TECENTRIQ®
Intravenous Infusion 1200mg
Product Overview

Mikio Sakai
TECENTRIQ Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.
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Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
**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
History of Development of Tecentriq

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

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: Analysis results for OAK Study reported at ESMO

OAK Study

October: Results for Japanese sub-group analysis reported at JLCS Annual Meeting

2017
September: Approved in the EU (locally advanced or metastatic NSCLC in patients previously treated with chemotherapy)

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

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

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

October: Analysis results for OAK Study reported at ESMO

TBP: Treatment beyond disease progression
TMB: Tumor mutational burden

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

## 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

### Important Missing Information
- None

## 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)

## 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)

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

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### Important Missing Information
- None

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- Interstitial lung disease
- Hepatic dysfunction
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### Risk Minimization Plan

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### All-patient surveillance:
- 1000 patients
- Registration for 12 months from market launch
## Ongoing Clinical Studies of Tecentriq in the Lung Cancer Field

### NSCLC

<table>
<thead>
<tr>
<th>Plus molecular targeted drugs</th>
<th>CBDCA + PTX ± BEV : IMpower150</th>
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<tr>
<td>CBDCA + nab-PTX : IMpower130</td>
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<td>CBDCA + PTX/nab-PTX : IMpower131</td>
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<td>CBDCA/CDDP + PEM : IMpower132</td>
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<tr>
<td>IMpower110</td>
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<tr>
<td>IMpower010</td>
<td></td>
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<tr>
<td>B-FAST (TMB assessment)</td>
<td></td>
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</table>

| Tecentriq alone               |
| CBDCA + ETP : IMpower133      |

### SCLC

| Plus chemotherapy             |
| CBDCA + ETP : IMpower133      |

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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/
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 1** Release of cancer antigen

**Step 2** Presentation of cancer antigen to T cell

**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)

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

The author is Genentech employee.
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)

**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

The Cancer-Immunity Cycle

Step 1
Release of cancer antigen

Step 2
Presentation of cancer antigen by dendritic cell

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 3. Priming and Activation of Naive T Cells

**Lymph node**

**Naive CD8⁺ T cell**
- **Cancer antigen**
- **MHC Class I molecule**
- **CD28**

**Activation, clonal proliferation, differentiation**
- **Cytokines** (IL-2, IFN-γ)

**Naive CD4⁺ T cell**
- **Cancer antigen**
- **MHC Class II molecule**
- **CD28**

**Activation, clonal proliferation, differentiation**

**Dendritic cell**
- **B7-1, B7-2**
- **Cancer antigen**

**CTL:** Cytotoxic T cell (CD8⁺ T cell)
- **CD28**
- **B7-1, B7-2**

**Th:** Helper T cell (CD4⁺ T cell)
- **CD28**

**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

**Co-stimulatory molecules:** Promote T cell activation via stimulatory signals

- B7-1, B7-2
- CD137L
- GITRL
- OX40L
- ICOSL
- CD28

**Co-inhibitory molecules:** Inhibit T cell activation via inhibitory signals

- PD-1
- PD-L1
- PD-L2
- B7-1, B7-2
- CTLA-4
- MHC Class II
- GAL-9
- HVEM
- TIM-3
- BTLA
- LAG-3

**T cell**

**Immune checkpoint molecule**

**Acceleration of the immune system**

**Braking of the immune system**

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

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
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);
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.
The Cancer-Immunity Cycle

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

Step 1: Release of cancer antigen
Step 2: Priming and T cell activation
Step 3: Trafficking of CTL to tumor
Step 4: Infiltration of CTL into the tumor
Step 5: Recognition of cancer cell by CTL
Step 6: Killing of cancer cell by CTL (Extinction of cancer cells)

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

Tecentriq: Three Features of its Mode of Action

**Direct**

Targets PD-L1 on the surface of tumor cells and immune cells, reactivating T cells

**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.

**Selective**

No interference to the PD-L2/PD-1 pathway, thereby potentially maintaining immune homeostasis.

