300th since 1717

Development Pipeline Progress Status

ONO PHARMACEUTICAL CO.,LTD.

November 7, 2017

Development status of OPDIVO (nivolumab) ①

Target disease	JAPAN	US/EU	KR/TW
Melanoma (1st)	Approved	Approved	Approved
Non-small cell lung cancer (2nd～)	Approved	Approved	Approved *)
Non-small cell lung cancer (1st)	Ⅲ	Ⅲ	Ⅲ
Renal cell carcinoma (2nd～)	Approved	Approved	Approved (TW) Approved (KR)
Renal cell carcinoma (1st)	Ⅲ	Ⅲ	Ⅲ
Hodgkin lymphoma	Approved	Approved	Approved
Head and neck carcinoma	Approved	Approved	Approved
Urothelial cancer	Ⅲ	Approved (US) Approved (EU)	Approved
Gastric cancer	Approved	Ⅲ	Filing (TW) Ⅲ (KR)
Gastro-esophageal junction cancer and esophageal cancer	Ⅲ	Ⅲ	Ⅲ
Small cell lung cancer	Ⅲ	Ⅲ	Ⅲ
Hepatocellular carcinoma	Ⅲ	Approved (US) Ⅲ (EU)	Ⅲ

*) : Additionally approved for non-squamous NSCLC in Taiwan

Red : Hematologic malignancy

Green : Change from the announcement in May 2017

Development status of OPDIVO (nivolumab) ②

Target disease	JAPAN	US/EU	KR/TW
Esophageal cancer	Ⅲ	Ⅲ	Ⅲ
Glioblastoma	Ⅲ	Ⅲ	–
Multiple myeloma	Ⅱ	Ⅲ	–
Malignant pleural mesothelioma	Ⅲ	Ⅲ	–
Ovarian cancer	Ⅲ	Ⅰ / Ⅱ	–
Central nervous system lymphoma, Primary Testicular Lymphoma	Ⅱ	Ⅱ	–
Cervix carcinoma, Uterine body cancer, Soft tissue sarcoma	Ⅱ	–	–
Diffuse large B cell lymphoma (Non-Hodgkin lymphoma)	–	Ⅱ	–
Follicular lymphoma (Non-Hodgkin lymphoma)	–	Ⅱ	–
Colorectal cancer	–	Approved (US) Ⅰ / Ⅱ (EU)	–
Virus positive/negative solid carcinoma	Ⅰ / Ⅱ	Ⅰ / Ⅱ	Ⅰ / Ⅱ
Pancreatic cancer, Triple negative breast cancer (CheckMate-032 study)	–	Ⅰ / Ⅱ	–
Biliary tract cancer	Ⅰ	–	–
Chronic myeloid leukemia	–	Ⅰ	–

Red : Hematologic malignancy

Green : Change from the announcement in May 2017

Clinical trials in combination therapy
OPDIVO (nivolumab) & other I-O compounds ①

Combination therapy	Cancer type	Japan	US/EU	KR/TW
Nivolumab + Ipilimumab	Melanoma	Filing	Approved	Approved
	Renal cell carcinoma	Ⅲ	Ⅲ	Ⅲ
	Non-small cell lung cancer	Ⅲ	Ⅲ	Ⅲ
	Small cell lung cancer	Ⅲ	Ⅲ	Ⅲ
	Head and neck cancer	Ⅲ	Ⅲ	Ⅲ
	Gastric cancer	Ⅲ	Ⅲ	Ⅲ
	Malignant pleural mesothelioma	Ⅲ	Ⅲ	–

Green : Change from the announcement in May 2017

Clinical trials in combination therapy
OPDIVO (nivolumab) & other I-O compounds ②

Combination therapy with nivolumab	Cancer type	Japan	US/EU	KR/TW
ONO-4483／Lirilumab (Anti-KIR antibody)	Solid tumor	Ⅰ	Ⅰ／Ⅱ	–
ONO-4482／Relatlimab (Anti-LAG-3 antibody)	Solid tumor	Ⅰ	Ⅰ／Ⅱ	–
ONO-4481／Urelumab (CD137 receptor agonist)	Solid tumor, Non-Hodgkin lymphoma	Ⅰ	Ⅰ／Ⅱ	–
Mogamulizumab (Anti-CCR4 antibody)	Solid tumor	Ⅰ	Ⅰ／Ⅱ	–
ONO-4686 (Anti-TIGIT antibody)	Solid tumor	Ⅰ／Ⅱ	Ⅰ／Ⅱ	–
ONO-4687／Cabiralizumab (Anti-CSF-1R antibody)	Solid tumor, Hematologic malignancy	Ⅰ	Ⅰ	–
ONO-7701 (IDO1 inhibitor)	Solid tumor, Hematologic malignancy	Ⅰ	Ⅰ／Ⅱ	–

Green : Change from the announcement in May 2017

Development pipeline in Japan (Oncology, other than OPDIVO)

Product name/its candidate /development code	Target indication	Japan
KYPROLIS (Additional dosage and administration)	Multiple myeloma	Approved
KYPROLIS (Change in dosage and administration)	Multiple myeloma	Ⅲ
ONO-7643 (Anamorelin)	Cancer anorexia/cachexia (in all types of cancer)	Ⅲ
ONO-7702 (Encorafenib)	Melanoma	Ⅲ
ONO-7703 (Binimetinib)	Melanoma	Ⅲ
ONO-5371 (Metyrosine)	Pheochromocytoma	Ⅰ / Ⅱ
ONO-4686 (BMS-986207)	Solid tumor	Ⅰ / Ⅱ
ONO-4059 (Tirabrutinib)	Central nervous system lymphoma	Ⅰ / Ⅱ
ONO-4481 (Urelumab)	Solid tumor	Ⅰ
ONO-4482 (Relatlimab)	Solid tumor	Ⅰ
ONO-4687 (Cabiralizumab)	Solid tumor and hematologic cancer	Ⅰ
ONO-7701 (BMS-986205)	Solid tumor and hematologic cancer	Ⅰ
ONO-4483 (Lirilumab)	Solid tumor	Ⅰ
ONO-4578	Solid tumor	Ⅰ

Green : Change from the announcement in May 2017

Development pipeline in Japan (Non-oncology)

