Development Pipeline Progress Status

ONO PHARMACEUTICAL CO.,LTD.

Development status of ONO-4538(nivolumab)①

Development Code	Target Disease	JAPAN	US/EU	KOR/TAI
ONO-4538	Melanoma(2nd～)	Launched	Launched (US) Filing (EU)	Approved(KOR) Filing(TAI)
ONO-4538	Melanoma(1st) (combination with Ipilimumab)	Ⅱ	Ⅲ	—
ONO-4538	Non-small cell lung cancer(2nd～)	Filing	Launched (US) Filing (EU)	Ⅱ (KOR) Filing(TAI)
ONO-4538	Non-small cell lung cancer(1st)	Ⅲ	Ⅲ	Ⅲ
ONO-4538	Renal cell carcinoma(2nd)	Ⅲ	Ⅲ	—
ONO-4538	Renal cell carcinoma(1st) (combination with Ipilimumab)	Ⅲ	Ⅲ	—
ONO-4538	Head and neck carcinoma	Ⅲ	Ⅲ	Ⅲ
ONO-4538	Gastric cancer	Ⅲ	Ⅰ/Ⅱ	Ⅲ
ONO-4538	Glioblastoma	—	Ⅲ	—

yellow：up-date after Nov. 2014

Development status of ONO-4538(nivolumab)②

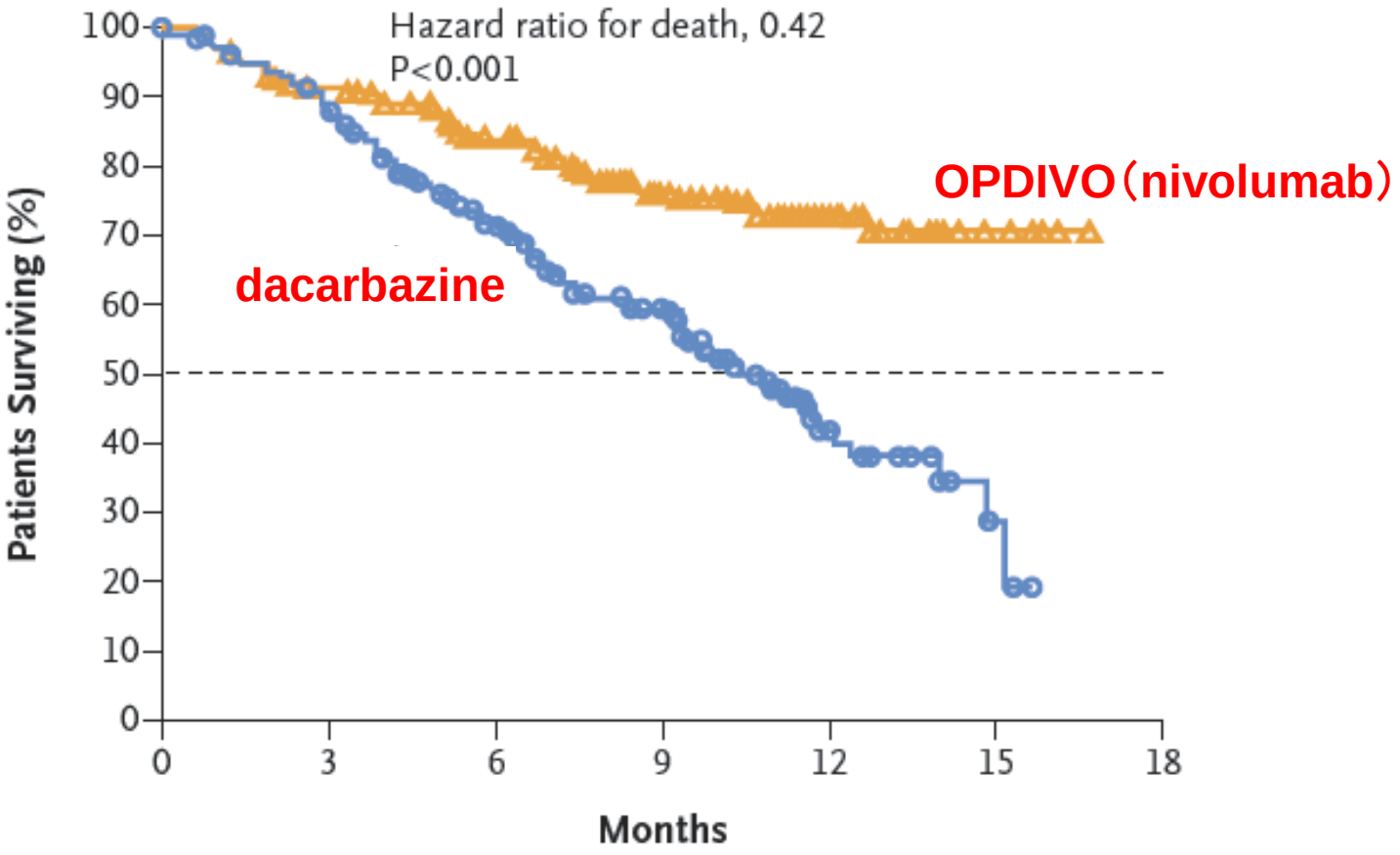
Development Code	Target Disease	US/EU	JAPAN
ONO-4538	Diffuse large B cell lymphoma (Non-Hodgkin lymphoma)	Ⅱ（BMS）	—
ONO-4538	Follicular lymphoma(Non-Hodgkin lymphoma)	Ⅱ（BMS）	—
ONO-4538	Hodgkin lymphoma	Ⅱ（BMS）	Ⅱ
ONO-4538	Esophageal cancer	—	Ⅱ
ONO-4538	Ovarian cancer(investigator initiated trial)	—	Ⅱ
ONO-4538	Bladder cancer	Ⅱ（BMS）	—
ONO-4538	Colon cancer	Ⅰ／Ⅱ（BMS）	—
ONO-4538	Pancreatic cancer, Small cell lung cancer, Triple negative breast cancer, Bladder cancer	Ⅰ／Ⅱ（BMS）	—
ONO-4538	Hepatocellular carcinoma	Ⅰ（BMS）	Ⅰ
ONO-4538	Hematologic malignancies	Ⅰ（BMS）	—
ONO-4538	Chronic myelogenous leukemia	Ⅰ（BMS）	—