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

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

Anti-PD-1 antibodies
- Pembrolizumab
- Nivolumab

Anti-PD-L1 antibody
- Tecentriq

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.

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.

Future Possibilities for Cancer Immunotherapy

Step 1
Release of cancer antigen
- Immunogenic cell death
- Tolerogenic cell death

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 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 4
Trafficking of CTL to tumor
- CX3CL1
- CXCL9
- CXCL10
- CCL4

Step 5
Infiltration of CTL into the tumor
- LFA1/ICAM1
- Selectin
- VEGF
- Endothelin B receptor

Step 6
Recognition of cancer cell by CTL
- 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

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

Effects of Anti-VEGF Therapy on the Tumor Microenvironment

*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.

**Ongoing Clinical Studies**

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<th>RG7446 (MPDL3280A)</th>
<th>NSCLC [2nd line]</th>
<th>Approved (18/01)</th>
<th>Phase III Multinational study</th>
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<th>Roche Tecentriq</th>
<th>Engineered anti-PDL1 monoclonal antibody</th>
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#: Additional indication

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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

<table>
<thead>
<tr>
<th>Name of lead presenter</th>
<th>Yuichiro Ohe</th>
<th>Institution or company/position</th>
<th>Deputy-director National Cancer Center Hospital</th>
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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.


COI: One or more of the authors have received lecture fees from Chugai Pharmaceutical Co., Ltd.
Non-Small Cell Lung Cancer

INITIAL CYTOTOXIC THERAPY

SUBSEQUENT THERAPY

Systemic immune checkpoint inhibitors (preferred)
- **Nivolumab (category 1)**
- **Pembrolizumab (category 1)**
- **Atezolizumab (category 1)**

Other systemic therapy:
- Docetaxel or pemetrexed or gemcitabine or ramucirumab+docetaxel

Best supportive care

See NCCN Guidelines for Palliative Care
Stage IV non-small cell lung cancer: Mutation negative, PD-L1<50% or unknown

**Second-line treatment and beyond**

- **Gene mutation-negative, PD-L1<50%, or unknown**
  - **PS 0-2**
    - **PD-L1≥1%**
      - PD-1 Inhibitors
      - Cytotoxic anticancer drugs
    - **PD-L1<1%**
      - Non-quamous cell carcinoma
      - Cytotoxic anticancer drugs or Nivolumab
    - **PD-L1 Unknown**
      - Squamous cell carcinoma
      - Nivolumab
    - **Drug therapy not recommended**
  - **PS 3-4**

*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).*
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

Locally advanced or metastatic NSCLC whose disease progressed on or after treatment with platinum-based chemotherapy
n=1,225 (Japan: 101)

Efficacy analysis set (ITT)
n=850 (Japan: 64)

Randomization
1 : 1

Docetaxel
75 mg/m² IV q3w
n=425 (Japan: 28)

Tecentriq
1,200 mg IV q3w
n=425 (Japan: 36)

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.

IHC Scoring Standards for PD-L1 Expression

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

<table>
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<tr>
<th>PD-L1 expression in tumor cells (TC)</th>
<th>PD-L1 expression in tumor-infiltrating immune cells (IC)</th>
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<td>TC score</td>
<td>PD-L1 expression ratio</td>
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<tr>
<td>TC3</td>
<td>$\geq 50%$</td>
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<tr>
<td>TC2</td>
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Staining in TC