Product name/its candidate /development code	Target indication	Japan
Orencia IV (Pediatric)	Juvenile idiopathic arthritis	Filing
Orencia IV (Additional indication)	Lupus nephritis	Ⅲ
Orencia SC (Additional indication)	Untreated rheumatoid arthritis	Ⅲ
Orencia SC (Additional indication)	Primary Sjögrens syndrome	Ⅲ
Orencia SC (Additional indication)	Polymyositis / Dermatomyositis	Ⅲ
ONO-1162 (Ivabradine)	Chronic heart failure	Ⅲ
ONO-5704	Osteoarthritis	Ⅲ
Onoact (Pediatric)	Tachyarrhythmia in low cardiac function	Ⅱ / Ⅲ
Onoact (Additional indication)	Ventricular arrhythmia	Ⅱ / Ⅲ
ONO-2370 (Opicapone)	Parkinson's disease	Ⅱ
ONO-8577	Overactive bladder	Ⅱ
ONO-5704	Enthesopathy	Ⅱ
Opdivo (Additional indication)	Sepsis	Ⅰ / Ⅱ

Green : Change from the announcement in May 2017

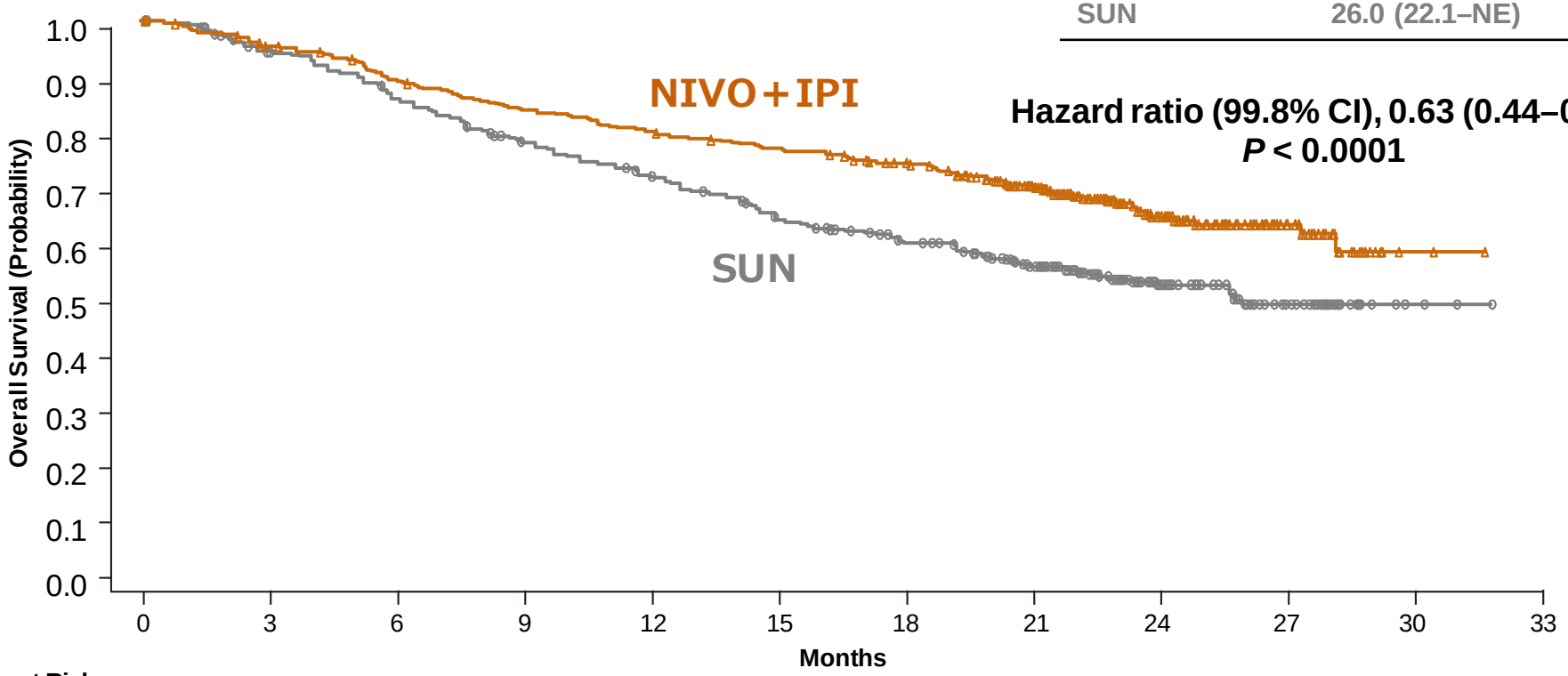
Global development projects (Other than OPDIVO)

Development code /Generic name	Target indication /Pharmacological Action	Phase	Area
ONO-7702 (Encorafenib)	Colorectal cancer /BRAF inhibitor	Ⅲ	KR
ONO-7702 (Encorafenib)	Melanoma /BRAF inhibitor	Ⅲ	KR
ONO-7703 (Binimetinib)	Colorectal cancer /MEK inhibitor	Ⅲ	KR
ONO-7703 (Binimetinib)	Melanoma /MEK inhibitor	Ⅲ	KR
ONO-4059 (Tirabrutinib)	B cell lymphoma /Btk inhibitor	Ⅱ	EU
ONO-4059 (Tirabrutinib)	Sjögrens syndrome /Btk inhibitor	Ⅱ	US
ONO-4474	Osteoarthritis /Trk inhibitor	Ⅱ	EU
ONO-7579	Solid tumor /Trk inhibitor	Ⅰ / Ⅱ	US/EU
ONO-7475	Acute leukemia / Axl / Mer inhibitor	Ⅰ	US
ONO-8055	Underactive bladder /PG receptor (EP2 / EP3) agonist	Ⅰ	EU

Green : Change from the announcement in May 2017

OS: IMDC intermediate/poor risk

Median OS, months (95% CI)	
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)



