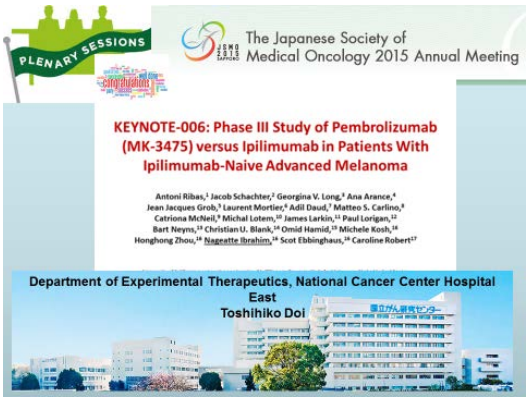
KEYNOTE-006: Phase III Study of Pembrolizumab (MK-3475) versus Ipilimumab in Patients with Ipilimumab-Naive Advanced Melanoma

Title slide



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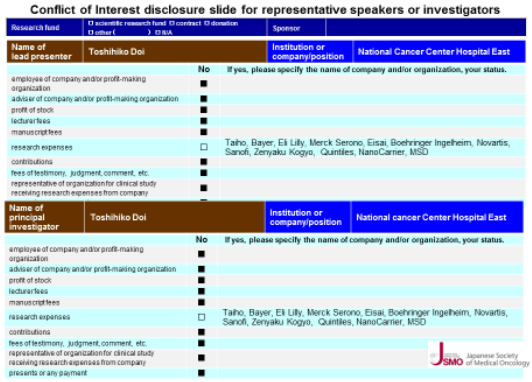

Conflict of Interest disclosure slide for representative speakers or investigators

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Name of lead presenter	Toshihiko Doi	Institution or company/position	National Cancer Center Hospital East

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Name of principal investigator	Toshihiko Doi	Institution or company/position	National cancer Center Hospital East

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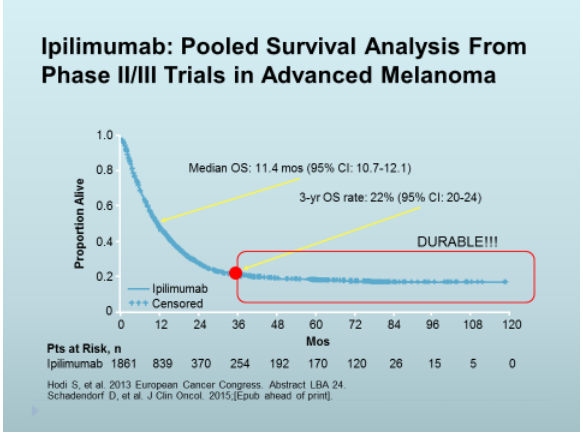
JSMO Japanese Society of Medical Oncology

Firstly, I want to thank the Organizing Committee for allowing me to present my discussion on the homepage. I am sorry to be unable to present all my slides due to copyright and confidentiality issues, so I will shorten my KEYNOTE-006 discussion of patients with advanced melanoma.

As you know, ipilimumab is a human monoclonal antibody that targets CTLA-4. CTLA-4 is a receptor on cytotoxic T-cells that downregulates the immune system and prevents it from recognizing and destroying cancer cells. Ipilimumab turns off the inhibitory mechanism, and allows the T cells to continue to kill cancer cells. Ipilimumab is becoming a standard treatment option for advanced melanoma.

Pooled analysis of patients with advanced melanoma treated by ipilimumab showed that their median overall survival was 11.4 months, and 22% were still alive after three years. Even limited number of patients who showed clinical benefits had durable responses [Slide 1].

Slide 1

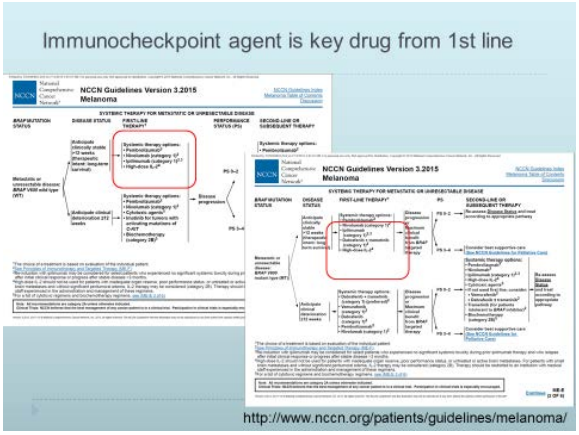


Key points of this trial are

1. Pembrolizumab showed significant and clinically meaningful improvements in progression-free survival, overall survival and objective response rate compared with ipilimumab. Pembrolizumab was also safer than ipilimumab.
2. The efficacy and safety were not dependent on dosing schedules of pemblolizumab

