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Nivolumab (brand name: Opdivo)

Benefit and harm on survival offset each other: strict restriction on use is needed

GLP-1 Agonists (liraglutide)

No evidence of improving prognosis in patients with diabetes: Not recommended

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Don't be misled by new "mab" drugs

Translated from the editorial in Med Check-TIP (in Japanese) Jul 2016 : 16 (66)

The human body, through the activation of its immune system, eliminates foreign substances from both outside and inside itself, including tissues damaged by ischemia and cancer cells. Autoimmune diseases and malignant tumors develop and are aggravated by excessive stimulation and/or failure of the immune surveillance system. The idea that excessive stimulation can be mitigated and the failure of immune surveillance reversed by using an antibody that binds to a causative molecule, or that the growth of cancer cells can be stopped by suppressing excess expression of a certain kinase receptor on cancer cells, has led to the development of "mab" and "nib" agents.

The new drugs featured in this issue all include "mab" in their generic names, namely nivolumab, bevacizumab, and ranibizumab. "Mab" is an abbreviation of monoclonal antibody, and indicates that the drugs whose generic names end with it are monoclonal antibodies. The prefix "Mono" means one, and "clonal" is an adjective form of clone, which is a cell or organism that is genetically identical to the unit or individual from which it was derived. A monoclonal antibody is an antibody made by proliferated B lymphocytes with a single gene that produces a particular antibody.

There are also many drugs that have "nib", especially "tinib", at the end of their generic names. This signifies that the drugs inhibit kinase enzymes, which activate protein in the body. "Tinib" indicates that the drugs are tyrosine kinase inhibitors. The first "nib" drug in Japan was gefetinib (brand name: Iressa), an inhibitor of the epithelial growth factor receptor (EGFR) tyrosine kinase and anti-lung cancer agent approved in 2002.

As of June, 2016, 35 "mab" and 28 "nib" drugs (total 63) were on the market in Japan. Among these, 16 "mab" and 16 "nib" drugs (total 32) were first marketed in 2013 or later, showing a recent rapid increase in the number of these drugs.

In Japan, since rituximab was launched in 2001, many "mab" drugs have been approved as anticancer and antirheumatic agents. In cases of severe rheumatoid arthritis, monoclonal antibodies may mitigate inflammation caused by excessive cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6. However, they also weaken the function of cytokines to eliminate foreign substances from both outside and inside the body, leading to aggravation of infections such as tuberculosis and sepsis, as well as proliferation of cancer cells.

Nivolumab was approved in Japan for treatment of non-small-cell lung cancer in 2015. It is a monoclonal antibody that works on PD-1, an important protein on cytotoxic T lymphocytes (killer T cells), which attack cancer cells. By binding to PD-1 on killer T cells, nivolumab protects the function of PD-1 and restores the lost cancer-fighting power of killer T cells suppressed by cancer cells with PD-L1. When one considers only this action, nivolumab indeed seems to be a dream-like new drug.

Videos posted by the manufacturer of drugs explain the drugs' mechanisms from start to finish. Misleading and deceptive wording such as "the world's first new immunotherapy", "a long-awaited new drug that will save lives", and "a new drug that prolongs lives of patients", are often found on the internet or in other media. Medical professionals also explain drugs to their patients using such phrases.

However PD-L1, which binds to PD-1 and suppresses the action of killer T cells, is also expressed on other immune cells, such as antigen-presenting cells (APCs) and regulatory T cells. Toxicity and clinical studies, as well as post-marketing spontaneous reports, have shown that nivolumab may suppress the functions of these normal immune cells, and thereby promote cancer or cause aggravation of infection and development of autoimmune diseases.

Neither "mab" nor "nib" drugs are dream-like new drugs. Their risk factors for shortening life have already been identified. The harm-benefit balance of these drugs should be accurately reassessed.

New anticancer drug Nivolumab (brand name: Opdivo)

Benefit and harm on survival offset each other: strict restriction on use is needed

Translated from Med Check-TIP (in Japanese) Mar. 2016 ; 16 (66):79-82

Abstract

● Nivolumab (brand name: Opdivo) is a monoclonal antibody (Note 1) against Programmed cell Death-1 (PD-1), approved for treatment of non-small-cell lung cancer.

● Receptor protein PD-1 which is expressed on cytotoxic T cells (killer T cells or killer cells) to promote apoptosis of foreign cells. They eliminate cancer cells and viral-infected cells. However, cancer cells on which one of the ligand proteins (PD-L1) that binds to PD-1 is expressed can escape attack by cytotoxic T cells and proliferate.

● It is believed that when nivolumab binds to PD-1 receptors, it prevents PD-L1 on cancer cells from binding to PD-1, restoring the ability of cytotoxic T cells. Cytotoxic T cells promote apoptosis of cancer cells, thus shrink cancer.

● However, PD-L1 is expressed not only on cancer cells, but also on normal immune cells such as antigen-presenting cells (APCs), monocyte-macrophages, vascular endothelial cells, and regulatory T cells. Nivolumab may disrupt the functions of these normal immune cells and suppress immunity, causing serious harms such as aggravation of infection, and development of autoimmune diseases and worsening of cancer .

● Among cases with squamous cell non-small-cell lung cancer and those with nonsquamous-cell non-small-cell lung cancer, only those with a high PD-L1 expression level (Note 2) showed significantly higher response rate to nivolumab and improved overall survival. Among nonsquamous-cell lung cancer patients with a low PD-L1 expression level, nivolumab was associated with higher mortality rate at the initial stage of the trial. Patients with a high PD-L1 expression level represent only approximately 35% of non-small-cell lung cancer patients.

● In non-small-cell lung cancer (especially nonsquamous-cell lung cancer) patients with a low PD-L1 expression level, nivolumab is not only ineffective, but also harmful as it increases death at the initial phase. Moreover, nivolumab might be ineffective or harmful in patients aged 75 years or older and those who have previously received two or more anticancer drugs.

●The use of nivolumab should be restricted to patients with cancer of a high proportion of PD-L1 expression determined by the PD-L1 expression level testing. After considering age and other factors, it should not be used to patients in whom favorable effect is not expected.

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Note 1 (monoclonal antibody):*The prefix "Mono" means one, and "clonal" is an adjective form of clone, which is a cell or organism that is genetically identical to the unit or individual from which it was derived. A monoclonal antibody is an antibody made by proliferated B lymphocytes with a single gene that produces a particular antibody. Names of monoclonal antibody drugs end with "mab", an abbreviation of monoclonal antibody. For instance, rituximab and ranibizumab are also monoclonal antibodies.*

Note 2: *"Patients with a high PD-L1 expression level" were defined as those whose proportion (%) of cells with PD-L1 among cancer cells is high. The cut-off value (%) which is used to determine whether a patient has a "high expression level" or "low expression level" were 1%, 5% and 10%. Among thsese, 10% or higher may be appropriate for "high expression level (positive)".*

Introduction:

Nivolumab (brand name: Opdivo) is believed to boost the immune system. As such an effect has been highlighted, a high drug price was set, and 30-40 million yen is required for annual drug cost per patient. In September, 2014, the drug was indicated for malignant melanoma in which radical excision was impossible. In December, 2015, it was indicated for non-small-cell lung cancer. Based on the estimation by the National Cancer Center Japan **[1]**, the number of lung cancer patients is increasing and was reported to reach 130,000 in 2015. Among them, approximately 80% is non-small-cell lung cancer patients. Suppose that Opdivo is used for approximately 50,000 patients at the least, estimated 1.75 trillion yen is needed annually just for the medication **[2]**.

One reason why such a high price was set for Opdivo is that in the previous indication, malignant melanoma, the number of targeted patients was only less than 1,000 **[2]**. Another reason is that a new mechanism of its action, immune checkpoint inhibition, was recognized. This means that the drug inhibits immune checkpoint, boosts immunity, and attacks cancer cells, producing safe and effective anti-cancer effect.

This article reviews scientific evidence to examine its safety, especially, whether the drug also attacks normal cells or not. It also discusses whether its benefit-harm balance meets the high drug price. The first indication, malignant melanoma, will be discussed in the next issue.

