Questions for this podcast (2): The Advances of Treatment in Lung Cancer

1. **Dr. Ma, in your first podcast you discussed the basics of lung cancer treatment including the stages, types, and treatment options. In this podcast, we want to focus on the advances in lung cancer treatment. Can you begin with describing the changes in lung cancer treatment over the last decade?**

Ma: Yeah, absolutely. So let me first give you an overview of the key advances in lung cancer treatment over the last decade. As a practicing oncologist and a researcher, its actually been very, very inspiring journey for myself to witness these changes over this key period of time.

Marking the dawn of the targeted therapy era in lung cancer, on November 18, 2004, the U.S. Food and Drug Administration (FDA), approved the molecular targeted therapy drug "erlotinib" (with the brand name TARCEVA) for the treatment of patients with advanced non-small cell lung cancer (NSCLC). This therapy is used after failure of at least one previous chemotherapy regimen. Survival of Tarceva-treated patients resulted in better treatment outcome comparing to standard-of-care. However, the absolute survival difference was not huge, in these "unselected" patient populations. Soon after the drug's approval, scientists have then discovered that there are actually specific DNA mutations within the so-called "EGFR" gene, which stands for the "Epidermal Growth Factor Receptor" gene, in those patients with remarkable drug response. The EGFR gene mutation actually remarkably sensitizes the tumor to the drug and therefore is the major driver of the treatment response.

With the birth of this game-changing clinical-translational cancer research discovery in "molecular targeted therapy" or as some people call it "precision therapy", it basically set the stage for a new paradigm of "genomics-guided therapy" that is using specific "driver cancer gene mutations" to guide treatment decisions. So, we now call these gene alterations "Actionable Mutations". Nowadays, we can molecularly profile these cancer gene mutations not just one by one, but using high throughput DNA sequencing techniques in "comprehensive molecular tumor profiling" over many hundreds of cancer genes simultaneously, or even over the whole cancer genome.

This means that we, as lung cancer oncologists would look at lung cancer not just as one disease any more, but many different "molecular diseases" even if the tumor cells look totally identical under the microscope. This "genomics-guided lung cancer therapy" has pretty much matured well over the past 10-15 years. And now just when we think we are reaching a plateau of the benefits of targeted therapy, we enter a new revolution of cancer immunotherapy. This has already brought about several new options of FDA-approved immunotherapy drugs for lung cancer treatment over the past few years.

2. **You mention the new revolution of cancer immunotherapy. What is cancer immunotherapy?**

Ma: Cancer Immunotherapy is a very broad term. But it is considered a real breakthrough in recent years. For lung cancer, immunotherapy refers to the new cancer treatment that targets the so-called PD-1/PD-L1 immune checkpoint pathway (i.e. the Programmed Death-1 and Programmed Death-Ligand 1 Pathway). This is pathway that some lung cancer cells managed to exploit or highjack for them to escape the otherwise normal immune surveillance in the patient's body against any foreign invading cells, such as infectious germs/viruses or the "transformed" cancer cells.

Generally speaking, the FDA-approved lung cancer immunotherapy drugs are biologically-engineered antibody drugs. They are given to patients intravenously, similar to most chemotherapy administration. However, the side effects profile of immunotherapy is mostly immune-related, like an autoimmune or inflammatory overdrive, and is very different from chemotherapy. Immunotherapy usually does not suppress ones bone marrow functions like most chemotherapies do.

In a nutshell, "immune checkpoint" cancer therapy blocks the tumor cells against their "corrupting influence" over the patients' immune cells, and then it leads to the "reactivation" of the immune cells in the patient's body, allowing them to ultimately "awaken", "recognize" and then "attack" to "kill" the lung cancer cells. So if you think of it this way, this is a very empowering concept for our patients to understand in terms their cancer therapy, as the drug is simply a "facilitator" and the patient's own immune system is the one that does the heavy-lifting and finishes the battle.

