300th since 1717

Development Pipeline Progress Status

ONO PHARMACEUTICAL CO.,LTD.

May 12, 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)
Renal cell carcinoma (1st)	Ⅲ	Ⅲ	Ⅲ
Hodgkin lymphoma	Approved	Approved	Filing (TW)
Head and neck carcinoma	Approved	Approved	Filing (TW) Ⅲ (KR)
Urothelial cancer	Ⅲ	Approved (US) Filing (EU)	Ⅲ
Gastric cancer	Filing	Ⅲ	Ⅲ
Gastro-esophageal junction cancer and esophageal cancer	Ⅲ	Ⅲ	Ⅲ
Small cell lung cancer	Ⅲ	Ⅲ	Ⅲ
Hepatocellular carcinoma	Ⅲ	Ⅲ	Ⅲ
Esophageal cancer	Ⅲ	Ⅲ	Ⅲ

*) : Approved only for squamous NSCLC and under filing for non-squamous NSCLC in Taiwan

Red : Hematologic malignancy

Green : Change from the announcement in May 2016

Development status of OPDIVO (nivolumab) ②

Target disease	JAPAN	US/EU	KR/TW
Glioblastoma	Ⅲ	Ⅲ	–
Multiple myeloma	–	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	–
Colon cancer	–	Filing (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 2016

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

Combination therapy	Cancer type	Japan	US/EU	KR/TW
Nivolumab + Ipilimumab	Melanoma	Ⅱ	Approved(US) Approved(EU)	Filing(TW)
	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 2016

Main 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 (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 2016

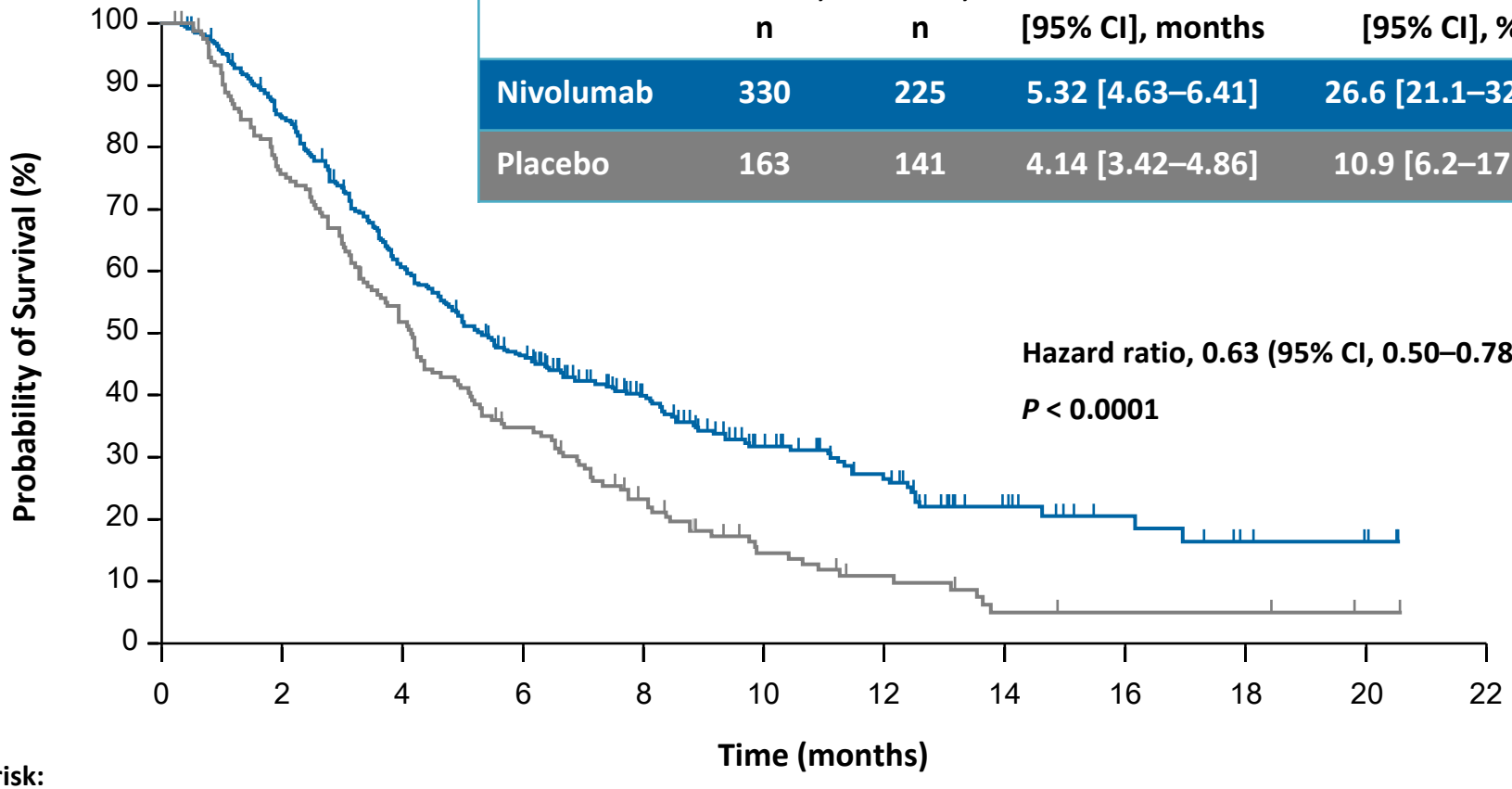
Development pipeline in Japan (Late stage)