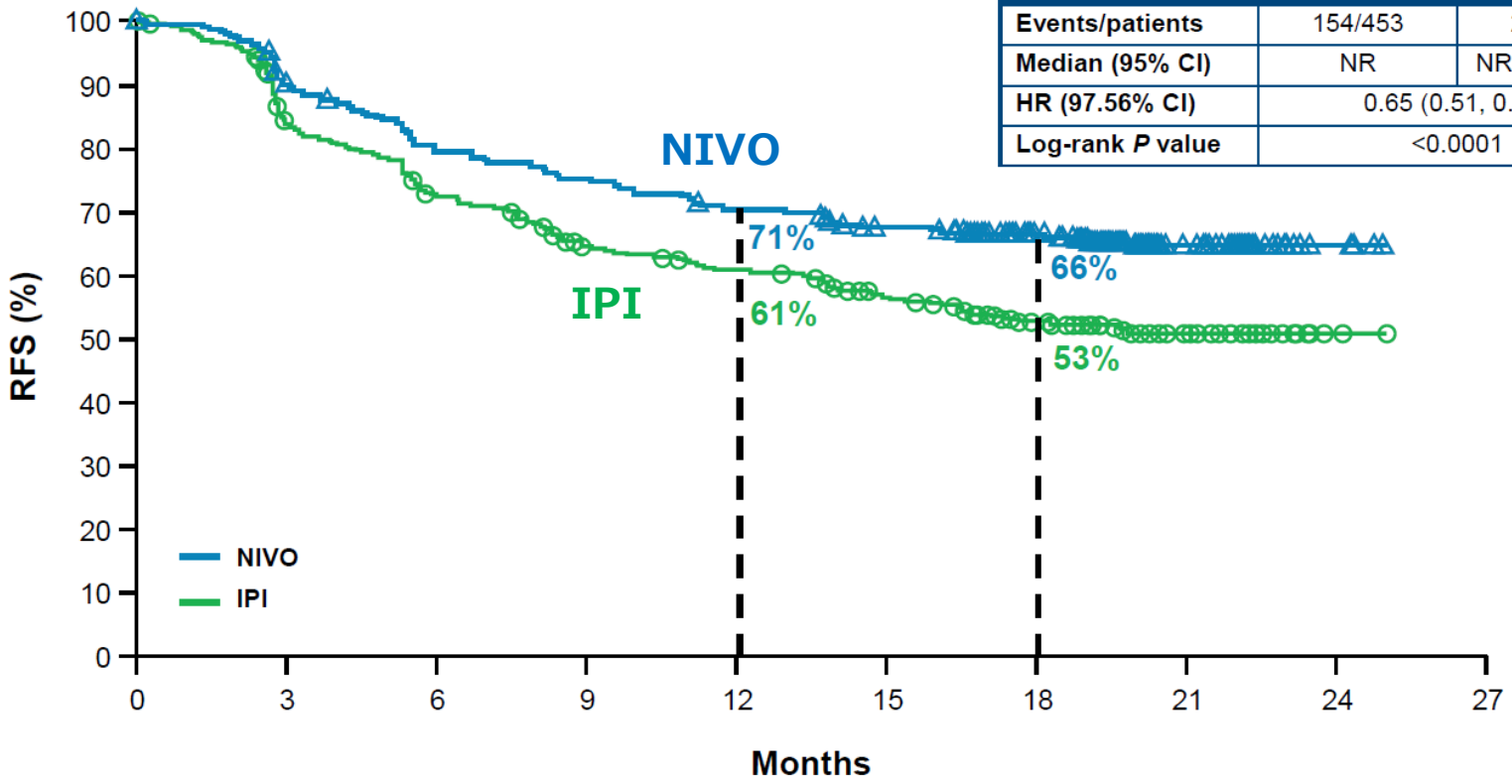
No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

Co-primary endpoint

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: A Randomized, Double-blind, Phase 3 Trial (CheckMate 238)

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



Number of patients at risk

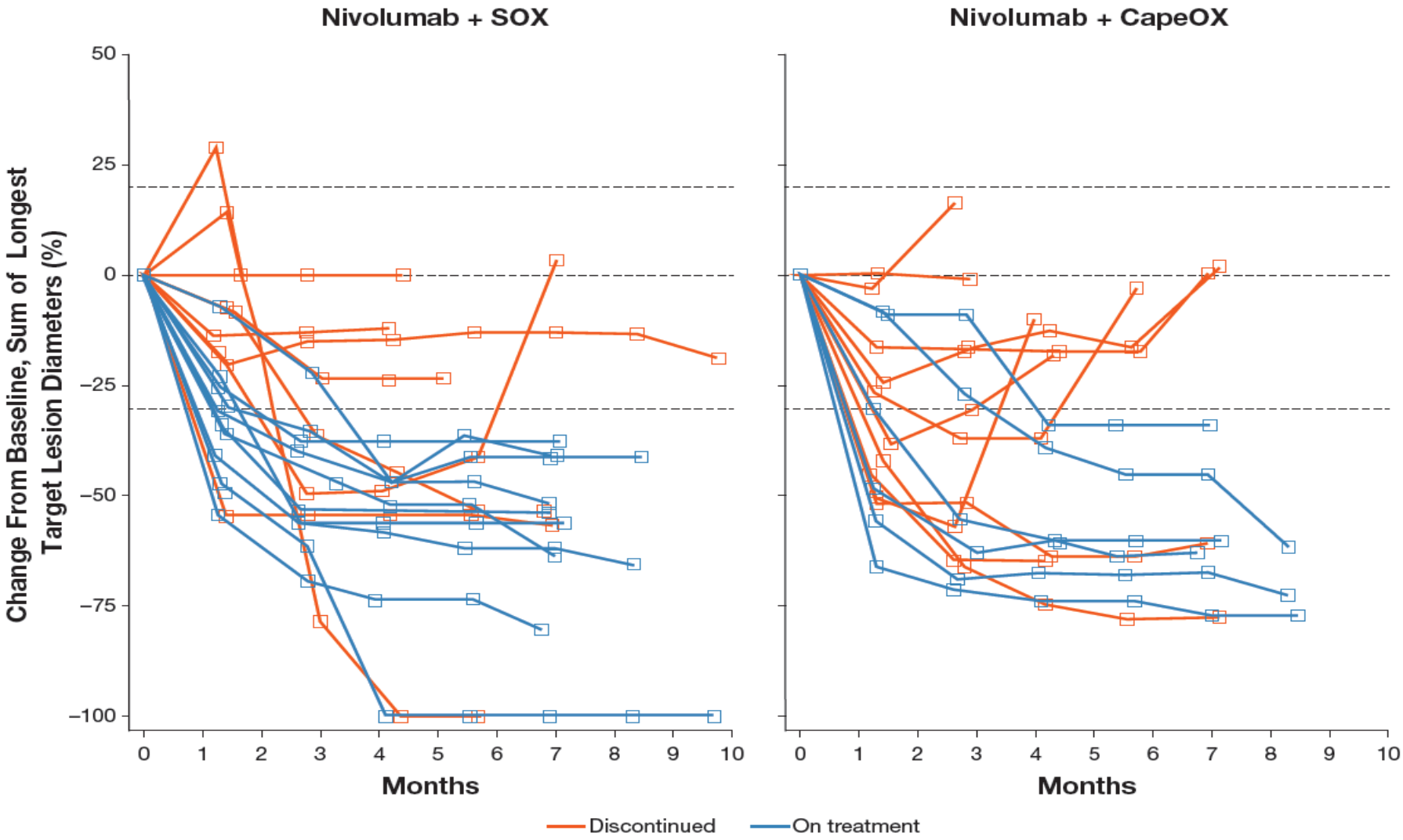
NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