3. Can you talk more about the potential of immunotherapy to improve the survival rates for lung cancer patients?

Ma: yeah, sure. One of the key reasons for our excitement about cancer immunotherapy, especially in lung cancer, is that it has the capacity to improve the overall survival rates of patients and to induce durable cancer response rate.

Although it is currently still being adopted for use predominately only in advanced metastatic stage lung cancer patients, and not to be considered a "curative" type of treatment, cancer immunotherapy has been shown to be capable of "prolonging the overall survival time" of metastatic patients.

Furthermore, it is being actively tested now in earlier stage lung cancer e.g. in post-operative (adjuvant) therapy setting after a curative lung cancer surgery, in order to further improve the overall "cure rates" of these early stage patients.

For the benefits of our audience, here is the current list of FDA-approved non-small cell lung cancer immunotherapy drugs available at the present time:

(i) **Nivolumab** (with brand name: **OPDIVO**),
(ii) **Pembrolizumab** (i.e. **KEYTRUDA**), and

(iii) **Atezolizumab** (i.e. **TECENTRIQ**).

Most recently, there was a major game-changing breakthrough again as a publication of the results of a phase III clinical trial, called the Pacific trial, with the use of a novel immune checkpoint drug in **stage III**, inoperable non-small cell lung cancer patients, after curative-intent chemoradiation combination treatment. Excitingly, the study showed remarkable and significant improvement in clinical outcomes of those patients treated with immunotherapy.

The drug tested here is called "**Durvalumab** – (with the brand name: **IMFINZI**)". And it is now newly approved by the FDA in February of this year, 2018. this provides clear improvement in the outcome, with up to 11 months of time before one experienced disease progression, i.e. essentially 3-times of that in the current standard-of-care chemoradiation alone. It also resulted in consistent improvement in response rate, and also decrease in the development of metastatic disease, even including brain metastases.

4. **That's excellent news. Are these cancer immunotherapy drugs used alone or in combination?**

Ma: Yeah, so essentially it is both. As of now, the approved lung cancer immunotherapy drugs can be used either alone, or in combination with chemotherapy, depends on the setting. For second-line use, after prior first-line chemotherapy-failure, all of the immunotherapy drugs mentioned here earlier, would be used alone as single-agent (i.e. Opdivo, Keytruda and Tecentriq).

However, for Keytruda, it has been approved by FDA to be used in combination with doublet chemotherapy (using Carboplatin and Alimta) as first-line treatment for advanced <u>non-squamous</u> non-small cell lung cancer.

Furthermore, for those non-small cell lung cancer patients with the tumors demonstrating "strong expression" of the so-called "PD-L1" protein biomarker for the immunotherapy (reported as 50% or more, from 0-100% scale), they would be eligible for single-agent Keytruda immunotherapy as upfront first-line treatment, which is shown to be more superior than chemotherapy itself in that setting.

5. **Where will the research go from here? Do you have any closing comments for us?**

Ma: There are actually many new exciting directions that cancer immunotherapy research are taken on these days. There are now many more immunotherapy drug combinations that are being tested in various clinical trial research, both nationally and internationally, beyond the PD-1/PD-L1 pathway. The possibilities are actually quite breathtaking. I am certain this new revolution would continue to impact and improve patients' long term survival in the near future in lung cancer.

Most recently, there are emerging novel **personalized-design immunotherapy** known by the short-name **"CAR-T" therapy** now newly approved already recently for use in leukemia and lymphoma; and it is quickly finding its way in applications to solid tumors such as lung cancer.

Besides, research on better ways to predict immunotherapy responders is also very important. Research work on unravelling the mechanism of drug resistance is also crucial in our effort to maximize the impact of future cancer immunotherapy.

So, it goes without saying conclusion, we are expecting a lot of ground-breaking new research findings and novel applications of lung cancer immunotherapy in the coming years. We should all definitely stay-tuned and feel hopeful.