December 9, 2016

Press Release,

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Information on the Initiation of Neoantigen (Genetic Variant Antigen) Peptide Vaccine Development

We announce that the development of a neoantigen[*4] (genetic variant antigen) peptide vaccine for non-small cell lung cancer[*3] will begin based on a patent transferred from the Kanagawa Prefectural Hospital Organization: "Antigen peptide originated from the T790M point mutated[*2] sequence of epidermal growth factor receptor (EGFR)[*1]".

Many patients with lung cancer are already at an advanced stage or have metastasis at the time of their diagnosis, which leads to a poor prognosis. Approximately 220,000 individuals[1] in the United States and 130,000 individuals[2] in Japan reportedly develop lung cancer. More than 80% of patients are diagnosed with non-small cell lung cancer. EGFR tyrosine kinase inhibitors (EGFR-TKI) are selected as conventional and effective drugs for patients with an EGFR activation mutation (primary mutation), accounting for approximately 10% of non-small cell lung cancer patients (Japanese: 30%). However, many patients acquire resistance to EGFR-TKI one to 1.5 years after the start of treatment, which results in disease progression. Previous studies reported that a gene mutation, the EGFR-T790M point mutation (secondary mutation), was detected in approximately 60% of EGFR-TKI-resistant patients. We will develop a peptide vaccine against the EGFR-TKI-resistant gene mutation as an antigen (neoantigen).

Neoantigen refers to an antigen involving a gene mutation related to cell canceration. It only appears on cancer cells, clarifying the border between cancer and normal cells. In the immune system, neoantigen is recognized as "non-self", and its immunogenicity is high. Since it may efficiently induce antigen-specific T cells, the development of cancer vaccines against neoantigen as an antigen is an important issue for next-generation cancer immunotherapy. The T790M point mutation may be a driver mutation directly involved in the transformation of cancer, which is caused by EGFR-TKI-attacked cancer cells acquiring attack tolerance. If this mutation is targeted, antigen expression may persist on cancer cells with drug (EGFR-TKI) administration, and antigen loss-related escape from immune surveillance mechanisms may not occur. Furthermore, the incidence of the T790M point mutation is higher (approximately 60%) than that of spontaneous mutations related to cancer transformation, and this may be because this gene mutation is induced

by drug administration. Internationally, cancer immunotherapy targeting drug resistance-inducing gene mutations represents a new approach.

We will introduce a peptide involving the EGFR-T790M point mutation from the Kanagawa Prefectural Hospital Organization: neoantigen*5 identified by Dr. Sasada et al., Director, Department of Cancer Immunotherapy Research and Development, Kanagawa Cancer Center Research Institute (Kanagawa Prefectural Hospital Organization), who developed this patent as a cancer immunity-inducing peptide. Lymphocytes in peripheral blood from patients with lung cancer were confirmed to show neoantigen-specific immune responses.

A tyrosine kinase inhibitor against the EGFR-T790M mutation recently became commercially available, and, due to its clinical molecule-targeting efficacy, generic products are now being developed, leading to blockbuster products. Therefore, drugs against the EGFR-T790M mutation will play an important role in the treatment of lung cancer worldwide. We will develop a discriminated product as a cancer vaccine that has a different action mechanism from these low-molecular-weight compounds. A clinical trial will be initiated in 2017.

We have performed a collaborative study on neoantigen exploration in cooperation with the Kanagawa Cancer Center since July 2016. By focusing on the mechanisms underlying antigen presentation in the cancer microenvironment*6, we are also investigating methods to identify driver and passenger mutation antigens (driver mutations: mutations directly involved in cancer transformation) (passenger mutations: mutations not related to canceration, potentially with high immunogenicity and numbers).

This matter will not markedly influence the achievements of our company in March 2017.

[Term explanation]

*1: Epidermal growth factor receptor (EGFR): Receptor that binds to epidermal growth factor, which regulates cell proliferation or growth, thereby contributing to signal transmission. Cell differentiation/proliferation may occur when this receptor is activated. Furthermore, EGFR is detected in many cells, and is involved in canceration or infiltration/metastasis when a mutation occurs.

*2: T790M point mutation: A mutation of the 790th amino acid of the EGFR protein from threonine to methionine. This mutation shows resistance to conventional tyrosine kinase inhibitors, such as Tarceva and Iressa.

