TECENTRIQ®
Intravenous Infusion 1200mg
Product Overview

Mikio Sakai
TECENTRIQ Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

TECENTRIQ®
atezolizumab

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

TECENTRIQ® atezolizumab

Product Outline

【Product name】
Anti-cancer agent / Humanized anti-PD-L1 monoclonal antibody
TECENTRIQ® Intravenous Infusion 1200mg

【Generic name】
atezolizumab (Genetical recombination)

【Package unit】
TECENTRIQ® Intravenous Infusion 1200mg: 20.0mL×1 vial

TECENTRIQ®
atezolizumab

History of Development of Tecentriq

2018

January: Approved in Japan
(Unresectable advanced or recurrent non-small cell lung cancer [NSCLC])

2017

September: Approved in the EU (locally advanced or metastatic NSCLC in patients previously treated with chemotherapy)

2016

October: Approved in the US (metastatic NSCLC in patients whose disease progressed during or after chemotherapy)

2014

March: Phase III multinational study (OAK) started

2013

August: First clinical trial in Japan (Phase I) started

2011

June: First clinical trial overseas (Phase I) started

OAK Study

2017

October: Results for Japanese sub-group analysis reported at JLCS Annual Meeting[2)]

September: Results of investigation into association between efficacy of Tecentriq and TMB in blood reported at ESMO[3)]

September: Results of re-evaluation of the association between PD-L1 expression and OS by SP142 and 22C3 assay reported at ESMO[4)]

June: Results of investigation into the clinical benefit of Tecentriq treatment beyond disease progression (TBP) reported at ASCO[5)]

2016

October: Analysis results for OAK Study reported at ESMO[1)]

TBP: Treatment beyond disease progression
TMB: Tumor mutational burden

1) Barlesi F, et al.: Ann Oncol 27 (suppl 6): Abst. LBA44-PR
2) Kubo T, et al.: Jpn J Lung Cancer 57 (5): O46-5
3) Gandara DR, et al.: Ann Oncol 28 (suppl 5): Abst. 1295O
4) Gadgeel S, et al.: Ann Oncol 28 (suppl 5): Abst. 1296O
5) Gandara DR, et al.: J Clin Oncol (suppl 15): Abst. 9001

Indications and Usage

Unresectable advanced or recurrent NSCLC

Precautions for Indications

1. Efficacy and safety of Tecentriq in chemotherapy-naive patients have not been established.
2. Efficacy and safety of Tecentriq in postoperative adjuvant chemotherapy have not been established.
3. Eligible patients should be selected after closely reading the Clinical Studies section, which provides information such as the prior treatment history of patients in the clinical studies, to gain a thorough understanding of the efficacy and safety of Tecentriq.

The usual dose for adults is 1200 mg of atezolizumab (recombinant) every 3 weeks, administered by intravenous infusion over 60 minutes. If the first dose is well tolerated, the times for the second and subsequent infusions may be shortened to 30 minutes.

Precautions for Usage

1. Efficacy and safety in coadministration with other anticancer drugs have not been established.
2. To prepare for use, draw 20 mL of Tecentriq into a syringe, add to about 250 mL of physiological saline JP, then administer by intravenous infusion.
3. In the event of an adverse reaction due to this product, consider whether to withhold Tecentriq or take other action, in accordance with the following criteria.

From the package insert prepared January 2018 (Version 1).

Overview of Tecentriq RMP

Revised in March 2018

Safety Specification

Important Identified Risks

- Interstitial lung disease
- Hepatic dysfunction
- Colitis or severe diarrhea
- Pancreatitis
- Type 1 diabetes mellitus
- Endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction)
- Encephalitis or meningitis
- Neuropathies (including Guillain-Barré syndrome)
- Myasthenia gravis
- Severe skin disorder
- Renal dysfunction (e.g., tubulointerstitial nephritis)
- Myositis or rhabdomyolysis
- Infusion reaction

Important Potential Risks

- Myocarditis
- Hemolytic anemia
- Immune thrombocytopenic purpura
- Use in patients with a history of organ transplantation (including a history of hematopoietic stem cell transplantation)
- Embryofetal toxicity

Risks Not Included in the Package Insert

Important Missing Information

None

Six months from market launch
Periodic site visits

Pharmacovigilance Plan

Routine activities

- Collection and evaluation of individual cases
- Collection and evaluation of literature etc.
- Collection and evaluation of information on overseas regulatory actions
- Signal detection and evaluation through means such as data mining techniques for adverse events (including deaths)

Additional activities

- Early post-marketing phase vigilance (EPPV)
- Drug-use surveillance in patients with NSCLC
- Post-marketing clinical studies (extension study of OAK Study, extension study of BIRCH Study)

All-patient surveillance:
1000 patients
Registration for 12 months from market launch

Risk Minimization Plan

Routine activities

- Preparation of package insert (revisions)
- Medication Guide for Patients

Additional activities

- Provision of information from EPPV
- Provision of information to healthcare providers (Guidance for Appropriate Use)
- Provision of information to patients (Patient Handbook)

Ongoing Clinical Studies of Tecentriq in the Lung Cancer Field

First-line
adjuvant

NSCLC

Plus molecular targeted drugs	CBDCA＋PTX ± BEV : IMpower150
Plus chemotherapy	CBDCA＋nab-PTX : IMpower130
	CBDCA＋PTX/nab-PTX : IMpower131
	CBDCA/CDDP＋PEM : IMpower132
Tecentriq alone	IMpower110
	IMpower010
	B-FAST (TMB assessment)

SCLC

Plus chemotherapy	CBDCA＋ETP : IMpower133

CBDCA: carboplatin; PTX: paclitaxel; BEV: bevacizumab; CDDP: cisplatin; nab-PTX: nab-paclitaxel; PEM: pemetrexed; ETP: etoposide
SQ: squamous cell carcinoma; NSCLC: non-small cell lung cancer; TMB (tumor mutation burden): number of mutations in tumor tissue

ClinicalTrials.gov.
https://clinicaltrials.gov/

TECENTRIQ® atezolizumab

The Anti-PD-L1 Antibody Tecentriq Mode of Action and Future Outlook

Hiroyoshi Nishikawa, M.D., Ph.D.
Department of Immunology, Nagoya University Graduate School of Medicine
Exploratory Oncology Research & Clinical Trial Center, Research Institute,
National Cancer Center

COI Disclosure

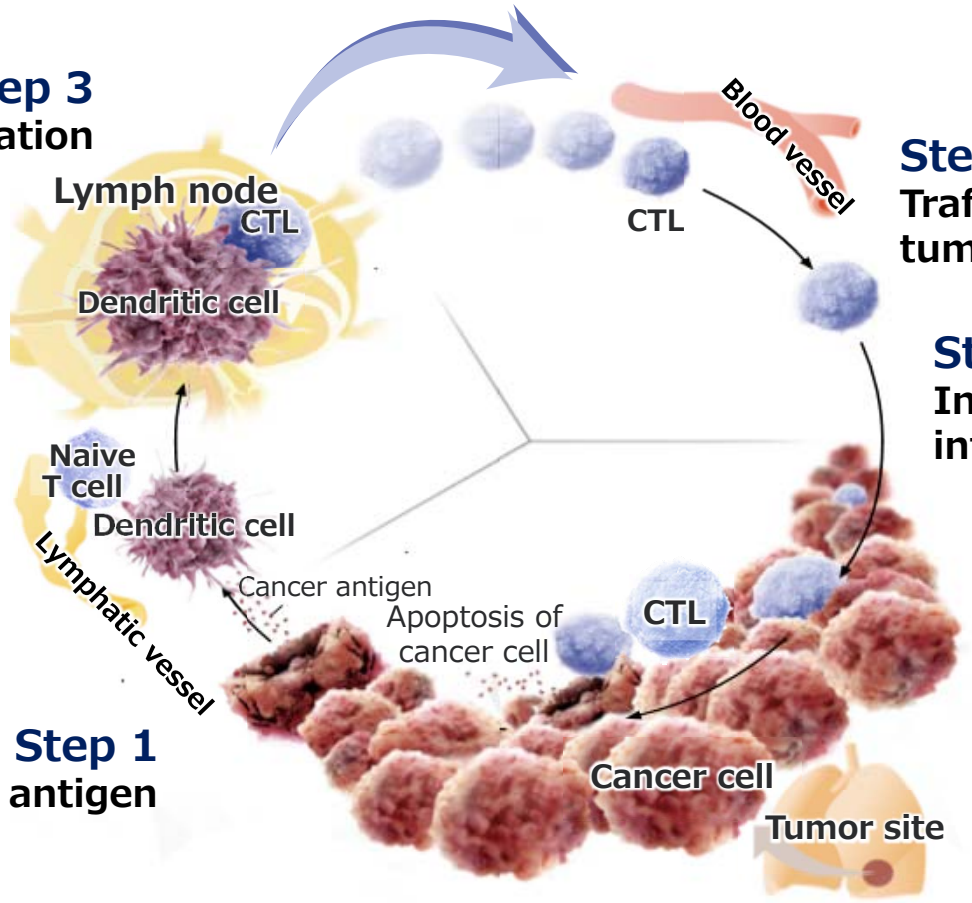
Name of presenter: Hiroyoshi Nishikawa

Institution: Nagoya University, National Cancer Center

In connection with my presentation, I have following relationships to disclose.

- Lecture fee, etc.
  Ono Pharmaceutical, Bristol-Myers Squibb and Chugai Pharmaceutical
- Research fund
  Ono Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, Kyowa Hakko Kirin, Daiichi Sankyo, Zenyaku Kogyo, Sysmex, Chugai Pharmaceutical and Asahi Kasei

The Cancer-Immunity Cycle



Step 3
Priming and T cell activation

Step 4
Trafficking of CTL* to tumor

Step 5
Infiltration of CTL into the tumor

Step 6
Recognition of cancer cell by CTL

Step 7
Killing of cancer cell by CTL (Extinction of cancer cells)

Step 2
Presentation of cancer antigen to T cell

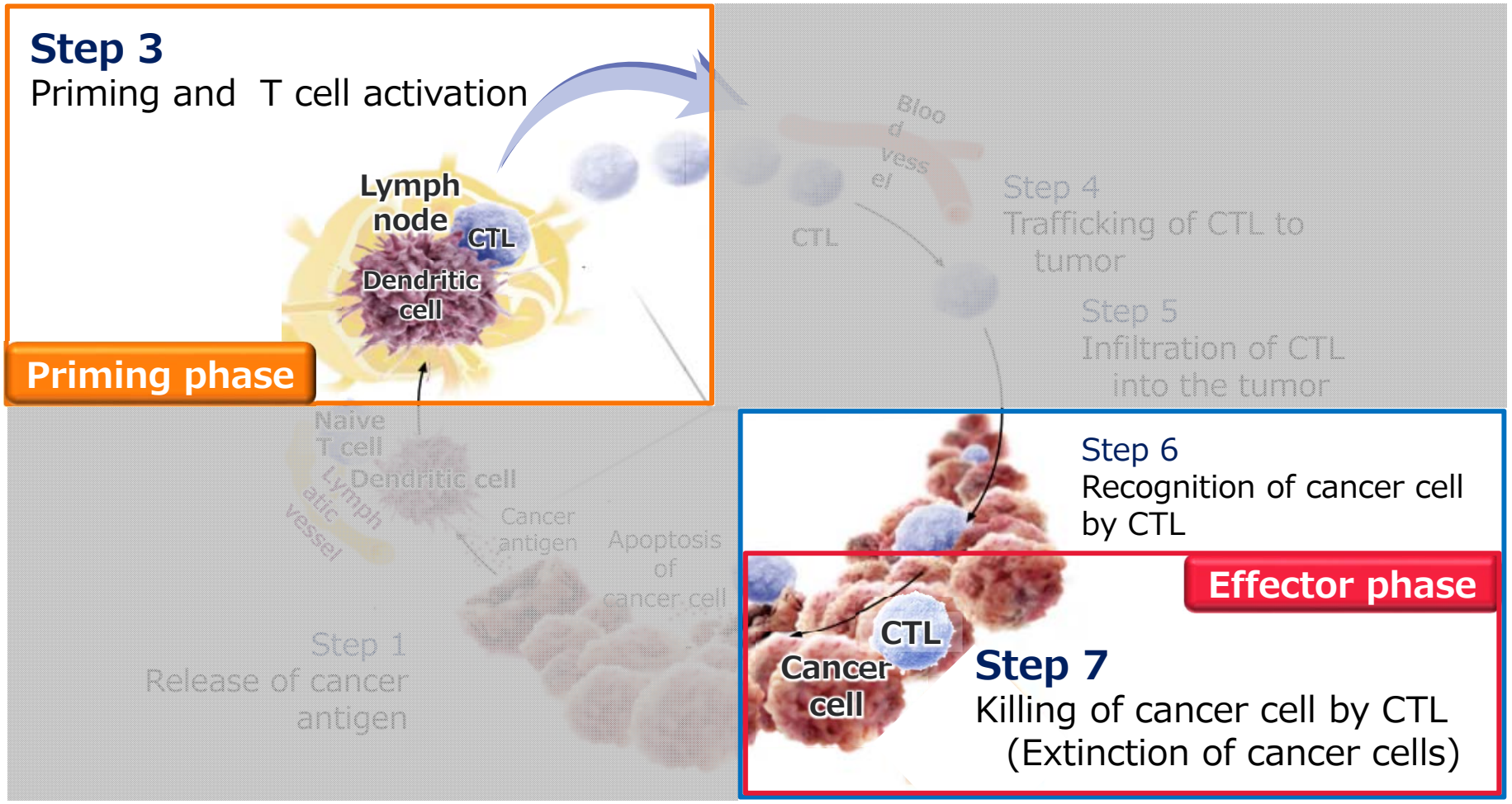
Step 1
Release of cancer antigen

(Conceptual diagram)

* CTL (cytotoxic T lymphocyte): Cytotoxic T cell ($CD8^+$ T cell)

Modified from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10
The author is Genentech employee.

