CH3.

Slide 1

We have recently become aware than a gene can fuse with another gene to become a powerful oncogene. As shown in the slide, gene A and gene B fuse to create a fusion gene consisting of gene A+gene B. This fusion gene can become a powerful oncogene, as recent studies have demonstrated.

Slide 2

I will now explain the role of the ALK, ROS1, and RET fusion genes in lung cancer and the role of the BCR-ABL fusion gene in chronic myeloid leukemia.

Slide 3

I will now explain ALK fusion genes.

In 2007, the research group led by Tatsuo Mano of the University of Tokyo discovered an ALK fusion gene that could serve as a therapeutic target for lung cancer. As shown in the slide, its frequency in lung cancer is 3.8%, so it is extremely rare. EML4 and ALK kinase on chromosome 2 fuse, as shown in the slide. This creates activated EML4-ALK fusion kinase, which heavily promotes oncogenesis. This gene is heavily involved in the growth of cancer to the extent that it is known as “the champion oncogene.”

Slide 4

Crizotinib (an ALK inhibitor) has proven to be efficacious in treating lung cancer with an ALK fusion gene, and it was approved in Japan in 2010. Crizotinib was therapeutically effective in this patient. The tumor that was present in the left lung prior to treatment clearly disappeared after crizotinib was administered. Thus, an ALK inhibitor was found to be highly therapeutically effective in treating ALK fusion gene-positive lung cancer.

Slide 5

Crizotinib (an ALK inhibitor) significantly improved survival for patients with ALK fusion gene-positive lung cancer compared to a conventional cytotoxic anticancer agent.

This slide shows the progression-free survival curve from a phase III trial comparing crizotinib and chemotherapy for initial treatment of ALK fusion gene-positive lung cancer. The group receiving crizotinib (indicated in blue) had a median progression-free survival of 10.9 months, so crizotinib significantly prolonged survival compared to a median progression-free survival of 7.0 months for patients receiving chemotherapy. As a result of this clinical trial, crizotinib (an ALK inhibitor) became the standard treatment for ALK fusion gene-positive lung cancer, and it is used in routine clinical practice. Recently, highly therapeutically effective ALK inhibitors such as alectinib and ceritinib have been developed and used.

Slide 6

Shown here is the antitumor action of crizotinib (an ALK inhibitor) and chemotherapy.

This figure is a waterfall plot. The further down the bar extends, the greater the rate of tumor shrinkage. The further up the bar extends, the more the tumor is likely to grow.

The response rate to an ALK inhibitor was 74%, extending far down the bar. In most patients, the tumor shrank. In contrast, the response rate to chemotherapy was 45%. The bar only extended slightly downwards compared to that for an ALK inhibitor. This indicates that an ALK inhibitor clearly shrinks a tumor substantially.

Slide 7

Cancers with an abnormal ALK gene besides lung cancer have been reported.

As shown in the slide, ALK and EML4 fuse in lung cancer, ALK and NPM1 fuse in lymphoma, ALK and TPM3 fuse in an inflammatory myofibroblastic tumor, and ALK and VCL fuse in kidney cancer to become powerful oncogenes. Studies reported that inhibiting the ALK protein is therapeutically effective in treating cancer with these fusion genes, which is why those cancers have recently been referred to as ALKoma.

Slide 8

I will now explain ROS1 fusion genes.

A mutation in ROS1 is a rare mutation found in about 1% of lung cancers. ROS1 is located on the long arm of chromosome 6, and 14 genes can fuse with it. CD74, EZR, SLC34A2, and SDC4 account for 70% of those mutations.

ROS1 has a high level of affinity for the tyrosine kinase domain of ALK, and an ALK inhibitor has the ability to inhibit ROS1 tyrosine kinase, so crizotinib (an ALK inhibitor) is now used as a treatment, as I explained a moment ago.

Slide 9

Shown here are results of a clinical trial of crizotinib to treat ROS1 fusion gene-positive lung cancer and patients who benefited it. The therapeutic effectiveness of monotherapy was already reported in the NEJM. In 36 of 50 patients (72%), the cancer shrank. The bar in the waterfall plot, which I explained a moment ago, extends far down for almost all of the patients, indicating that the tumor shrank substantially. On the right are FDG-PET findings. On the left are intrapulmonary metastases and lymph node metastases, which appeared as dark spots prior to treatment. The tumors almost disappeared 7 weeks after crizotinib therapy.

Slide 10

I will now explain RET fusion genes. These genes are a rare genetic mutation noted in 1.9% of lung cancers. Facilities such as the National Cancer Center and the Japanese Foundation for Cancer Research identified these genes as a new target in lung cancer in 2012. RET fuses with another gene on chromosome 10 to create a driver gene.

Slide 11

RET-positive lung cancer was examined during genomic testing for lung cancer at the national level primarily at the National Cancer Center's Eastern Hospital. An organization known as LC-SCRUM-Japan screened 1,536 patients and identified 34 patients with RET-positive lung cancer. A clinical trial was conducted to determine whether or not vandetanib, a molecularly targeted drug that inhibits RET tyrosine kinase, could treat RET-positive lung cancer, and 17 eligible patients were enrolled.