*3: Non-small cell lung cancer (NSCLC): Lung cancer is classified into two types: small and non-small cell lung cancers. The latter progresses more slowly than the former, but does not

respond to chemotherapy or radiotherapy. In Japan, ≥80% of lung cancer patients have non-small cell lung cancer. This cancer has been sub-classified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

*4: Neoantigen: An antigen involving gene mutations (amino acid mutations) related to unique gene abnormalities in cancer cells. It is a cancer-specific antigen expressed through unique gene mutations in the cancer cells of individual patients, and does not exist in normal cells. Cancer cell-killing immunity may be efficiently induced by targeting neoantigen, which is recognized as "non-self" by the immune system. Neoantigen may be available as the antigen of cancer vaccines, as a biomarker to select patients for whom an immune checkpoint antibody is effective, and as a high accuracy target of T-cell therapy (CAR-T: chimera antigen receptor T-cell therapy, TCR-T: T-cell receptor therapy, and T-iPS: iPS regenerative T cells), which has recently been introduced.
However, neoantigen includes tumor-specific gene mutation antigens and those related to post-translational modifications, such as phosphorylation, glycosylation, and methylation.

*5: EGFR T790M mutation as a possible target for immunotherapy; identification of HLA-A*0201-restricted T cell epitopes derived from the EGFR T790M mutation, Yamada et al. PLoS One. 2013 Nov 5; 8(11): e78389.

A peptide antigen derived from EGFR T790M is immunogenic in non-small cell lung cancer, Ofuji et al. Int J Oncol. 2015 Feb; 46(2): 497–504.

*6: Cancer microenvironment: A state characteristic of a tissue in which cancer cells aggregate. In the presence of various factors secreted by cancer cells, macrophages and immature myelocytes aggregate, and these immunocytes may be involved in the infiltration/malignancy /transformation of cancer cells.

[1] American Cancer Society

http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

[2] National Cancer Center

http://www.ncc.go.jp/jp/information/press_release_20150428.html

About Green Peptide Co., Ltd.

Green Peptide is a drug discovery venture company responsible for the development of innovative "cancer immunotherapy" as the 4th cancer treatment following surgery, radiotherapy, and chemotherapy. Clinical trials on cancer peptide vaccines are being conducted in Japan and the United States, and we recently started the development of new T-cell therapy involving the iPS regeneration of antigen-specific T cells.

About Kanagawa Prefectural Hospital Organization

Five prefectural hospitals (Kanagawa Prefecture) are managed by the Kanagawa Prefectural Hospital Organization. The Research Institute of Kanagawa Cancer Center, one of the five hospitals, has a 30-year history since its establishment, and has many opinions for cancer immunotherapies, including cancer peptide vaccine therapy, which was developed by our company.

Neoantigen/peptide vaccine development

GreenPeptide (Securities code: 4594)

December 9, 2016

Contents

Highlight

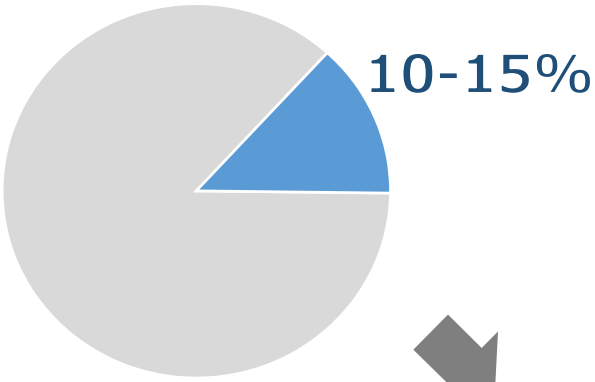
Highlight

1 Cancer immunotherapy for a drug-resistant gene mutation (EGFR T790M point mutation) involved in resistance to a primary treatment for lung cancer, EGFR-TKI

- Annual number of newly diagnosed patients: 500,000 patients → Approximately 80% of these had non-small cell lung cancer.

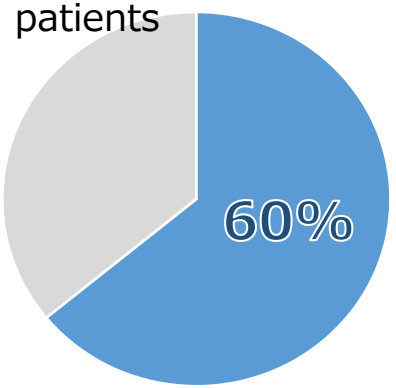
(United States: 210,000 patients, EU (Top 5 countries): 200,000 patients, Japan: 100,000 patients)[1]

- Primary EGFR mutation rate



EGFR tyrosine kinase inhibitors (EGFR-TKI)[2] are used as standard therapy.

- T790M mutation (secondary EGFR mutation) rate in EGFR-TKI-resistant patients



1 Source: GLOBOCAN 2012

2 Tarceva (erlotinib, sales amount in 2015: $1.59 bn), Iressa (gefitinib), and Giotrif (afatinib) were approved by 3 bureaus.

Highlight (cont.)