671P

Interim Safety and Clinical Activity of Nivolumab in Combination With S-1/Capecitabine Plus Oxaliplatin in Patients With Previously Untreated Unresectable Advanced or Recurrent Gastric/Gastroesophageal Junction Cancer: Part 1 Study of ATTRACTION-04 (ONO-4538-37)

Yoon-Koo Kang,[1] Ken Kato,[2] Hyun Cheol Chung,[3] Keiko Minashi,[4] Keun-Wook Lee,[5] Haruhiko Cho,[6] Won Ki Kang,[7] Yoshito Komatsu,[8] Masahiro Tsuda,[9] Kensei Yamaguchi,[10] Hiroki Hara,[11] Souiti Fumita,[12] Mizutomo Azuma,[13] Narikazu Boku,[2] Li-Tzong Chen[14]

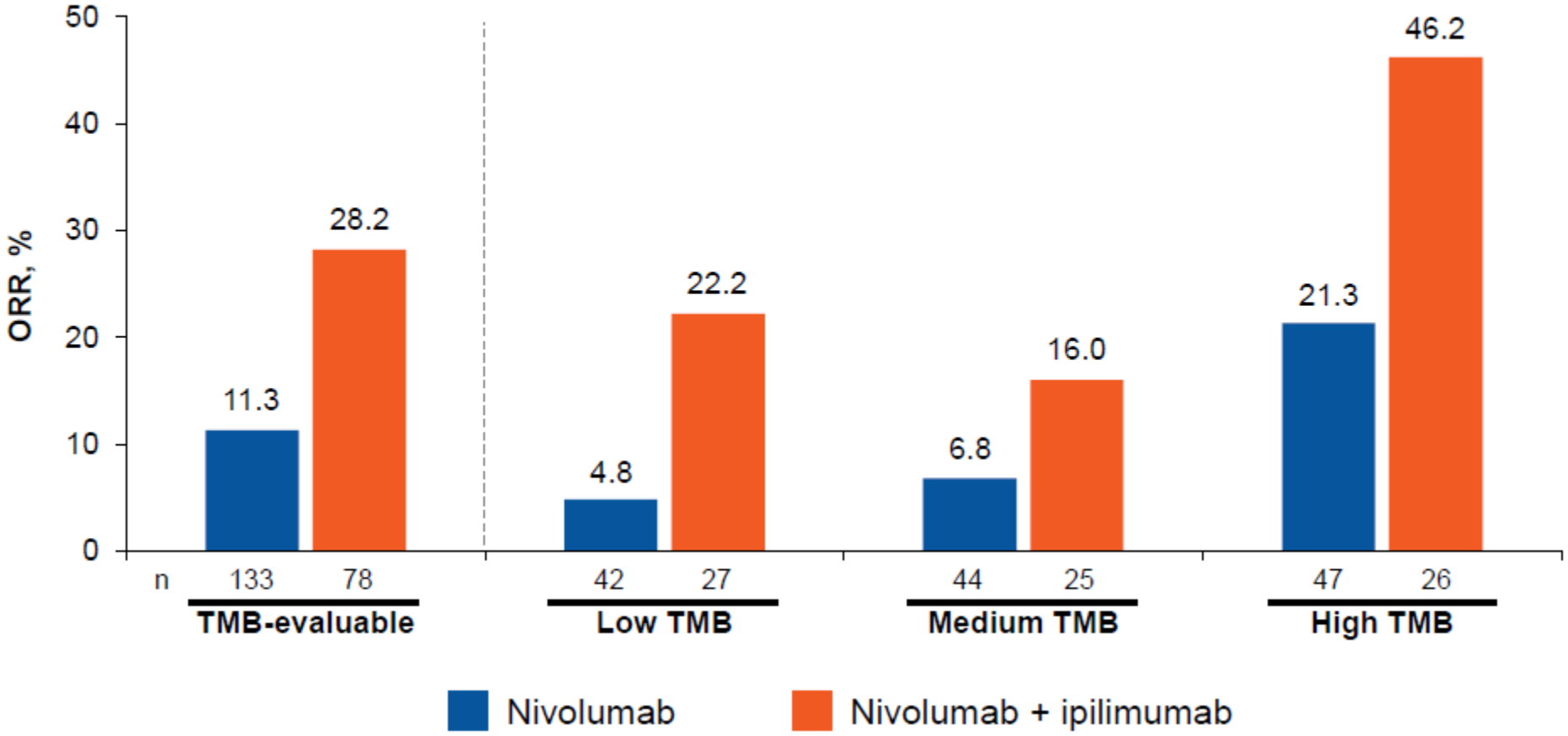
[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Yonsei Cancer Center, Song Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea; [4]Chiba Cancer Center, Chiba, Japan; [5]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [6]Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital (previous Kanagawa Cancer Center), Yokohama, Japan; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Hokkaido University Hospital Cancer Center, Sapporo, Japan; [9]Hyogo Cancer Center, Akashi, Japan; [10]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [11]Saitama Cancer Center, Saitama, Japan; [12]Nara Hospital Kindai University, Ikoma, Japan; [13]Kitasato University School of Medicine, Kanagawa, Japan; [14]National Institute of Cancer Research, National Health Research Institutes, and National Cheng Kung University Hospital, Tainan, Taiwan