red : Hematologic malignancies

Combination clinical trials (OPDIVO & other I-O compounds)

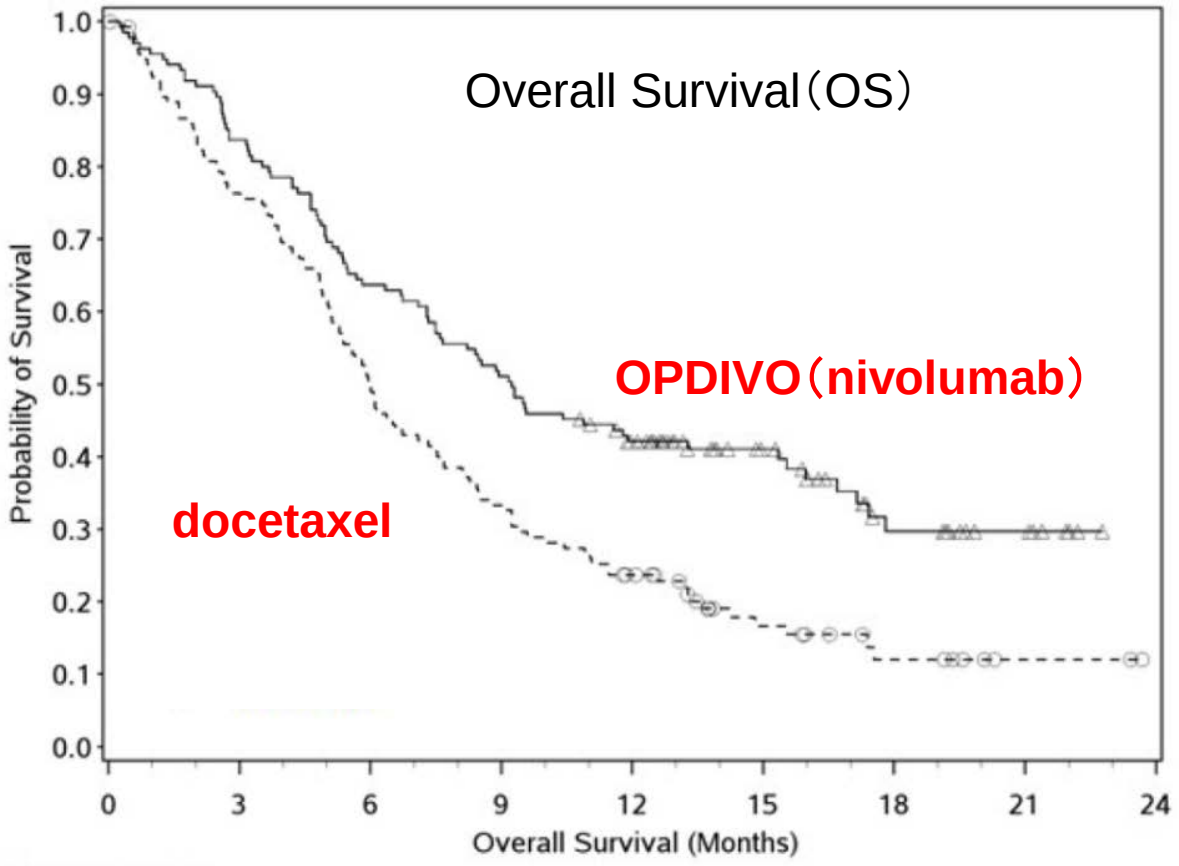
Company	Combination	Cancer type	Phase	Area
BMS	Nivolumab＋Ipilimumab	Renal cell carcinoma	Ⅲ	US,EU JP
		Melanoma	Ⅲ	US
			Ⅱ	JP
BMS	Nivolumab＋Lirilumab （Anti-KIR antibody）	Solid tumor	Ⅰ	US
BMS	Nivolumab＋BMS-986016 （Anti-LAG-3 antibody）	Solid tumor	Ⅰ	US, EU
BMS	Nivolumab＋Urelumab （CD137 receptor agonist）	Solid tumor, Non-Hodgkin lymphoma	Ⅰ/Ⅱ	US, EU
Kyowa Hakko Kirin	Nivolumab＋ Mogamulizumab	Solid tumor	Ⅰ	JP