The Cancer-Immunity Cycle

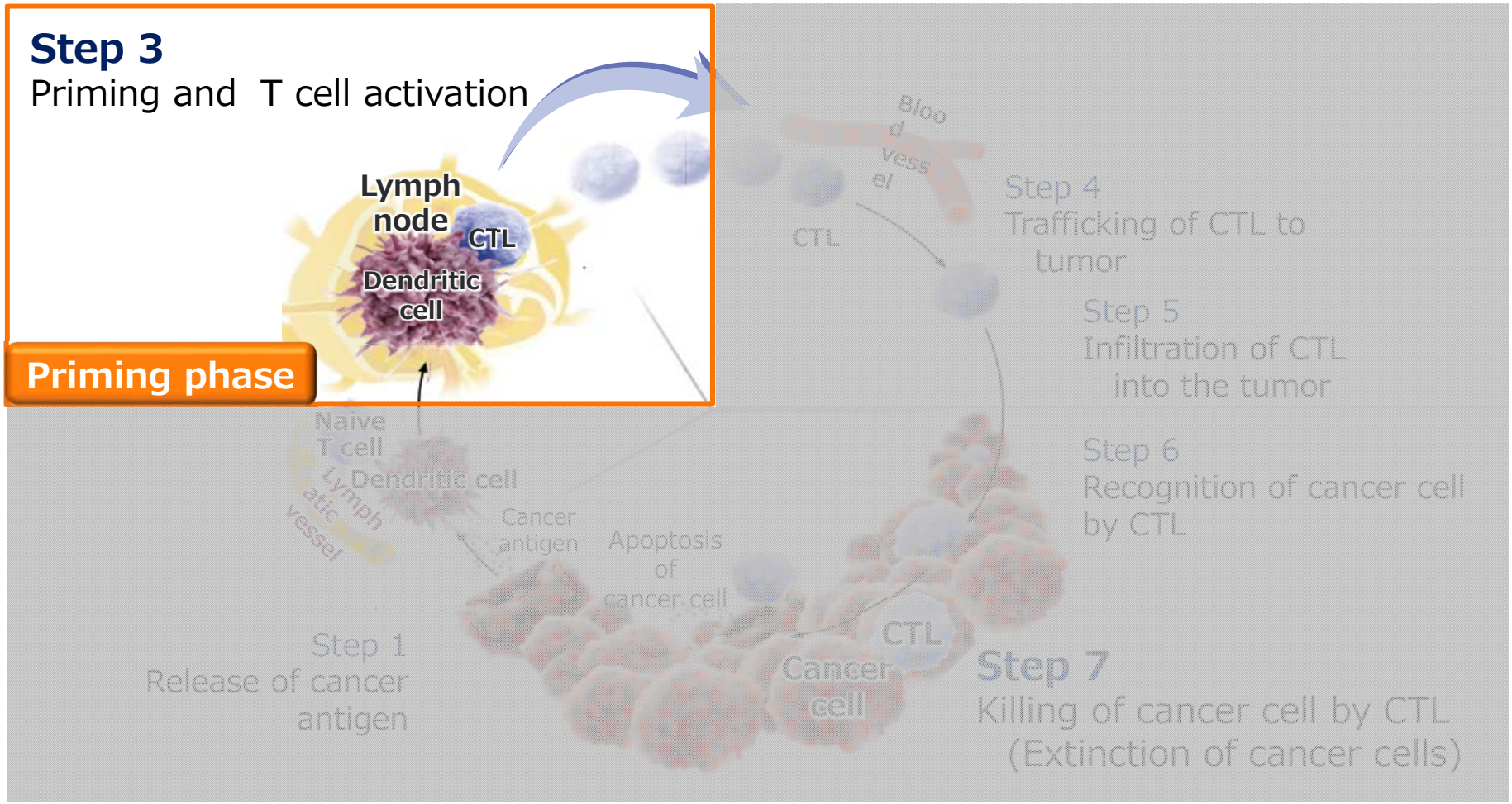


Priming: First stimulus for initiation of immunity
Priming phase: The stage in which naive T cells are first stimulated by antigen
Effector phase: The stage in which the functional immune response occurs, using information memorized in the priming phase

(Conceptual diagram)

Modified from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10

The Cancer-Immunity Cycle



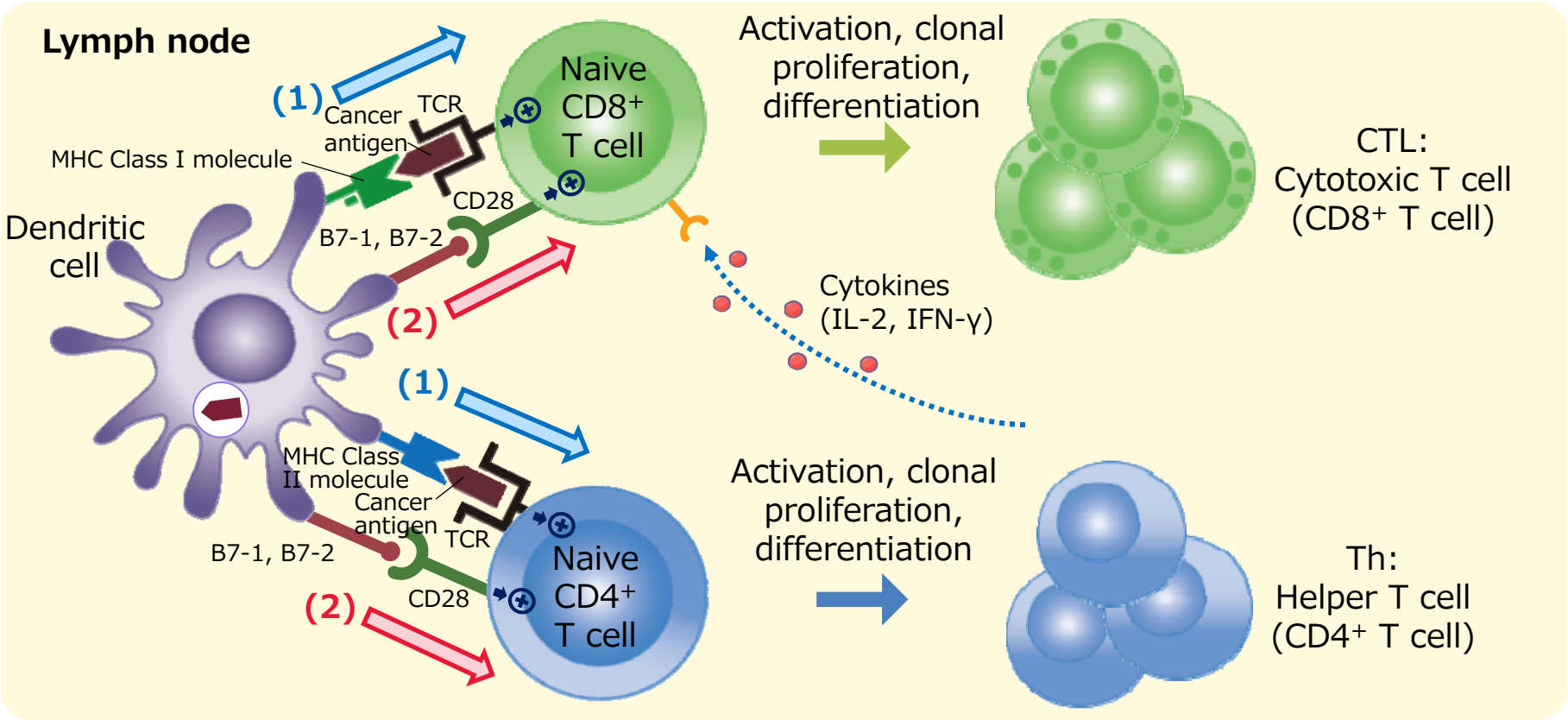
(Conceptual diagram)

Modified from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10

T Cell Activation in the Priming Phase

Step 3. Priming and Activation of Naive T Cells

Priming phase

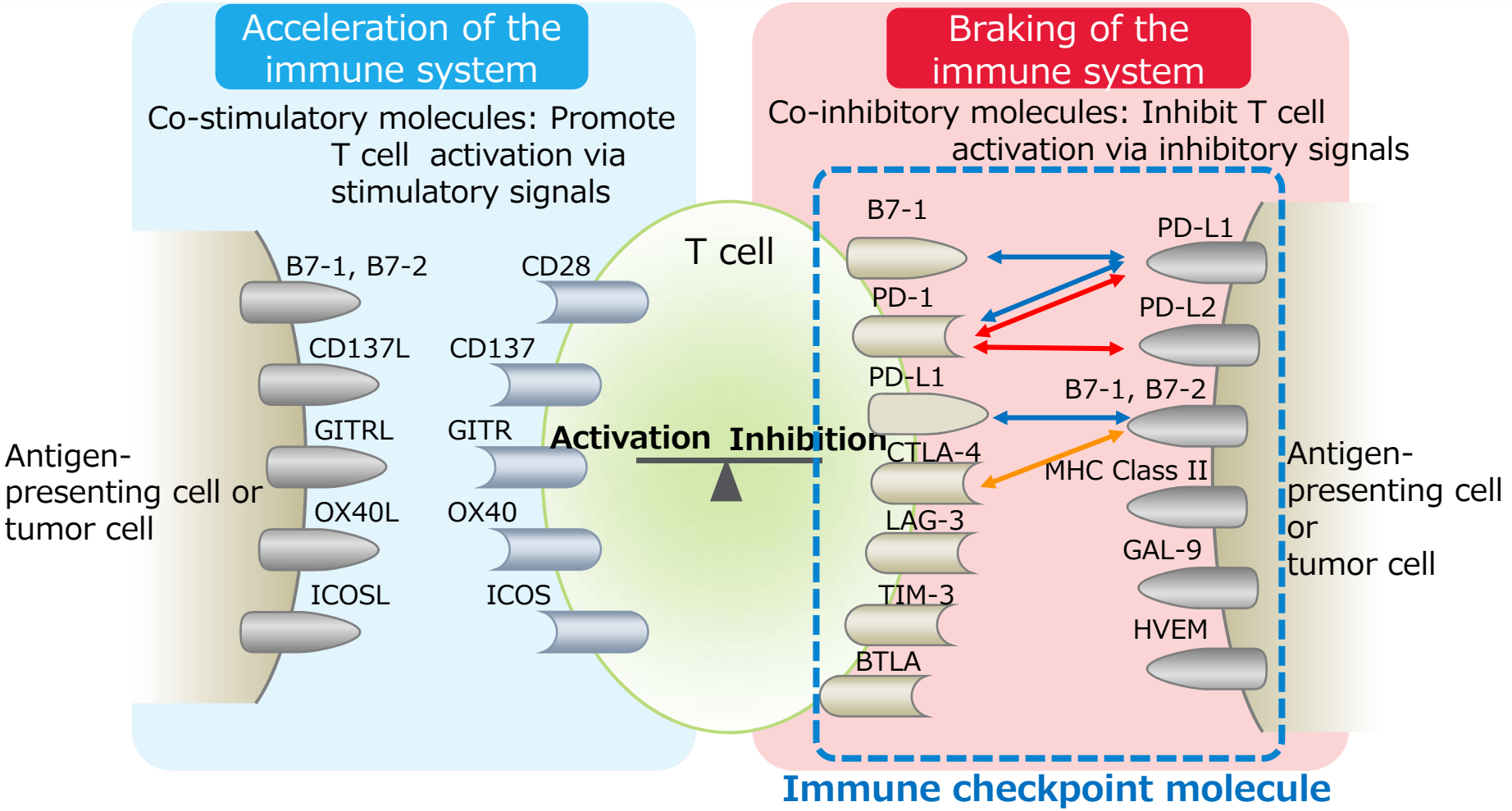


(Conceptual diagram)

Priming: First stimulus for initiation of immunity
MHC: Major histocompatibility complex
TCR: T cell receptor
IFN: Interferon
IL-2: Interleukin-2

Graphic prepared from Abbas AK, et al.: Basic immunology: Functions and disorders of the immune system. 4th edition; 2014

Interactions of Key Cell-Surface Factors in the PD-1/PD-L1 Pathway

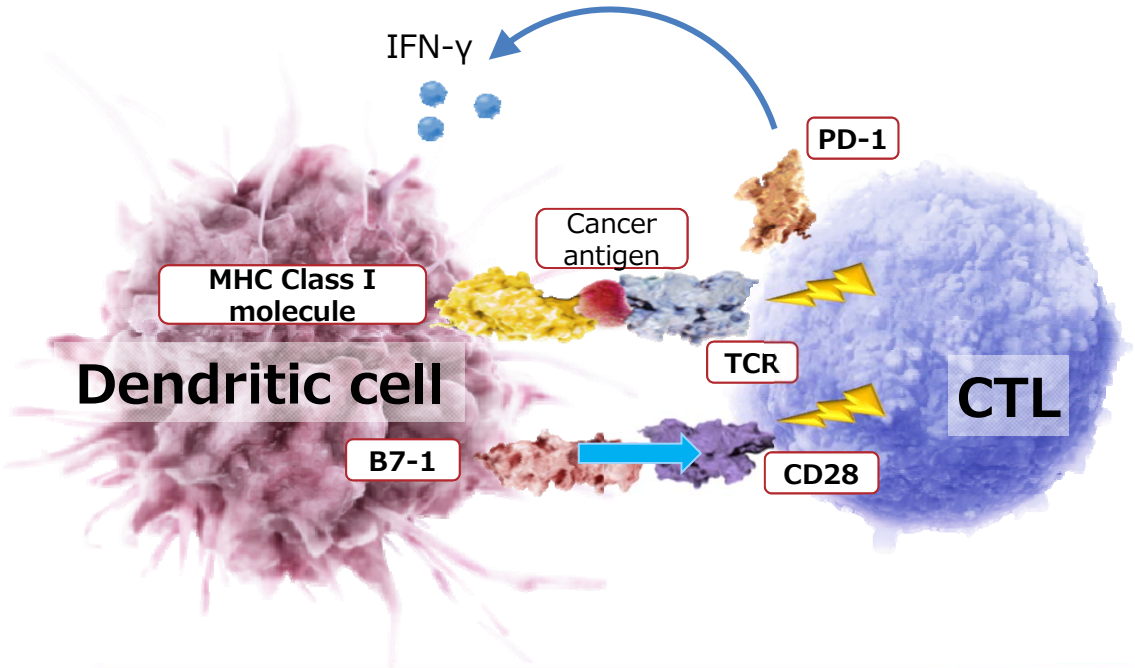


PD-1: Programmed (cell) death 1
PD-L1: Programmed (cell) death ligand 1

Modified from Sakaguchi S, Nishikawa H (eds). Cancer and Immunity [Gan to Men'eki] 2015, Nanzando

T Cell Activation in the Priming Phase Inhibitory Mechanism and the Role of Tecentriq

Priming phase



(Conceptual diagram)

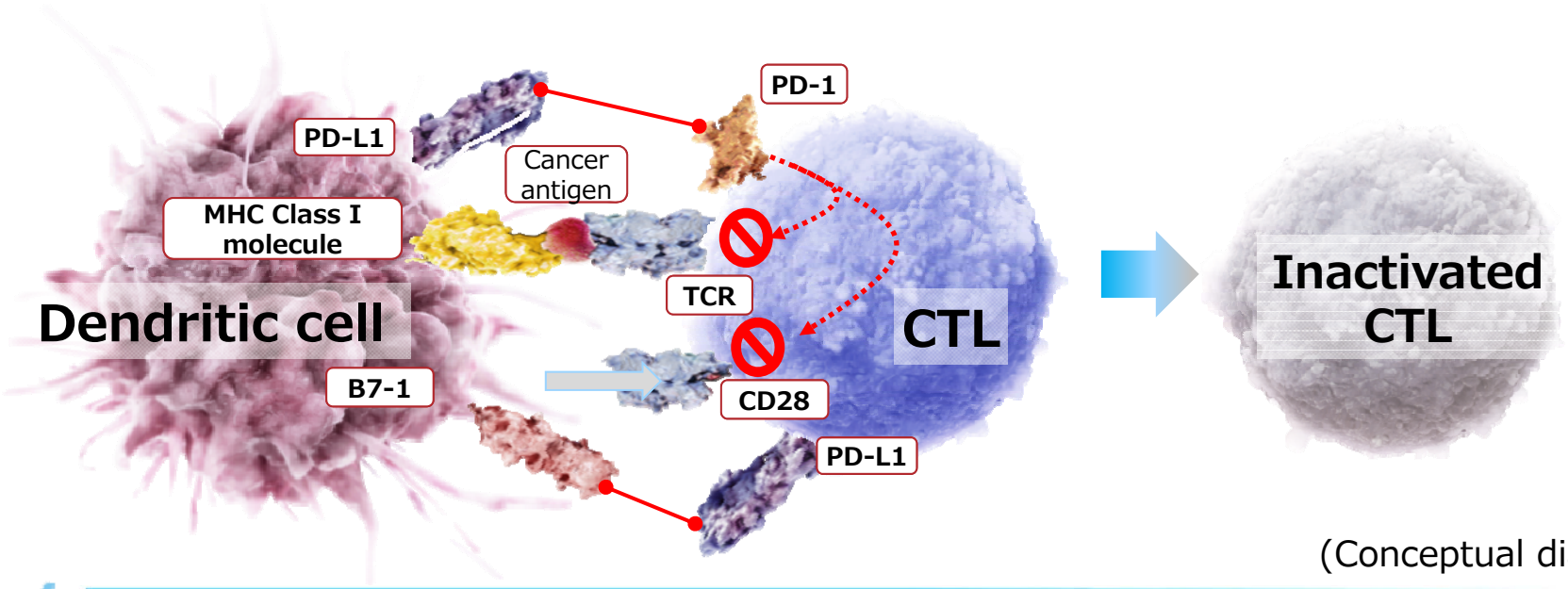
In the lymph nodes, T cells are activated by (1) Presentation of cancer antigen and (2) transduction of co-stimulatory signals by antigen-presenting cells to T cells

TCR: T cell receptor
CTL (cytotoxic T lymphocyte): Cytotoxic T cell

Graphic prepared from Abbas AK, et al.: Basic immunology: Functions and disorders of the immune system. 4th edition; 2014

T Cell Activation in the Priming Phase Inhibitory Mechanism and the Role of Tecentriq