Product name/its candidate /development code	Target indication	Japan
Parsabiv (ONO-5163)	Secondary hyperparathyroidism	Approved
KYPROLIS (Additional dosage and administration)	Multiple myeloma	Filing
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
KYPROLIS (Change in dosage and administration)	Multiple myeloma	Ⅲ
ONO-1162 (Ivabradine)	Chronic heart failure	Ⅲ
ONO-7643 (Anamorelin)	Cancer anorexia/cachexia (in all types of cancer)	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-5371 (Metyrosine)	Pheochromocytoma	Ⅰ / Ⅱ

Green : Change from the announcement in May 2016

Overall Survival Time of Nivolumab in 3rd Line Therapy in Gastric Cancer（ATTRACTION-2）

	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



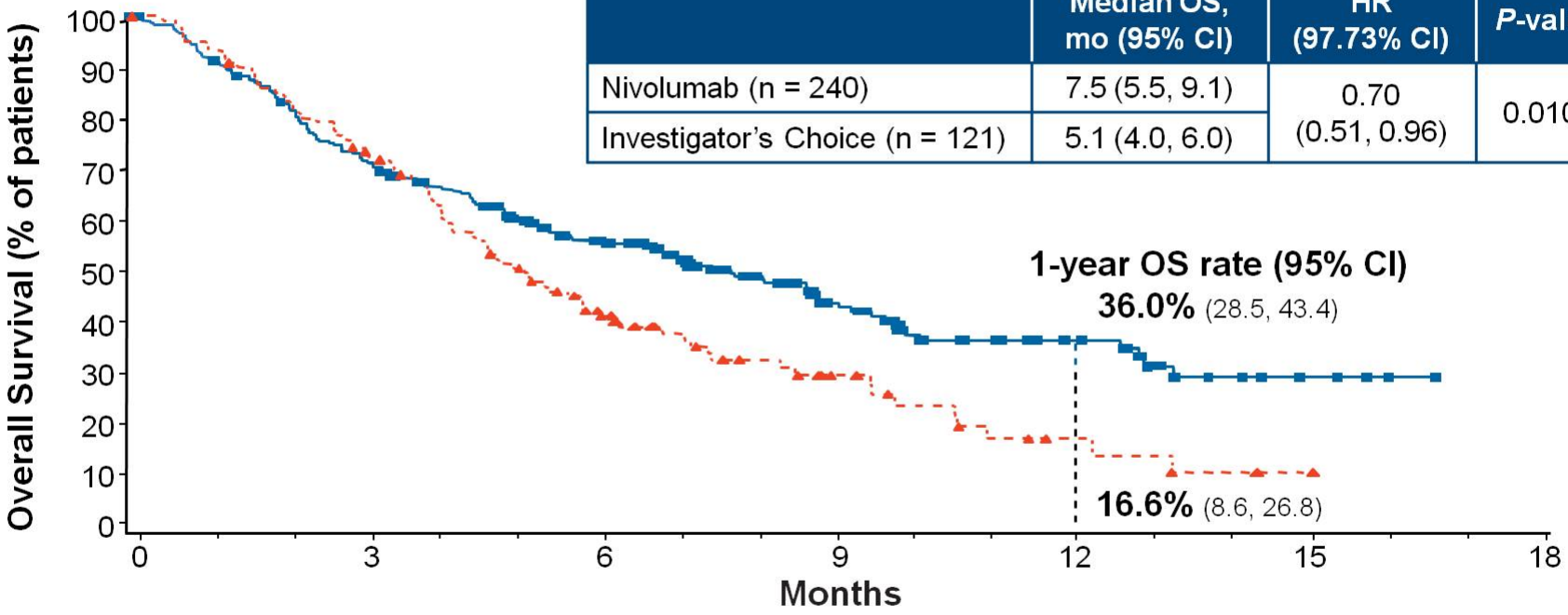
At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Presented by Yoon-Ko Kang at 2017 Gastrointestinal Cancers Symposium