Slide 12

Shown here is the therapeutic effective of vandetanib in treating RET-positive lung cancer. On the right is a waterfall plot, and in 9 of 17 patients (53%) the cancer shrank. CT findings before and after treatment are shown on the far right. A tumor adjacent to the heart was clearly found to have shrunk. Vandetanib is not available for treatment of RET-positive lung cancer in routine clinical practice, but it likely could be in the future.

Slide 13

I will now explain BCR-ABL. As shown in the slide, chromosomal translocation of the ABL gene on chromosome 9 and the BCR gene on chromosome 22 results in the BCR-ABL fusion gene, which causes cancer cells to proliferate, leading ot chronic myeloid leukemia. In previous clinical trials, imatinib caused the Philadelphia chromosome to mostly disappear compared to standard treatment, and it is currently used as standard treatment.

Slide 14

I will now explain gastrointestinal stromal tumors (GISTs).

Slide 15

I will now explain KIT. Studies have reported that KIT-activating gene mutations are a major cause of GIST. A KIT mutation is noted in exons 9, 11, 13, and 17 at a frequency of about 90%. Imatinib (an ABL kinase inhibitor) has potent action as a KIT kinase inhibitor and has become a treatment for a GIST. A clinical trial used imatinib to treat a GIST in 147 patients, and the tumor shrank in 79 (53.7%). Imaging findings on the right indicate that a massive GIST in the abdomen generally shrank as a result of treatment. The fact that imatinib was so therapeutically effective in treating a GIST that did not respond to chemotherapy was a major finding, and imatinib is currently used in routine clinical

practice.

Slide 16
I will now explain HER2.

Slide 17-18
HER2 is a transmembrane tyrosine kinase receptor in the EGFR family. It is a major oncogene, and its amplification and overexpression are noted in many types of cancer. As shown in the slide, the HER family consists of HER1 (EGFR), HER2, HER3, and HER4. HER1, HER2, and HER3 are known to be involved in the proliferation, survival, and differentiation of tumor cells, but the role of HER4 in breast cancer is unclear. HER1 is an EGFR, as I explained a moment ago.

Slide 19
A humanized anti-HER2 monoclonal antibody, trastuzumab is known to be a drug that specifically binds to HER2 protein (a product of the HER2 gene), and trastuzumab is used to treat HER2-positive breast cancer and gastric cancer.

Slide 20
Shown here are results of a clinical trial on trastuzumab to treat breast cancer. This trial compared chemotherapy alone and combined therapy with chemotherapy and trastuzumab in 234 patients with breast cancer with a high level of HER2 expression.
You can see the curve for progression-free survival. Survival significantly improved in the group receiving trastuzumab in addition to chemotherapy.

Slide 21
Shown here are results of a clinical trial on trastuzumab to treat gastric cancer.
3,807 patients were screened, and 810 with HER2-positive cancer were identified. 584 patients were eligible for this clinical trial. Its design compared survival. Two hundred and ninety patients were treated with capecitabine, 5FU, and cisplatin while 294 were also treated with trastuzumab.

As shown in the slide, the survival curve for the group that also received trastuzumab surpassed that for the group that did not receive trastuzumab. Median survival was 13.8 months for the group that also received trastuzumab and 11.1 months for the group that did not receive trastuzumab, so trastuzumab significantly improved survival. Based on these findings, trastuzumab is now used in routine clinical practice to treat HER2-positive gastric cancer.

Slide 22
I will now explain mutations in the BRAF gene.

Slide 23

BRAF is located on chromosome 7 (7q34) and consists of 18 exons. When a mutation occurs in the codon for valine at amino acid 600 (V600) of BRAF, BRAF kinase is constantly activated.

V600E accounts for about 91% of BRAF mutations, and other mutations are extremely rare.

The frequency of a mutation in the BRAF gene in different types of cancer is shown in the slide. As you can see, it is most frequent in malignant melanoma (43%), followed by thyroid cancer (27%), ovarian cancer (15%), and colon cancer (14%). Its frequency in lung cancer is rare (3%). A BRAF inhibitor (vemurafenib) that selectively inhibits BRAF kinase and that inhibits the proliferation of cancer cells is known to be efficacious in treating BRAF mutation-positive patients.

Slide 24

Shown here are data from a clinical trial on a BRAF inhibitor (vemurafenib) to treat malignant melanoma.

When overall survival after dacarbazine and vemurafenib therapy (standard treatment) to treat BRAF V600E-positive malignant melanoma was compared, vemurafenib significantly improved survival, and it is currently used as standard treatment.

Slide 25

Also shown here are progression-free survival and antitumor action. Vemurafenib significantly improved progression-free survival. As shown in the waterfall plot, the response rate to vemurafenib was 40% while the response rate to dacarbazine was 5%. Vemurafenib yielded satisfactory results in terms of antitumor action.

Slide 26

The therapeutic effectiveness of a BRAF inhibitor (vemurafenib) in treating cancer other than malignant melanoma is shown in the table. There were few patients with each type of cancer, but its antitumor action against different types of cancer was 42% for non-small-cell lung cancer, 0% for colon cancer, 12% for cholangiocarcinoma, and 29% for thyroid cancer. The therapeutic effectiveness of vemurafenib was found to have differed depending on the type of cancer. That said, the response rate of BRAF V600E-positive malignant melanoma and non-small-cell lung cancer to vemurafenib was about 40%, and the tumors were found to have similarly shrunk.