Based on these clinical trials, pembrolizumab, ipilimumab and nivolumab are all used as 1st line therapeutic options for advanced melanoma, both with and without *BRAF* mutations [Slide 2].

Slide 2

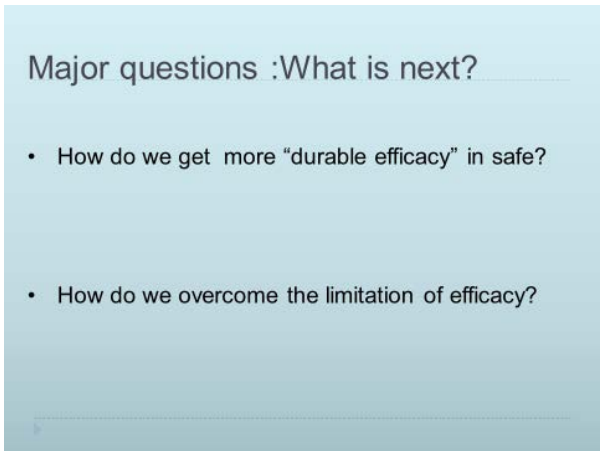


Several questions remain. The minor questions include: [No slide shown]

1. Which PD-1 inhibitor will become the pre-eminent front-line drug? In their drug trial results, both drugs appeared to have quite similar efficacies and safety profiles as front-line agents for advanced or metastatic melanoma.
2. Another minor question is: Which dosing schedule is better? We don’t know the optimal dosing schedule. Right now, it depends on the investigators’ choice in terms of costs, scheduling, toxicity etc.

The major questions include [Slide 3]:

Slide 3



How do we get a durable, efficacious response while minimizing adverse effects?

Durability is a key aspect of immune checkpoint therapy. In fact, the reason we have not been able to define the optimized initial dose is because so many patients required dose modifications due to adverse effects.

And note that immunotherapy toxicities are more similar to autoimmune diseases than to the usual chemotherapy effects, and might not be familiar to medical oncologists.

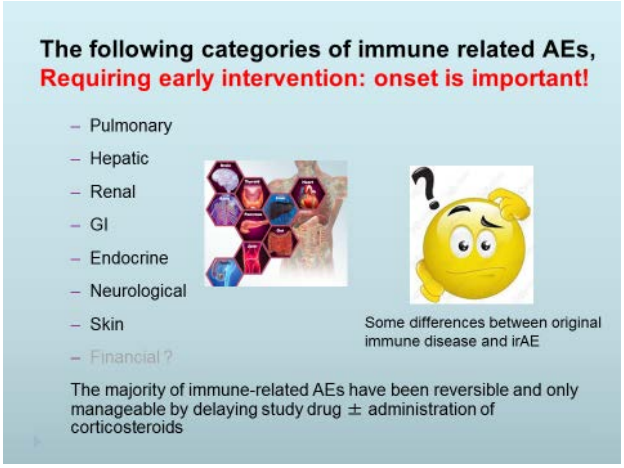
Most immune-related AEs have been reversible and can be managed by delaying or decreasing the study drug and/or use of corticosteroids. But if patients do not respond to these interventions, their adverse effects can be very difficult to manage. Catching and treating these problems early is important!

Also, immunotherapy toxicities and autoimmune diseases differ in some ways, so we have to develop new methods to suppress immune responses in these patients.

Financial adverse effects are not caused by the immune system.