Interaction between PD-1 and PD-L1 is essential for normal immune reaction:

Programmed cell Death-1 (PD-1) is a receptor protein that is expressed on activated lymphocytes such as T cells and B cells **[3-5]**. PD-L1 is a substance that binds specifically to PD-1 receptor, and is called a ligand. When PD-L1 binds to PD-1 receptor, cells on which PD-1 is expressed is inactivated **[3-5]**.

PD-L1 plays a key role in the normal immune function that eliminates foreign objects **[6]**. For instance, PD-L1 is expressed on dendritic cells **[3-6]**, which functions as antigen presenting cells (APCs), monocyte-macrophages, vascular endothelial cells, and regulatory T cells **[6] (Table 1)**. While these immune cells are involved in treating and eliminating foreign substances (thus, they include foreign substances in them and they themselves become like foreign substances), they express PD-L1 to escape attack by cytotoxic T cells (killer T cells) to maintain their normal functions **(Figure 1, A)**. Regulatory T cells plays an essential role in terminating inflammatory reaction at the final stage of tissue repair **[6]**.

Cancer cells without PD-L1 are attacked by killer T cells and disappear through apoptosis **(Figure 1, B)**. There are several mechanisms with which cancer cells escape the attack by immune system in order to proliferate. Expression of PD-L1 on cancer cells is one of them **[3-5]**.

The reaction pathway through which PD-L1 binds to PD-1 (PD-1/PD-L1 pathway) is believed to be an immune checkpoint. It is essential when cancer cells escape attack by immune cells and proliferate. Drugs that inhibits the binding is believed to be useful for treating cancer as immune checkpoint inhibitors **[7, 8]**.

Nivolumab is a human monoclonal antibody against human PD-1. It prevents PD-L1 from binding to PD-1 by binding to extracellular domain of PD-1 (ligand binding domain), activates killer T cells and enhances their cytotoxic activity, regulating the proliferation of tumors **[3-5]**.

At the same time, normal immune cells expressed with PD-L1, which is essential for normal immune reaction may be exposed to attack by killer (cytotoxic) T lymphocytes because PD-L1 on the normal immune cell cannot bind to PD-1 on the killer T cells and cannot escape the attack of killer T cells. For example, PD-L1 is expressed on antigen-presenting cells (APCs), which recognize foreign substances and play an important role at the initial stage of immune reaction, as well as monocyte-macrophages, vascular endothelial cells, and regulatory T cells. Therefore, a monoclonal antibody against PD-1 might inhibit such normal immune functions and downregulate immunity, reducing the function that recognizes cancer cells as foreign substances. As a result, this might aggravate infection and/or facilitate growth of cancers.

Moreover, if regulatory T cells, key players in terminating inflammatory reaction at the final stage of tissue repair, are attacked by killer T cells, immune/inflammatory response would not end, and inflammation might become chronic, leading to serious adverse reactions such as autoimmune diseases including thyroid diseases **[6]**.

Toxicity test showed hypothyroidism:

Cynomolgus monkeys (6 males and 6 females per dose group) were treated with saline control, nivolumab 10 mg/kg, or 50 mg/kg. Lowered thyroid hormone T3 was observed with nivolumab 50 mg/kg. However, it was not interpreted as a sign of toxicity and no-observed-effect-level (NOEL) was set at 50 mg/kg, because it was claimed that no abnormality was found in other indicators by the pharmaceutical company. Based on the ratio of AUC for 50 mg/kg in monkeys and 3 mg/kg in human, the safety factor was set at 105 fold **[9]**. However, considering the mechanism of action of nivolumab, lowered thyroid hormone T3 is a sign of toxicity, NOEL should be estimated to be 10 mg/kg, and the safety factor would be only 20 fold.

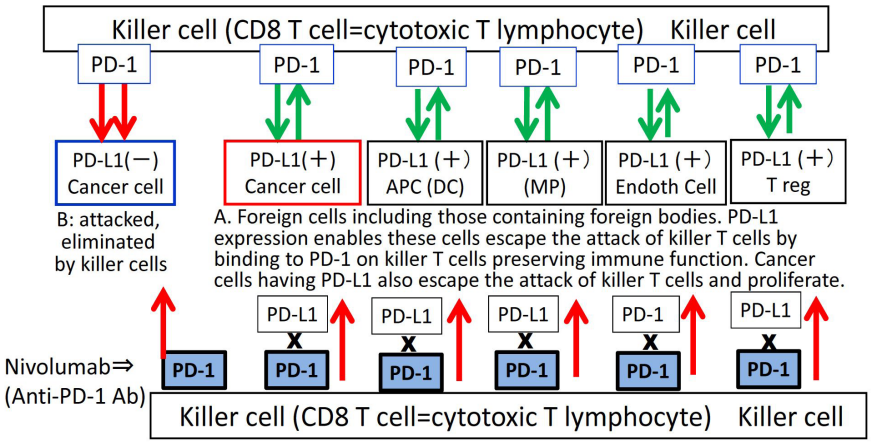
Homology of human PD-1 to cynomolgus monkey PD-1 is not mentioned. Even if they are 100% homologous at

Table 1 :
Cells expressing PD-1, PD-L1, and PD-L2 and the expression degree

immune cells	PD-1	PD-L1	PD-L2
CD4 T cells	+++	+++	—
CD8 T cells	+++	+++	—
CD4 T reg	+++	+++	—
B cells	++	+	++
APC (DCs)	+-	+++	++
Monocytes/macrophages	+-	+++	++
Mast cells *a	?	+++	++
Vascular endotheliuml	—	+++	—

PD-1: Programmed cell Death-1
PD-L1, PD-L2: There are 2 types of ligand that bind to PD-1. PD-L1 is the main ligand.
CD4 T cells: so-called "helper T cells"
CD8 T cells: cytotoxic T cells, so-called "killer T cells" or "killer cells"
CD4 T reg: regulatory T cells
APC (DCs): antigen-presenting cells (dendritic cells)
The table is an extract of Fig.1 in Francisco et al. [6].
a*: extracted from the text in ref [6]..

Figure 1: PD-L1 plays essential role for normal immune function



PD-1: Programmed cell Death-1, **PD-L1**: main ligand of PD-1. **APC (DCs)**: antigen-presenting cells (dendritic cells), **MP:** macrophage, **Endoth cell:** endothelial cells, **T reg**: regulatory T cells,
Nivolumab, an anti-PD-1 antibody protects PD-1 on killer T cells and escaps PD-L1 on various cells to bind to PD-1 to inactivate killer cells. This causes killer cells to attack not only cancer cells, but also immune cells expressing PD-L1 for maintaining normal immune function and causes reduced immunity. As a result, cancer might progress and infection might aggravate. Reduced function of regulatory T cells (T reg) interrupts termination of inflammation, leading to induction of autoimmune diseases.

extracellular domain, it does not mean that they totally match **[10]**. Therefore, even a slight sign should not be missed. In fact, many cases of hypothyroidism have been reported in human.

Similar to nivolumab, anti-LAG-3 antibody activates killer T cells, inactivates regulatory T cells, and induces autoimmune diseases **[11]**. In a toxicity study with monkeys, anti-LAG-3 antibody and nivolumab were administered concurrently. In this study, one of the 3 animals exhibited systemic symptoms and was sacrificed in extremis (classified as dead). Pathologically, vasculitis in the brain and the spinal cord, and inflammation in the testicle and the epididymis were found [9]. Although the details are unknown, it is highly possible that autoimmune inflammatory diseases were induced in the brain and the testicle.

Clinical studies on non-small-cell lung cancer:

Phase I to III clinical studies on non-small-cell lung cancer were conducted abroad, involving patients in which platinum-based chemotherapy had been ineffective **[4, 12]**. In the phase I, three trials were conducted with five dose levels on malignant melanoma, non-small-cell lung cancer, and renal cancer. In the phase II, one trial was conducted only on squamous-cell non-small-cell lung cancer (SQ-NSCLC). In the phase II and III, all the patients in nivolumab groups received 3 mg/kg every two weeks. In the phase III, non-blind controlled studies were conducted on nonsquamous non-small-cell lung cancer (NSQ-NSCLC) **[7, 12]** and squamous-cell non-small-cell lung cancer **[8, 12]** separately.