Survival Benefit of OPDIVO for Melanoma



	dacarvadine	nivolumab
12M survival rate	42.1 %	72.9 %

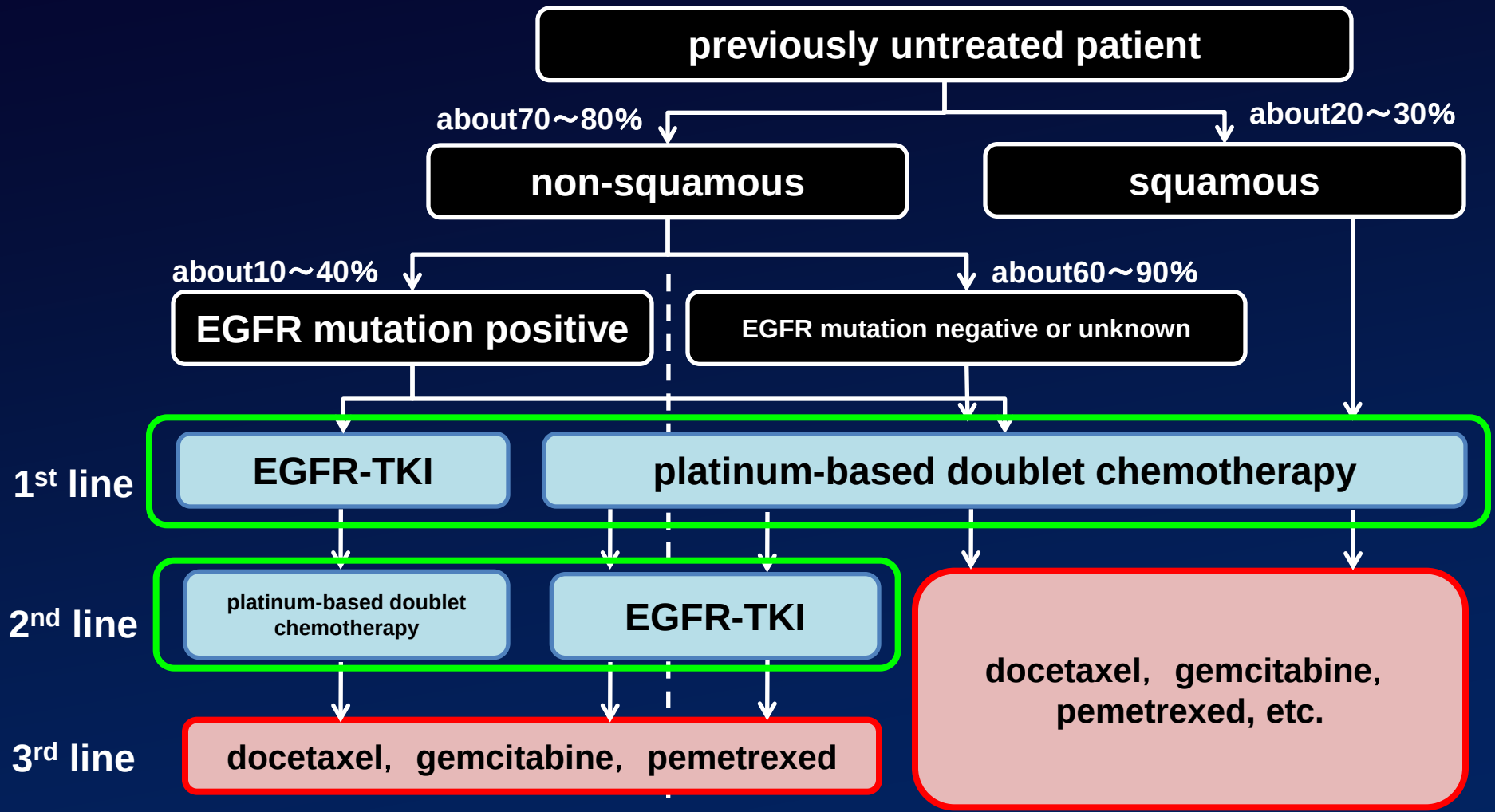
OPDIVO：NSCLC（Squamous）



HR＝0.59, P = 0.00025

	median OS
nivolumab	9.2M
docetaxel	6.0M