Checkmate 032 Nivolumab+ipilimumab Small Cell Lung Cancer

ORR by Tumor Mutation Burden Subgroup

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC



INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER 2017

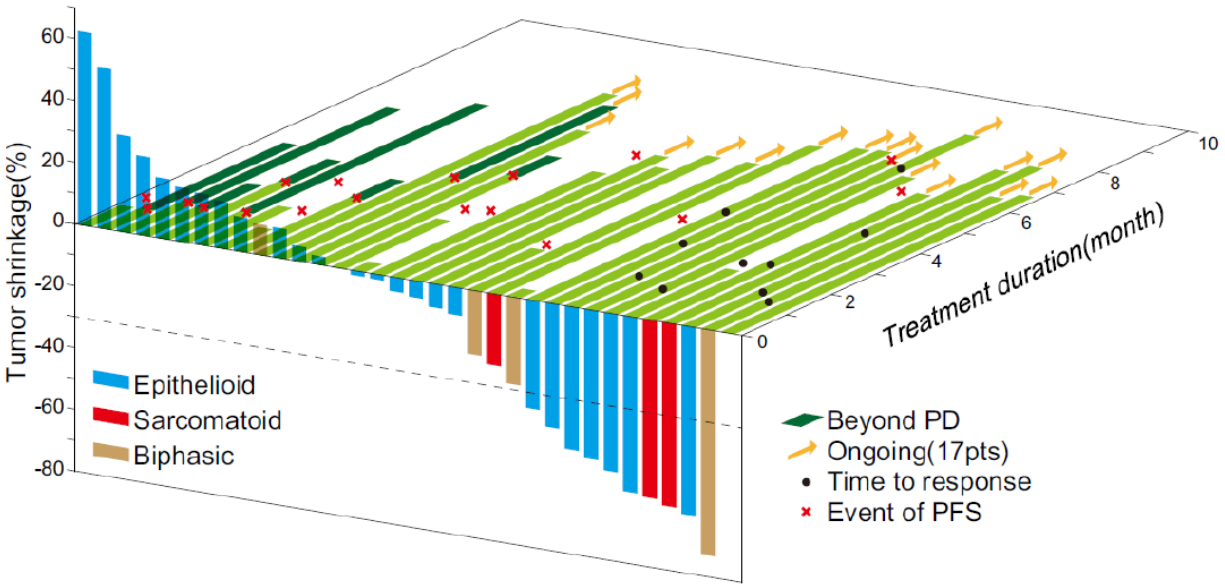
A Phase II Study of Nivolumab in Malignant Pleural Mesothelioma

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Efficacy: Tumor Response assessment after first 6 months

Data cut off: April 21, 2017

Tumor Response [CI 95%]		
ORR	(n=34)	10, 29.4% [16.8, 46.2]
Epithelioid	(n=27)	7, 25.9% [13.2, 44.7]
Sarcomatoid	(n=3)	2, 66.7% [20.8, 93.9]
Biphasic	(n=4)	1, 25.0% [4.6, 69.9]
DCR	(n=34)	23, 67.6% [50.8, 80.9]



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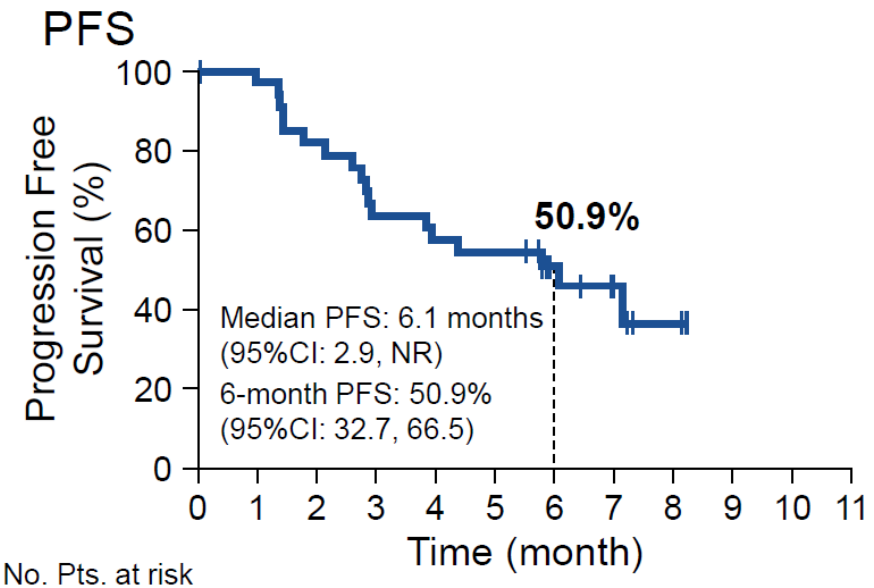
Efficacy: Progression Free Survival (PFS) and Overall Survival (OS) after minimum 6 months follow up