In the phase III trial on NSQ-NSCLC **[7, 12]**, the median overall survival (OS) (95% CI) was 12.2 months (9.7-15.0) with nivolumab and 9.4 months (8.1-10.7) with docetaxel. Hazard ratio (HR) (95%CI) was 0.73 (0.59-0.89, p=0.002), and OS was significantly longer with nivolumab (median, 2.8 months longer).

In the phase III trial on squamous-cell lung cancer **[8, 12]**, median OS (95% CI) was 9.2 months (7.3-13.3) with nivolumab and 6.0 months (5.1-7.3) in docetaxel group (3.2 months longer). HR (95% CI) was 0.59 (0.44-0.79, p<0.001), and OS was significantly longer in the nivolumab group.

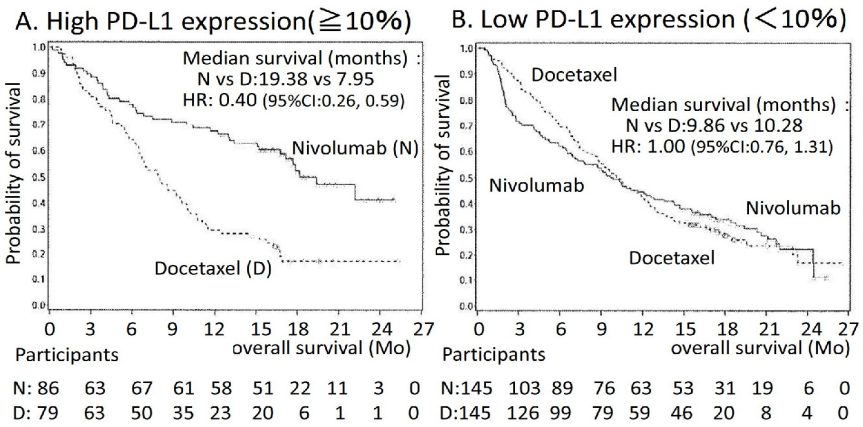
However, it should be noted that in best response, there were more cases of progressive disease (PD) in the nivolumab group. In squamous-cell lung cancer, the odds ratio for PD was 1.3 (p=0.275). Furthermore, in nonsquamous lung cancer, cases of PD represented 44% of the nivolumab group as compared with 29 % in the docetaxel group. Odds ratio was 1.91 (95% CI 1.36-2.69, p=0.0002). Tumor progression was observed almost twice more frequently with nivolumab, and it was significant **(Table 2).** The significant increase of tumor progression should be considered as an adverse reaction of nivolumab.

Table 2: Response rate and progression rate

	Nivolumab		Docetaxel		OR(95%CI)	p value
Non Squamous, Non Small Cell Lung Cancer (NSQ-NSCLC)	N=292		N=290			
	人	%	人	%		
CR+PR	56	19.2	36	12.4	1,67(1.06-2.64)	0.0254
PD (progressive diseases)	129	44.2	85	29.3	1.91(1.36-2.69)	0.0002
Squamous, Non Small Cell Lung Cancer (SQ-NSCLC)	N=135		N=137		OR(95%CI)	p value
	人	%	人	%		
CR+PR	27	20.0	12.0	8.8	2.60(1.26-5.39)	0.0083
PD (progressive diseases)	56	41.5	48	35.0	1.31(0.80-2.15)	0.275

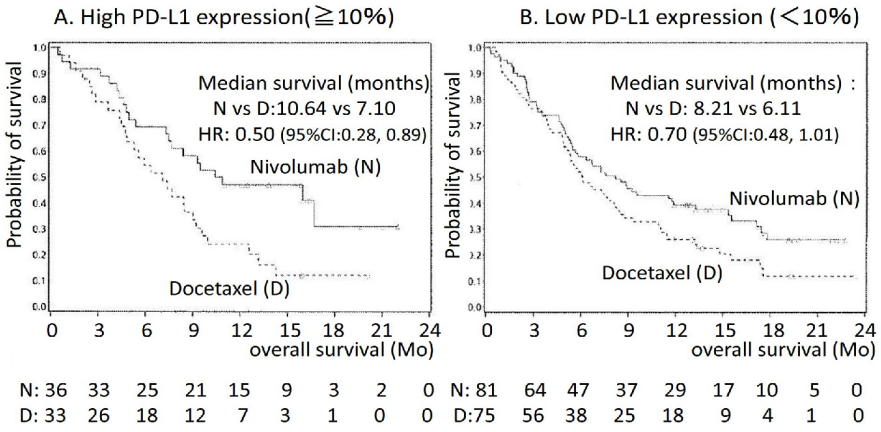
The response rates (CR+PR) are significantly higher in the nivolumab group than docetaxel group. However the progression rates are also higher in the nivolumab group. Especially in the NSQ-NSCLC, the progression rate is significantly higher in the nivolumab group than in the docetaxel group and even higher than the response rate.

Figure 2 Overall survival (OS) of nonsquamous non-small-cell lung cancer: comparison of nivolumab and docetaxel



Overall survival (OS) of cancer with high PD-L1 expression (≧10%) was significantly higher in nivolumab group than control, but no difference was found in patients with low PD-L1 expression (＜10 %). Note higher mortality in Nivolumab group during very early phase of the trial indicating essential role of testing for PD-L1 expression level before Nivolumab use to NSCLC.

Figure 3 Overall survival (OS) of squamous cell lung cancer by the level of PD-L1 expression level



Overall survival (OS) of cancer with high PD-L1 expression (≧10%) was significantly higher in nivolumab group than control, but no significant difference was found in patients with low PD-L1 expression (＜10%). As one of the reasons why OS showed tendency of improved survival, PD-L2 on the cancer cells as one of the other ligands that bind to PD-1 on the killer cells.

In Japan, 2 uncontrolled phase 2 trials were conducted, involving 76 nonsquamous lung cancer patients and 35 squamous lung cancer patients **[5, 12]**.

Survival benefit is expected only when various conditions are met:

If we can identify for what kind of patients a drug is effective, ineffective or harmful, we can efficiently utilize the drug. In published papers **[7, 8]**, no information was included to analyze such conditions. However, thorough analysis is given in the summary basis of approval (SBA).

Ineffective in patients with a low PD-L1 expression level, especially with nonsquamous lung cancer:

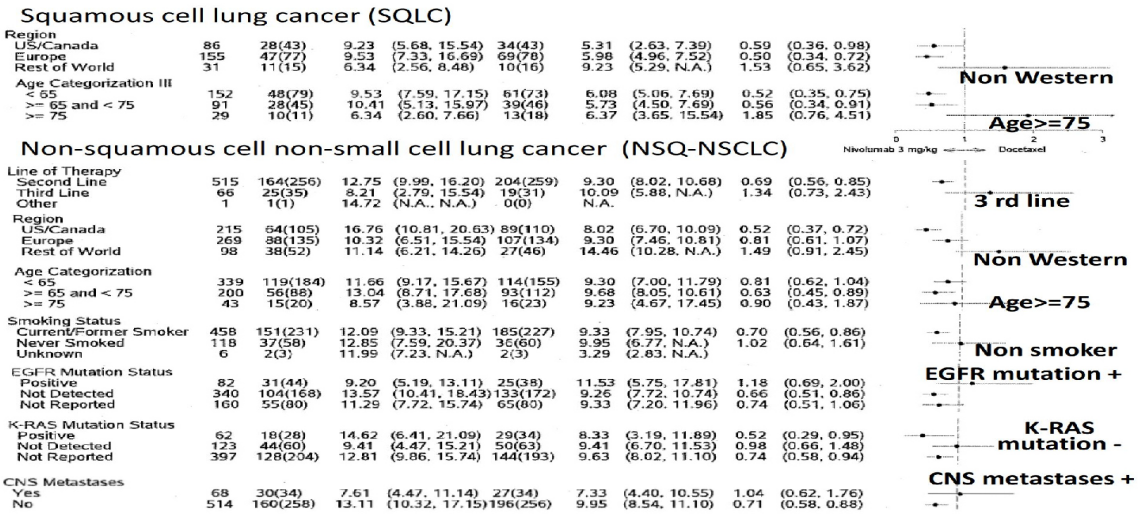
Nivolumab specifically inhibits binding of PD-L1 to PD-1. It is logical and easily presumed that if a ligand that binds to PD-1, particularly PD-L1, is not expressed at a high level, the drug is likely to be ineffective.