Priming phase



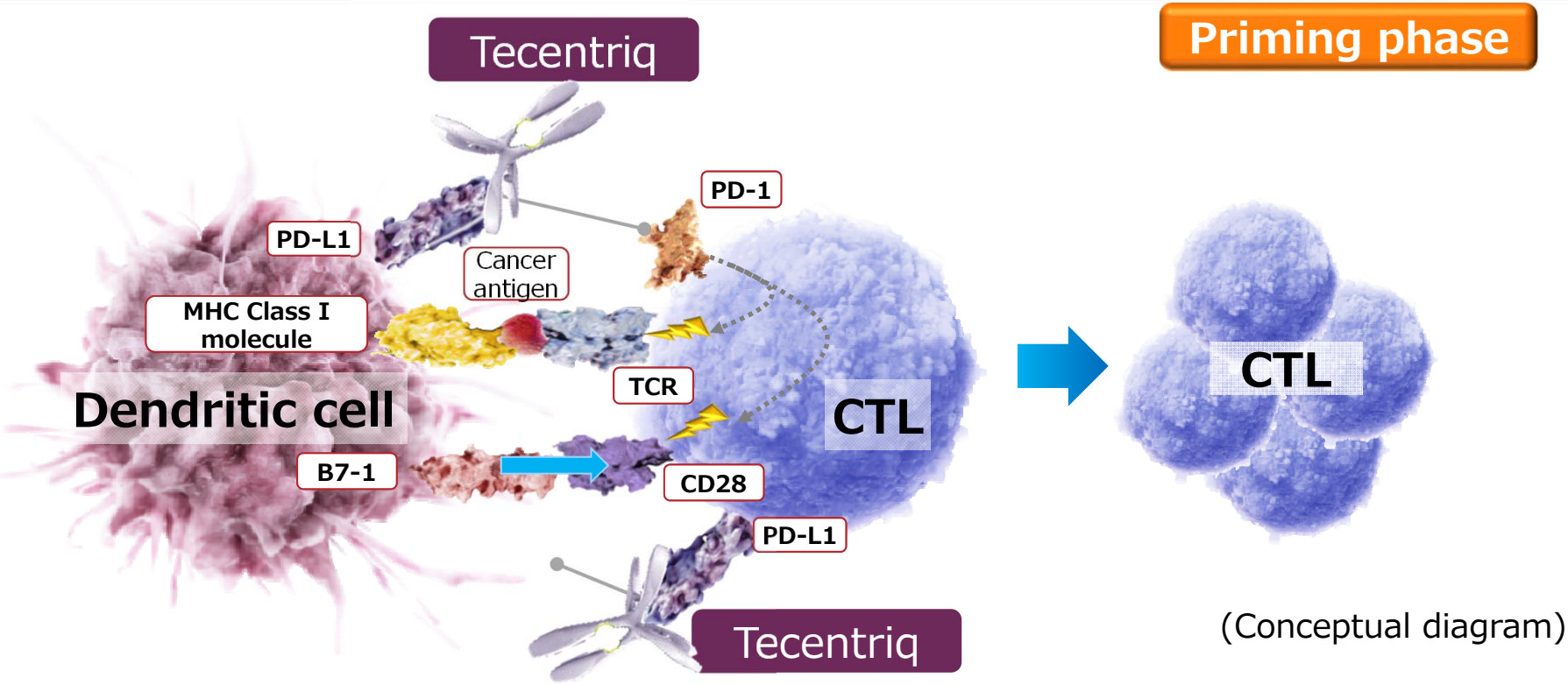
(Conceptual diagram)

When PD-L1 binds to PD-1,
(1) TCR signal transduction and (2) co-stimulatory signals are suppressed, leading to suppression of T cell activation and proliferation

TCR: T cell receptor
CTL (cytotoxic T lymphocyte): Cytotoxic T cell

Graphic prepared from Hui et al.: Science 355, 1428–1433 (2017);
Abbas AK, et al.: Basic immunology: Functions and disorders of the immune system. 4th edition; 2014

T Cell Activation in the Priming Phase Inhibitory Mechanism and the Role of Tecentriq

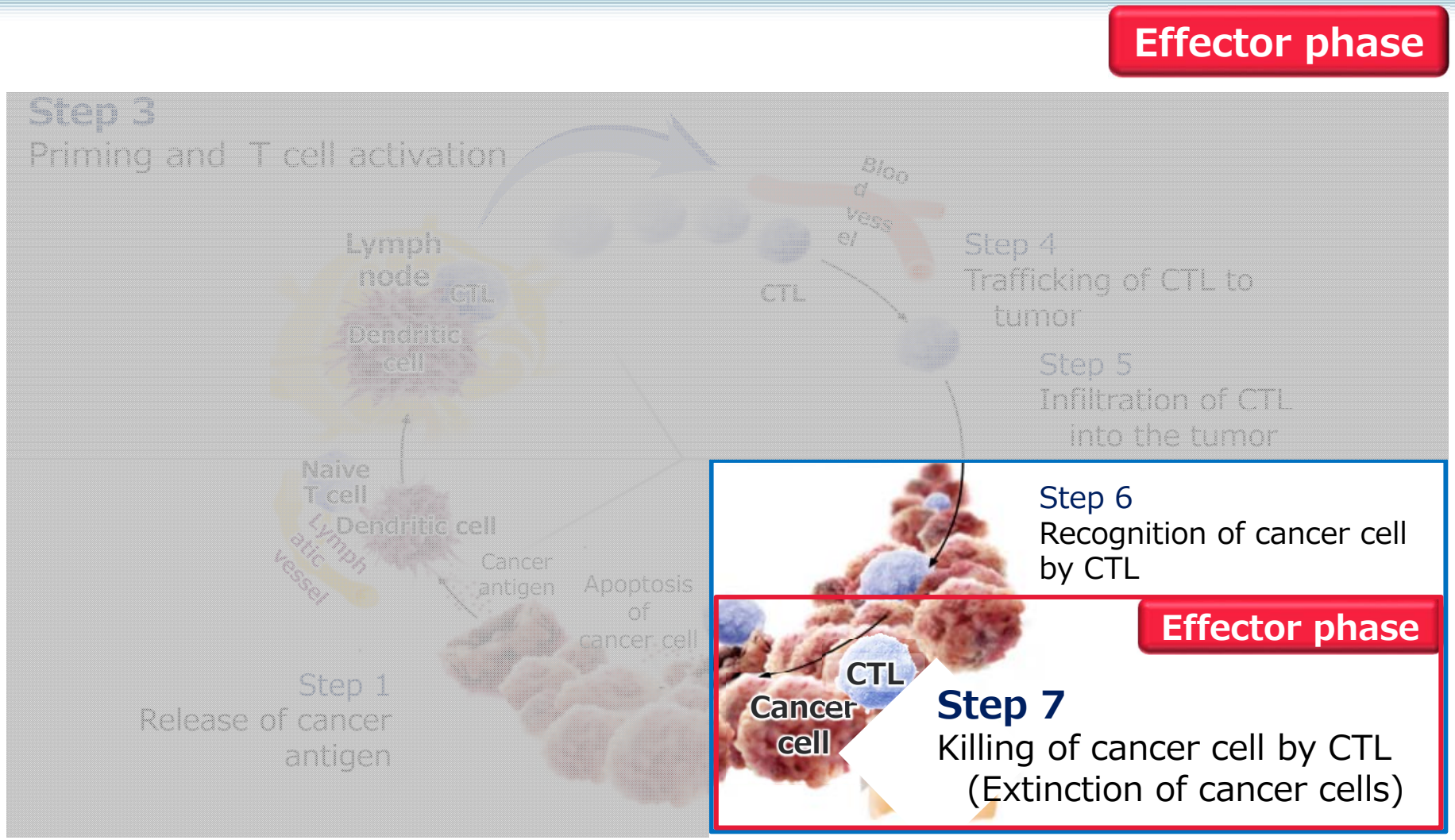


(Conceptual diagram)

When Tecentriq binds to PD-L1,
binding of (1) PD-L1 to PD-1 and (2) PD-L1 to B7-1 is inhibited,
TCR signals and co-stimulatory signals are transduced, and T cell activation is enhanced

Graphic prepared from Abbas AK, et al.: Basic immunology: Functions and disorders of the immune system. 4th edition; 2014

The Cancer-Immunity Cycle

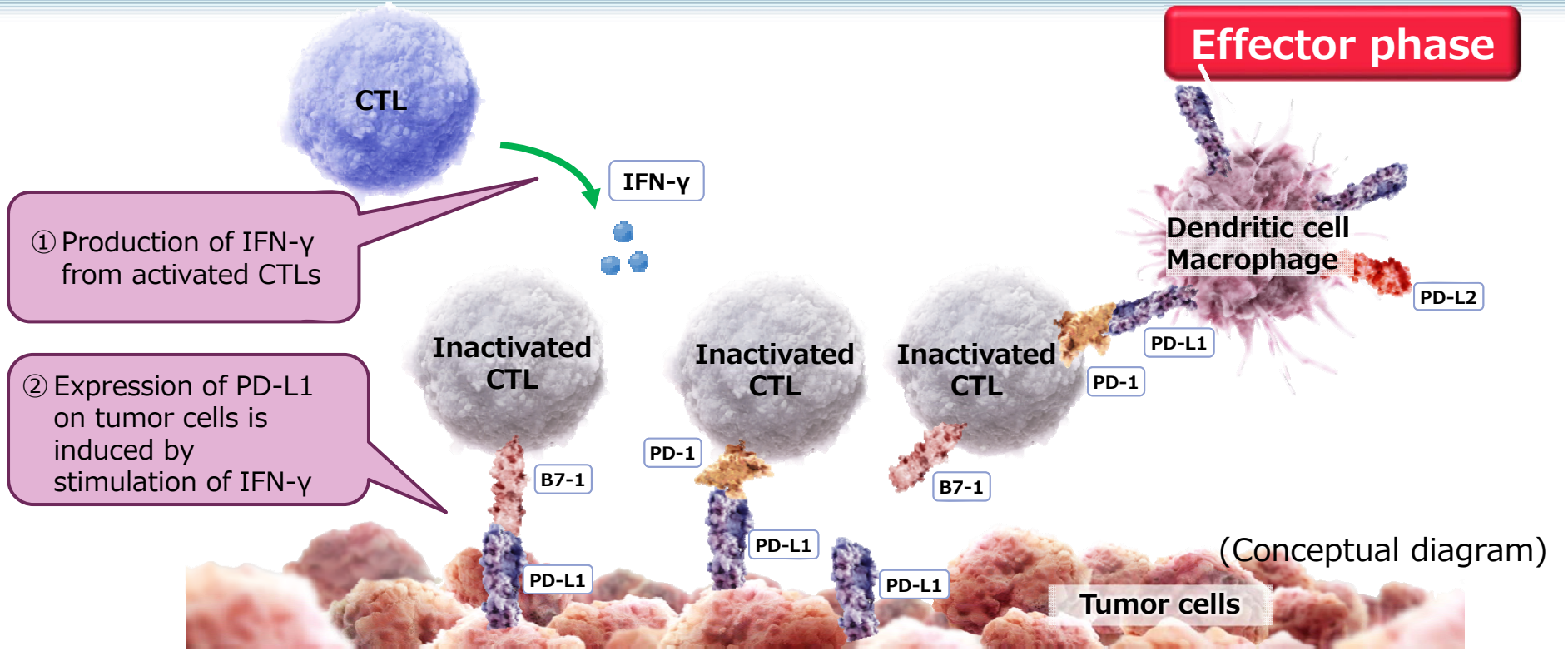


(Conceptual diagram)

Effector phase: The stage in which the functional immune response occurs, using information memorized in the priming phase

Modified from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10

T Cell Inhibitory Mechanism in the Effector Phase and the Role of Tecentriq

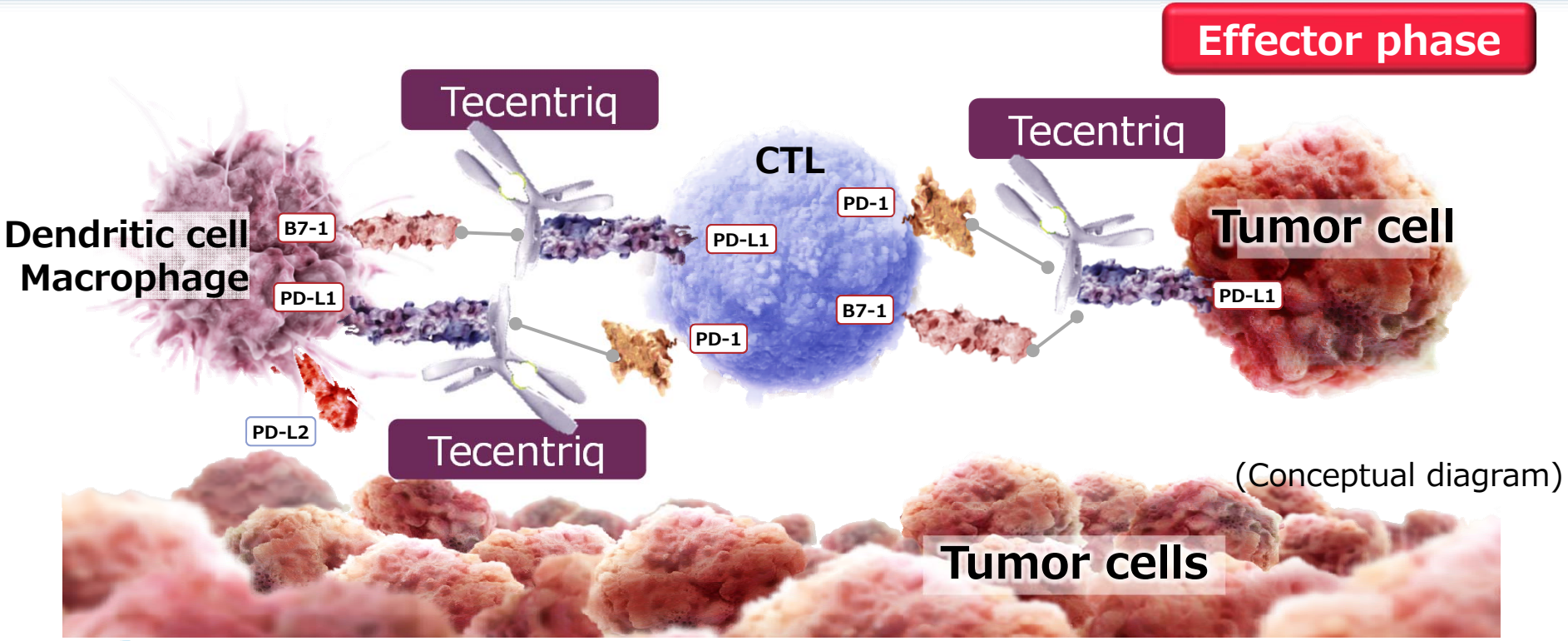


When PD-L1 on tumor cells and immune cells binds with (1) PD-1 and (2) B7-1 on T cells, the antitumor immune response is inhibited

CTL (cytotoxic T lymphocyte): Cytotoxic T cell
IFN: Interferon
IL-2: Interleukin-2

Zou W, Chen L. Nat Rev Immunol. 2008; 8 (6): 467-77.
Chen DS, Mellman I. Immunity. 2013; 39 (1): 1-10.; Herbst RS, et al.: Nature. 2014; 515 (7528): 563-7.

T Cell Inhibitory Mechanism in the Effector Phase and the Role of Tecentriq



(Conceptual diagram)

When Tecentriq binds to PD-L1 on tumor cells and immune cells binding of (1) PD-L1 to PD-1 and (2) PD-L1 to B7-1 is inhibited, and T cells are reactivated, enhancing the antitumor immune response

Chen DS, et al.: Clin Cancer Res 2012; 18 (24): 6580-7.; Herbst RS, et al.: Nature. 2014; 515 (7528): 563-7.; Powles T, et al.: Nature. 2014; 515 (7528) : 558-62.; Hui E, et al.: Science. 2017; 355 (6332) : 1428-1433.; Kamphorst AO, et al.: Science. 2017; 355 (6332) : 1423-1427.

