



## **Lung Cancer Video Library**

### **General Non Small Cell Lung Cancer**

#### **Immunotherapy in Patients with Driver Mutations**

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Dr. Ben Levy: I'm Ben Levy and I'm associate professor at Johns Hopkins School of Medicine. So it's important to talk about the role of immunotherapy for patients with driver mutations. These are patients that harbor specific genetic alterations in which we usually deliver targeted therapies rather than chemotherapy or immunotherapy. And this is an evolving field, so much so, that when in the field of lung cancer, they're really two separate fields. One that delves into immunotherapy therapy approaches and one that delves into targeted therapy approaches. And when we hit the convergence of these, when we start to think about, well, for patients with targets, we'll usually offer oral targeted therapies. This is different than immunotherapy. How does immunotherapy perform for those patients? And we do have some early data that immunotherapy, at least as a single agent, does not offer meaningful responses for patients that have driver mutations, which is quite confusing to patients and quite confusing to oncologists.

So, if you have a patient who has a driver mutation like an EGFR mutation, those patients, no matter what their PD-L1 status is, should probably receive a targeted agent without immunotherapy at any point in time of their treatment continuum. And the data we have on this is several fold. First, there's been data out of France, looking at the role of single agent immunotherapy for patients with multiple different driver mutations. So specifically looking at the role of immunotherapy EGFR mutation patients, looking at the role of immunotherapy for ALK rearrange patients, looking at the role of immunotherapy for ROS3 rearranged patients. And this was a retrospective analysis when they look back and look at chart reviews, to see how these patients performed when they got immunotherapy. And the long story short, and the bottom line here is that immunotherapy as a single agent does not work well for patients that have driver mutations.

The one exception or two exceptions to this would be patients that have a B RAF V 600e mutation. Those are patients that may respond to immunotherapy and patients with K RAS mutations may respond to immunotherapy, but other driver mutation positive patients generally do not respond to single agent immunotherapy. So that's one set of data that we have. The second set of data comes from a prospective study. So the study that was design prospectively, and in this study, they look at a very small number of patients that were EGFR mutated. This is a driver mutation that should deserve to receive a targeted therapy, not



immunotherapy, but in the trial design, these patients, the investigators decided rather than give patients targeted therapy, why not give them immunotherapy and see what happens? So all of these patients had EGFR mutation and received single agent pembrolizumab, an immunotherapy drug. And incredibly the response rate was 0%.

No one had tumor shrinkage who received immunotherapy and this really underscores and highlights the importance of understanding the molecular features of the tumor so that you don't quickly move to immunotherapy. And instead you can treat patients with targeted therapy. What we also know is patients that have a target who receive immunotherapy first mistakenly, who then go onto receive targeted therapy. Those patients may have toxicities from the targeted therapy that has to do with the overlap of immunotherapy and targeted therapy. So the bottom line from the second piece of information is that immunotherapy as a frontline strategy for patients that are EGFR mutated did not work, which is something we kind of already knew from the retrospective data and [inaudible] France. The third element of this, that creates confusion is that we just don't know if immunotherapy may work with chemotherapy for patients that are on targeted therapy.

So, a patient who has EGFR mutated lung cancer, who receives a targeted therapy pill, who then unfortunately developed disease progression. There may be a role of not single agent immunotherapy, but looking at immunotherapy plus chemotherapy. And we have some ongoing data that's looking at this. We have one trial called the Empower 150 Trial that showed that there may be a role of immunotherapy in combination with chemotherapy, for patients that are EGFR mutated and ALK rearranged, after they experienced disease progression with the tyrosine kinase inhibitor or the oral therapy. And so, this is a regimen of carboplatin, paclitaxel bevacizumab, and atezolizomab. Those are two chemotherapies, one anti-angiogenesis strategy with bevacizumab and atezolizomab immunotherapy. And the four drug regimen seems to be quite active for patients that were EGFR mutated who had experienced disease progression on a targeted therapy.

So, I think in some, what we know is one single agent immunotherapy probably doesn't work well for patients with targets or genotypes. The acceptance of that of course, is the B RAFV 600e mutation or K RAS mutations. They may work as single-agent. Two, there may be toxicity problems. If you give a patient single agent immunotherapy first and then decide to give them a targeted therapy next, there may be real challenges with toxicity. And finally, just because immunotherapy by itself does not work for patients with genotype. It doesn't mean it may not work with chemotherapy. And I think we're still trying to understand all of this, it's so complicated. So stay tuned. 2020 has been an incredible year for lung cancer and hopefully in 2021, we'll have more answers about the specific role of immunotherapy for patients with driver mutations.