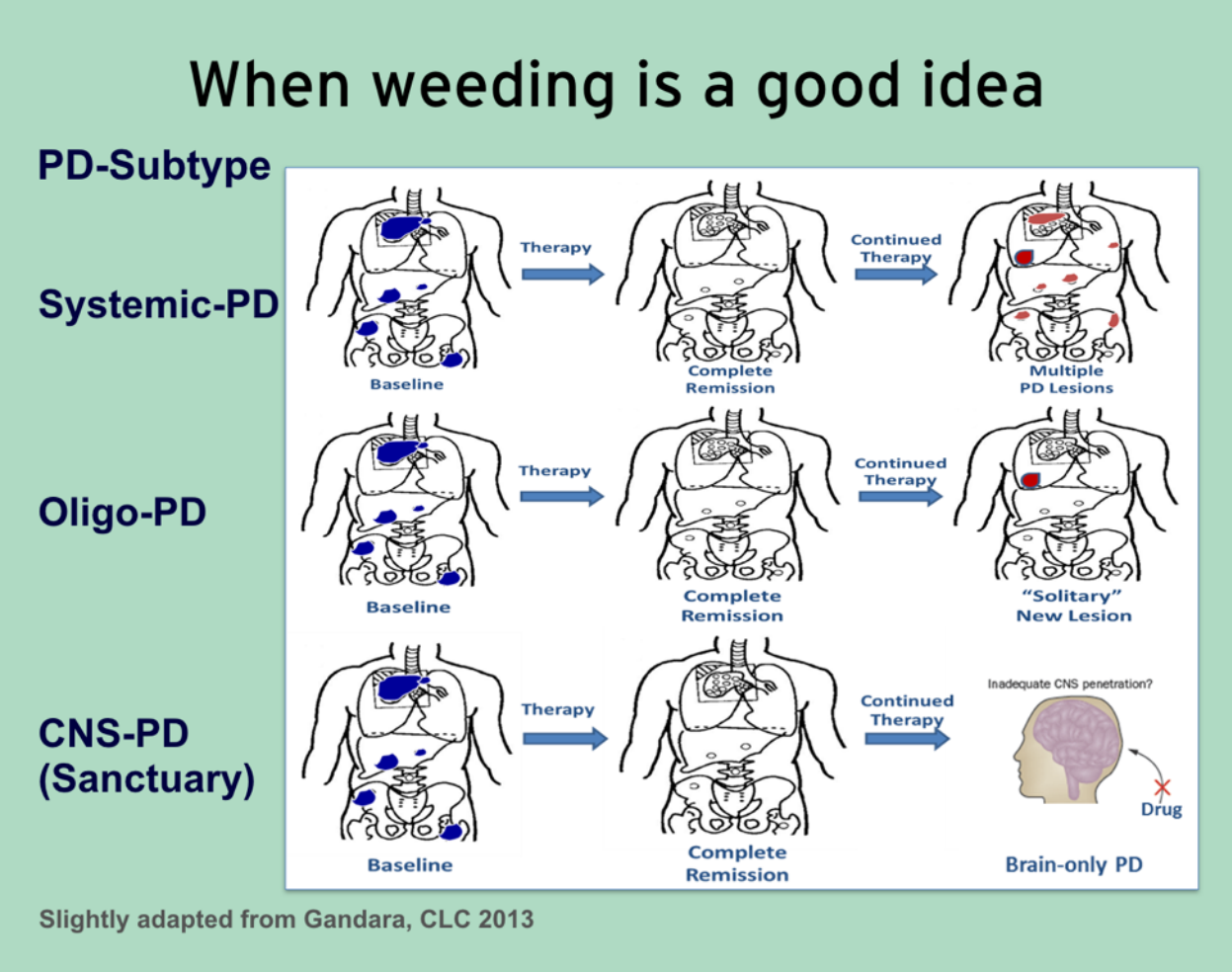
Crizotinib for ALK: Like erlotinib for EGFR, better than chemo, but again, now what should be done?