Medical Treatment Flow for NSCLC



: this time, the group ONO-4538（mono therapy）aims the additional indication

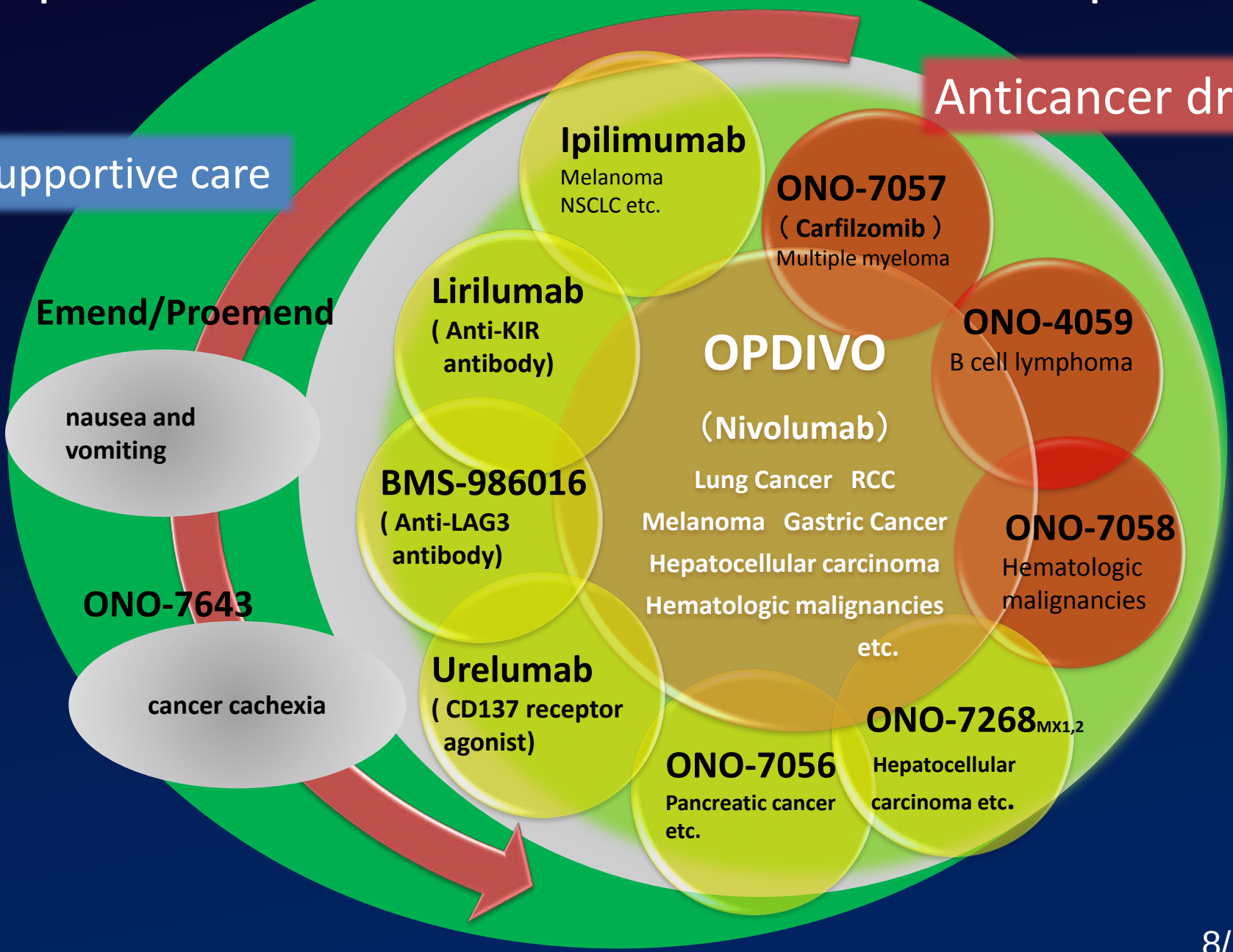
: the future, the group ONO-4538（combination or mono therapy）aims the additional indication