Overall Survival

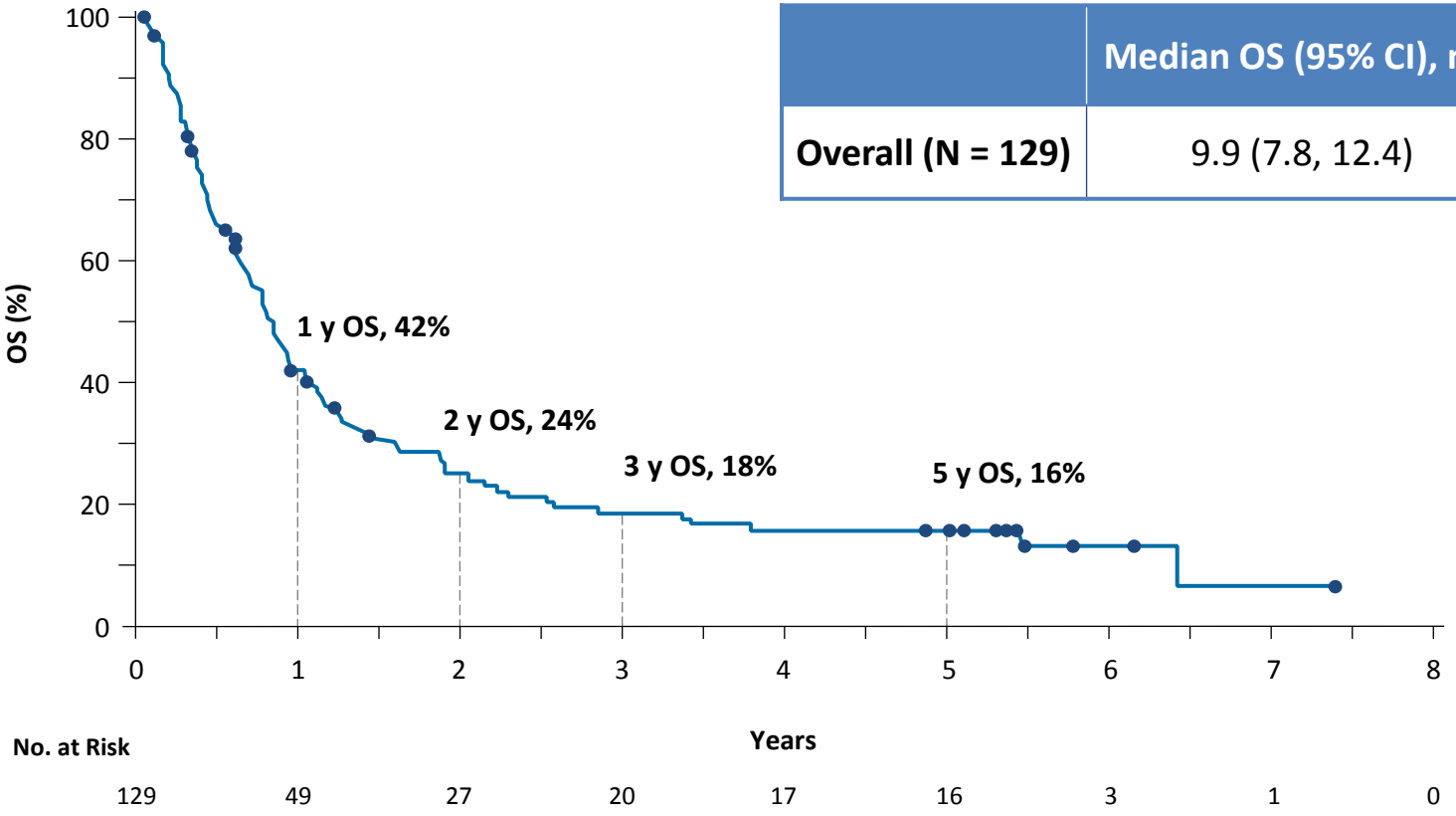
Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