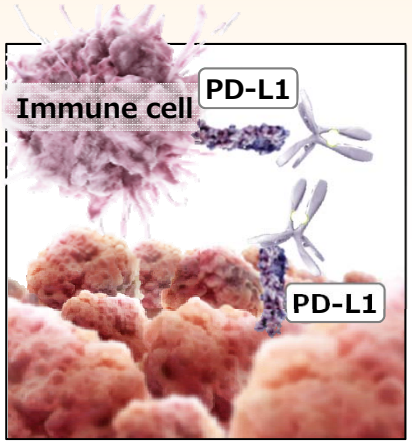
T Cell Inhibitory Mechanism in the Effector Phase and the Role of Tecentriq

Tecentriq: Three Features of its Mode of Action

Effector phase

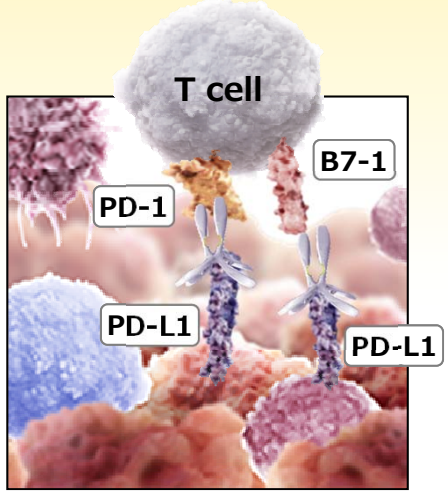
Direct

Targets PD-L1 on the surface of tumor cells and immune cells, reactivating T cells[1,2]



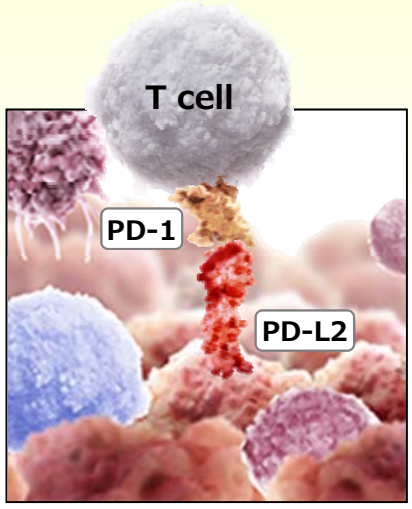
Complete

Blocks the PD-1/PD-L1 pathway necessary for T cell activation and blocks the pathway of B7-1 and PD-L1 involved in co-stimulatory signals, thereby resulting in dual blockade.[3]



Selective

No interference to the PD-L2/PD-1 pathway, thereby potentially maintaining immune homeostasis.[4,5,6,7,8]



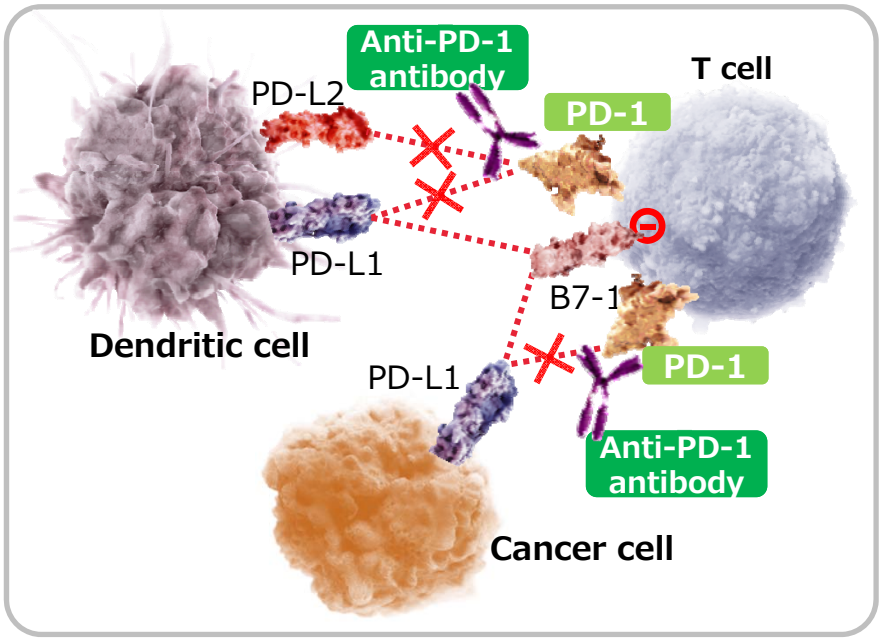
1. Chen DS, Mellman I. Immunity. 2013; 39 (1): 1-10.; 2. Sznol M, Chen L. Clin Cancer Res 2013; 19 (5): 1021-34.;
3. Paterson AM, et al.: J Immunol. 2011; 187 (3): 1097-105.; 4. Chen DS, et al.: Clin Cancer Res. 2012; 18 (24): 6580-7.;
5. Latchman Y. et al.: Nat Immunol. 2001; 2 (3): 261-8.; 6. Akbari O, et al.: Mucosal Immunol 2010; 3 (1): 81-91.;
7. Brown JA, et al.: J Immunol 2003; 170 (3): 1257-66.; 8. Matsumoto K, et al. Biochem Biophys Res Commun. 2008; 365 (1): 170-5.

Differences Between Anti-PD-L1 Antibodies and Anti-PD-1 Antibodies

Effector phase

Anti-PD-1 antibodies

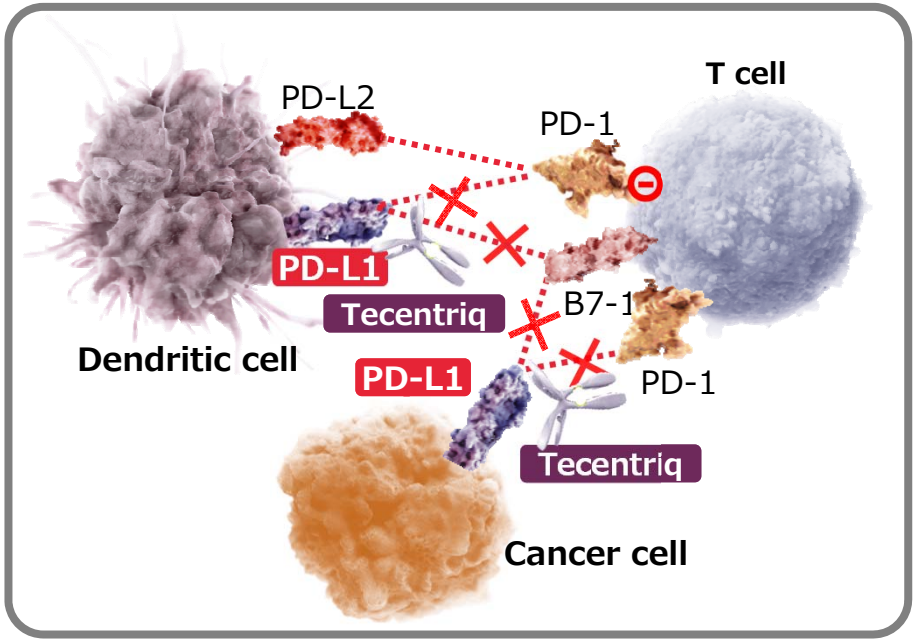
Nivolumab　Pembrolizumab



- PD-1/PD-L1 pathway: Blocked
- B7-1/PD-L1 pathway: Maintained
- PD-1/PD-L2 pathway: Blocked

Anti-PD-L1 antibody

Tecentriq



- PD-1/PD-L1 pathway: Blocked
- B7-1/PD-L1 pathway: Blocked
- PD-1/PD-L2 pathway: Maintained

(Conceptual diagram)

The clinical relevance of differences in the maintenance and blockade of the B7-1/PD-L1 and PD-1/PD-L2 pathways is a question for further research

Chen DS, et al.: Clin Cancer Res 2012; 18 (24): 6580-7. Paterson AM, et al.: J Immunol 2011; 187 (3): 1097-105.
Yang J, et al.: J Immunol 2011; 187 (3): 1113-9. Brahmer JR, et al.: N Engl J Med 2012; 366 (26): 2455-65.

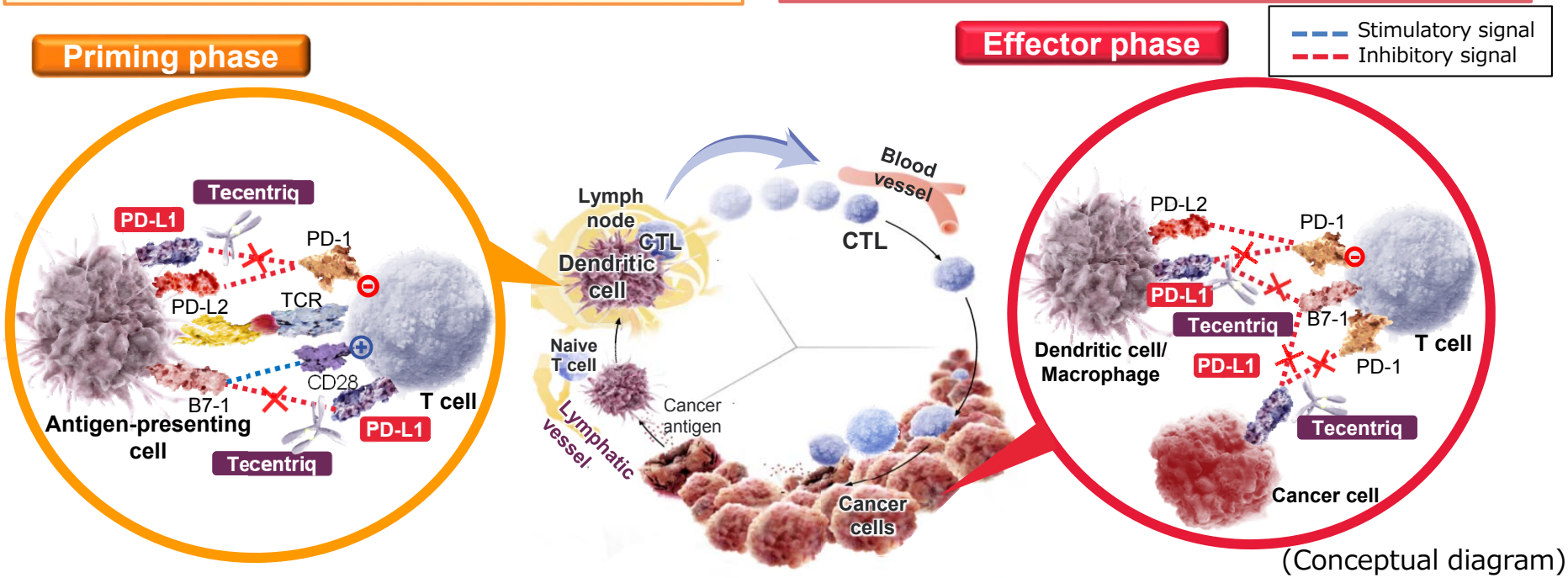
Summary of the MOA of Tecentriq

Effects in lymph nodes

Tecentriq binds to PD-L1 on the surface of antigen-presenting cells and T cells in the lymph nodes, blocking the PD-L1/PD-1 and PD-L1/B7-1 pathways that suppress the activation of T cells.
Additionally, T cell priming and activation is promoted by maintenance of the binding of B7-1 to CD28, which transduces co-stimulatory signals.

Effects on the tumor microenvironment

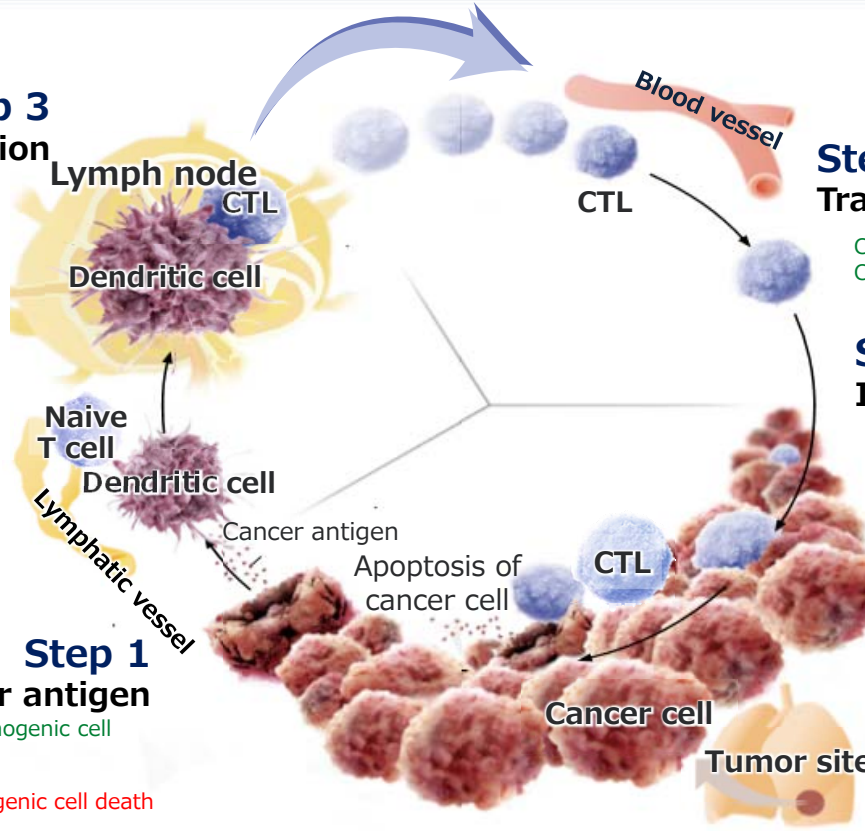
Tecentriq binds to PD-L1 on the surface of tumor cells and immune cells in the tumor microenvironment, blocking binding to PD-1 and B7-1 on the T cell surface, thereby reactivating T cells.
Meanwhile, as Tecentriq does not bind to PD-L2, the PD-L2/PD-1 pathway is maintained.



(Conceptual diagram)

Graphic prepared from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10 (the authors are Genentech staff);
Abbas AK, et al.: Basic immunology: Functions and disorders of the immune system. 4th edition; 2014;
Chen DS, et al.: Clin Cancer Res. 2012; 18 (24): 6580-6587 (the authors are Genentech staff);
Herbst RS, et al.: Nature. 2014; 515 (7528): 563-567; Powels T, et al.: Nature. 2014; 515 (7528): 558-562;
Hui E, et al.: Science. 2017; 355 (6332): 1428-1433.; Kamphorst AO, et al.: Science. 2017; 355 (6332): 1423-1427.