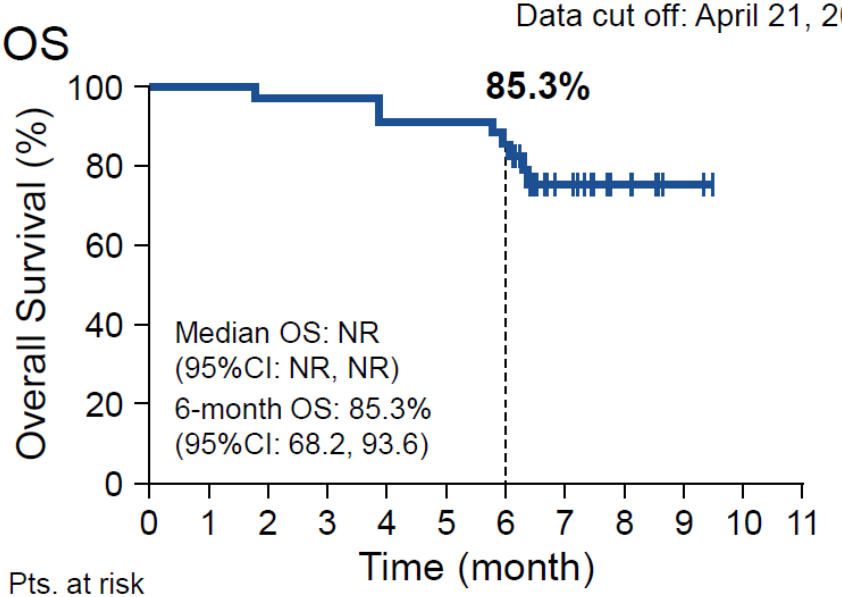
Data cut off: April 21, 2017



No. Pts. at risk

Time (month)	0	1	2	3	4	5	6	7	8	9	10	11
ONO-4538	34	32	27	21	19	18	10	5	2	0	0	0

Full Analysis Set

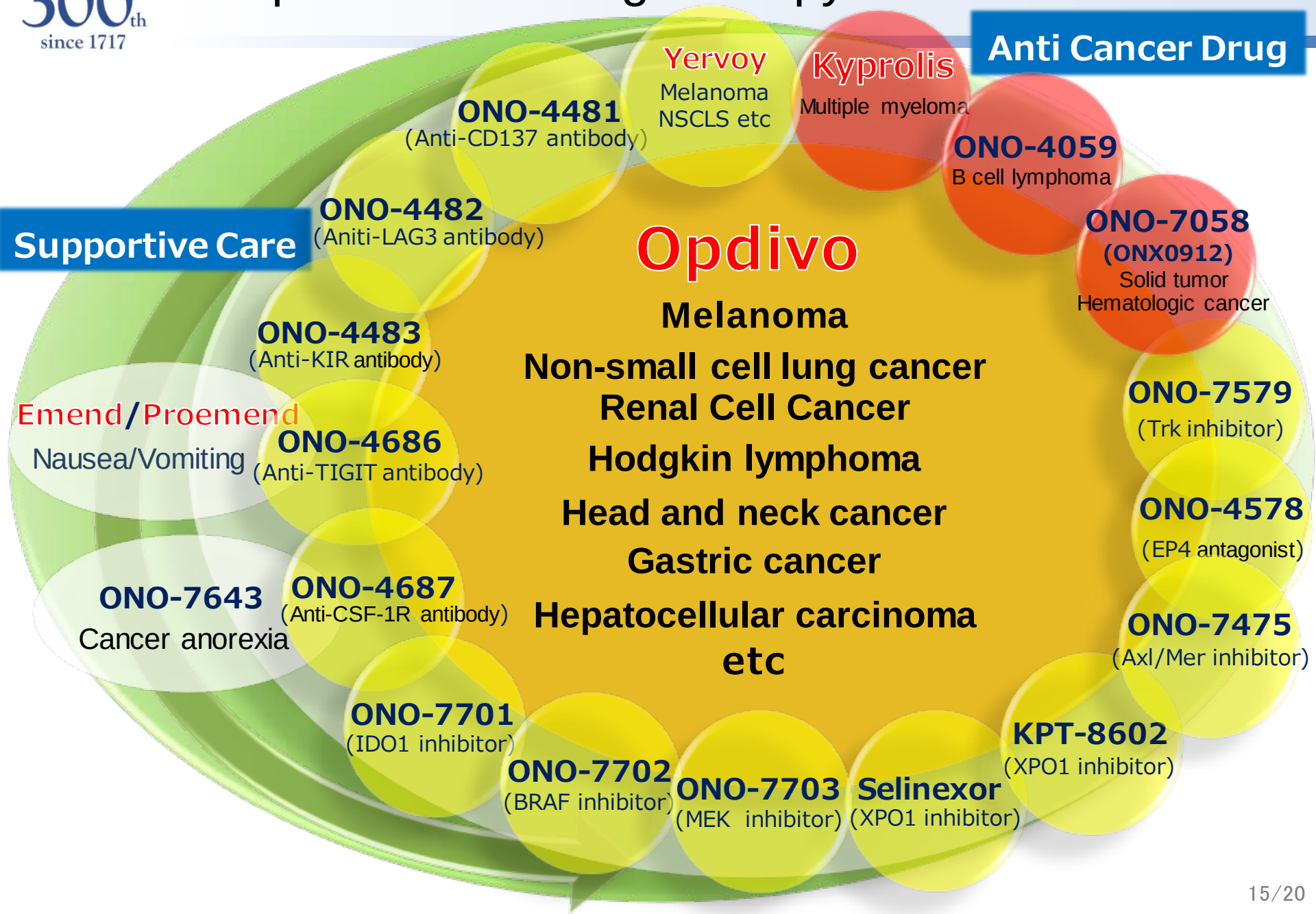


No. Pts. at risk

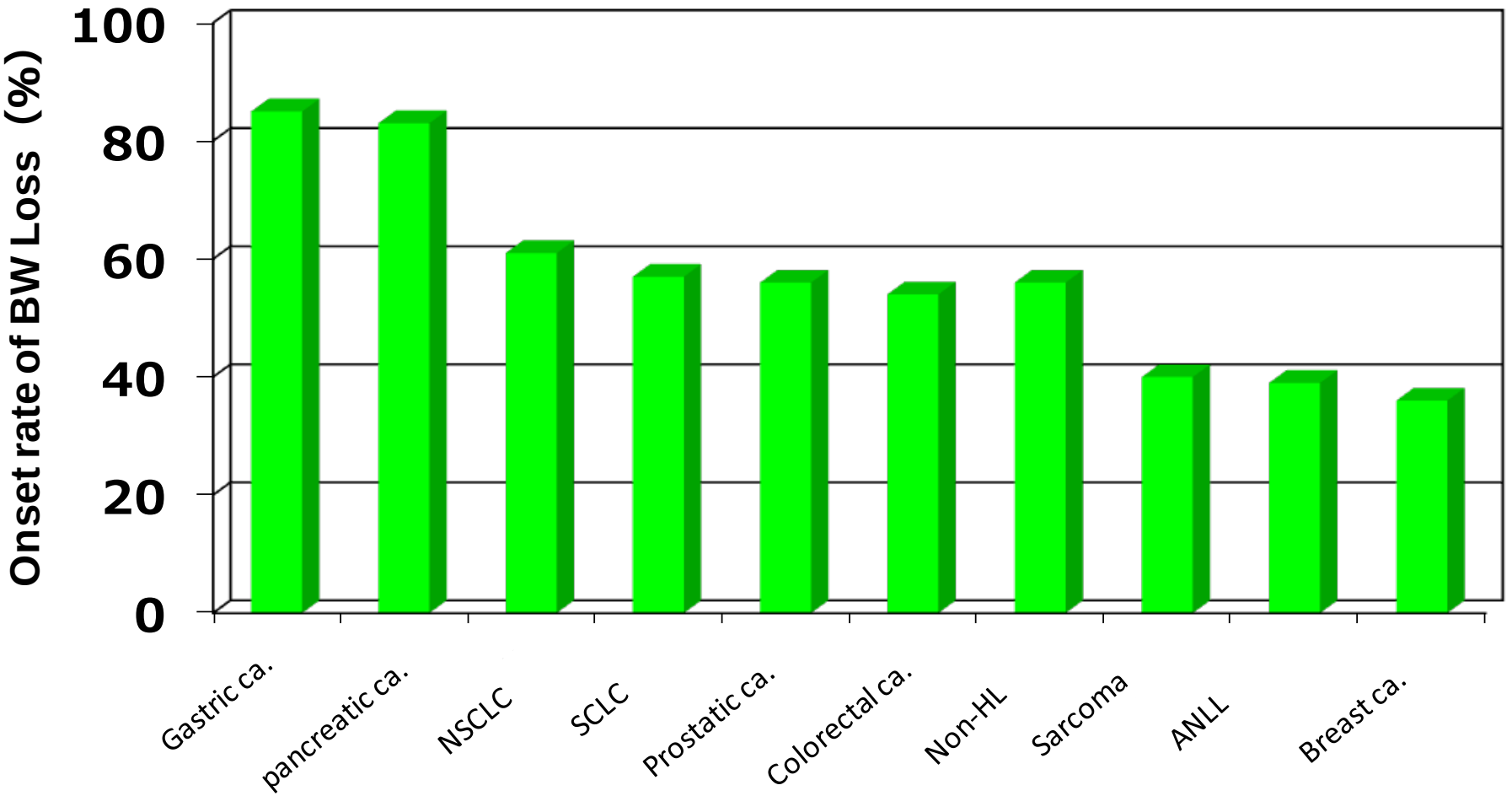
Time (month)	0	1	2	3	4	5	6	7	8	9	10	11
ONO-4538	34	34	33	33	31	31	29	14	6	2	0	0