2 The neoantigen T790M gene mutation is a target of cancer immunotherapy.

1. Antigen epitope (peptide) of which the immunogenicity was confirmed
   → A patent was granted in the United States

2. Only appear on cancer cells.

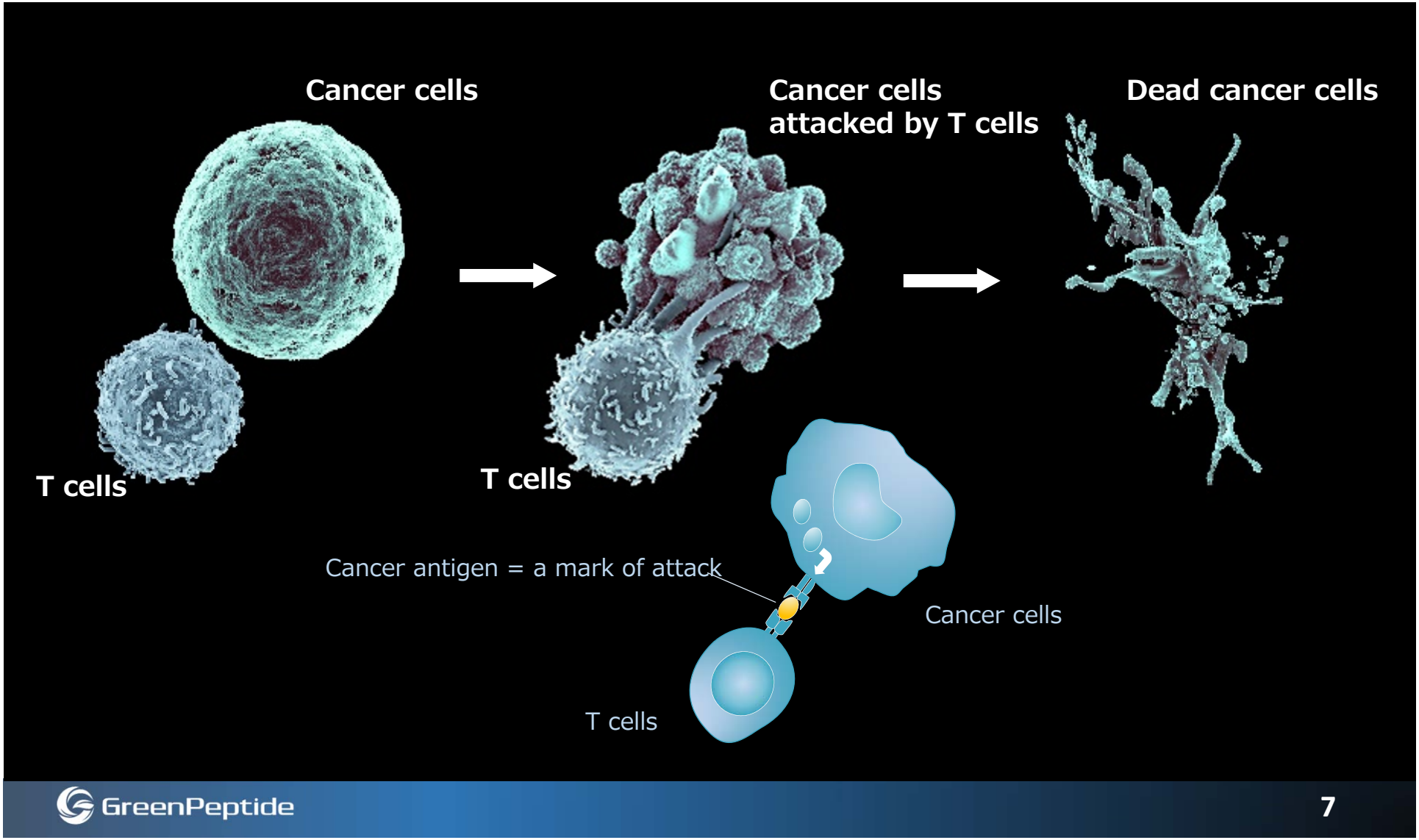
3. Escape (antigen loss) from immune surveillance mechanisms may not occur.
   →Driver mutations are essential for cancer malignancy, which occurs against a challenge by EGFR-TKI (primary treatment)

4. A relatively high incidence.

What is neoantigen?