Staining in TC and IC

Staining in IC

### Baseline Characteristics (OAK Study)

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<th>Docetaxel (n=425)</th>
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<td><strong>Age ≥65 years</strong></td>
<td>190 (45%)</td>
<td>207 (49%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>261 (61%)</td>
<td>259 (61%)</td>
</tr>
<tr>
<td>Female</td>
<td>164 (39%)</td>
<td>166 (39%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>302 (71%)</td>
<td>296 (70%)</td>
</tr>
<tr>
<td>Asian</td>
<td>85 (20%)</td>
<td>95 (22%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (1%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Other*</td>
<td>13 (3%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (5%)</td>
<td>14 (3%)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>155 (36%)</td>
<td>160 (38%)</td>
</tr>
<tr>
<td>1</td>
<td>270 (64%)</td>
<td>265 (62%)</td>
</tr>
<tr>
<td><strong>Tobacco use history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>84 (20%)</td>
<td>72 (17%)</td>
</tr>
<tr>
<td>Current</td>
<td>59 (14%)</td>
<td>67 (16%)</td>
</tr>
<tr>
<td>Previous</td>
<td>282 (66%)</td>
<td>286 (67%)</td>
</tr>
</tbody>
</table>

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

## Baseline Characteristics (OAK Study)

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

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

#### PD-L1 Expression Level

<table>
<thead>
<tr>
<th>By expression of PD-L1</th>
<th>Efficacy analysis set (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong positive sub-group: 16% (TC3 or IC3)</strong></td>
<td>Excluding the strong positive sub-group: 84% (TC0/1/2 and IC0/1/2)</td>
</tr>
<tr>
<td><strong>Efficacy analysis set expressing PD-L1: 54% (TC1/2/3 or IC1/2/3)</strong></td>
<td>Negative sub-group: 45% (TC0 and IC0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>By histology</th>
<th>Efficacy analysis set (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-squamous cell carcinoma sub-group (Non-Sq)</strong></td>
<td>Non-squamous cell carcinoma sub-group (Non-Sq)</td>
</tr>
<tr>
<td><strong>Squamous cell carcinoma sub-group (Sq)</strong></td>
<td>Squamous cell carcinoma sub-group (Sq)</td>
</tr>
</tbody>
</table>
Overall Survival in ITT Population (OAK Study)

Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>No. at risk</th>
<th>Month</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=425)</td>
<td>425 363 305 248 218 188 157 74 28 1</td>
<td>13.8 months (11.8-15.7)</td>
<td></td>
</tr>
<tr>
<td>Docetaxel (n=425)</td>
<td>425 336 263 195 151 123 98 51 16 –</td>
<td>9.6 months (8.6-11.2)</td>
<td></td>
</tr>
</tbody>
</table>

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

* Stratified HR
† Stratified Log-rank test

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

Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=241)</td>
<td>15.7 months (12.6-18.0)</td>
</tr>
<tr>
<td>Docetaxel (n=222)</td>
<td>10.3 months (8.8-12.0)</td>
</tr>
</tbody>
</table>

HR*: 0.74 (95% CI: 0.58-0.93)\(^+\), \(p^†=0.0102\)

\* Stratified HR
\+ Censored

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

**TC1/2/3 or IC1/2/3**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=241)</td>
<td>15.7 mo (12.6-18.0)</td>
</tr>
<tr>
<td>Docetaxel (n=222)</td>
<td>10.3 mo (8.8-12.0)</td>
</tr>
</tbody>
</table>

**TC3 or IC3**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=72)</td>
<td>20.5 mo (17.5-NE)</td>
</tr>
<tr>
<td>Docetaxel (n=65)</td>
<td>8.9 mo (5.6-11.6)</td>
</tr>
</tbody>
</table>

**TC0/1/2 and IC0/1/2**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=348)</td>
<td>12.6 mo (10.2-14.2)</td>
</tr>
<tr>
<td>Docetaxel (n=356)</td>
<td>9.8 mo (8.6-11.8)</td>
</tr>
</tbody>
</table>

**TC0 and IC0**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=180)</td>
<td>12.6 mo (9.6-15.2)</td>
</tr>
<tr>
<td>Docetaxel (n=199)</td>
<td>8.9 mo (7.7-11.5)</td>
</tr>
</tbody>
</table>