EGFR: epidermal growth factor receptor , TKI: tyrosine kinase inhibitor

＊: In case ALK translocation is positive, the treatment with ALK inhibitor as mono therapy is recommended.

（Japan Lung Cancer Society, Lung Cancer Medical Treatment Guideline 2012）

Comprehensive medical treatment for cancer patients



Planned presentation about nivolumab in ASCO 2015：overseas clinical trial

Non small lung cancer
An ongoing phase IIIb/IV safety trial of nivolumab (NIVO) in patients (pts) with advanced or metastatic non-small-cell lung cancer (NSCLC) who progressed after receiving 1 or more prior systemic regimens.
A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC).
Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC).
First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 [PD-1]) in advanced non-small cell lung cancer (NSCLC): Safety, efficacy and correlation of outcomes with PD-1 ligand (PD-L1) expression.
Renal cell cancer
Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma (mRCC): Association of biomarkers with clinical outcomes.
Updated survival results from a randomized, dose-ranging phase II study of nivolumab (NIVO) in metastatic renal cell carcinoma (mRCC).
Expanded cohort results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC).
Melanoma
Efficacy and safety results from a phase III trial of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients (pts) with advanced melanoma (MEL) (CheckMate 067).
Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase III study (CheckMate 066).
Survival, biomarker, and toxicity analysis of nivolumab (NIVO) in patients that progressed on ipilimumab (IPI).
Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase II study (CheckMate 069).

Planned presentation about nivolumab in ASCO 2015：overseas clinical trial

Melanoma(continued)
Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): A pooled analysis.
Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study.
Nivolumab in resected and unresectable melanoma: Immune-related adverse events and association with survival outcomes
Hepatocellular carcinoma
Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040.
Small cell lung cancer
Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032.
Glioblastoma
Preliminary safety and activity of nivolumab and its combination with ipilimumab in recurrent glioblastoma (GBM): CHECKMATE-143

Planned presentation about nivolumab in ASCO 2015：clinical trial in Japan

Non small cell lung cancer

Phase II studies of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients with advanced squamous (sq) or non-squamous (non-sq) non-small cell lung cancer (NSCLC).

Ovarian cancer

Durable tumor remission in patients with platinum-resistant ovarian cancer receiving nivolumab.