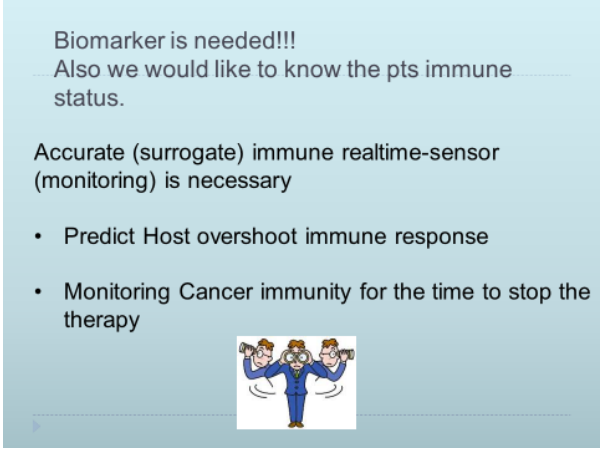
[Slide 4].

Slide 4



Ideally, we would like to have both predictive biomarkers and also markers for patients' immune status. However, we do not currently have a reliable, qualified immune monitoring method. A validated immune-monitoring system is an unmet medical need. [Slide 5]

Slide 5



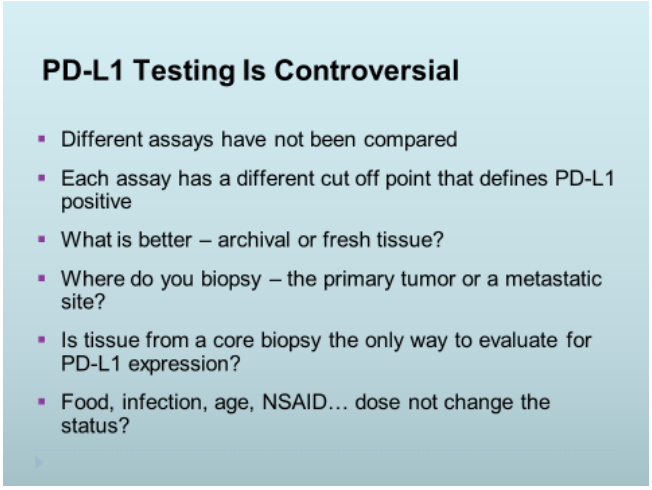
How do we expand the efficacy of these treatments?

Although a few patients achieve long-term durable responses, most patients withdraw during the initial short treatment period without clinical benefits. To maximize therapeutic response, we need biomarkers to identify patients who are likely to benefit from this therapy—especially considering, among other things, how costly these therapies are.

Research for these biomarkers is promising, and includes such characteristics as mutation rates, immune scores/ cytokine profiling, CD8+/T-cell ratios, tumor-infiltrating lymphocytes, neo-epitopes, gene signatures, and RNA expression profiles, in both cancer and stromal cells. [No slide shown]

However, the most common clinical method now uses IHC staining for programmed death ligand-1, PD-L1. The utility of this method is debatable. In particular, this assay needs to be standardized as to method, materials, and testing algorithm, so to provide a reproducible threshold assessment. [Slide 6]