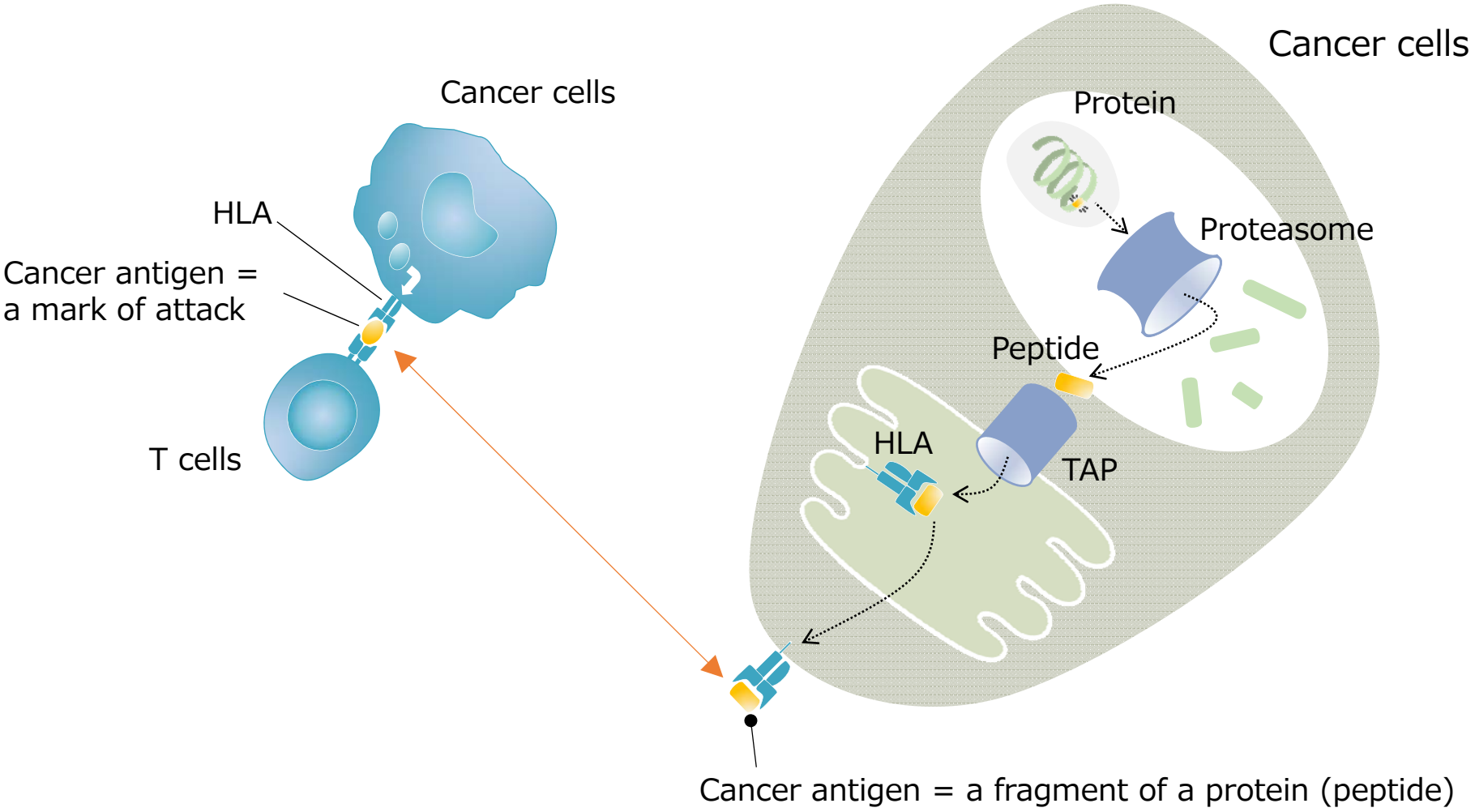
Cancer Antigen

Cancer antigen is a mark of cancer, presented on the surfaces of cancer cells, for T cells.



Identification of cancer antigens

An antigen recognized by T cells as a mark of attack consists of a sequence of 8 to 12 amino acids (peptide) prepared/expressed by cancer cells.



Cancer antigen ideal for cancer immunotherapy

mark of attack

1. *In vivo* immune responses in cancer patients (immunogenicity).
   → *In the immune system, cancer is recognized/eliminated as "non-self".*

2. Cancer antigens only appear on cancer cells.
   → *The immune system does not damage normal cells.*

3. Escape (antigen loss) from immune surveillance mechanisms may not occur.
   → *Immunity does not lose a mark of attack.*

4. A high incidence.*
   → *Cancer antigens are available for many patients, and may be readily developed.*

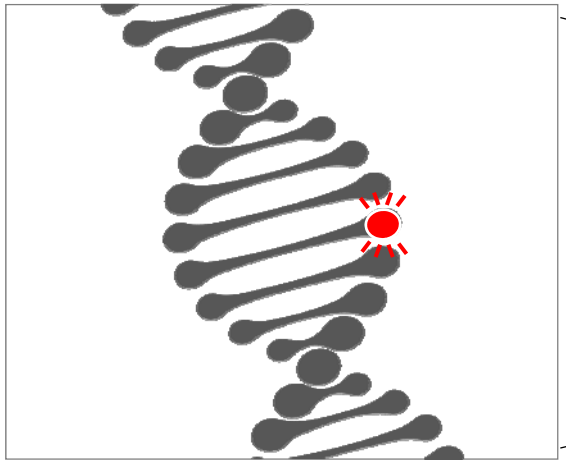
* A gene abnormality with a low incidence (neoantigen: described below) has also recently been investigated as a target for cancer vaccine development.