Future Possibilities for Cancer Immunotherapy



● Stimulatory factor
● Inhibitory factor

Step 3
Priming and T cell activation

CD28/B7-1
CD137/CD137L
OX40/OX40L
CD27/CD70
HVEM
GITR
IL-2
IL-12

CTLA-4/B7-1, B7-2
PD-L1/PD-1
B7-1/PD-L1
Prostaglandin

Step 2
Presentation of cancer antigen to T cell

TNF-α
IL-1
IFN-α
CD40L/CD40
CDN
ATP
HMGB1
TLR

IL-10
IL-4
IL-13

Step 1
Release of cancer antigen

Immunogenic cell death

Tolerogenic cell death

Step 4
Trafficking of CTL to tumor

CX3CL1
CXCL10
CXCL9
CCL4

Step 5
Infiltration of CTL into the tumor

LFA1/ICAM1
Selectin

VEGF
Endothelin B receptor

Step 6
Recognition of cancer cell by CTL

T cell receptor

Reduced expression of pMHC on cancer cells

Step 7
Killing of cancer cell by CTL

IFN-γ
Granular T cell components

PD-1/PD-L1
B7-1/PD-L1
IDO
TGF-β
BTLA
VISTA

LAG-3
Arginase
MICA/MICB
B7-H4
TIM-3/phospholipids

(Conceptual diagram)

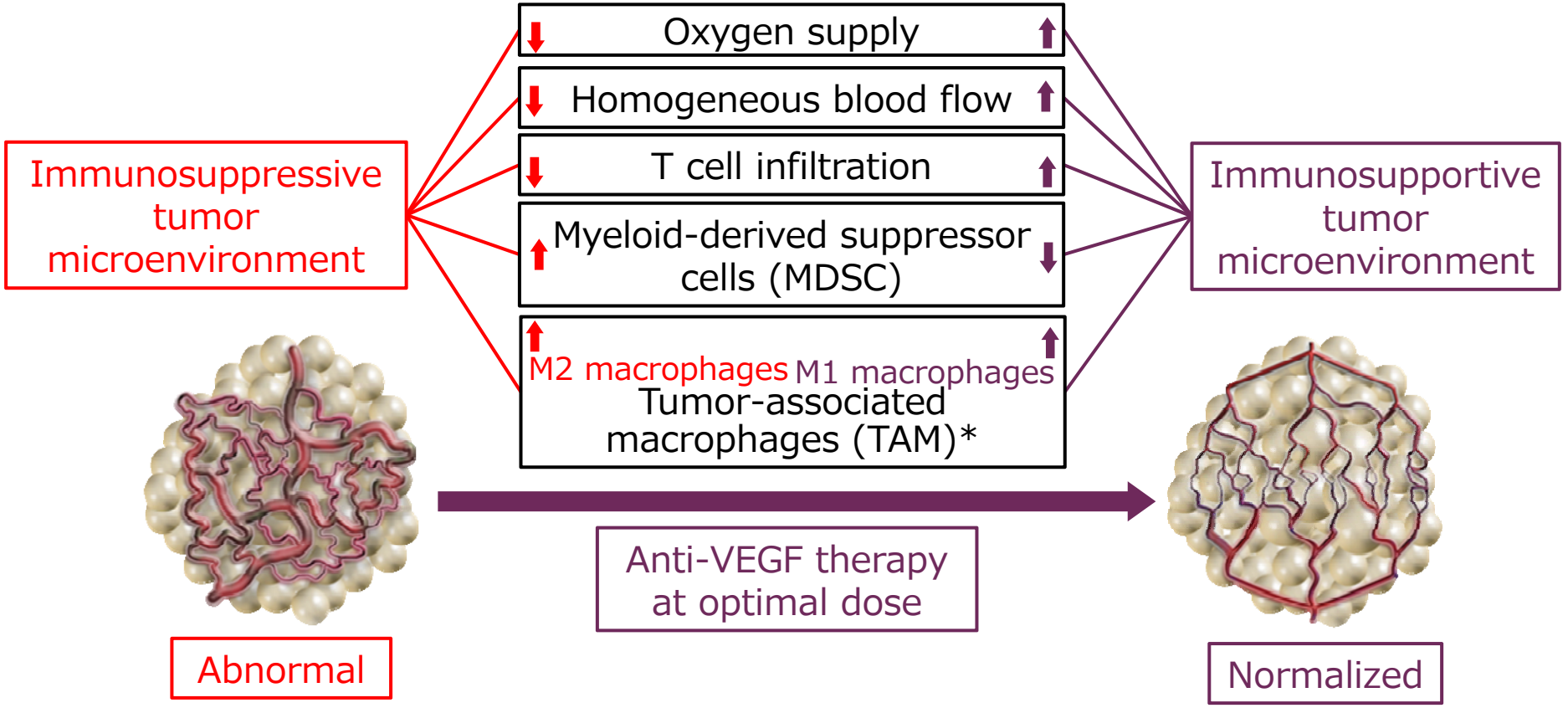
CTL (cytotoxic T lymphocyte): Cytotoxic T cell ($CD8^+$ T cell)
Priming: First stimulus for initiating immunity

Various factors are involved in the cancer-immune set point, including cancer-derived factors, drugs, environmental factors, microbiota-derived factors, and genes.

⇒Research is advancing into use in combination with chemotherapy drugs, molecular targeted drugs, and other cancer immunotherapy drugs

Modified from Chen DS, Mellman I.: Immunity. 2013; 39 (1): 1–10

Effects of Anti-VEGF Therapy on the Tumor Microenvironment



(Conceptual diagram)

*Tumor-associated macrophages (TAM) are divided into two subsets, depending on their function: M1 macrophages and M2 macrophages. M1 macrophages promote the anti-tumor immune response, while M2 macrophages suppress the anti-tumor immune response.

Modified from Huang Y, et al.: Cancer Res 2013; 73 (10): 2943-2948

Ongoing Clinical Studies

RG7446 (MPDL3280A)	NSCLC [2nd line]	Approved (18/01)	atezolizumab Tecentriq Injection	Roche Tecentriq	Engineered anti-PDL1 monoclonal antibody
	NSCLC [1st line] #	Phase lll Multinational study			
	NSCLC (adjuvant) #	Phase III Multinational study			
	Small cell lung cancer #	Phase III Multinational study			
	Urothelial carcinoma #	Phase III Multinational study			
	Muscle invasive urothelial carcinoma (adjuvant) #	Phase III Multinational study			
	Renal cell carcinoma #	Phase III Multinational study			
	Renal cell carcinoma (adjuvant) #	Phase III Multinational study			
	Breast cancer #	Phase III Multinational study			
	Ovarian cancer #	Phase III Multinational study			
	Prostate cancer #	Phase III Multinational study			

#: Additional indication

Clinical studies for combinations with other drugs are already in progress.

Treatment Overview of Non-Small Cell Lung Cancer and Clinical Trials for Tecentriq®

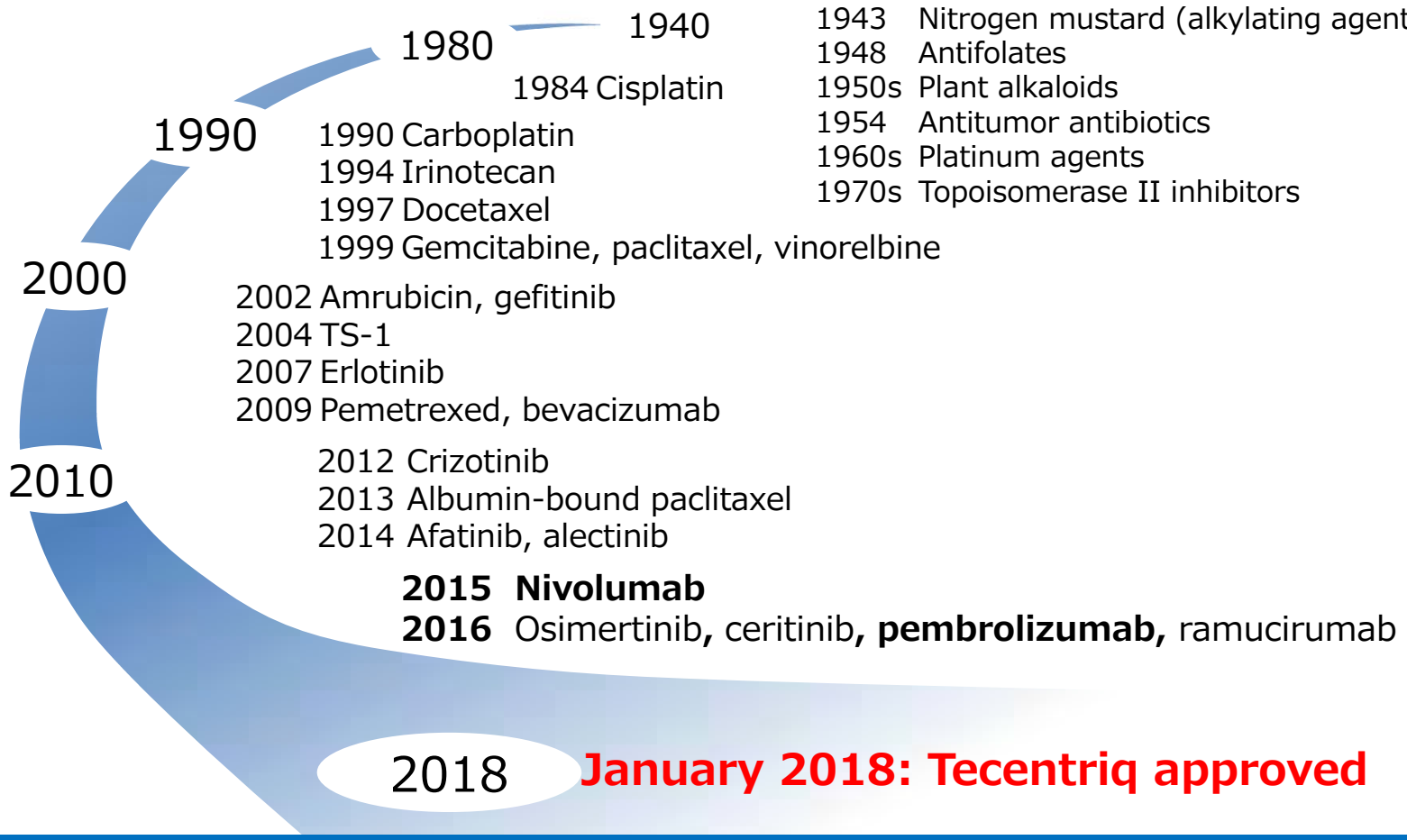
Yuichiro Ohe, M.D.
Deputy Director, Chief,
Division of Thoracic Oncology
National Cancer Center Hospital, Japan

COI Disclosure

Name of lead presenter	Yuichiro Ohe	Institution or company/position	Deputy-director National Cancer Center Hospital

	No	If yes, please specify the name of company and/or organization, your status.
employee of company and/or profit-making organization	☑	
adviser of company and/or profit-making organization	☑	
profit of stock	☑	
lecturer fees	☐	AstraZeneca, Chugai, Lilly, ONO, BMS, Daiichi-Sankyo, Nipponkayaku, Boehringer Ingelheim, Bayer, Pfizer, MSD, Taiho
manuscript fees	☑	
research expenses	☐	AstraZeneca, Chugai, Lilly, ONO, BMS, Kyorin, Dainippon-Sumitomo, Pfizer, Taiho, Novartis, Kissei, Ignyta
contributions	☑	
fees of testimony, judgment, comment, etc.	☐	AstraZeneca, ONO, BMS
representative of organization for clinical study receiving research expenses from company	☑	
presents or any payment	☑	

Evolution of Drug Treatment for Non-Small Cell Lung Cancer in Japan

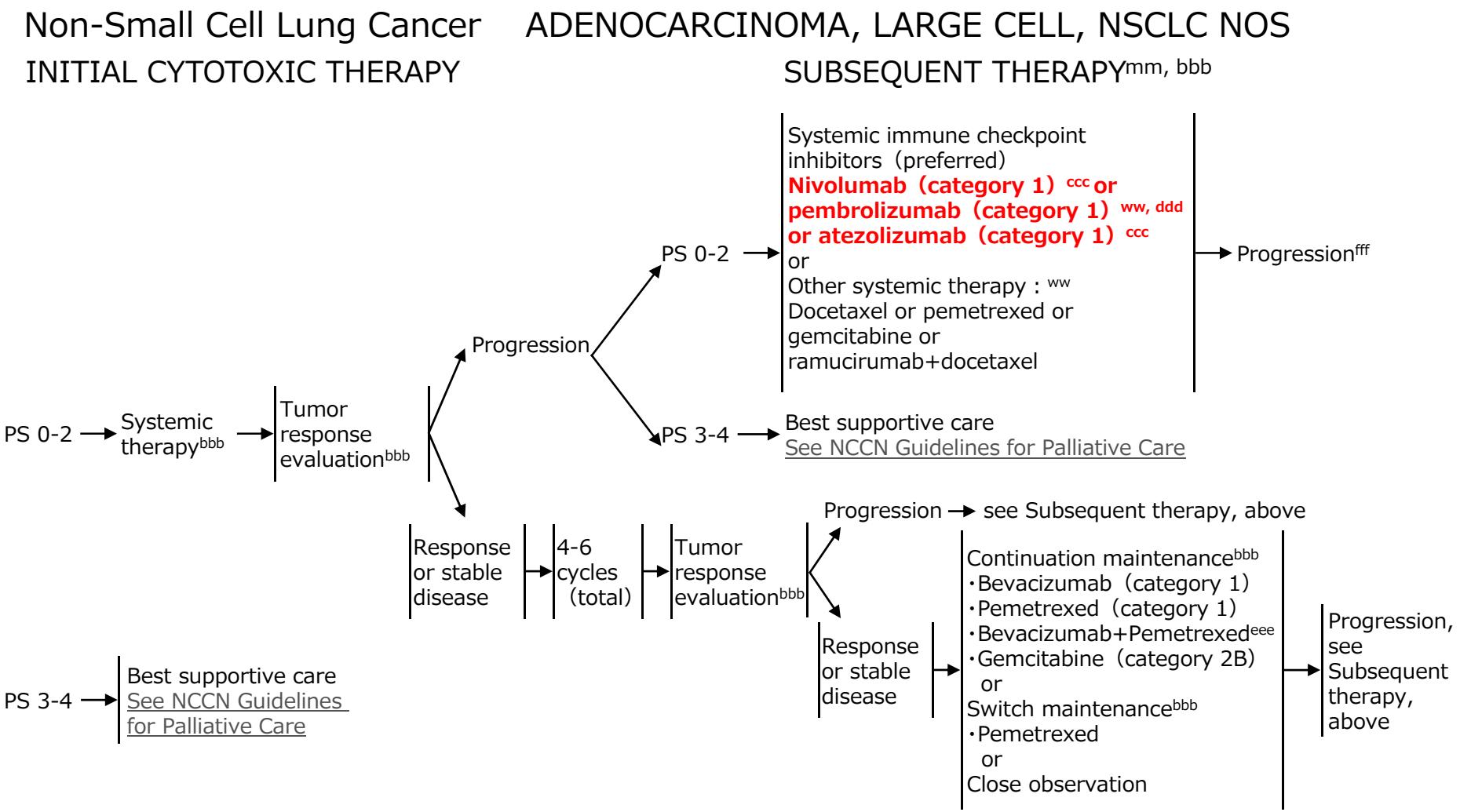


With the development of cytotoxic anticancer drugs, molecular targeted drugs, and cancer immunotherapy (immune checkpoint inhibitors), the drug treatment options for non-small cell lung cancer have widened.

NB: Years represent the dates of approval (additional indication) for non-small cell lung cancer in Japan

Modified from Kudo K, and Kiura K: Annals of the Japanese Respiratory Society 2014; 3 (1): 35-42
COI: One or more of the authors have received lecture fees from Chugai Pharmaceutical Co., Ltd.

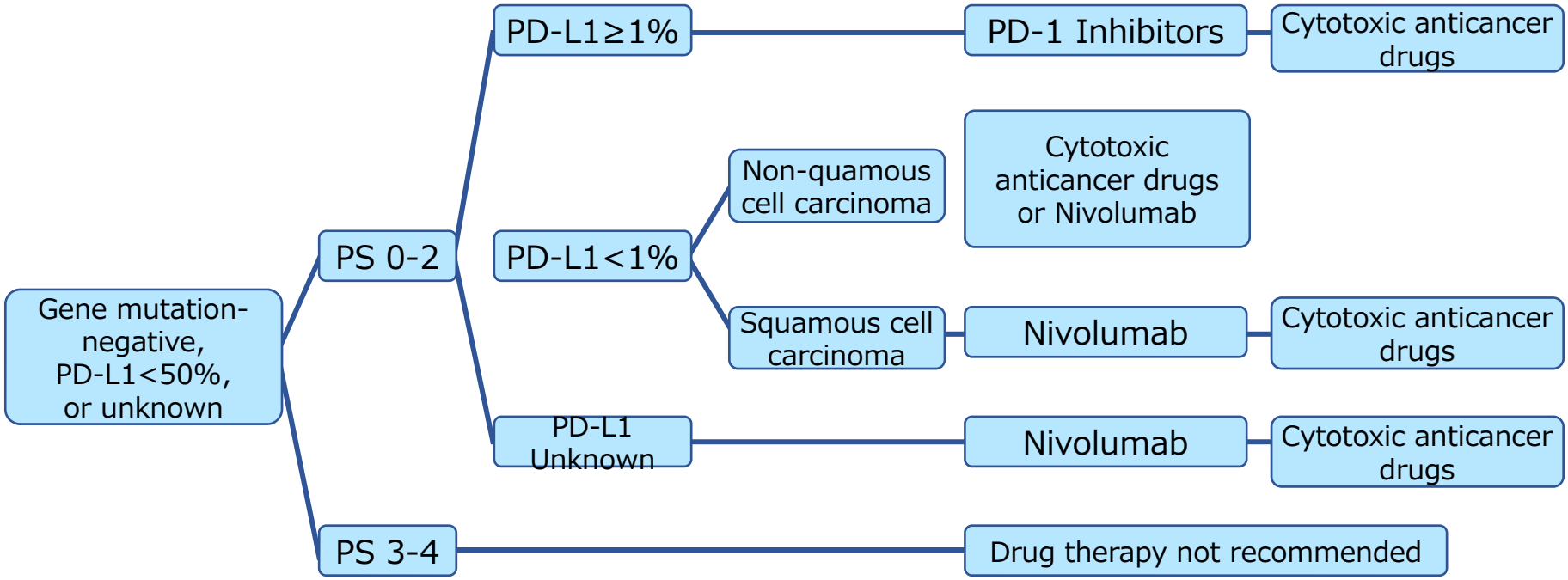
NCCN Guideline (Version 2. 2018)



Clinical Guidelines for the Management of Lung Cancer 2017

Stage IV non-small cell lung cancer: Mutation negative, PD-L1<50% or unknown

Second-line treatment and beyond



* For mutation-positive patients with exacerbation after treatment with kinase inhibitors and patients with PD-L1≥50% and exacerbation after treatment with pembrolizumab too, consider the treatment options in accordance with the tree diagram below (after prior treatment with pembrolizumab however, efficacy and safety of second-line treatment and beyond with a PD-1 inhibitor remains unclear).