* 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)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Median OS (month)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Tecentriq</strong></td>
<td><strong>Docetaxel</strong></td>
</tr>
<tr>
<td><strong>ITT population†</strong></td>
<td>850 (100)</td>
<td>13.8</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>TC3 or IC3‡</strong></td>
<td>137 (16)</td>
<td>20.5</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>TC2/3 or IC2/3‡</strong></td>
<td>265 (31)</td>
<td>16.3</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>TC1/2/3 or IC1/2/3†</strong></td>
<td>463 (54)</td>
<td>15.7</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>TC0/1/2 and IC0/1/2‡</strong></td>
<td>704 (83)</td>
<td>12.6</td>
<td>9.8</td>
</tr>
<tr>
<td><strong>TC0 and IC0‡</strong></td>
<td>379 (45)</td>
<td>12.6</td>
<td>8.9</td>
</tr>
</tbody>
</table>

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

---

In favour of Tecentriq  In favour of Docetaxel

OS: Subgroup Analysis by Histology (OAK Study)

Non-squamous cell carcinoma

- **Tecentriq** vs **Docetaxel**
- **Median OS (month)**
  - Non-squamous cell carcinoma:
    - Tecentriq: 11.2 mo (95% CI: 9.3-12.6)
    - Docetaxel: 15.6 mo (95% CI: 13.3-17.6)
- **HR = 0.73** (95% CI: 0.60-0.89) *p* = 0.0015

Squamous cell carcinoma

- **Tecentriq** vs **Docetaxel**
- **Median OS (month)**
  - Squamous cell carcinoma:
    - Tecentriq: 7.7 mo (95% CI: 6.3-8.9)
    - Docetaxel: 8.9 mo (95% CI: 7.4-12.8)
- **HR = 0.73** (95% CI: 0.54-0.98) *p* = 0.0383

**Minimum follow up = 19 months**

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Median OS (month)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tecentriq</td>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>850 (100)</td>
<td>13.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>628 (74)</td>
<td>15.6</td>
<td>11.2</td>
</tr>
<tr>
<td>Squamous</td>
<td>222 (26)</td>
<td>8.9</td>
<td>7.7</td>
</tr>
</tbody>
</table>

* ITT: Stratified HR, Subgroup: Non-stratified HR
### OS: Subgroup Analysis by Baseline Characteristics (OAK Study)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Median OS (month)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tecentriq</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Female</td>
<td>330 (39)</td>
<td>16.2</td>
<td>11.2</td>
</tr>
<tr>
<td>Male</td>
<td>520 (61)</td>
<td>12.6</td>
<td>9.2</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>453 (53)</td>
<td>13.2</td>
<td>10.5</td>
</tr>
<tr>
<td>≥65 years</td>
<td>397 (47)</td>
<td>14.1</td>
<td>9.2</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>315 (37)</td>
<td>17.6</td>
<td>15.2</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>535 (63)</td>
<td>10.6</td>
<td>7.6</td>
</tr>
<tr>
<td>1 prior therapy</td>
<td>640 (75)</td>
<td>12.8</td>
<td>9.1</td>
</tr>
<tr>
<td>2 prior therapies</td>
<td>210 (25)</td>
<td>15.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>628 (74)</td>
<td>15.6</td>
<td>11.2</td>
</tr>
<tr>
<td>Squamous</td>
<td>222 (26)</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Never smokers</td>
<td>156 (18)</td>
<td>16.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Current/previous smokers</td>
<td>694 (82)</td>
<td>13.2</td>
<td>9.3</td>
</tr>
<tr>
<td>CNS metastasis</td>
<td>85 (10)</td>
<td>20.1</td>
<td>11.9</td>
</tr>
<tr>
<td>No CNS metastasis</td>
<td>765 (90)</td>
<td>13.0</td>
<td>9.4</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>59 (7)</td>
<td>17.2</td>
<td>10.5</td>
</tr>
<tr>
<td>KRAS wildtype</td>
<td>203 (24)</td>
<td>13.8</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>EGFR mutant</strong></td>
<td>85 (10)</td>
<td>10.5</td>
<td>16.2</td>
</tr>
<tr>
<td><strong>EGFR wildtype</strong></td>
<td>628 (74)</td>
<td>15.3</td>
<td>9.5</td>
</tr>
<tr>
<td>ITT population</td>
<td>850 (100)</td>
<td>13.8</td>
<td>9.6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>In favour of Tecentriq</th>
<th>In favour of Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