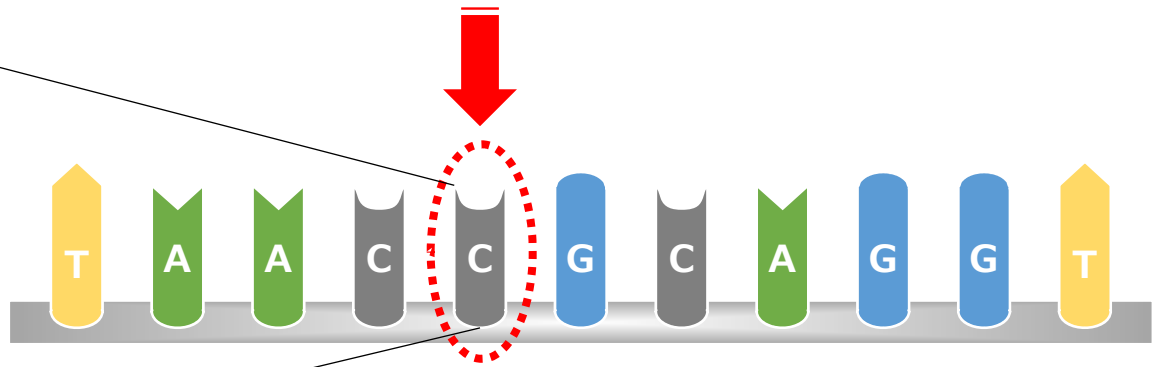
Neoantigen

Neoantigen is a product of cancer-cell-specific gene abnormalities.

Original amino acid sequence (in normal cells)

Point gene mutation





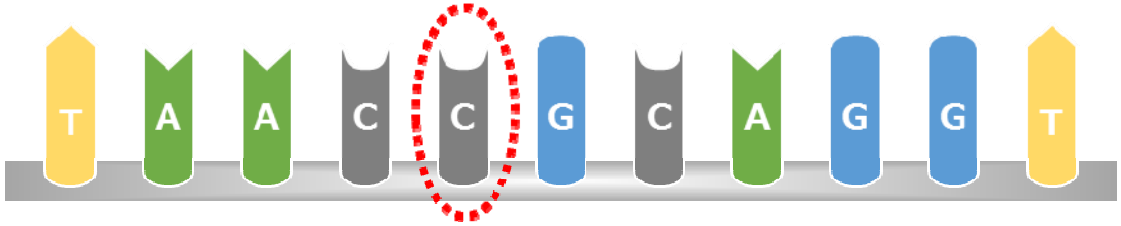
An amino acid sequence in which some amino acids are substituted for other amino acids through a point gene mutation (in cancer cells)

Immunogenicity of neoantigen

In immune surveillance mechanisms, neoantigen specifically appearing on cancer cells is recognized as “non-self” and attacked/eliminated.

■ Original amino acid sequence

■ Neoantigen (sequence involving a point gene mutation)



- Low immunogenicity

The immune system recognizes neoantigen as “self”

▼

Does not attack

- High immunogenicity

The immune system recognizes neoantigen as “non-self”

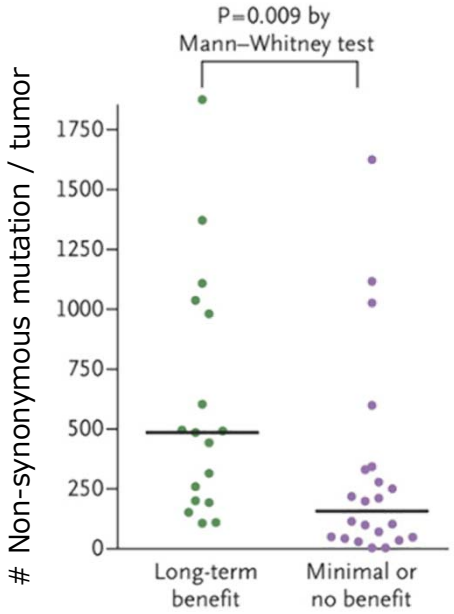
▼

Attacks to eliminate the foreign body

Why is neoantigen being focused on?