The Japan Lung Cancer Society (ed): EBM-Based Clinical Guidelines for the Management of Lung Cancer. 2017

Tecentriq—Key Clinical Studies

Clinical studies involving Japanese sites

2014

OAK Study (Phase III)
Patients with locally advanced or metastatic non-small cell lung cancer (second or third-line treatment)

BIRCH Study (Phase II)
Patients with PD-L1-positive (TC2/3 or IC2/3) locally advanced or metastatic non-small cell lung cancer (first, second, third-line treatment, or beyond)

2013

POPLAR Study (Phase II)
Patients with locally advanced or metastatic non-small cell lung cancer (second or third-line treatment)

FIR Study (Phase II)
Patients with PD-L1-positive (TC2/3 or IC2/3) locally advanced or metastatic non-small cell lung cancer (first, second-line treatment, or beyond)

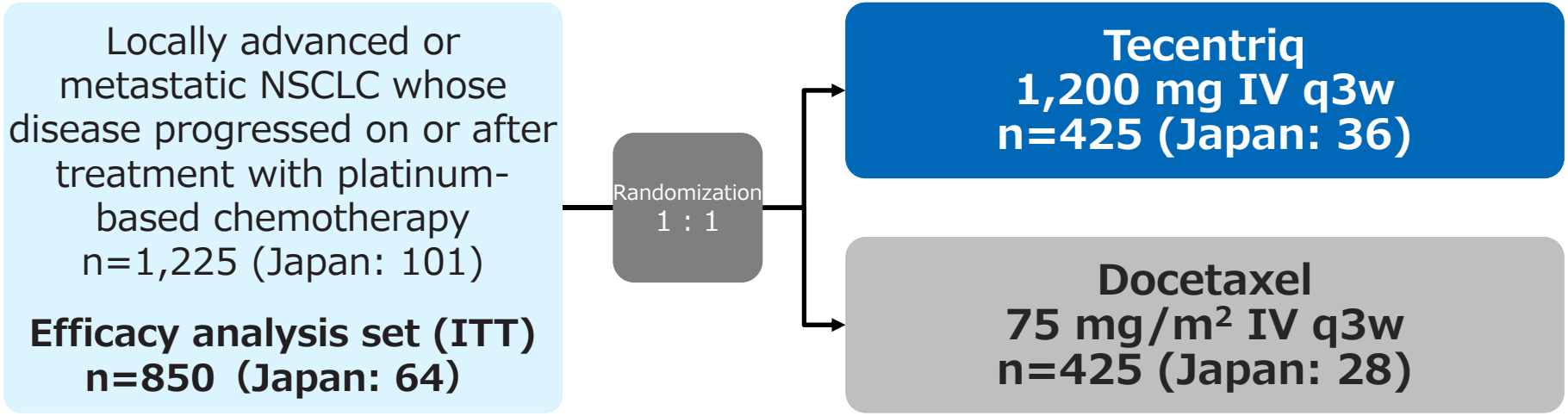
JO28944 Study (Phase I)
Japanese patients with advanced or recurrent solid cancers

2011

PCD4989g Study (NSCLC Cohort) (Phase I)
Patients with locally advanced or metastatic non-small cell lung cancer*
* Patients eligible for the overall study were those with locally advanced or metastatic solid tumors or hematopoietic malignancies.

Clinical study designs mainly intended for evaluation of efficacy
In-house source: Evaluation dossier for Tecentriq approval

Study Design of OAK Study



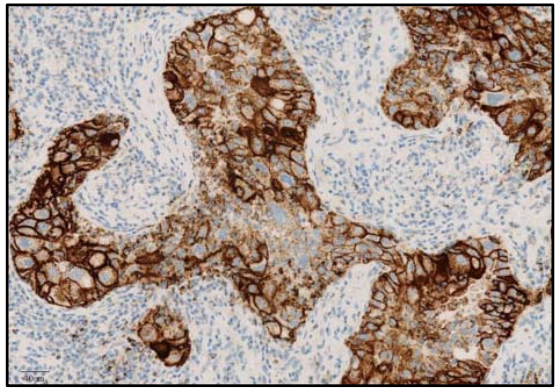
Stratification factors:
- PD-L1 expression (IC0, IC1, IC2, IC3)
- Prior chemotherapy regimens (1 or 2)
- Histology (non-squamous or squamous cell carcinoma)

Primary endpoint: OS in the ITT population and PD-L1 subgroups
Secondary endpoints: PFS, ORR, DOR (RECIST v1.1, investigator assessed)
Analysis plan: ITT for primary endpoint analysis was the first 850 enrolled patients. Subgroup analysis was conducted based on pre-planned IHC for PD-L1 expression and histology.

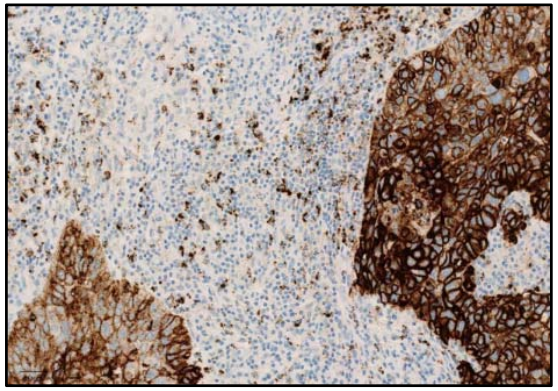
Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

IHC Scoring Standards for PD-L1 Expression

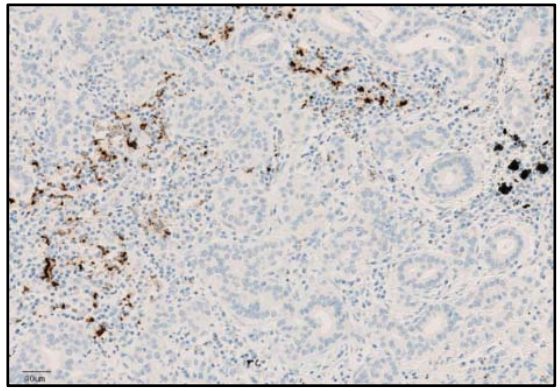
Calculated from Immunohistochemistry (IHC) using SP142 antibody (Ventana)



Staining in TC



Staining in TC and IC



Staining in IC

PD-L1 expression in tumor cells (TC)		PD-L1 expression in tumor-infiltrating immune cells (IC)	
TC score	PD-L1 expression ratio	IC score	PD-L1 expression ratio
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

Baseline Characteristics (OAK Study)

Characteristic	Tecentriq (n=425)	Docetaxel (n=425)
Age, (years)		
Median	63.0	64.0
Range	33-82	34-85
Age ≥65 years	190 (45%)	207 (49%)
Sex		
Male	261 (61%)	259 (61%)
Female	164 (39%)	166 (39%)
Race		
White	302 (71%)	296 (70%)
Asian	85 (20%)	95 (22%)
Black	5 (1%)	11 (3%)
Other*	13 (3%)	9 (2%)
Unknown	20 (5%)	14 (3%)
ECOG performance status		
0	155 (36%)	160 (38%)
1	270 (64%)	265 (62%)
Tobacco use history		
Never	84 (20%)	72 (17%)
Current	59 (14%)	67 (16%)
Previous	282 (66%)	286 (67%)

*Other includes American Indian, Alaska native, Hawaiian native, other Pacific Islander, other

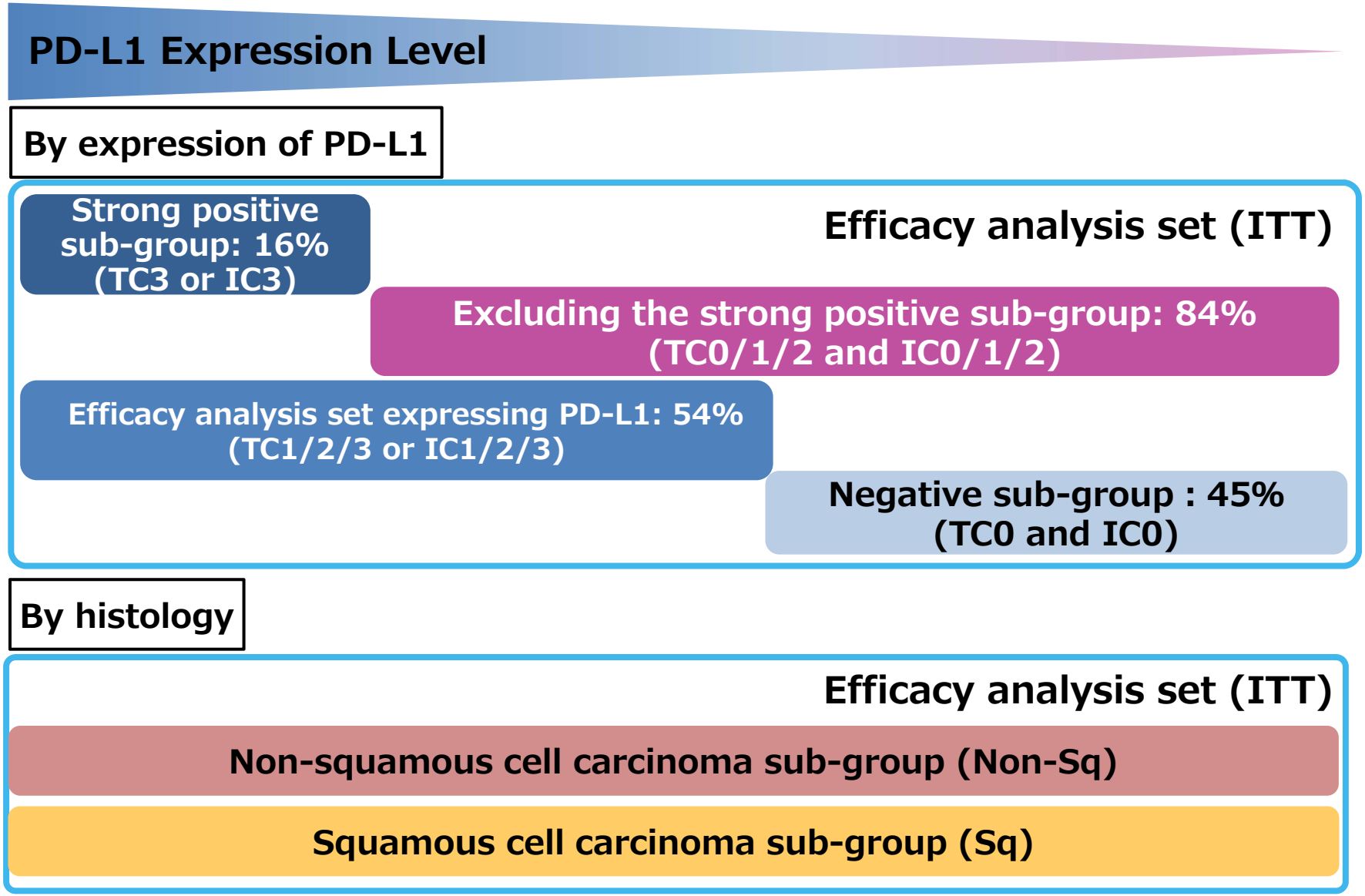
Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

Baseline Characteristics (OAK Study)

Characteristic	Tecentriq (n=425)	Docetaxel (n=425)
EGFR mutation		
Positive	42 (10%)	43 (10%)
Negative	318 (75%)	310 (73%)
Unknown	65 (15%)	72 (17%)
EML4-ALK mutation		
Positive	2 (<1%)	0
Negative	223 (52%)	201 (47%)
Unknown	200 (47%)	224 (53%)
Histology		
Non-Squamous	313 (74%)	315 (74%)
Squamous	112 (26%)	110 (26%)
PD-L1 subgroups		
TC3 or IC3	72 (17%)	65 (15%)
TC2/3 or IC2/3	129 (30%)	136 (32%)
TC1/2/3 or IC1/2/3	241 (57%)	222 (52%)
TC0 and IC0	180 (42%)	199 (47%)
Unknown	4 (1%)	4 (1%)
Number of prior therapies in the locally advanced or metastatic setting		
1	320 (75%)	320 (75%)
2	105 (25%)	105 (25%)

Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

Sub-groups for which Efficacy was Investigated in the OAK Study



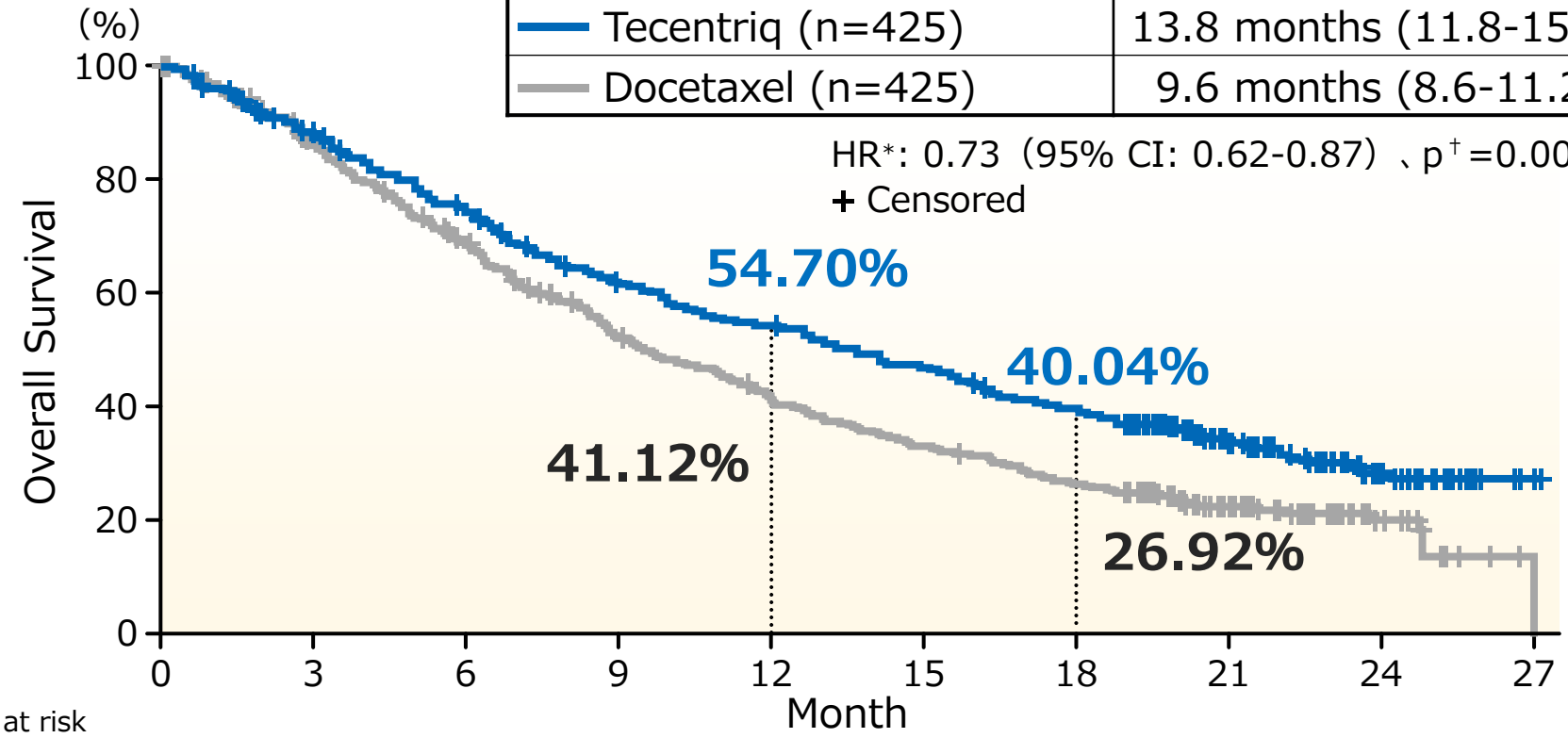
Overall Survival in ITT Population (OAK Study)