5-Year Estimates of OS
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

2017 AACR, Julie Brahmer et.al

AACR American Association for Cancer Research
ANNUAL MEETING 2017 WASHINGTON, DC
Abstract Number CT075

Overall Survival Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (CheckMate 067)

James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] Dana Walker,[16] Linda Rollin,[16] Christine Horak,[16] F. Stephen Hodi,[17,*] Jedd D. Wolchok[18,*]

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AACR American Association for Cancer Research
ANNUAL MEETING
2017 WASHINGTON, DC

Impact of Tumor Mutation Burden on the Efficacy of First-Line Nivolumab in Stage IV or Recurrent Non-Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 026

Solange Peters,[1] Benjamin Creelan,[2] Matthew D. Hellmann,[3] Mark A. Socinski,[4] Martin Reck,[5] Prabhu Bhagavatheeswaran,[6] Han Chang,[6] William J. Geese,[6] Luis Paz-Ares,[7] David P. Carbone[8]

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

MEL
Overall survival (OS) analysis from an expanded access program (EAP) of nivolumab (NIVO) in combination with ipilimumab (IPI) in patients with advanced melanoma (MEL).
Management of gastrointestinal (GI) toxicity associated with nivolumab (NIVO) plus ipilimumab (IPI) or IPI alone in phase II and III trials in advanced melanoma (MEL).
Association of distinct baseline tissue biomarkers with response to nivolumab (NIVO) and ipilimumab (IPI) in melanoma: CheckMate 064.
Efficacy and safety of nivolumab (NIVO) in patients with advanced melanoma (MEL) and poor prognostic factors who progressed on or after ipilimumab (IPI): Results from a phase II study (CheckMate 172).
Phase II multicenter, single arm, open label study of nivolumab (NIVO) incombination with ipilimumab (IPI) as first line in adult patients (pts) withmetastatic uveal melanoma (MUM): GEM1402 NCT02626962.
The safety and early efficacy of high-dose ipilimumab (IPI) and the combination nivolumab plus ipilimumab (NIVO + IPI) in patients (pts) with uveal melanoma (UM).
Exploratory analysis of multiprotein serum predictors at baseline of progression-free survival of ipilimumab or ipilimumab and nivolumab in the Checkmate-069 study.
Neoadjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage III melanoma: Updated data from the OpACIN trial and first immunological analyses.
Phase 1 study to evaluate safety and efficacy of ipilimumab + nivolumab + external beam radiotherapy in patients with metastatic melanoma.
SECOMBIT (sequential combo immuno and target therapy study): A three arms prospective, randomized phase II study to evaluate the best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with metastatic melanoma and BRAF mutation.