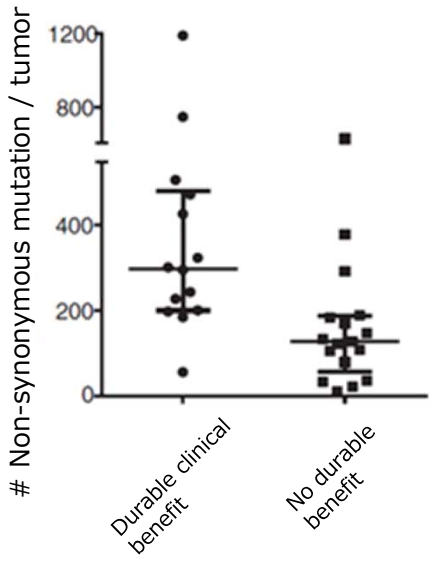
- **Immune checkpoint antibodies are more effective for patients with a larger number of gene mutations (neoantigen) in their cancer cells; the immunogenicity of neoantigen may be useful.**

Ipilimumab (anti-CTLA-4) melanoma



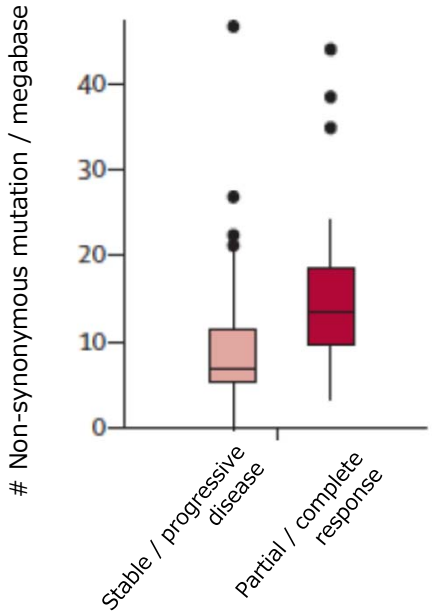
Snyder, NEJM, 2014

Pembrolizumab (anti-PD-1) non-small cell lung cancer



Rizvi, Science, 2015

Atezolizumab (anti-PD-1) non-small cell lung cancer



Rosenberg, lancet, 2016

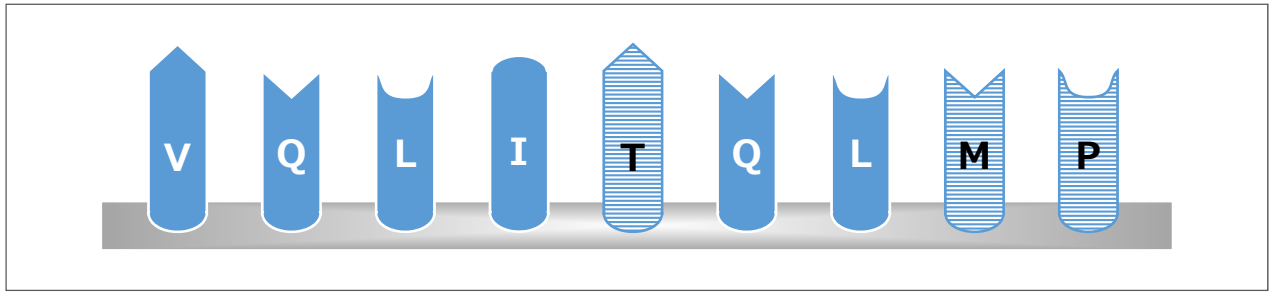
- **However, a gene mutation does not always have immunogenicity (≤1/100), and mutations vary among patients; the incidence is low (≤1%).**

Characteristics of seeds

T790M point mutation

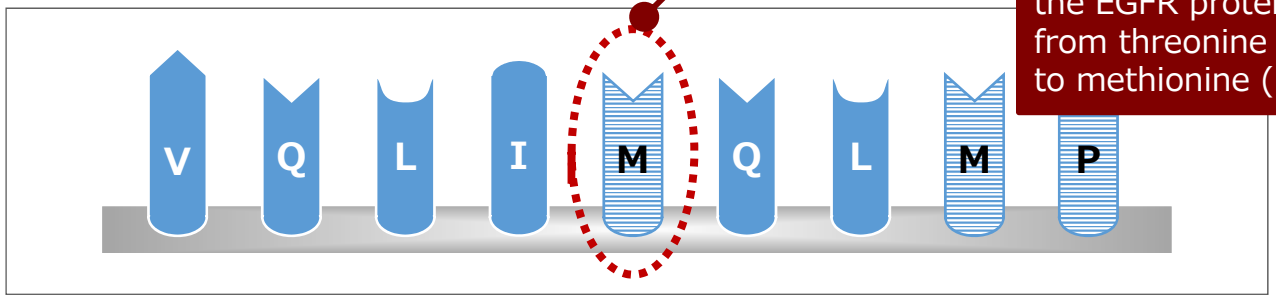
Amino acid sequence of the EGFR peptide appearing on small cell lung cancer cells

Before the administration of EGFR-TKI (tyrosine kinase inhibitors)*



Administration of EGFR-TKI

After its administration



Mutation of the 790th amino acid of the EGFR protein from threonine (T) to methionine (M)

Resistance gene mutations appear in approximately 60% of treatment-resistant patients.