### Secondary endpoints

<table>
<thead>
<tr>
<th>ITT</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=58*)</td>
<td>13.6%</td>
<td>16.3 months</td>
</tr>
<tr>
<td>Docetaxel (n=57*)</td>
<td>13.4%</td>
<td>(95% CI: 10.0-NE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 0.34 (0.21-0.55) p&lt;0.0001, Cochran-Mantel-Haenszel test</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TC3 or IC3</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=22*)</td>
<td>30.6%</td>
<td>12.5 months</td>
</tr>
<tr>
<td>Docetaxel (n=7*)</td>
<td>10.8%</td>
<td>6.3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TC2/3 or IC2/3</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=29*)</td>
<td>22.5%</td>
<td>14.7 months</td>
</tr>
<tr>
<td>Docetaxel (n=17*)</td>
<td>12.5%</td>
<td>9.2 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TC1/2/3 or IC1/2/3</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=43*)</td>
<td>17.8%</td>
<td>16.0 months</td>
</tr>
<tr>
<td>Docetaxel (n=36*)</td>
<td>16.2%</td>
<td>(95% CI: 9.7-NE)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TC0 and IC0</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq (n=14*)</td>
<td>7.8%</td>
<td>Not reached</td>
</tr>
<tr>
<td>Docetaxel (n=21*)</td>
<td>10.6%</td>
<td>6.2 months</td>
</tr>
</tbody>
</table>

* CR/PR patients
NE: Not Estimable

## Follow-up Treatments: ITT Population

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

※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

## Summary of Safety Profiles

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

### Summary of Adverse Events (Tecentriq)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades</th>
<th>Grade 3 or higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>interstitial lung disease</td>
<td>14 (2.3%)</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>hepatic dysfunction/hepatitis</td>
<td>18 (3.0%)</td>
<td>67 (11.0%)</td>
</tr>
<tr>
<td>colitis</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>diarrhea</td>
<td>4 (0.7%)</td>
<td>94 (15.4%)</td>
</tr>
<tr>
<td>pancreatitis</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>type 1 diabetes</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>thyroid dysfunction</td>
<td>0%</td>
<td>34 (5.6%)</td>
</tr>
<tr>
<td>adrenal gland dysfunction</td>
<td>3 (0.5%)</td>
<td>0%</td>
</tr>
<tr>
<td>pituitary gland dysfunction</td>
<td>0%</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>encephalitis/meningitis</td>
<td>5 (0.8%)</td>
<td>0%</td>
</tr>
<tr>
<td>neurological disorder</td>
<td>3 (0.5%)</td>
<td>39 (6.4%)</td>
</tr>
<tr>
<td>myasthenia gravis</td>
<td>0%</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>skin disorder</td>
<td>12 (2.0%)</td>
<td>159 (26.1%)</td>
</tr>
<tr>
<td>renal dysfunction</td>
<td>12 (2.0%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>myositis</td>
<td>0%</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>rhabdomyolysis</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>12 (2.0%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

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.
Phase III multinational study (OAK study)
### Immune Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>All (n=609)</th>
<th>Japan (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3 or higher</td>
</tr>
<tr>
<td>interstitial lung disease</td>
<td>14 (2.3%)</td>
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</tr>
<tr>
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<td>67 (11.0%)</td>
<td>18 (3.0%)</td>
</tr>
<tr>
<td>colitis</td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>diarrhea</td>
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</tbody>
</table>

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Phase III multinational study (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

1\textsuperscript{st} dose
60 minutes

2\textsuperscript{nd}/subsequent dose
30 minutes

*If well tolerated*

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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