In fact, in nonsquamous lung cancer, in which PD-L1 is expressed at a high level (10% or higher) on cancer cells, nivolumab significantly improved OS, and survival benefit was confirmed **(Fig. 2, A)**. However, in patients with a low PD-L1 expression level (lower than 10%), no survival benefit was observed at all **(Fig.2, B)**. The drug rather increased the initial mortality.

Likewise, in squamous lung cancer patients with a high PD-L1 expression level, survival benefit was clearly observed **(Fig. 3, A)** while in those with a low PD-L1 expression level, survival benefit was not significant **(Fig. 3, B)**. In squamous lung cancer, even in the cases with a low PD-L1 expression level, OS improved more than in nonsquamous lung cancer. The possible association between this tendency and PD-L2, another ligand that binds to PD-1, needs to be examined.

Because PD-L1 antibody has already been marketed **[13]**, PD-L1 expression level testing should be conducted as one of the preconditions for using nivolumab.

Figure 4 : Factors related with no survival benefit or risk of mortality



Ineffective or harmful in patients aged 75 years or older:

In addition to presence or absence of a high PD-L1 expression level, HRs and 95% CIs of OS are described by various characteristics of the participants in details in the SBA for clinical trials [12]. Among them, factors with which the drug might be ineffective on survival benefit or adversely shorten life are extracted and shown in **Figure 4.** The factors with which the drug might not prolong progression free survival (PFS) or adversely shorten it are extracted and shown in **Figure 5.**

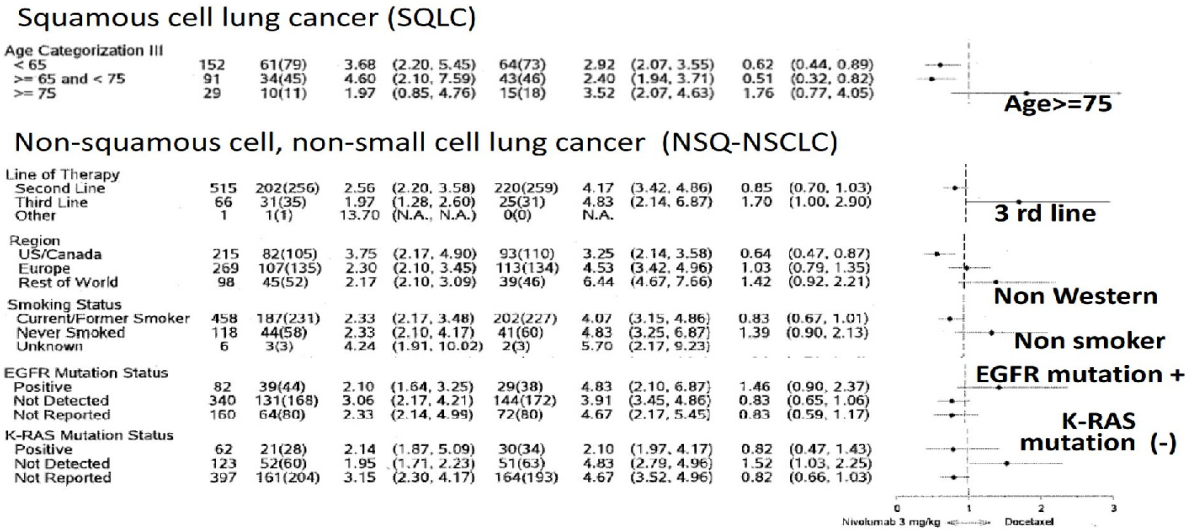
In squamous-cell lung cancer, in "rest of the world (regions other than Europe and North America) (HR=1.53)" and "patients aged 75 years or older (HR=1.85)", nivolumab is possibly ineffective or more harmful.

In nonsquamous lung cancer, in "patients with prior treatment with 2 or more drugs (HR=1.34)" and "rest of the world (HR=1.49)", harm might outweigh with nivolumab. In "patients aged 75 years or older (HR=0.90)", "non-smoking (HR=1.02)", "patients with EGFR mutations (HR=1.18)", "patients without K-RAS mutations (HR=0.98)" and "patients with metastases to central nervous system (CNS) (HR=1.04)", the drug was found to be ineffective.

PFS (**Fig.5**) was significantly shortened in nonsquamous lung cancer in "patients with prior treatment with more than one drug (HR=1.70, 95%CI: 1.00-2.90)" and "patients without K-RAS mutations (HR=1.52: 1.03-2.25)". In patients in which K-RAS mutation was undetected, in particular, PFS was 1.95 months versus 4.83 months, and was more than twice shorter. The data also showed that the drug might shorten PFS in "patients aged 75 years or older" with squamous lung cancer (HR=1.76), and "rest of the world (HR=1.42)", "non-smoking (HR=1.39)" and "patients with EGFR mutation-positive (HR=1.46)" with nonsquamous lung cancer.

EGFR mutation and K-RAS mutation are mechanisms for escaping immune surveillance. In many patients with EGFR mutation-positive, PD-L1 is not expressed while K-RAS mutation is associated with expression of PD-L1. Further analysis is needed to determine the factors with which the drug is expected to be more effective, ineffective or harmful.

Figure 5 : Factors related with no benefit or risk of PFS



Limited financial resource must be efficiently utilized.

On adverse reactions:

In the phase 3 trials, serious adverse events occurred less frequently with nivolumab than with docetaxel in squamous-cell lung cancer. Contrarily, it occurred more frequently with nivolumab in nonsquamous lung cancer. In general, diarrhea, alopecia and hematologic disorders caused by the cytotoxic effect were observed frequently with docetaxel. Cancer progression and resulting hypercalcemia (7.7% versus 0% in squamous lung cancer), and hypothyroidism (5.3% versus 0% in squamous lung cancer, 6.6% versus 0% in nonsquamous lung cancer) were more marked with novolumab. These are considered to be adverse reactions caused by the mechanism of action of the drug **[12]**).

Cancer progression with respect to the best response was observed almost twice more frequently with nivolumab, particularly in nonsquamous lung cancer, and it was significant. As the drug inhibits PD-1 on antigen-presenting cells (APCs), it might reduce the function that recognizes cancer cells as foreign bodies, promoting the proliferation of the cancer cells. Furthermore, considering that hypothyroidism occurred significantly more frequently with nivolumab in both trials on squamous lung cancer and nonsquamous lung cancer, and that thyroid hormone T3 was reduced in animal toxicity studies, the drug certainly increases autoimmune diseases. In fact, deaths were reported and warnings for autoimmune diseases have been issued **[14, 15]**.

Therefore, based on the mechanism of action of nivolumab, cancer progression and increased autoimmune diseases are adverse reactions to the drug.

In practice:

When nivolumab is used for treating non-small-cell lung cancer with a high PD-L1 expression level, it prolongs median survival for approximately 3 months.

However, when a PD-L1 expression level is low, nivolumab might shorten life under some conditions. The drug is worthless as it possibly shortens life while the annual drug cost amounts to as high as 35 million yen. Conditions in which the drug is ineffective or harm outweighs, such as “aged 75 or older”, “EGFR mutation”, “K-RAS mutation”, “non-smoking” and “types of prior medications”, should be determined. Under such conditions, the drug should not be used.