If there is an immune response, neoantigen with immunogenicity is synthesized.

* Molecule-targeting drugs as a primary treatment for non-small cell lung cancer: epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKI), such as Tarceva (erlotinib, sales amount in 2015: $1.59 bn), Iressa (gefitinib), and Giotrif (afatinib), were approved by 3 bureaus.

Characteristics of the T790M point mutation

1. *In vivo* immune responses in cancer patients (immunogenicity)

→*The response of human T cells to the T790M mutation-derived antigen was confirmed.*

- The immunogenicity of the T790M mutation-derived peptide was higher than that of the original sequence (wild-type) peptide.
- T cells, which specifically responded to the T790M mutation-derived peptide, exhibited cytotoxic activity against an EGFR-expressing lung cancer cell line with the T790M mutation.

Article by seeds developers

"EGFR T790M mutation as a possible target for immunotherapy; identification of HLA-A*0201-restricted T cell epitopes derived from the EGFR T790M mutation" *Yamada et al.* PLoS One. 2013 Nov 5;8(11):e78389.

"A peptide antigen derived from EGFR T790M is immunogenic in non-small cell lung cancer" *Ofuji et al.* Int J Oncol. 2015 Feb; 46(2): 497–504.

Characteristics of the T790M point mutation (cont.)

2. Appearance on cancer cells

→Secondary gene mutation after the administration of EGFR-TKI (molecule-targeting drugs as primary treatments for non-small cell lung cancer)

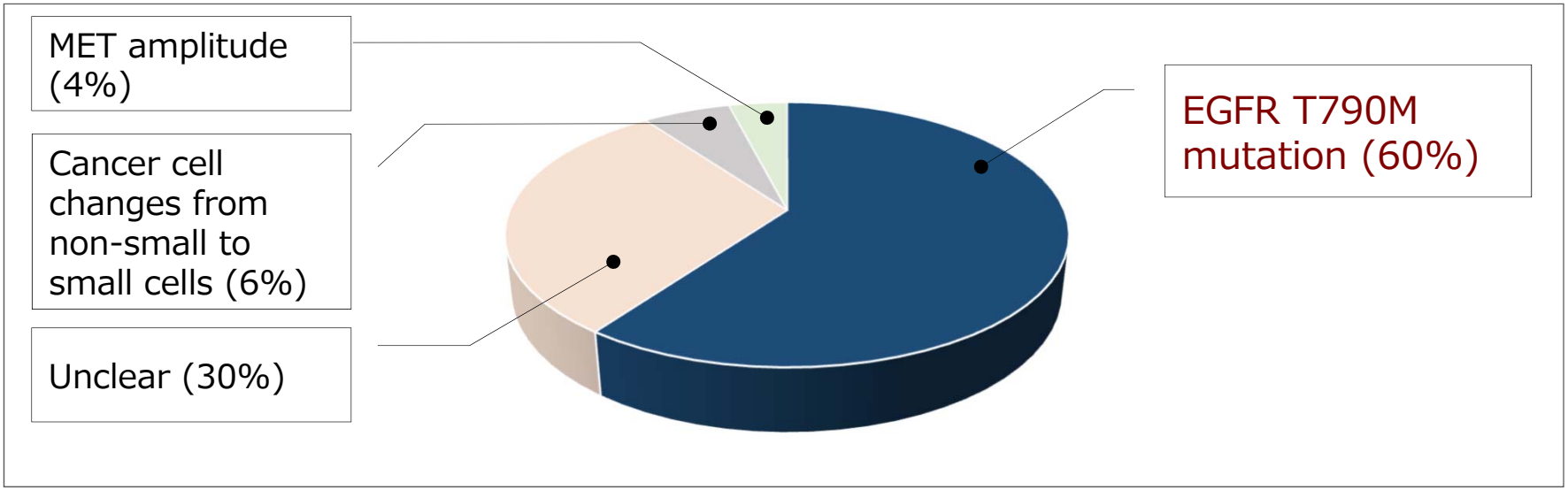
3. Escape (antigen loss) from immune surveillance mechanisms may not occur.

→Since the gene mutation is necessary to acquire resistance to a challenge by EGFR-TKI (cancer malignancy), the appearance of the antigen persists with a continuous EGFR-TKI treatment.