Global Development Projects

*The most advanced stage is shown

Development Code	Target Disease	Overseas*	JAPAN*
ONO-6950	Bronchial asthma	Ⅱ	Ⅱ
ONO-4053	Allergic rhinitis	Ⅱ	Ⅱ
ONO-2952	Irritable bowel syndrome（IBS）	Ⅱ	—
ONO-9054	Glaucoma, Ocular hypertension	Ⅱ	—
ONO-4059	B-cell lymphoma	Ⅰ	Ⅰ
ONO-8055	Underactive bladder	Ⅰ	—
ONO-2160/CD	Parkinson’s disease	—	Ⅰ
ONO-1266	Portal hypertension	Ⅰ	—
ONO-4232	Acute heart failure	Ⅰ	—
ONO-4474	Osteoarthrosis	Ⅰ	—

Development pipeline list in Japan（1）

*The most advanced stage is shown

Development code /Product name/Product candidate name	Planned indication	JAPAN
Opalmon (additional formulation)	Thromboangiitis obliterans, Lumbar spinal stenosis	Launched
Rivastach Patch (Additional dosing regimen)	Dementia of the Alzheimer's type	Filing
Proemend (pediatric)	Chemotherapy-induced nausea and vomiting	Ⅲ
ONO-4164IV (Orencia IV)	Juvenile idiopathic arthritis	Ⅲ
ONO-4164IV (Orencia IV)	Lupus nephritis	Ⅲ
ONO-7057 (Carfilzomib)	Multiple myeloma	Ⅲ
ONO-5163	Secondary hyperparathyroidism	Ⅲ
Onoact (pediatric)	Tachyarrhythmia in low cardiac function	Ⅱ／Ⅲ

Development pipeline list in Japan（2）

*The most advanced stage is shown

Development code /Product name/Product candidate name	Planned indication	JAPAN
ONO-7643	Cancer cachexia	Ⅱ
ONO-1162	Chronic heart failure	Ⅱ
ONO-6950	Bronchial asthma	Ⅱ
ONO-4053	Allergic rhinitis	Ⅱ
ONO-7056	Solid Tumor	Ⅰ
ONO-7268MX1	Hepatocellular carcinoma	Ⅰ
ONO-7268MX2	Hepatocellular carcinoma	Ⅰ
ONO-2160/CD（levodopa pro-drug）	Parkinson’s disease	Ⅰ
ONO-2370（COMT inhibitor）	Parkinson’s disease	Ⅰ
ONO-4059	B-cell lymphoma	Ⅰ

Number of Cancer Patients

Cancer	Incident per year				Mortality per year			
	Japan	Korea	USA	EU	Japan	Korea	USA	EU
Oesophagus	19,683	2,223	16,968	45,983	12,440	1,551	15,982	39,523
Stomach	107,898	31,269	21,155	139,667	52,326	10,746	11,758	107,314
Colorectum	112,675	33,773	134,349	447,136	49,345	9,169	55,259	214,814
Liver	36,168	16,900	30,449	63,462	32,518	12,275	24,312	62,175
Gallbladder	21,417	5,228	9,431	29,744	19,309	4,176	3,845	20,877
Pancreas	32,899	5,379	42,885	103,845	31,046	5,086	41,509	104,535
Larynx	3,615	1,087	12,373	39,921	977	394	3,880	19,772
Lung	94,855	22,873	214,226	410,220	75,119	17,848	167,545	353,723
Melanoma of skin	1,371	649	69,109	100,442	691	263	10,224	22,212
Breast	55,710	17,140	232,714	464,202	13,801	2,274	43,909	131,257
Cervix uteri	9,390	3,299	12,966	58,373	3,645	1,113	6,605	24,385
Corpus uteri	11,449	2,016	49,645	98,984	2,783	291	6,925	23,733
Ovary	8,921	2,349	20,874	65,584	4,986	1,054	15,377	42,737
Prostate	55,970	10,351	233,159	417,137	11,644	1,696	30,383	92,318
Kidney	16,830	5,651	58,222	115,252	8,124	1,264	14,900	48,988
Bladder	22,042	4,097	68,639	151,297	7,630	1,330	16,468	52,395
Brain, nervous	5,510	1,978	21,611	57,132	2,229	1,270	15,746	45,003
Thyroid	9,290	32,992	52,126	52,956	1,764	430	1,965	6,334
Hodgkin lymphoma	1,061	246	8,601	17,584	148	54	1,295	4,622
Non-hodgkin lymphoma	20,978	4,717	63,066	93,518	11,157	1,611	21,732	37,886
Multiple myeloma	4,984	1,317	19,626	38,956	4,334	856	11,978	24,296
Leukaemia	10,182	3,002	39,658	82,329	8,583	1,751	24,729	53,796

※WHO GLOBOCAN 2012