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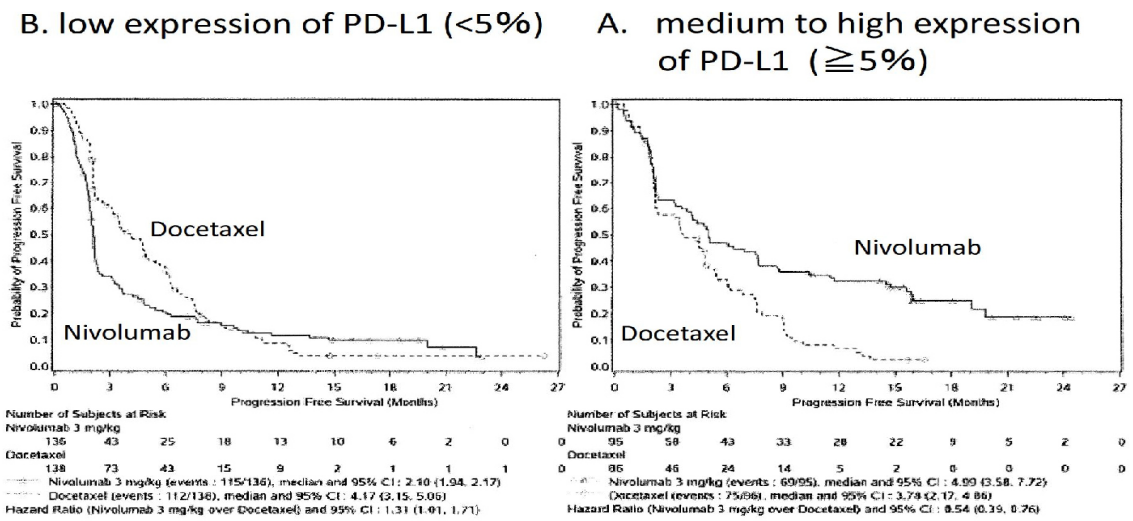
Appendix

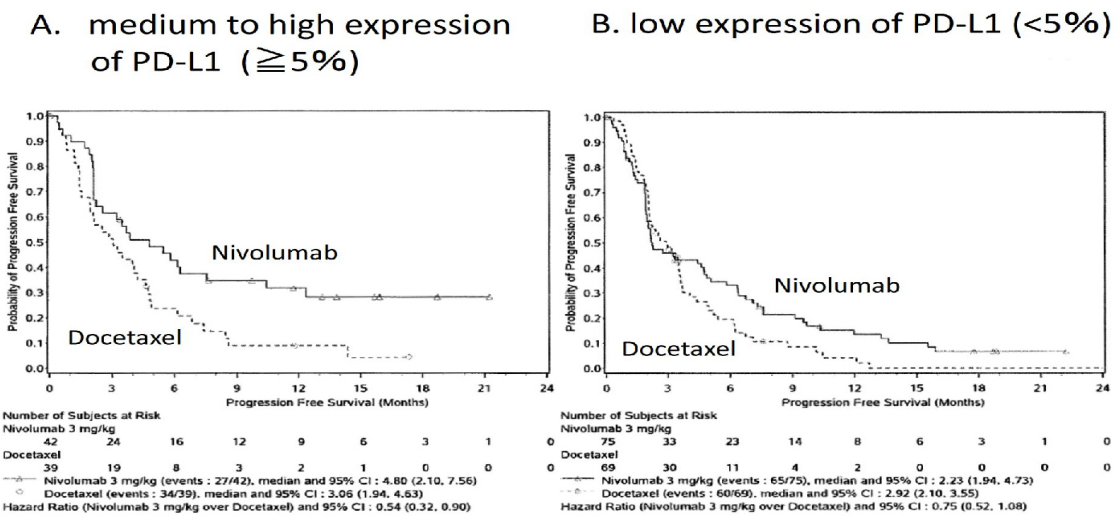
Figure 6： PFS of NSQ-NSCLC by expression level of PD-L1



Note that the cut off level of PD-L1 expression is 5 %. Kaplan-Meier curves using 10% for cut off level were not provided by the SBA. If provided, the difference might be more distinct.

Appendix

Figure 7： PFS of SQLC by expression level of PD-L1



Note that the cut off level of PD-L1 expression is 5 %. Kaplan-Meier curves using 10% for cut off level were not provided by the SBA. If provided, the difference might be more distinct.

GLP-1 Agonists (liraglutide etc.)

No evidence of improving prognosis in patients with diabetes
Not recommended

Translated from Med Check-TIP (in Japanese) Mar. 2016 ; 16 (67):108-112

Abstract

A anti-diabetic medicine is valuable only if it can prolong life or at least it tends to prolong life and significantly reduce serious complications such as retinopathy, renal failure, cardiovascular disease and cancers. Incretin related drugs (DPP-4 inhibitors and GLP-1 agonists) were introduced from 2009 onwards in Japan. Just like other agents for diabetes, they were approved only because they lowered HbA1c levels, which is merely a surrogate endpoint, without proof of survival prolongation.

In June 2016, a randomized controlled trial (RCT) comparing placebo reported for the first time that liraglutide, a GLP-1 agonist, had improved cardiovascular events. However, as a result of close examination, we conclude that this claim is not reliable because of the highly probable blinding failure presumed from various contradicting data in the trial. Moreover, increased pancreatic cancer, combined with results of animal tests and other clinical and epidemiological findings, suggests that the agent has carcinogenicity. Therefore, Med Check-TIP recommends not to use these agent.

Introduction

For the treatment of a diseases with certain mortality, the strongest and unbiased endpoint is whether the treatment can improve survival or not **[1]**. The purpose of a diabetic medicine is to prevent complications (retinopathy, nephropathy, neuropathy, cardiovascular events, and malignant tumor) by improving systemic metabolism, and prolong life (decrease total mortality).

DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1 agonists) are incretin related medicines, which have been in clinical use since 2009. Their unique feature is claimed that they do not usually cause hypoglycemia **[2, 3]**. They are widely used as they are expected to be new dream-like medicines **[2]**. Six DPP-4 inhibitors (5 ingredients) were ranked among 100 top-selling medicines in fiscal year 2015. In particular, the total sales of two products of sitagliptin amounted to over 100 billion yen **[4]**.

However, just like other hypoglycemic agents, they were approved as "new products" only for their lowering effect on glycohemoglobin (HbA1c), a surrogate endpoint. Later on, because of the reasons described in the **column** (P.38)of this issue, placebo controlled non-inferiority trials (***Note 1***) for these drugs were conducted.

Among incretin related drugs, none of the DPP-4 inhibitors (saxagliptin **[5]**, alogliptin **[6]**, sitagliptin **[7]**) nor a GLP-1 agonist (lixisenatide) improved prognosis of patients with diabetes. Among these trials, one trial **[5]** aimed at proving

Note 1: *Non-inferiority and superiority trials*

Superiority trial: a trial to show the superiority of an intervention by showing the risk reduction of the primary outcome expressed by the hazard ratio, odds ratio or risk ratio and their upper limit of the 95% confidence interval (95%CI) less than 1.0.

Non-inferiority trial: *a trial to show the non-inferiority of an intervention comparing the control group by showing the hazard ratio, odds ratio or risk ratio and their upper limit of the 95% confidence interval (95%CI) less than a certain level for instance 1.3. The risk may be considered to be within a permissible level compared with control.*

On the protocol, the LEADER trial was designed as a non-inferiority trial, whose upper limit of 95% CI for hazard ratios (HR) was set at 1.3. Superiority analysis was not included even as a secondary analysis in the protocol [9, 10].

Table 1 : Fundamental design and the results of pivotal RCTs of incretin related agents

group	generic name	Trial name	Publication	fundamental design and the results *a	
				Primary	Secondary
DPP-4 inhibitors	saxsgliptin	SAVOR-TIMI53	Oct. 2013	superiority: No	non-inferiority: yes
	alogliptin	EXAMINE	Oct 2013	non-inferiority: yes	
	sitagliptin	TECOS	July 2015	non-inferiority: yes	superiority: No
GLP-1 agonists	lixisenatide	ELIXA	Oct 2015	non-inferiority: yes	superiority: No
	liraglutide	LEADER	June 2016	non-inferiority: yes	*b

*a : No : hypothesis was not proven Yes : hopothesis was proved

*b : Protocol of the LEADER did not state that it is conducted as a superiority study at all.

superiority (***Note 1***). All the other trials were designed to prove non-inferiority against a placebo. Although the goal was achieved, superiority was not proven (**Table1**).

In 2012, the Med Check stated that these incretin related drugs should not be used because non-clinical and clinical trials had shown their carcinogenicity and they were unlikely to bring benefit, including benefit on survival, even after long-term human use **[9]**. In June 2016, a clinical trial for liraglutide (LEADER study) reported for the first time that the drug reduced more cardiovascular events as compared with a placebo **[10,11]**. This paper verifies it.

Incretin related drugs

Food intake stimulates the cells of small-intestine to secrete hormones (intestinal hormones) which stimulate β cells in the pancreas, inducing secretion of insulin, while suppressing action of glucagon. The intestinal hormone is generally termed as an incretin. The major intestinal hormone is GLP-1 (glucagon-like peptide-1) **[12]**.