Mok, ASCO 2014

We say these drugs are lasting less than a year on average — now what? We're trying to find something other than chemotherapy. There are multiple promising approaches, including next generation drugs aimed at the targeted therapy, but I'm going to talk to you today about a slightly different approach. Before doing so, I want to just share that this story is very analogous for crizotinib and ALK and ROS1, it's the exact same story.

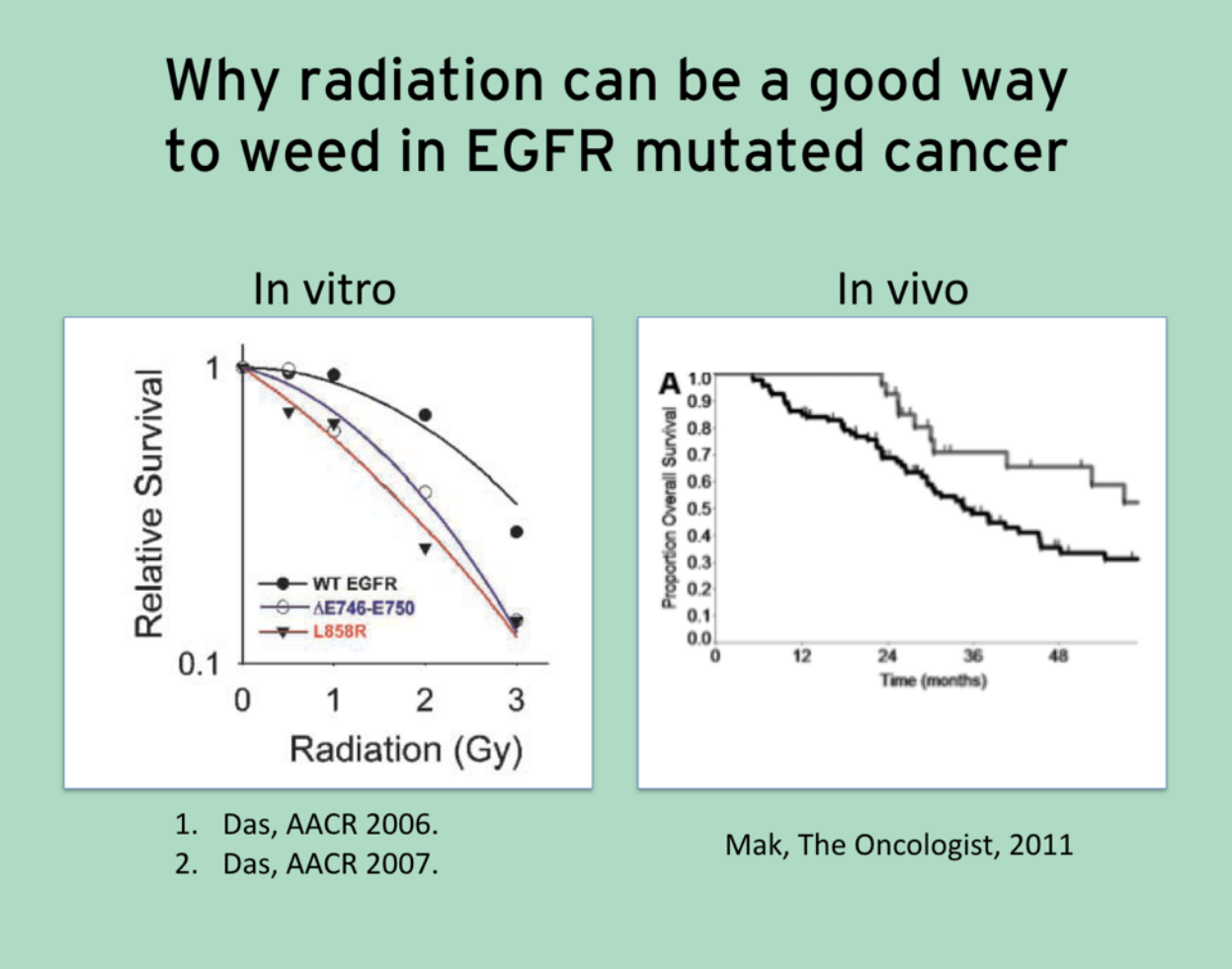
The approach I colloquially call "weeding the garden." This approach is what it sounds like — using some kind of local ablation or surgery to take out areas of progression, areas that are growing despite the targeted therapy, the areas that perhaps have a resistance mutation of some kind, and then using the original therapy for the rest of the cancer that's still well controlled.