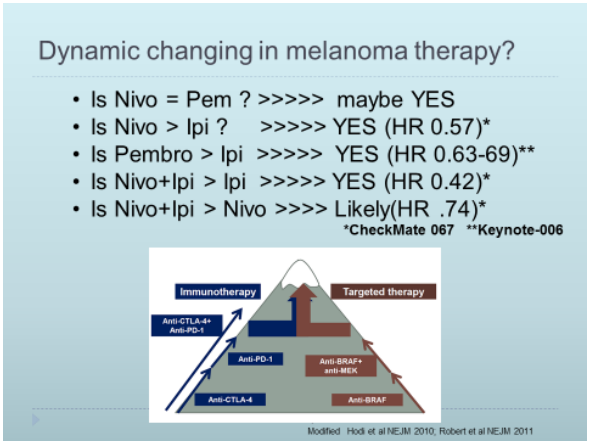
Slide 6



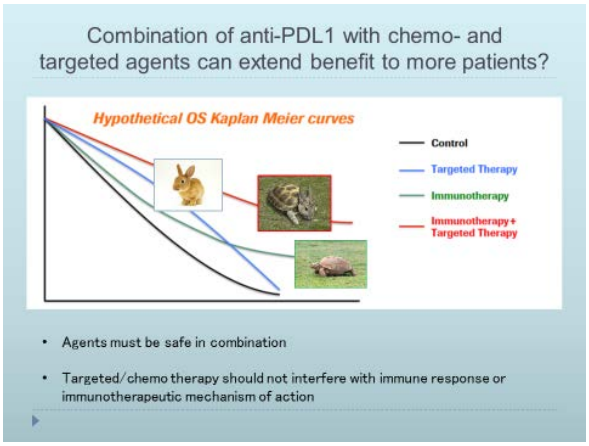
Although early trial data suggest that f PD-1–PD-L1 signaling is actively blockaded in a wide range of tumor types (melanoma, breast cancer, lung cancer, gastroesophageal cancer, Hodgkin’s lymphoma etc.), only a subset of patients in a few tumor types have enjoyed clinical benefits. To extend therapeutic benefits to a broader range of patients, clinical trials have investigated the synergistic potential of combining immune checkpoint inhibitors with other checkpoint agents, cytotoxic agents, anticancer vaccines, cytokines, and radiotherapy.[NO slide shown]

The CheckMate 067 trial of melanoma treatments showed improvements in both tumor response and patient survival with the combination of CTLA-4 antibody ipilimumab with the PD-1 antibody nivolumab compared to either therapy given alone. As expected, the combination arm had a greater rate of severe and potentially life-threatening adverse effects, but most can be prevented or reversed with management. This is not only a major advance for melanoma treatment, but also provides an approach that may be applicable to other cancer types, and other drug combinations. [Slide7,8]

Slide 7

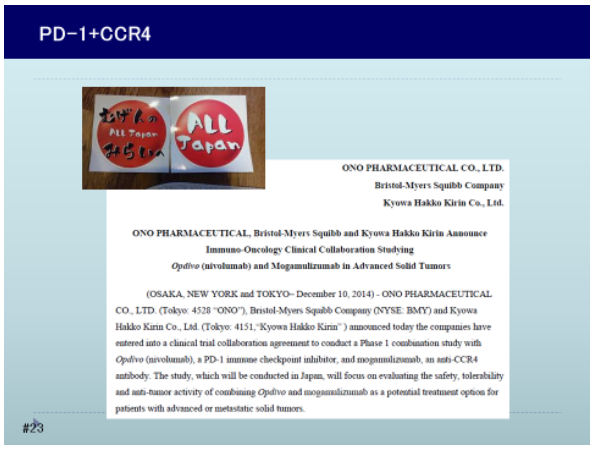


Slide 8



Another approach is to involve other effector cells such as regulatory T cells (T_{reg}s) or myeloid-derived suppressor cells (MDSCs). Now in Japan, a combination therapy with anti-PD-1 antibody and anti-CCR4 antibody targeted to T_{reg}s has recently begun. [Slide 9]

Slide 9



In any case, immune response to cancer is dynamic and systemic, and therefore, immunotherapy is not just a single agent or class of agents. There are many targetable molecules to manipulate, and many facets of the immune response against cancer.

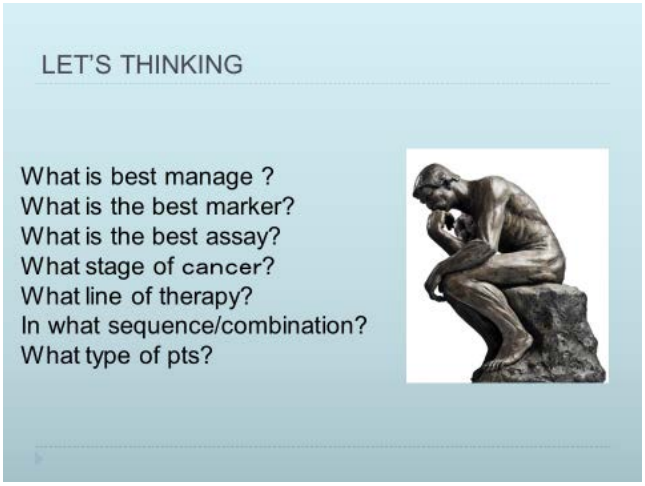
Checkpoint inhibition was just the beginning.

We should consider

- What is best way to manage this disease?
- What are the best markers?
- What is the best assay?
- What stage of cancer responds best to which therapy?
- What is the optimal sequence or combination of treatment?
- Which patients are most likely to benefit?

[Slide10]

Slide 10



Acknowledgments

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