GLP-1 receptors, on which GLP-1 acts, exist on pancreatic β cells, and cells on the peripheral and central nervous systems, cardiovascular system, heart, kidneys, lungs and gastrointestinal mucosa. When GLP-1 binds to a GLP-1 receptor, it increases intracellular cAMP and alters activity of ion channels. In pancreatic β cells, insulin synthesis is enhanced, and insulin is secreted by the cells **[12]**.

Endogenous GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) with a plasma half-life of 1 to 2 minutes. DPP-4 inhibitors were developed to prolong the activity of endogenous GLP-1. Contrarily, GLP-1 agonists act like GLP-1 which is not easily inactivated by DPP-4 and has very long half-life. Incretin related drugs include both DPP-4 inhibitors and GLP-1 agonists (**Table 2:** approved/marketed drugs as of August, 2016 in Japan).

It should be examined whether these agents activating short-acting biological substances for 24 hours, 365 days are beneficial or not for humans.

The LEADER trial: design, methods and baseline characteristics

The LEADER trial **[9, 10]** is a non-inferiority RCT (***Note 1***), involving 9340 patients with cardiovascular risk, who were on treatment for type 2 diabetes and had HbA1c level of 7.0% or higher (average 8.7%). In addition to the standard treatment they were assigned, in a 1:1 ratio, to receive either 1.8 mg of liraglutide (Group L: 4668 patients) or placebo (saline) (Group P: 4672 patients) subcutaneously per day. The primary outcome was the occurrence of composite cardiovascular events. The median follow-up was 3.8 years.

No marked difference was found in the baseline characteristics between the 2 groups. The average BMI was 32.5 and average body weight was 91.7 kg. 10% of the patients were from Asia (China, South Korea, Taiwan), but none was from Japan. It is also noteworthy that 1.8 mg/day of liraglutide (the approved dose in the West) is twice as high as the usual dose (0.9 mg/day) in Japan.

Table 2: List of incretin related drugs (as of August, 2016)

Class	Generic name (Brand name)	Tmax (h)/ t1/2 (h)	Dosage and administration: summary of labeling	Notes: renal excretion, contraindications and other relevant notes
GLP-1 agonists (injection)				
Short-acting	Exenatide (Byetta)	1.3-1.5h/ 1.27-1.35h	Twice daily before meals sc, start at 5μg/dose, can be increased up to 10μg/dose	Inactivated after glomerular filtration, contraindicated in patients with severe renal impairment
	Lixisenatide (Lyxumia)	1.5-1.75h/ 2.01-2.45h	Once daily before breakfast sc, start at 10 μg/dose, can be increased up to 20μg/dose	
Long-acting	Liraglutide(Victoza)	7.5-12h/ 10-15h	Once daily sc, start at 0.3mg/dose, can be increased up to 0.9mg/dose	
Prolonged-acting	Exenatide extended-release (Bydureon)	2h/不明	2 mg sc once every seven days (weekly)	Inactivated after glomerular filtration, contraindicated in patients with severe renal impairment
	Dulaglutide(Trulicity, Ateos)	48-50.33h/ 108h	0.75mg/dose sc once weekly	
DPP-4 inhibitors (oral tablets)				
Short-acting	Sitagliptin(Januvia, Glactiv)	2-5h/ 9.6-12.3h	50mg/dose, once daily, can be increased up to 100mg/dose	Renal excretion, decrease the dose in patients with renal impairment
	Vildagliptin(Equa)	1-1.5h 1.77-2.41h	50mg/dose, twice daily	Renal excretion (partial), decrease the dose in patients with renal impairment, contraindicated in patients with severe hepatic impairment
	Alogliptin(Nesina)	1.1h/17.1h	25mg/dose, once daily	Renal excretion, decrease the dose in patients with renal impairment
	Linagliptin(Trajenta)	6h/105h	5mg/dose, once daily	
	Teneligliptin(Tenelia)	1-1.8h/ 20.8-30.2h	20mg/dose, once daily, can be increased up to 40mg/dose	
	Anagliptin(Suiny)	0.92-1.8h/ 1.87-21.9h	100mg/dose, twice daily, can be increased up to 200mg/dose	Renal excretion (partial), decrease the dose in patients with renal impairment
	Saxagliptin(Onglyza)	0.8-1.5h/ 6.5-8.6h	5mg/dose, once daily	Renal excretion (partial), decrease the dose in patients with renal impairment
Prolonged-acting	Trelagliptin(Zafatek)	1.3-1.5h/ 17.6-18.5h	100mg/dose, once weekly	Renal excretion, decrease the dose in patients with renal impairment, contraindicated in patients with severe renal impairment that receive dialysis
	Omarigliptin(Marizev)	0.5-1.5h 38.9-82.5h	25mg/dose, once weekly	Renal excretion, decrease the dose in patients with renal impairment

Tmax (h): time to maximum plasma concentration. t1/2 (h): elimination half life, sc: subcutaneous injection

《column》

Why methods assessing anti-diabetic agents favor industry?

Translated from the editorial in the No67 issue of Med Check TIP (in Japanese) 2016

Since 2000, 55 products that contain 26 ingredients and belong to 4 classes of anti-diabetic agents have been approved. They include insulin analogues, GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors. The last three, which have completely new mechanisms of action, were first marketed internationally in 2005, followed by launching in Japan in 2009.

Drugs for the treatment of diseases that might be fatal are valuable if they prolong life. Even if they don't, they should at least show tendency to prolong life and significantly reduces serious complications of the disease, or relieve pains or serious discomforts. Serious complications, for example, of diabetes, are retinopathy, renal failure, cardiovascular disease and cancers. In order to assess this, in a randomized controlled trial (RCT) in which participants are all given with a standard treatment and are randomly assigned to a study agent or placebo, "superiority" of the agent over placebo have to be proven.

However, the long-term post marketing studies for these agents did not aim at establishing "superiority" but only "non-inferiority", except for one trial, in their protocols. This means that new products with high price are approved for marketing "if they are not inferior to or demonstrate the similar level of benefit and harm with placebo".

FDA officially guaranteed

It is the US Food and Drug Administration (FDA) that officially endorsed such strange evaluation methods. For all anti-diabetic agents marketed before 2008 in the United States, neither survival benefit nor reduction of cardiovascular (CV) diseases has been proven. Rosiglitazone even increased cardiovascular events. In December, 2008, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) confirmed the followings.

(1) Importance of glycemic control on microvascular risk reduction is affirmed
(2) HbA1c remains primary efficacy endpoint for drug approval
(3) CV benefit is not a requirement for approval of these drugs
(Glycemic control alone will be difficult to demonstrate CV risk reduction as observed in numerous outcomes trials)

FDA consulted the Panel inquiring "It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?" The majority answered "Yes: 14/16"

Non-inferiority trials for those approved drugs were conducted successively. It has been considered that the adverse effect may be acceptable unless the upper limit of the 95% confidence interval of the risk (hazard ratio) exceeds 1.3.

Reduction of HbA1c increased mortality (ACCORD study)

In fact, in June, 2008 about a half year before the Advisory Panel decided as above, the ACCORD study was published, which showed that the mortality of the intensive therapy group was higher than that of the standard therapy group.

This clearly indicates that HbA1c never be the appropriate primary efficacy endpoint for drug approval. The Panel ignored the evidence from the ACCORD study and decided that confirming no evidence of worsening is sufficient because it may be difficult to confirm significant improvement.
FDA and the National Institute of Health (NIH) endorsed these "weak" studies by funding them. Such an incoherent technique is unacceptable.

Superiority is reported only in the fraudulent studies

Masking failures and management differences were highly suspected in the studies for liraglutide and empagliflozin. Only in these fraudulent studies, the drugs showed superiority on the CV benefit over placebo. Why should we pay more than 200 billion yen (2 billion dollars) for these agents that have only the same benefit as placebos? The clinical study reports should be disclosed and closely examined.

Endpoints and major result

The primary composite outcome in the time-to-event analysis was "the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke" The results showed that these events occurred less frequently with liraglutide (13.0%) than with placebo (14.9%) (HR=0.87, 95% CI: 0.78-0.97, p=0.01 as superiority). Based on this result, the authors claimed the superiority of liraglutide than placebo. They also argued for the superiority of the drug with regard to total mortality (this point will be discussed later).