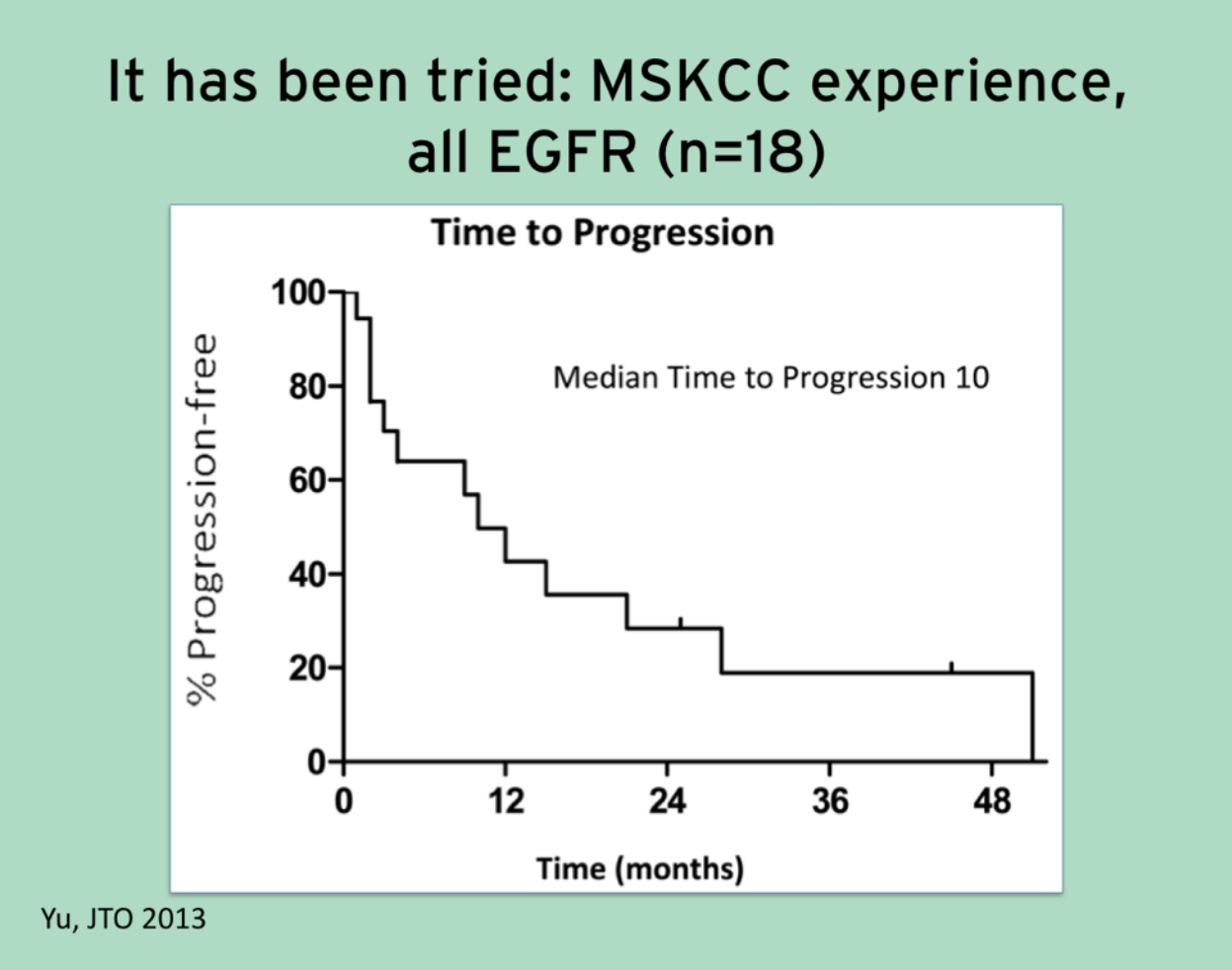
So when might this make sense, and when might it not? Well the situation where it surely does not make sense is classical progression. Prior to the advent of targeted therapies and immunotherapies, there was really only one pattern of progression that we mostly saw: when the cancer was going to grow, it grew everywhere and it grew in multiple new spots – not a time when weeding the garden makes good common sense.