Full Analysis Set

Comprehensive Drug Therapy for Cancer Patients



Onset Rate of Body Weight Loss in Each Cancer



Dewys WD, et al. Am J Med. 1980;69:491-497. Altered

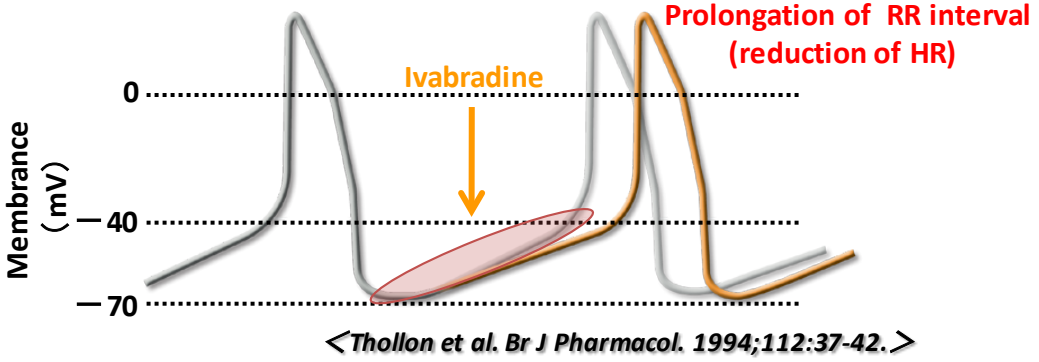
ONO-1162/Ivabradine (Chronic Heart Failure)

Licensor	Servier (France)
Generic name	Ivabradine
Mode of action	Selective If inhibitor（Effect of reducing heart rate）
Indication (abroad)	Chronic heart failure and stable angina pectoris
Dose and Dosage (abroad)	Start at 5 mg twice daily adjusting the dose at 2.5 mg, 5 mg or 7.5 mg according to heart rate and tolerance
Indication in Japan (planned)	Chronic heart failure
Characteristic	Reducing heart rate without affecting blood pressure（First in class）

No. of CHF pats (Japan)：

About 1.5 Mil

IMS Analysis



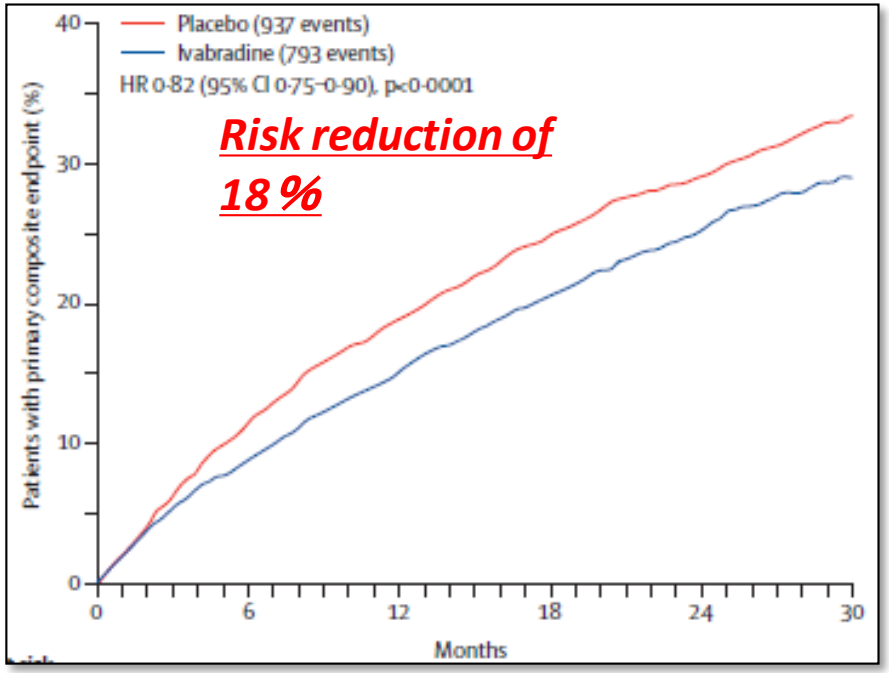
＜Thollon et al. Br J Pharmacol. 1994;112:37-42.＞