Characteristics of the T790M point mutation (cont.)

4. Its incidence is high.

→Approximately 60% are EGFR-TKI-resistant patients



(C) 2011 American Association for Cancer Research

The EGFR T790M mutation is the target of cancer immunotherapy.

Patent

- Name of development: Antigen peptide originated from t790m point-mutated sequence of epidermal growth factor receptor
- Patent No.: PCT/JP2013/071499
- Date of application: August 8, 2013 (date of priority: October 8, 2012)
- Applicant: Kanagawa Prefectural Hospital Organization
- Developer: Tetsuro Sasada, Tetsuya Nakaomote, and Kazuya Ofuji

- State of inspection

Country of transference	Date of transference	Application number	State of application
European Patent Office	06.03.2015	2013827804	Pending
Japan	05.02.2015	2014529551	Pending
United States of America	09.02.2015	14420561	Assessment of registration (US 9505824)

HLA restrictive of a peptide to be developed

HLA-A2 restrictive

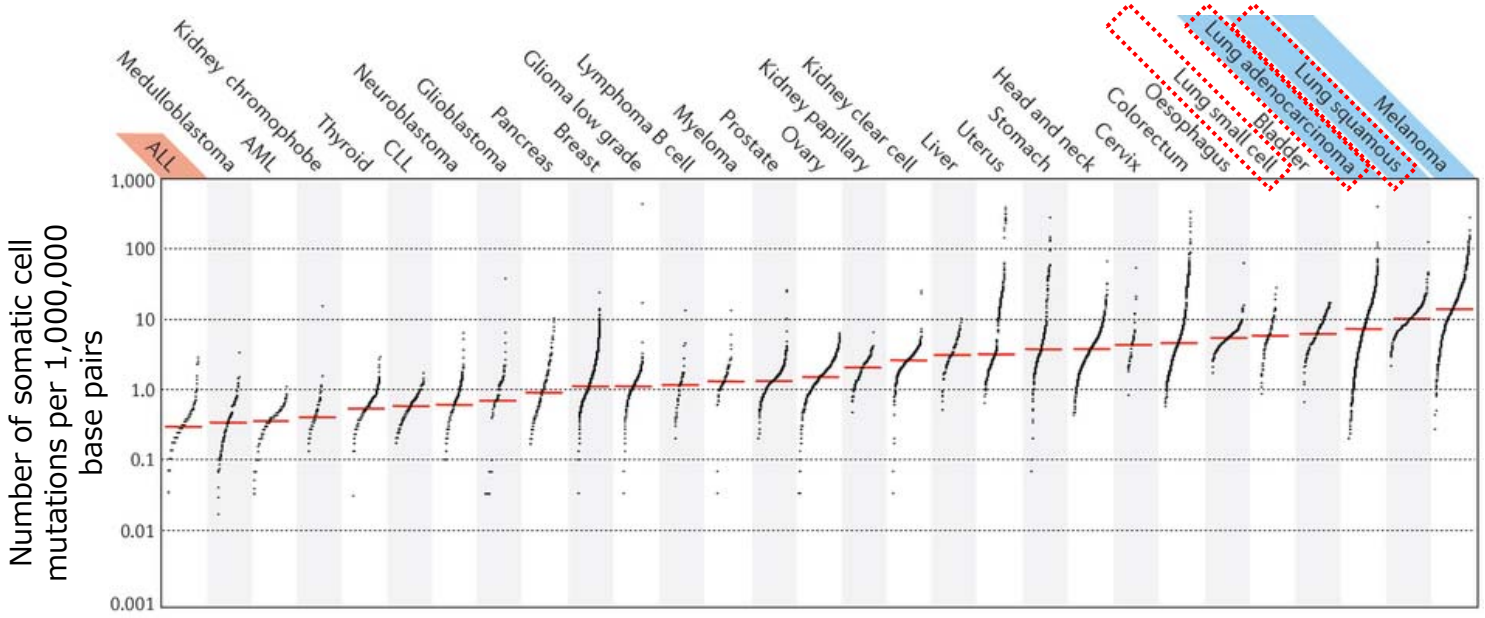
■ Positive reaction rate to the population

HLA type %	U.S.A	5 countries in Europe	Japan	China
A2	48	48	30	50
A1	22	28	6	3
A24	15	20	60	22

Possibilities for neoantigen

Possibilities for neoantigen

1. **Prediction of the effects of immune checkpoint inhibitors**
   →According to previous studies, cancer types with frequent gene mutations showed favorable clinical results.



Khalil, D. N. *et al*. (2016) The future of cancer treatment: immunomodulation, CARs and combination immunotherapy *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.25

2. **Design of new cancer vaccines**

3. **Targets for T-cell therapy (TCR-T and T-iPS)**