Primary endpoint

	Median OS (95% CI)
Tecentriq (n=425)	13.8 months (11.8-15.7)
Docetaxel (n=425)	9.6 months (8.6-11.2)

HR*: 0.73 (95% CI: 0.62-0.87) 、p†=0.0003

+ Censored



No. at risk										
Tecentriq	425	363	305	248	218	188	157	74	28	1
Docetaxel	425	336	263	195	151	123	98	51	16	–

＊ Stratified HR

† Stratified Log-rank test

Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

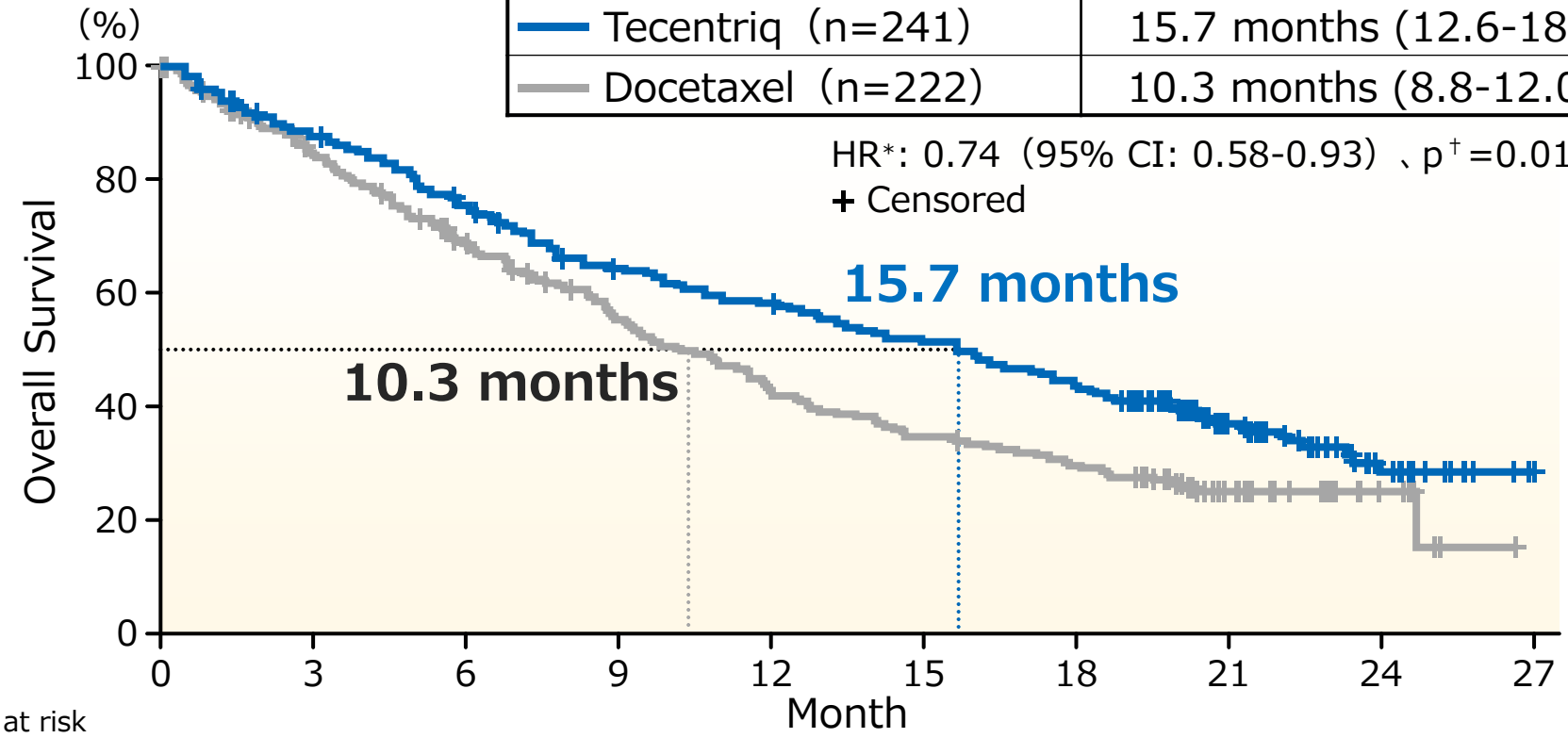
Overall Survival in PD-L1 Expressing Efficacy Analysis Set (OAK Study)

Primary endpoint

	Median OS（95% CI）
Tecentriq（n=241）	15.7 months (12.6-18.0)
Docetaxel（n=222）	10.3 months (8.8-12.0)

HR*: 0.74（95% CI: 0.58-0.93）、p†=0.0102

+ Censored



No. at risk										
Tecentriq	241	207	176	145	131	115	98	47	19	1
Docetaxel	222	172	136	105	81	65	55	28	8	–

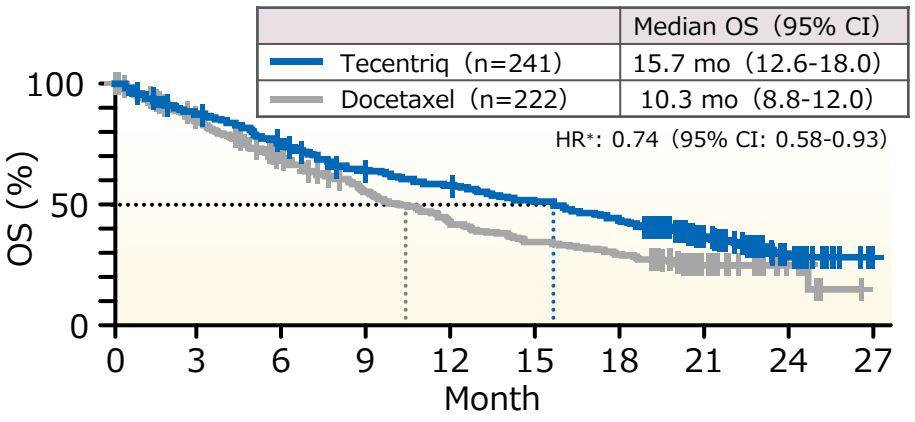
＊ Stratified HR

† Stratified Log-rank test

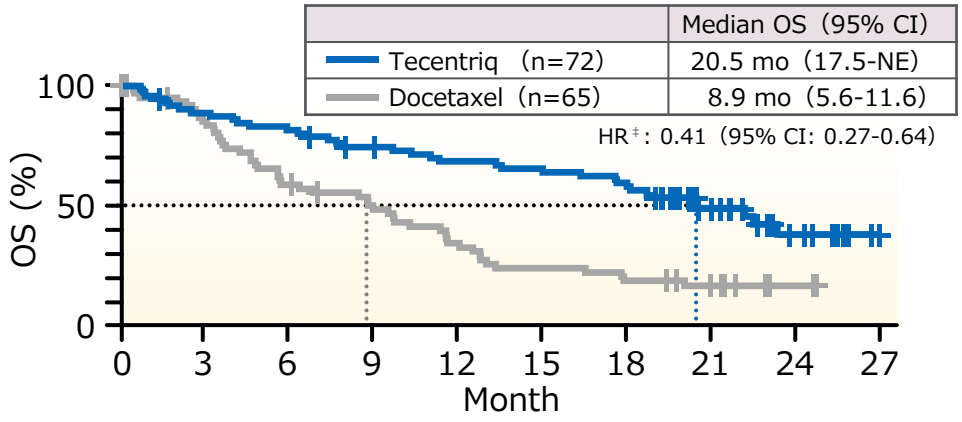
Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

Overall Survival in PD-L1 Expressing Subgroups (OAK Study)

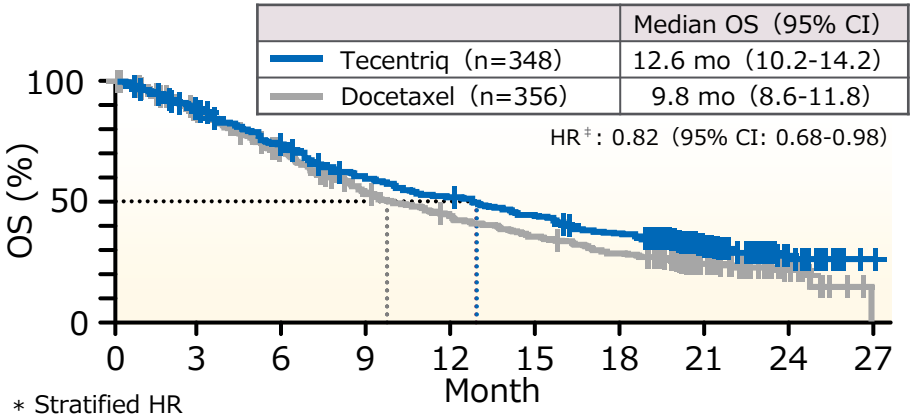
TC1/2/3 or IC1/2/3



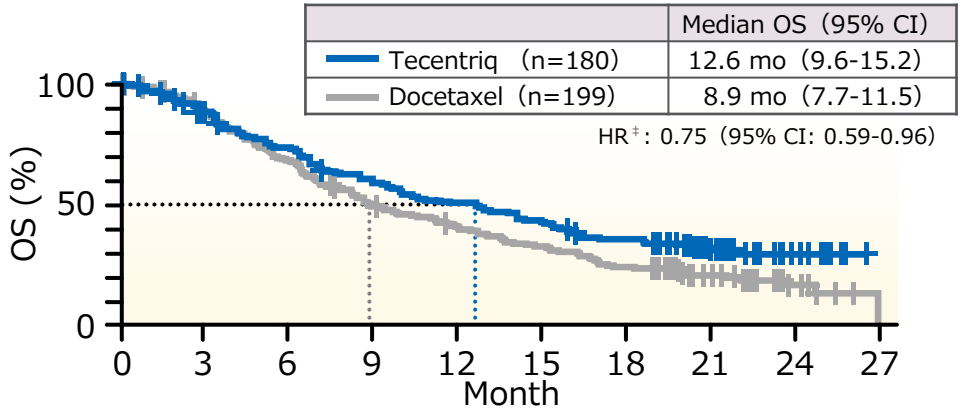
TC3 or IC3



TC0/1/2 and IC0/1/2



TC0 and IC0



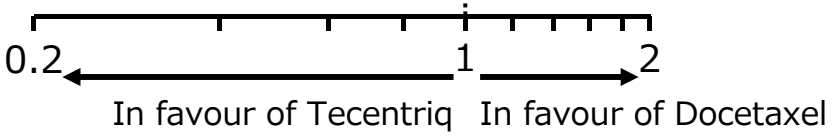
* Stratified HR
‡ Non-stratified HR
NE: Not Estimable

Phase III multinational study (OAK study)
In-house source: Evaluation dossier for Tecentriq approval

OS : Subgroup Analysis by PD-L1 Expression (OAK Study)

Primary analysis | Subgroup analysis

	n (%)	Median OS (month)		HR* (95% CI)
		Tecentriq	Docetaxel	
ITT population†	850 (100)	13.8	9.6	0.73 (0.62-0.87)
TC3 or IC3‡	137 (16)	20.5	8.9	0.41 (0.27-0.64)
TC2/3 or IC2/3‡	265 (31)	16.3	10.8	0.67 (0.49-0.90)
TC1/2/3 or IC1/2/3†	463 (54)	15.7	10.3	0.74 (0.58-0.93)
TC0/1/2 and IC0/1/2‡	704 (83)	12.6	9.8	0.82 (0.68-0.98)
TC0 and IC0‡	379 (45)	12.6	8.9	0.75 (0.59-0.96)

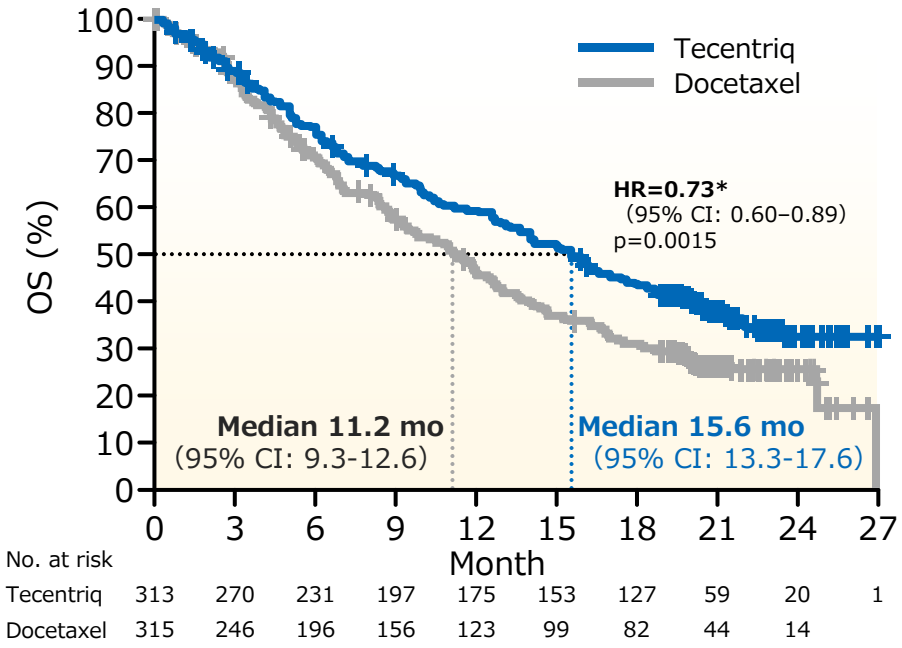


* ITT and TC1/2/3 or IC1/2/3: Stratified HR
Other subgroups: Non-stratified HR
† Primary endpoint
‡ Subgroup analysis

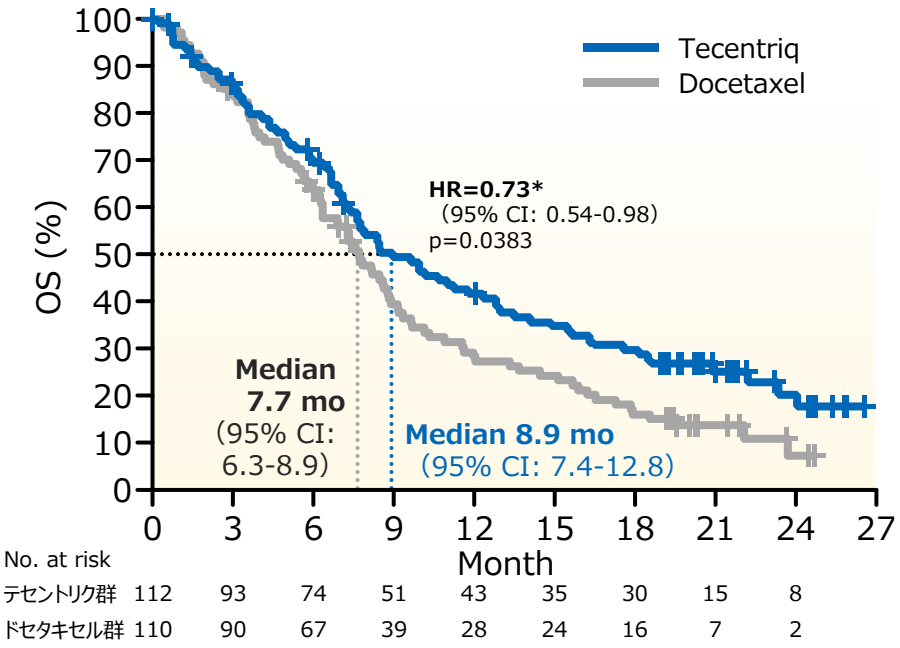
Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