However, although not significant, both benign and malignant tumors were observed more frequently with liraglutide (**Table 3**). Similar to cardiovascular diseases, malignant tumor heavily affects prognosis of diabetic patients, especially their survival, and is an important outcome. If malignant tumor is included in the primary composite outcome, no significant difference was found between the groups (**Table 3**).

Pancreatic cancer occurred in 5 patients in the placebo group and 13 patients in the liraglutide group (p=0.059). Although this is not significant at p less than 0.05 for the level of significance, considering the carcinogenicity of GLP-1 agonists and a possibility to miss true association (beta error: ***Note 2***), this has a biological significance. This will also be discussed later.

Note 2: *A significance level is commonly set at p=0.05. This value represents a "probability of erroneously assuming association when actually no association exist". In a statistical term, it is called "alpha error" or type 1 error. In contrast, an error "denying association when association actually exists" is called beta error or type 2 error.*

Problems in the LEADER trial

1)Change in the hypothesis

In the protocol [9, 10], the hypothesis was "non-inferiority against placebo (***Note 1***)". The prime goal was to verify this hypothesis, and proving superiority was not included in the protocol. In other words, liraglutide was expected to be no more effective than placebo.

In the analysis conducted after the trial, as the upper limit of 95% CI of HR was less than 1.0, the hypothesis was changed to claim superiority. However, this is inappropriate. Unless included in a hypothesis, it is not supposed to be claimed. Moreover, double blinding is extremely important, but in this study, it might not have been maintained, leading differences in management/care between the groups. This undermines the claim for superiority even further. This will be discussed later on.

2)Risk of blinding failure

The LEADER trial was conducted as double blinded manner. However, it was relatively easy to guess which group the patient had been assigned to if changes in glucose and HbA1c levels, and course of nausea, vomiting, anorexia, and body weight were considered.

a)Changes in HbA1c levels

The trial targeted to maintain HbA1c levels at 7.0% or below. In HbA1c levels at 3 months or later after the start of the trial, the degree of decrease was bigger with liraglutide than with placebo by 1.0%. Because change in glucose levels is faster than that in HbA1c level, it was probably easy to guess the assignment at the initial stage of the trial.

b)Significant increase in nausea and vomiting

Among all adverse events, nausea and vomiting were

Table 3: Risk of major outcomes and adverse events in the LEADER trial

	Liraglutide (N=4668)		Placebo (N=4672)		odds ratio (OR) and 95% CI *c			NNTB (- means NNTH)	P value
	n	%	n	%	OR	LL	UL		
Primary composite outcome*a	608	13.0	694	14.9	0.86	0.76	0.97	55	0.0107
Expanded composite outcome*b	948	20.3	1062	22.7	0.87	0.78	0.96	41	0.0044
Total mortality	381	8.2	447	9.6	0.84	0.73	0.97	71	0.0169
Cardiovascular death	219	4.7	278	6.0	0.78	0.65	0.93	79	0.0067
Non-cardiovascular death	162	3.5	169	3.6	0.96	0.77	1.19		0.7011
Adverse events leading to withdrawal	444	9.5	339	7.3	1.34	1.16	1.56	-44	< 0.0001
Serious	192	4.1	245	5.2	0.78	0.64	0.94	88	0.0097
Severe	164	3.5	188	4.0	0.87	0.70	1.08	196	0.1951
Non-serious	252	5.4	94	2.0	2.78	2.19	3.53	-30	<0.0001
Non-severe	280	6.0	151	3.2	1.91	1.56	2.34	-36	<0.0001
Nausea	77	1.6	18	0.4	4.34	2.59	7.26	-79	<0.0001
Vomiting	31	0.7	2	0.04	15.6	3.73	65.3	-161	<0.0001
Diarrhea	27	0.6	5	0.1	5.43	2.09	14.1	-212	<0.0001
Abdominal pain	11	0.2	3	0.1	3.68	1.02	13.2	-583	0.0323
Anorexia	11	0.2	2	0.0	5.52	1.22	24.9	-519	0.0124
Abdominal discomfort	10	0.2	0	0.0				-467	0.0015
Acute gallstone diseases	145	3.1	90	1.9	1.63	1.25	2.13	-85	0.0003
Acute cholecystitis	68	1.5	50	1.1	1.37	0.95	1.97	-259	0.0945
Choleithiasis	36	0.8	21	0.4	1.72	1.00	2.95	-311	0.0459
Other acute gallstone diseases	41	0.9	19	0.4	2.17	1.26	3.74	-212	0.0043
Acute pancreatitis	18	0.4	23	0.5	0.78	0.42	1.45		0.4355
Chronic pancreatitis	0	0.0	2	0.0	0.00				0.1575
Benign tumor	168	3.6	145	3.1	1.17	0.93	1.46		0.1835
Malignant tumor	296	6.3	279	6.0	1.07	0.90	1.26		0.4578
Tumor (benign+malignant)	464	9.9	424	9.1	1.11	0.96	1.27		0.1543
Pancreatic cancer	13	0.3	5	0.1	2.61	0.93	7.32	-583	0.0589
Primary endpoint+malignant tumor	904	19.4	973	20.8	0.91	0.83	1.01		0.0783

***a:** primary composite outcome: time to the first occurrence of any of the followings; cardiovascular death, non-fatal myocardial infarction and non-fatal stroke

***b:** expanded composite outcome: hospitalization due to coronary angioplasty, unstable angina or heart failure was added to the primary composite outcome

***c:** Hazard ratio (HR) and its 95% CI calculated by the Cox proportional hazard model were 0.87 (0.78-0.97) for the primary composite outcome, 0.88 (0.81-0.96) for the expanded composite outcome, and 0.85 (0.74-0.97) for total mortality. These values are almost consistent with the odds ratios (ORs) above and their 95% CIs calculated by univariate analysis.

observed over 4 times and 15 times more frequently with liraglutide than with placebo, respectively (both p<0.0001). Diarrhea, abdominal pain, anorexia, and abdominal discomfort were also experienced significantly more frequently with liraglutide (**Table 3**).

c)Changes in body weight

The patients in the placebo group hardly lost their body weights. The degree of body weight reduction was greater by 2.3 kg with liraglutide than with placebo.

GLP-1 agonists induce nausea and vomiting, enhance satiety, reduce hunger, and reduce body weight by delaying gastric emptying time peripherally and by the action on the central nervous system **[12-14]**. These were commonly observed in animal tests and clinical trials as the class effect of GLP-1 agonists based on some summary basis of approvals (SBAs) of GLP-1 agonists. Tolerance develops to the peripheral action such as delaying gastric emptying in a short-term, but the central action persists for a long-term [13]. It is presumed to act mainly on the arcuate nucleus in the hypothalamus [14]. In fact, the U.S. and European regulator approved a preparation of liraglutide 3.0 mg for reducing body weight in patients with obesity **[15-17]**.

Based on these, it is very likely that physicians can easily guess the assignment, and that double blinding failed at the early stage of the trial.

3)The data suggesting blinding failure

a)Discrepancy between serious and non-serious adverse event leding to withdrawal

The blinding failures seem resulted in contradicting data. The strangest point is found in discrepancy between serious and non-serious adverse events leading to withdrawal. In general, proportion of patients with serious and non-serious adverse events leading to withdrawal are linked to each other. However, in the LEADER trial, serious adverse events leading to withdrawal were observed 22% less with liraglutide (OR=0.78, p<0.0001), while the proportion of non-serious adverse events leading to withdrawal was 5.4% in liraglutide group and 2.0% in the placebo group (OR=2.78, p<0.0001). They occurred almost 3 times more frequently in patients who had received liraglutide.

The data suggest that the patients treated with the drug withdrew earlier before adverse events became serious while the patients treated with placebo continued the treatment until adverse events became serious. This suggests a gap between the 2 groups in the management of adverse events.

b)Acute gallstone diseases occurred frequently, but not pancreatitis.

In general, when acute gallstone diseases (choleithiatis, acute cholecystitis) increase, acute and chronic pancreatitis also increases because acute gallstone diseases are often accompanied by biliary obstruction. This is a common sense in medicine.