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

MEL
Multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO) (OpACIN-neo).
Initial efficacy of anti-lymphocyte activation gene-3 (anti-LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti-PD-1/PD-L1 therapy.
Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204.
A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC).
Association of changes in T regulatory cells (Treg) during nivolumab treatment with melanoma outcome.
NSCLC
Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer: A study on risk factors for fatal outcome.
Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer: A study on risk factors using interim results of post-marketing all-case surveillance.
Nivolumab (N) plus ipilimumab (I) as first-line (1L) treatment for advanced (adv) NSCLC: 2-yr OS and long-term outcomes from CheckMate 012.
Nivolumab (nivo) + nab-paclitaxel (nab-P) + carboplatin (C) in patients (pts) with non-small cell lung cancer (NSCLC): Interim results from a multicenter phase I study.
EA5142 adjuvant nivolumab in resected lung cancers (ANVIL): The newest study in the ALCHEMIST platform.

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

NSCLC
Checkmate 816: A phase 3, randomized, open-label trial of nivolumab plus ipilimumab vs platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC.
Randomized phase III trial of concurrent chemoradiation followed by nivolumab or placebo for locally advanced non-small cell lung cancer (NSCLC) (RTOG 3505).
NIVORAD: A randomised phase 2 trial of nivolumab and stereotactic ablative body radiotherapy in advanced non-small cell lung cancer, progressing after first or second line chemotherapy.
Ceritinib plus nivolumab (NIVO) in patients (pts) with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC).
Predictive impact of PD-L1-expressing circulating tumor cells in NSCLC patients treated with nivolumab.
Pre-treatment hematological markers as a predictive biomarker for survival in patients with non-small cell lung cancer treated with nivolumab.
Response to first-line chemotherapy regimen to predict efficacy of nivolumab in lung cancer.
Excision repair cross complementation group 1 (ERCC-1) gene polymorphisms and response to nivolumab in advanced non-small cell lung cancer (NSCLC).
Predictive and prognostic value of systemic inflammatory response biomarkers in patients receiving nivolumab for metastatic non-small cell lung cancer (NSCLC).
SCLC
Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032.

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

MPM
Checkmate 743: A phase 3, randomized, open-label trial of nivolumab (nivo) plus ipilimumab (ipi) vs pemetrexed plus cisplatin or carboplatin as first-line therapy in unresectable pleural mesothelioma.
Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial.
GC/EC
CheckMate 577: A randomized, double-blind, phase 3 study of adjuvant nivolumab (nivo) or placebo in pts with resected esophageal (E) or gastroesophageal junction (GEJ) cancer.
CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (nivo) + ipilimumab (ipi) or nivo + chemotherapy (CTX) vs CTX alone in pts with previously untreated advanced (adv) gastric (G) or gastroesophageal junction (GEJ) cancer.
FRACTION (Fast Real-time Assessment of Combination Therapies in Immuno-ONcology)-gastric cancer (GC): A randomized, open-label, adaptive, phase 2 study of nivolumab in combination with other immuno-oncology (IO) agents in patients with advanced GC.
A phase II, open-label, randomized study to evaluate the efficacy and safety of GS-5745 combined with nivolumab versus nivolumab alone in subjects with unresectable or recurrent gastric or gastroesophageal junction adenocarcinoma.
Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study.
H&N
An open-label, multicohort, phase I/II study to evaluate nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC).