We have two new patterns of progression where it does make more common sense. One is oligoprogression – that is what it sounds like, you have progression in just one or two spots, those spots maybe have T790m or

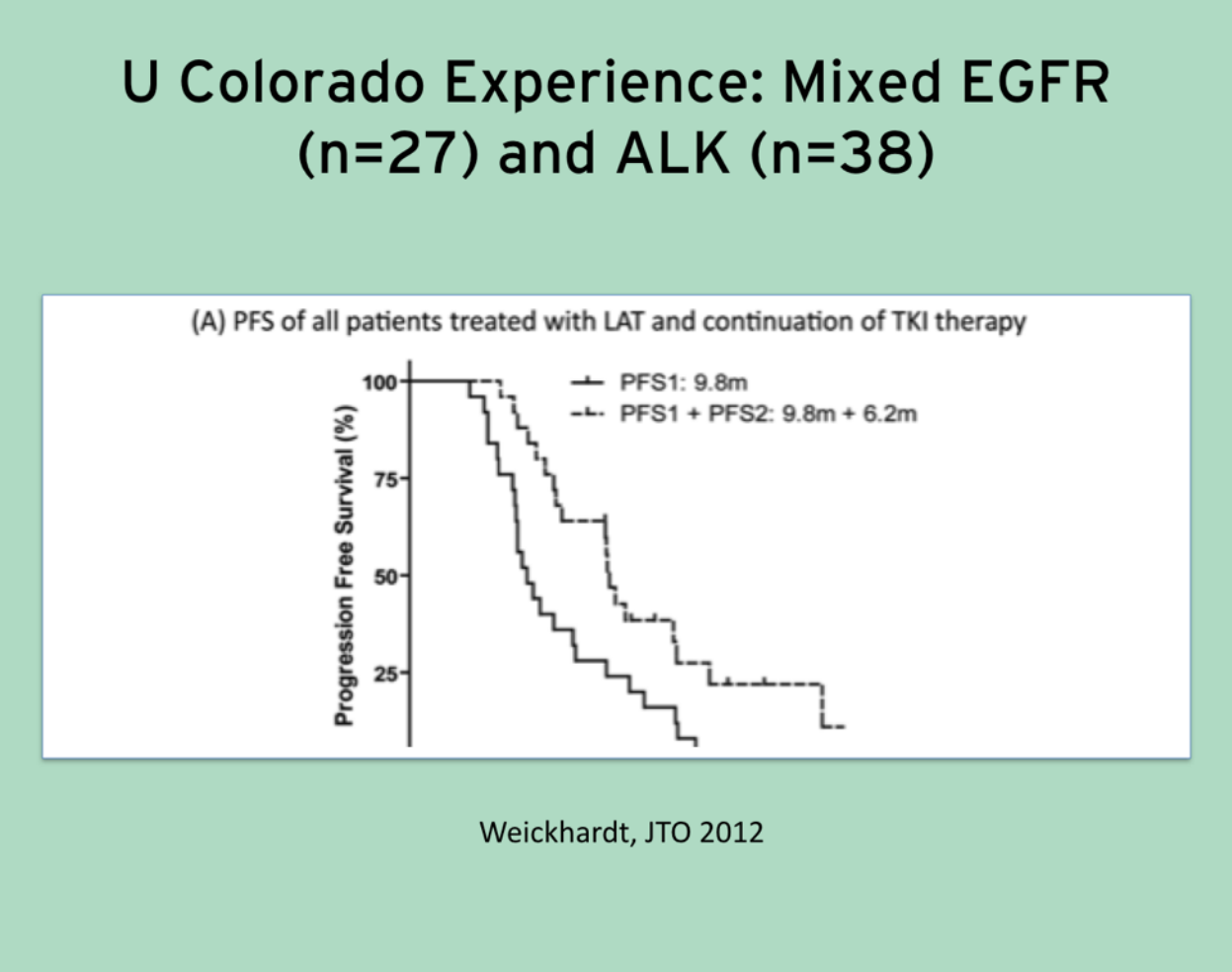
some other resistance change, where the rest of the cancer is beautifully controlled still on the targeted therapy. The other situation is when the progression is in an area that the drug doesn't get to so well. So there's this filter between the rest of the body and the brain called the blood-brain barrier. Its job is to keep poisons out of the brain and it appropriately sees most of our anti-cancer therapies as poisons and keeps them out of the brain. You can have cancer growing in the brain not because there's some resistance gene, some secondary mutation or amplification of some gene, but just because the drugs aren't getting there well. I think that's another area where it conceptually makes sense to consider weeding the garden.