OS: Subgroup Analysis by Histology (OAK Study)

Non-squamous cell carcinoma



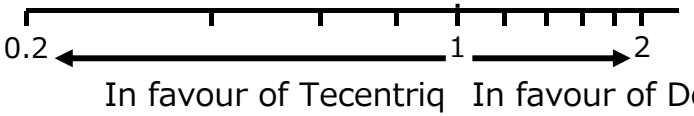
Squamous cell carcinoma



Minimum follow up=19 months

	n（%）	Median OS (month)		HR* (95% CI)
		Tecentriq	Docetaxel	
ITT	850（100）	13.8	9.6	0.73（0.62-0.87）
Non-squamous	628（74）	15.6	11.2	0.73（0.60-0.89）
Squamous	222（26）	8.9	7.7	0.73（0.54-0.98）

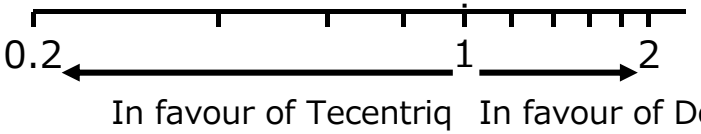
＊ ITT: Stratified HR, Subgroup: Non-stratified HR



Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

OS: Subgroup Analysis by Baseline Characteristics (OAK Study)

	n (%)	Median OS (month)		HR* (95% CI)
		Tecentriq	Docetaxel	
Female	330 (39)	16.2	11.2	0.64 (0.49-0.85)
Male	520 (61)	12.6	9.2	0.79 (0.64-0.97)
<65 years	453 (53)	13.2	10.5	0.80 (0.64-1.00)
≥65 years	397 (47)	14.1	9.2	0.66 (0.52-0.83)
ECOG PS 0	315 (37)	17.6	15.2	0.78 (0.58-1.04)
ECOG PS 1	535 (63)	10.6	7.6	0.68 (0.56-0.84)
1 prior therapy	640 (75)	12.8	9.1	0.71 (0.59-0.86)
2 prior therapies	210 (25)	15.2	12.0	0.80 (0.57-1.12)
Non-squamous	628 (74)	15.6	11.2	0.73 (0.60-0.89)
Squamous	222 (26)	8.9	7.7	0.73 (0.54-0.98)
Never smokers	156 (18)	16.3	12.6	0.71 (0.47-1.08)
Current/previous smokers	694 (82)	13.2	9.3	0.74 (0.61-0.88)
CNS metastasis	85 (10)	20.1	11.9	0.54 (0.31-0.94)
No CNS metastasis	765 (90)	13.0	9.4	0.75 (0.63-0.89)
KRAS mutant	59 (7)	17.2	10.5	0.71 (0.38-1.35)
KRAS wildtype	203 (24)	13.8	11.3	0.83 (0.58-1.18)
EGFR mutant	85 (10)	10.5	16.2	1.24 (0.71-2.18)
EGFR wildtype	628 (74)	15.3	9.5	0.69 (0.57-0.83)
ITT population	850 (100)	13.8	9.6	0.73 (0.62-0.87)

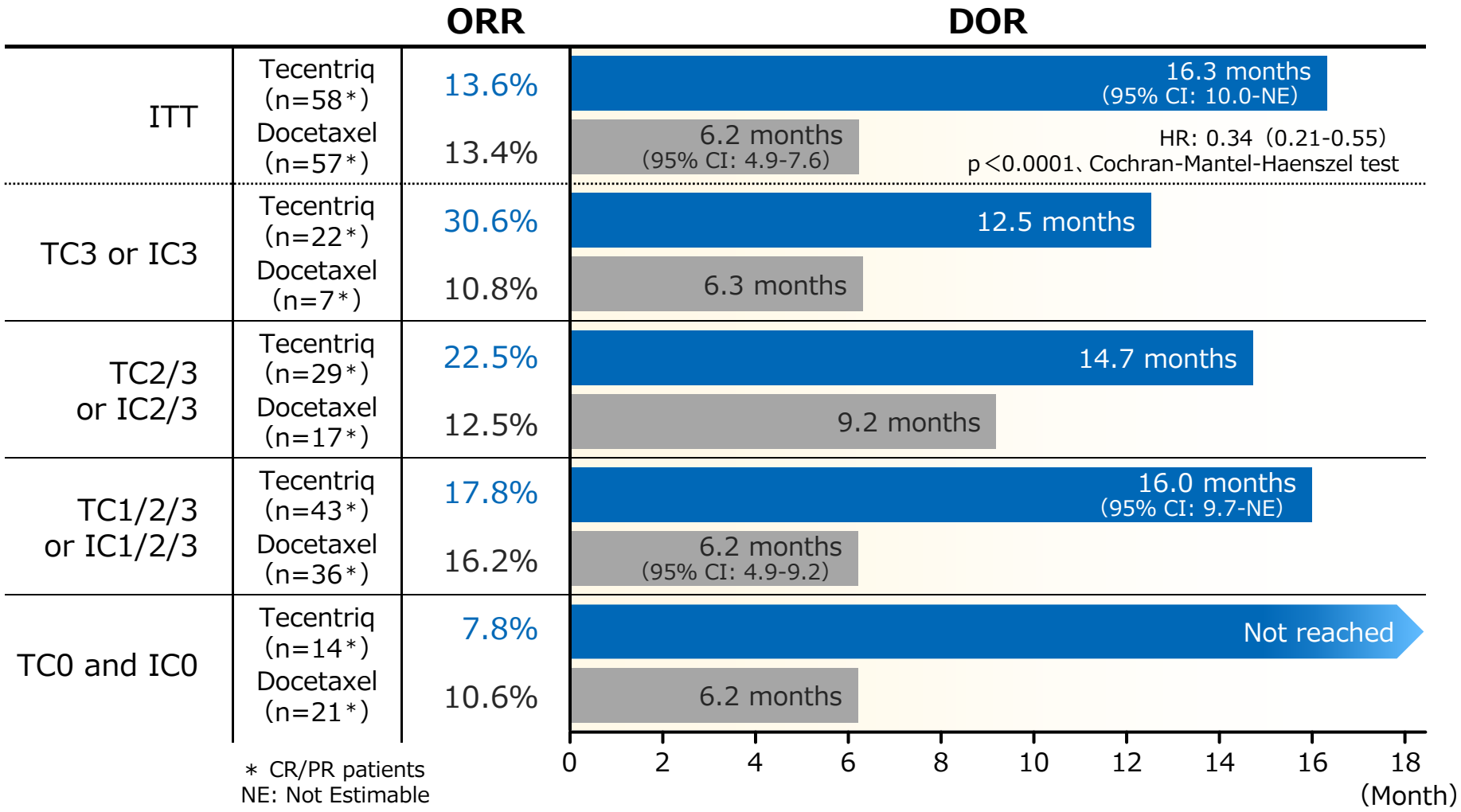


* ITT: Stratified HR, Subgroup: Non-stratified HR

Rittmeyer A, et al.: Lancet 2017; 389 (10066) : 255-65.

ORR/DOR: Subgroup Analysis by PD-L1 Expression (OAK Study)

Secondary endpoints



＊ CR/PR patients
NE: Not Estimable

Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65, Supplementary appendix

Follow-up Treatments: ITT Population

Treatments	Tecentriq (n=425)	Docetaxel (n=425)
Immunotherapy	19 (4.5%)	73 (17.2%)
Nivolumab	16 (3.8%)	58 (13.6%)
MEDI4736 (anti-PD-L1 monoclonal antibody)※2	0	7 (1.6%)
L-DOS47 (anti-CEACAM6 AFAIKL2 immunoconjugate)※2	2 (0.5%)	3 (0.7%)
Lambrolizumab※2	0	4 (0.9%)
Ipilimumab※1	0	2 (0.5%)
Durvalumab※2	0	1 (0.2%)
RO6958688 (T-cell bispecific monoclonal antibody)※2	1 (0.2%)	0
Tremelimumab※2	0	1 (0.2%)

※1 Not approved for NSCLC in Japan
※2 Not approved in Japan
Same types of treatments except protocol treatments were regarded as one time, different types were regarded as other treatments.
CEACAM6=carcinoembryonic antigen related cell adhesion molecule 6

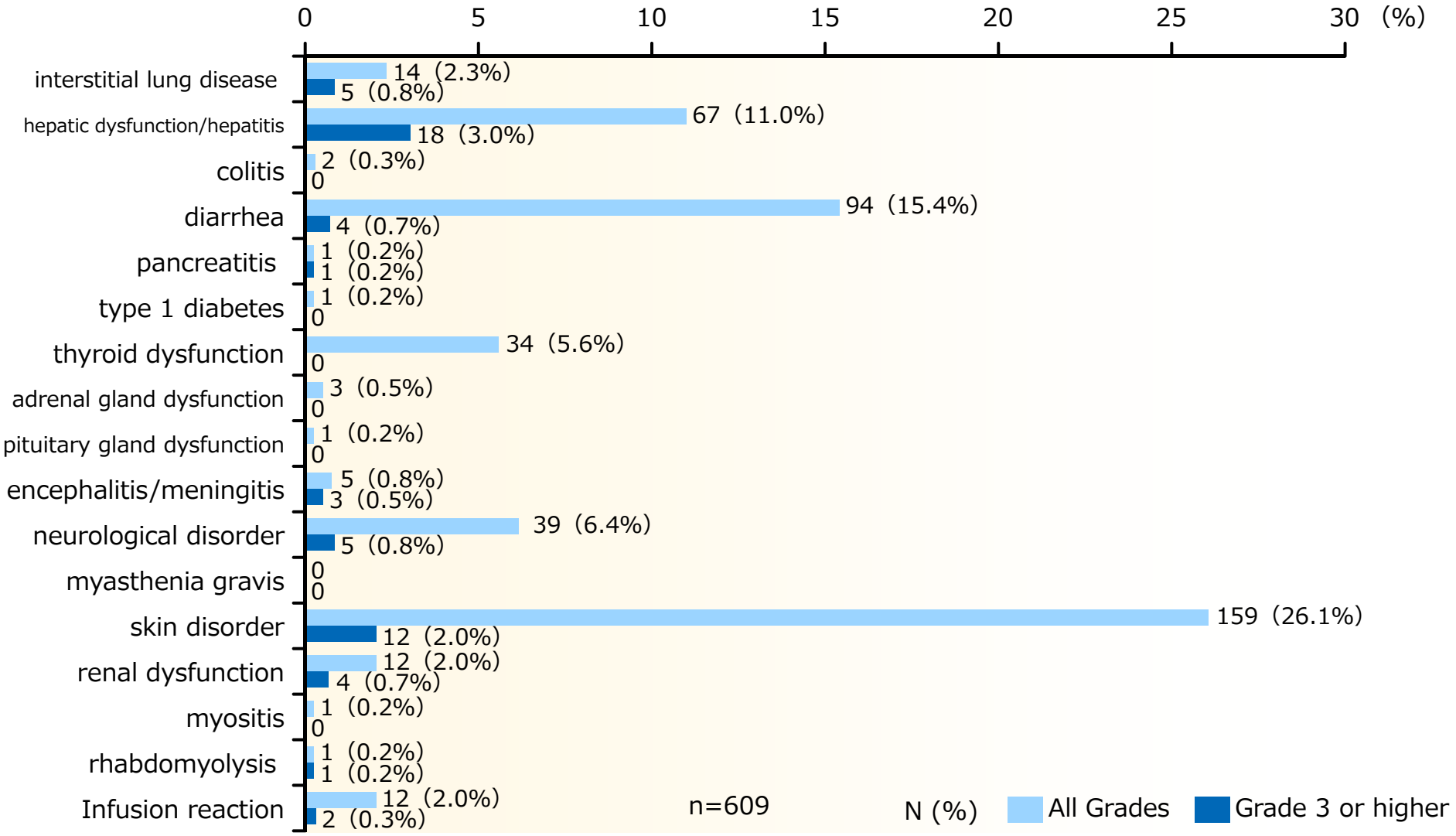
Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65, Supplementary appendix

Summary of Safety Profiles

	Tecentriq (n=609)	Docetaxel (n=578)
All adverse events (AEs)	573 (94.1%)	555 (96.0%)
Treatment-related AEs	390 (64.0%)	496 (85.8%)
Grade 3-4 AEs	227 (37.3%)	310 (53.6%)
Treatment-related Grade 3-4 AEs	90 (14.8%)	247 (42.7%)
All deaths	10 (1.6%)	14 (2.4%)
Treatment-related deaths	0	1 (0.2%)
Serious AEs	194 (31.9%)	181 (31.3%)
AEs leading to withdrawal from treatments	46 (7.6%)	108 (18.7%)
AEs leading to dose modification, delay, or interruption	152 (25.0%)	210 (36.3%)

Rittmeyer A, et al.: Lancet 2017; 389（10066）: 255-65.

Summary of Adverse Events (Tecentriq)



Cases with negative causal relationship are also included.
Definition of adverse events such as interstitial lung disease is consisted of multiple events.

This study was supported by F. Hoffmann-La Roche Ltd. and Genentech Inc.
Evaluation dossier for Tecentriq approval: Rittmeyer A, et al.: Lancet, 2017; 389（10066）: 255-65.
Phase III multinational study (OAK study)

Immune Related Adverse Events

Immune related adverse events (safety population)

	Tecentriq			
	All（n=609）		Japan（n=56）	
	All Grade	Grade 3 or higher	All Grade	Grade 3 or higher
interstitial lung disease	14（2.3%）	5（0.8%）	5（8.9%）	1（1.8%）
hepatic dysfunction/hepatitis	67（11.0%）	18（3.0%）	10（17.9%）	2（3.6%）
colitis	2（0.3%）	0	0	0
diarrhea	94（15.4%）	4（0.7%）	8（14.3%）	0
pancreatitis	1（0.2%）	1（0.2%）	0	0
type 1 diabetes	1（0.2%）	0	0	0
thyroid dysfunction	34（5.6%）	0	3（5.4%）	0
adrenal gland dysfunction	3（0.5%）	0	0	0
pituitary gland dysfunction	1（0.2%）	0	1（1.8%）	0
encephalitis/meningitis	5（0.8%）	3（0.5%）	4（7.1%）	3（5.4%）
neurological disorder	39（6.4%）	5（0.8%）	1（1.8%）	1（1.8%）
myasthenia gravis	0	0	0	0

This study was supported by F. Hoffmann-La Roche Ltd. and Genentech Inc.
Evaluation dossier for Tecentriq approval: Rittmeyer A, et al.: Lancet, 2017; 389（10066）: 255-65.
Phase III multinational study (OAK study)

Summary of OAK Study

- In the Phase III multinational study (OAK Study), Tecentriq significantly prolonged overall survival (OS) versus docetaxel, regardless of PD-L1 expression or histological type (non-squamous cell carcinoma or squamous cell carcinoma).
- The frequencies of adverse events were 94% in the Tecentriq group and 96% in the Docetaxel group, and those of Grade 3 or 4 adverse events were 37% and 54%, respectively.
- No treatment-related Grade 5 adverse events were seen in the Tecentriq group.

Indications of Tecentriq

INDICATIONS

Unresectable advanced or recurrent NSCLC

<Precautions for Indications>

1. Efficacy and safety of Tecentriq in chemotherapy-naive patients have not been established.
2. Efficacy and safety of Tecentriq in postoperative adjuvant chemotherapy have not been established.
3. Eligible patients should be selected after closely reading the Clinical Studies section, which provides information such as the prior treatment history of patients in the clinical studies, to gain a thorough understanding of the efficacy and safety of Tecentriq.

Dosage and Administration of Tecentriq

Every 3 weeks

1,200mg
Fix dose

1st dose
60 minutes

If well tolerated

2nd/subsequent dose
30 minutes

Excerpt from <Precautions for Usage>
2. To prepare for use, draw 20 mL of Tecentriq into a syringe, add to about 250 mL of physiological saline JP, then administer by intravenous infusion.

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Tomoyuki Shimamura