Key Results of Phase 3 Study in Abroad

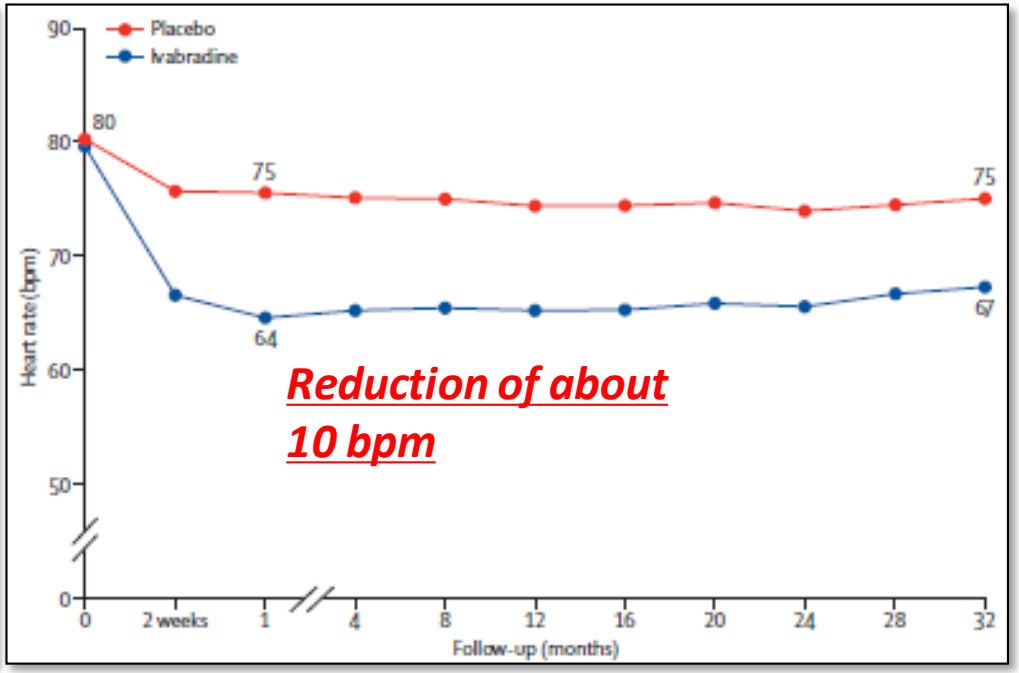
Phase 3 study in abroad （SHIFT study conducted by Servier）

Study sites：625 sites（37countries）
No. of patients：6505（Placebo 3264, ONO-1162 3241）
Study period：Sep 2006～March 2010（Average treatment period：20.1±9.0 months）

Change in event-onset rate of hospitalization due to CV death or aggravated heart failure

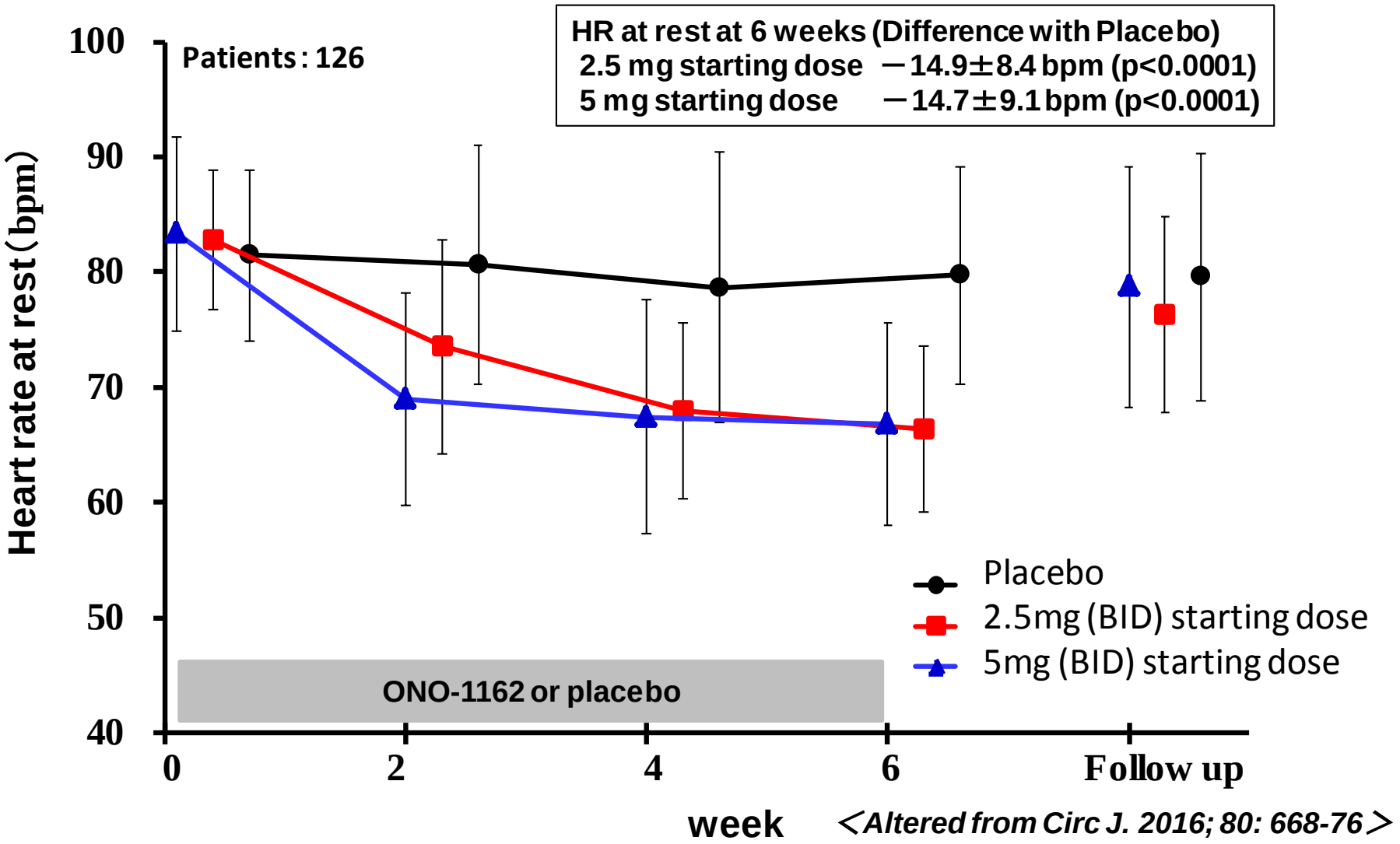


Change in heart rate



＜*Lancet 2010; 376: 875-85*＞

Key Results of Phase 2 Study in Japan



<Altered from Circ J. 2016; 80: 668-76>

ONO-5704/SI-613

Compound	**Compound chemically bound with hyaluronic acid and diclofenac**
Indication/ Stage	**①Osteoarthritis (OA): Knee joint P3, Other joints (shoulder, elbow, hip, leg, etc.) P3 under preparation** **②Enthesopathy (EP) (elbow, planta, shoulder, knee, Achilles, etc.) : P2**
Dose and dosage	**Inject into joint cavity at 3 mL every 4 weeks (prefilled syringe)**
Characteristic	• **Maintain pain relief effect by sustained release of diclofenac in joint cavity.** • **Low risk of systemic adverse drug reactions caused by diclofenac.**

Whole market of hyaluronic acid drugs: ¥ 40 - 50 billion/year