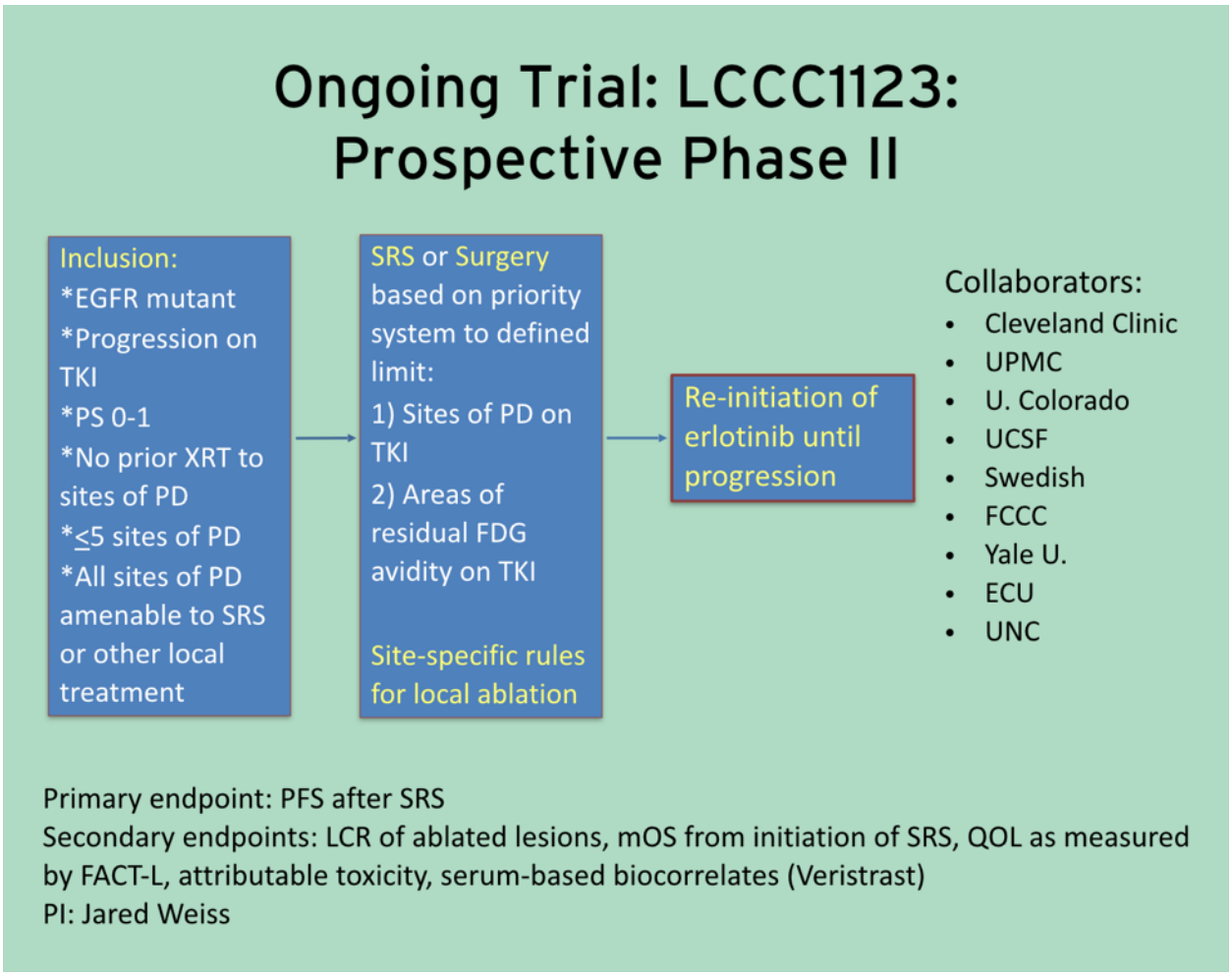
For EGFR, I think radiation is a particularly promising approach to do this – at left you can see data preclinically in the lab on why EGFR mutated cells seem to be more sensitive to radiation than non-mutated cells, and at right some human data to back up that this actually happens in real people.