However, in the LEADER trial, while acute gallstone diseases occurred 63% more frequently with liraglutide as compared with placebo (OR=1.63, p=0.0003), both acute (0.5% versus 0.4%) and chronic (2 patients versus 0) pancreatitis occurred less frequently with the drug.

As mentioned above, many cases of mild adverse events seem to have led to early withdrawal in the liraglutide group. Considering this tendency, it is possible that cases of mild biliary abnormalities led to withdrawal in the liraglutide group while they stayed on until they become more serious in the placebo group. This is another point that suggests some gaps in the management or care between groups.

4)Inappropriate control of glucose levels in the placebo group?

Failure in blinding is also suspected because of the contradicting results in glucose levels. Usually, when a glucose level is lowered, severe hypoglycemia increases. However, the trial showed an opposite tendency. In monitoring HbA1c levels, glucose levels are maintained obviously lower with liraglutide than with placebo. In fact, it is consistently lower by approximately 1 % . At the same time, the proportion of patients who developed severe hypoglycemia was 2.4% (114 patients) with liraglutide and 3.3% (153 patients) with placebo (p=0.02).

Significantly more glucose-lowering drugs, such as insulin preparations (liraglutide group 28.6% versus placebo group 43.2%, OR=0.53, p<0.0001) and SU agents (7.6% versus 10.8%, OR=0.68, p<0.0001), were used in combination with placebo than with liraglutide. Glitazone agents (OR=0.61), metformin (OR=0.82), GLP-1 agonists (OR=0.47) (***Note 3***), α -glycosidase (OR=0.56), glynides (OR=0.61) were all used significantly more frequently (p<0.001) with placebo. ORs for SGLT-2 inhibitors and DPP-4 inhibitors were 0.76 (p=0.046) and 0.87 (p=0.23) (***Note 3***), respectively.

Although glucose levels were maintained lower (1% lower by HbA1c), severe hypoglycemia was observed less frequently in the liraglutide group. Furthermore, in the same group, there were less cases of serious adverse events that led to withdrawal, but more cases of non-serious adverse events that led to withdrawal. These strange phenomena raise a doubt about appropriateness of treatment given to the patients in the placebo group. It suggests that there were some differences in management or care between the two groups.

Note 3: *On the protocol, concomitant use of GLP-1 agonists and DPP-4 inhibitors was contraindicated.*

5)BMI and contradicting results in Asian patients

HR for the primary outcome in patients whose BMI was over 30 was 0.82 (95%CI 0.71-0.94). On the other hand, it was 0.96 (0.81-1.15) in patients whose BMI was 30 or lower, and liraglutide was ineffective in this sub-group. When analyzed by region, HR for Asia was 0.62 (0.37-1.04). This was not significant, but there was substantial reduction in point estimation (***Note 4***). Although, in Asia (China, Taiwan and South Korea), there are probably less people whose BMI is over 30, the trial showed a significant favorable result, and it was nearly significant. This is possibly due to differences in management resulted by the blinding failure.

Note 4: *A statistical term. Degree of risk such as odds ratio (OR) and hazard ratio (HR) is presented as an estimate that indicates the highest probability (point estimate) and its 95% CI. For instance, for HR in Asia, the point estimate is 0.62 and its 95% CI is 0.37-1.04.*

6)Carcinogenicity

As mentioned in the section on adverse events, the frequent occurrence of pancreatic cancer (OR=2.6, p=0.059) is biologically significant. Moreover, when malignant tumor is added to the primary outcome (composite outcome), odds ratio is not significant.

In this section, we discuss the results of the meta-analysis of pre-approval clinical trials **[18, 19]** including those of another GLP-1 agonist, exenatide, and findings from toxicity studies.

a) Meta-analysis of clinical trials for approval and another GLP-1 agonist

In several RCTs for the approval of liraglutide **[19]**, serious neoplasms (mostly malignant tumors) were observed more frequently with liraglutide (OR=1.80, p=0.2) (***Note 5***). According to the SBA of exenatide, OR for malignant tumor was 5.06 (2.01-12.73, p=0.0001) (***Note 5***).

The combined odds ratio (fixed effect) for the LEADER trial and pre-approval trials for liraglutide and exenatide was 1.18 (1.01-1.39, p=0.048), and was significant (***Note 6***).

Note 5: *SBA of liraglutide reported that the trial involved 4211 patients (2241 person-years) in the liraglutide group and 2272 patients (1139 person-years) in the non-liraglutide group. Malignant neoplasms were found in 20 cases (19 patients) (8.9/1000 person-years) in the liraglutide group and 6 cases (5.3/1000 person-years) in the non-liraglutide group. According to the SBA of exenatide, combined database from 15 long-term RCTs and 8 long-term non-controlled studies (all are non-Japanese studies) showed that malignant neoplasms were found in 48 patients among 3504 patients (1.4%) in the exenatide group and 5 patients among 1826 patients (0.3%) in the control group (1108 patients treated with placebo and 718 with insulin).*

Note 6: *Pre-approval trials for lixisenatide and dulaglutide have not been reviewed. A long-term study for lixisenatide, ELIXA [8], reported the number of cases with neoplasms, but not with malignant neoplasms. Therefore, they were not included in the analysis in the note 5.*

b) Findings from toxicity studies

A 2-year rat carcinogenicity study showed a statistically significant dose-related increase of thyroid C cell adenoma and C cell cancer. Even the minimum dose, 0.075 mg/kg/day of liraglutide, led to a statistically significant increase or increasing trend in these diseases. NOAEL (no observable adverse effect level) was not determined for either of them.

In a 2-year mouse carcinogenicity study, NOAEL for thyroid C cell adenoma and C cell cancer was only 3-fold and 18-fold of the maximum recommended clinical dose for Japanese, respectively.

The pharmaceutical company insists that it does not suggest carcinogenicity in humans, and thyroid C cell adenoma and C cell cancer are rodent (mice and rats)-specific tumors. The Japanese Ministry of Welfare, Health and Labour accepted such an explanation by the pharmaceutical company **[18-21]**.

However, it is reported that in rodents, thyroid C cell adenoma and C cell cancer increase via GLP-1 receptors **[18-21]**. Moreover, human medullary thyroid cancer consists of mainly C cells **[22]**. In response to a request from the U.S. Food and Drug Agency (FDA), Novo Nordisk issued a warning about a risk of development of C cell tumors, including medullary thyroid cancer, and launched a registry system for medullary thyroid cancer **[23]**.

The fact that increased thyroid C cell adenoma and C cell cancer in mice and rats suggests that malignant cells even in the other organs might also be proliferated by GLP-1 agonist.

c) Findings from post marketing studies

The analysis of reported odds ratio (ROR), using adverse reaction cases reported to the FDA's Adverse Event Reporting System (AERS) showed that pancreatitis occurred 10.7 times and 6.7 times more frequently with the brand name drugs in the U.S., namely exenatide and sitagliptin, respectively. The incidence of pancreatic cancer was 2.9-fold and 2.7-fold with exenatide and sitagliptin, respectively. Thyroid cancer was also reported 4.7 times more frequently with exenatide. All of these were statistically significant **[24]**.

d) Importance of carcinogenicity in diabetics

Based on the discussion above, findings on increased malignant tumors (or serious tumors) were consistent in humans and animals. It can be concluded that "cancer" surely increases in humans using GLP-1 agonist.

Currently, in Japan, the number one cause of death in patients with diabetes is malignant neoplasms **[25]**. It has been reported that morbidity of cancer among diabetic patients is high **[25-27]**.

The Japan Diabetes Society is reluctant to accept the relationship between high incidence of cancer among diabetic patients and use of anti-diabetic drugs **[3]**. However, not only animal tests, but also clinical trials and epidemiological studies have pointed out carcinogenetic property of incretin related drugs **[11]**, pioglitazone **[28]** and new insulin preparations **[11]**.

In practice

The LEADER trial did not prove that liraglutide improves mortality from cardiovascular events and total mortality.

The evidence that suggests the possible serious harm of GLP-1 agonists in a long-term, such as carcinogenicity, has been gradually established just as the Med Check-TIP has been advocating. Neither GLP-1 agonists nor DPP-4 inhibitors are recommended for the treatment of type 2 diabetes.

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