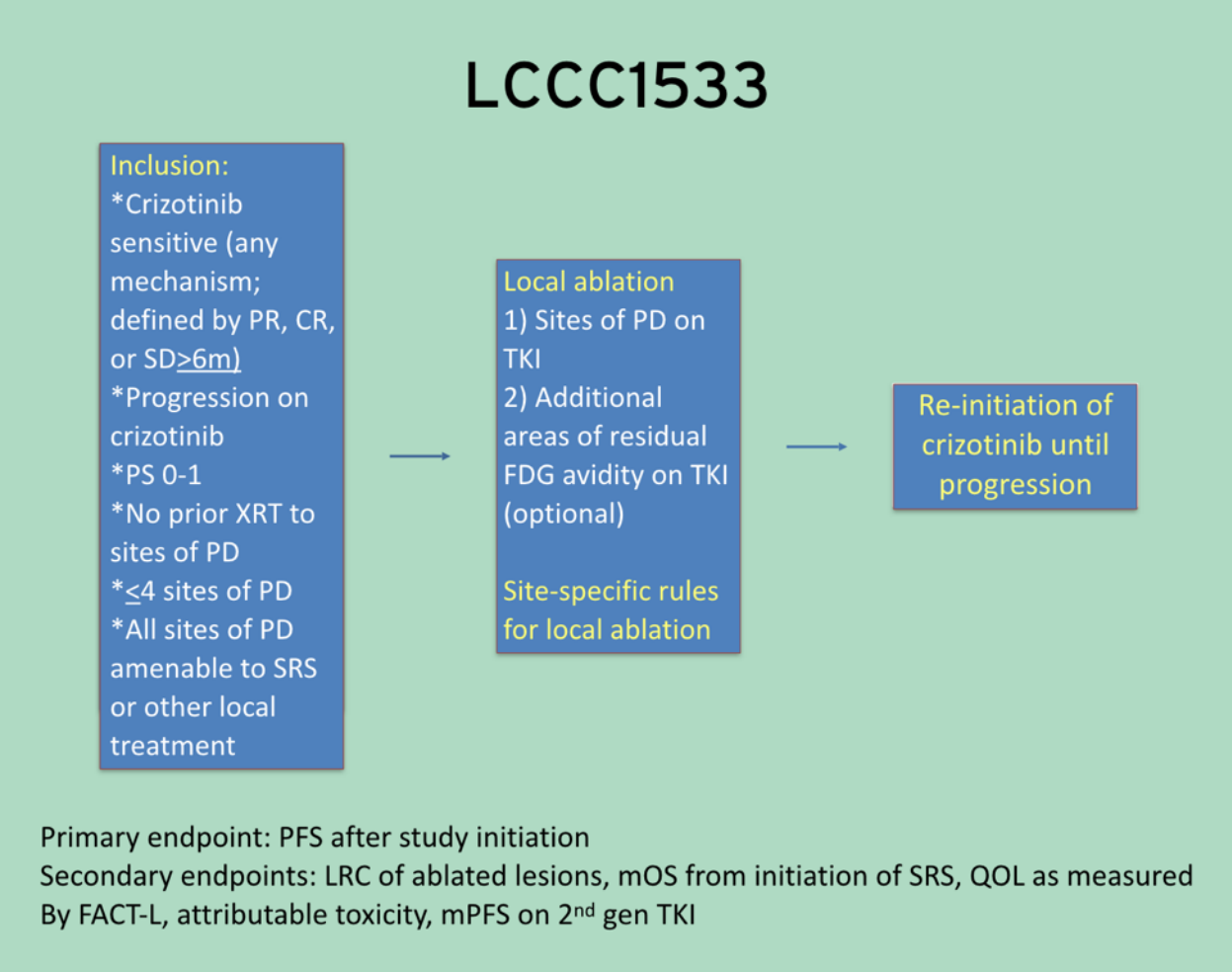
This approach has been tried retrospectively – the Memorial group here did a mostly surgical series where they got a median time until progression of another ten months after this approach, so they've mostly cut out the sites of progression and started TKI back up again.



Our colleagues at Colorado, where we happen to be taping today, have done this in a mixed series of EGFR and ALK patients; they show their data separately for whether the progression was primarily in the brain or elsewhere. When the brain was the primary site of progression, they got another 7.1 months out of targeted therapy. When it was outside of the brain, they got an additional four months.



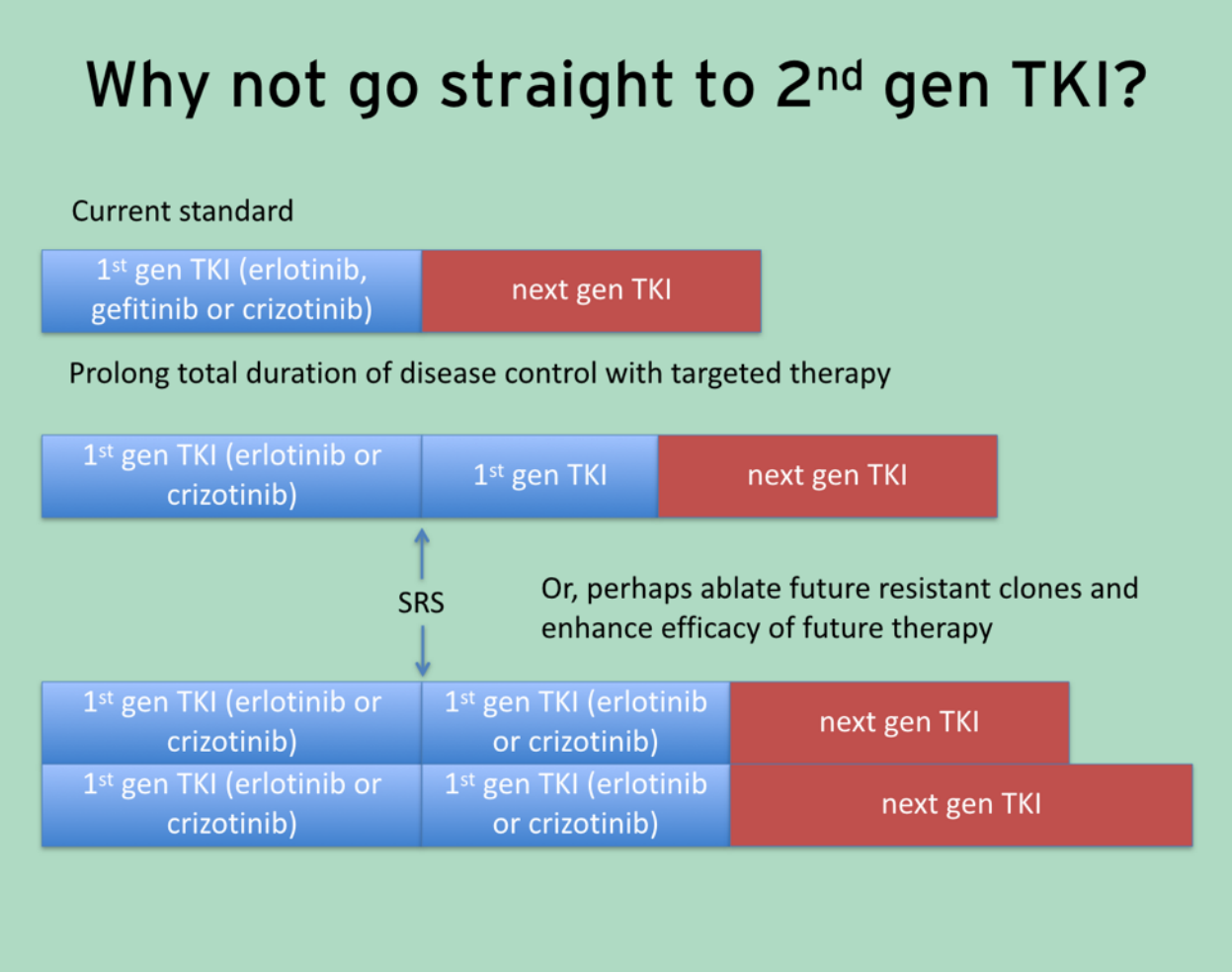
I have the privilege to lead a study prospectively evaluating this approach for patients with oligoprogression on EGFR mutation. The design is very simple, you have to have gotten benefit out of an EGFR TKI, typically erlotinib in the first line in this country, but no prohibition against gefitinib or afatinib, but now one or two sites, up to five sites, are growing. We do stereotactic radiosurgery to those sites of progression, and then restart a TKI for the remainder of the sensitive disease. My collaborators are shown at right, including many GRACE contributors.



[In 2015] Pfizer agreed to fund a very similar study for patients who have previously received a benefit on crizotinib but are now progressing. The design is rather similar here, where we do radiosurgery to the sites of progression, restart the crizotinib, and because which mutations are sensitive to crizotinib is evolving at the current time, we don't define this on a molecular basis but on a practical basis – patients who have received benefit but now have growth in four or less spots.

You might reasonably ask me the question, "well we have all these exciting next generation tyrosine kinase inhibitors we've heard about on GRACE, we

have the clovis compound and the AZ compound for EGFR, we have alectinib and ceritinib for ALK — why not just jump to one of those?" I actually think that would be a perfectly reasonable approach, perhaps the preferred approach when there's poly progression, but I can show you graphically why you might consider the approach that I'm talking about.



So here's the approach of starting with the first-gen TKI and moving straight to the next-gen TKI. Let's imagine that my approach of eliminating oligoprogressive disease only has minimal efficacy, only gets you a few extra months on the first line therapy, you might look at this graphically this way:

that you've inserted an additional therapy, you've squeezed a little more juice from the orange, in first line, before moving to that next line. But it's entirely possible that in reality we get something better than that. So the first of these alternative hypotheses is that we get a longer duration of control — perhaps ten months or a year, replicating the original experience with the first line targeted therapy. Here we have a larger advantage to total cancer control before moving on to chemotherapy. Alternatively, if we're radiating spots, we may be eliminating some of the spots that are eventually going to cause resistance on second line TKI, and so it's entirely possible, I would call it my professional fantasy, that we'll actually not only prolong the duration of benefit of the first line drug, but make the second line drug last longer when we get there. The possibility of that approach is shown at the very bottom — that fantasy phenomenon.

So I thank you for your kind attention.

GRACE.expert/GCVL