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

H&N
Cost-effectiveness of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck.
Characterization of potential predictive biomarkers of response to nivolumab in CheckMate 141 in patients with squamous cell carcinoma of the head and neck (SCCHN).
A randomized phase II study of chemoradiation (CRT) +/- nivolumab (Nivo) with sequential safety evaluations of Nivo +/- lirilumab (Liri) or ipilumumab (Ipi) concomitant with (C) RT in intermediate (IR) and high-risk (HR) head and neck squamous cell carcinoma (HNSCC) (RTOG 3504, NCT02764593).
Nivolumab (Nivo) vs investigator's choice (IC) for platinum-refractory (PR) recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN; Checkmate 141): Outcomes in first-line (1L) R/m patients and updated safety and efficacy.
Nivolumab (Nivo) vs investigator™s choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Efficacy and safety in CheckMate 141 by prior cetuximab use.
RCC
Efficacy and safety of nivolumab in patients with metastatic renal cell carcinoma (mRCC) and brain metastases: Preliminary results from the GETUG-AFU 26 (Nivoren) study.
Safety and efficacy of nivolumab for metastatic renal cell carcinoma (mRCC): Real world data from an Italian expanded access program (EAP).
Nivolumab treatment for patients with non-clear cell renal cell carcinoma: A multicenter retrospective analysis.
A phase III randomized study comparing perioperative nivolumab vs. observation in patients with localized renal cell carcinoma undergoing nephrectomy (PROSPER RCC).

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

UC
Health-related quality of life as a marker of treatment benefit with nivolumab in platinum-refractory patients with metastatic or unresectable urothelial carcinoma from CheckMate 275.
A phase I study of cabozantinib plus nivolumab (CaboNivo) and cabonivo plus ipilimumab (CaboNivoIpi) in patients (pts) with refractory metastatic (m) urothelial carcinoma (UC) and other genitourinary (GU) tumors.
HCC
Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study.
COL
Combination of nivolumab (nivo) + ipilimumab (ipi) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 study.
Concordance of DNA mismatch repair deficient (dMMR)/microsatellite instability (MSI) assessment by local and central testing in patients with metastatic CRC (mCRC) receiving nivolumab (nivo) in CheckMate 142 study.
GBM
Histopathologic review of suspected disease progression in patients with recurrent glioblastoma (GBM) receiving nivolumab ± ipilimumab: CheckMate 143.
Nivolumab combined with hypofractionated stereotactic irradiation (HFSRT) for patients with recurrent high grade gliomas: A phase I trial (NCT02829931).

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

Sarcoma
A multi-center phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (Alliance A091401).
PRO
Phase 2 biomarker-driven study of ipilimumab plus nivolumab (Ipi/Nivo) for ARV7-positive metastatic castrate-resistant prostate cancer (mCRPC).
nHL
CheckMate 436: A phase 1-2 study to evaluate safety and efficacy of nivolumab plus brentuximab vedotin in patients with CD30-expressing relapsed/refractory non-Hodgkin lymphomas.
AML
Phase IB/II study of nivolumab with azacytidine (AZA) in patients (pts) with relapsed AML.
MM
CheckMate 602: An open-label, randomized, phase 3 trial of combinations of nivolumab, elotuzumab, pomalidomide and dexamethasone in relapsed/refractory multiple myeloma.
Nivolumab in combination with daratumumab, with or without pomalidomide and dexamethasone, for relapsed/refractory multiple myeloma: 2 cohorts of the phase 1 CheckMate 039 safety study.

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OPDIVO (Nivolumab)-related presentation in ASCO 2017 Meeting

OTHER
An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers.
ADVL1412: Initial results of a phase I/II study of nivolumab and ipilimumab in pediatric patients with relapsed/refractory solid tumors-A COG study.
Preliminary results of a phase I/IIa study of BMS-986156 (glucocorticoid-induced tumor necrosis factor receptor-related gene [GITR] agonist), alone and in combination with nivolumab in pts with advanced solid tumors.
Phase 1 safety of ICOS agonist antibody JTX-2011 alone and with nivolumab (nivo) in advanced solid tumors; predicted vs observed pharmacokinetics (PK) in ICONIC.
A phase 1b study to evaluate TAK-659 in combination with nivolumab in patients (pts) with advanced solid tumors.
A phase I study of enadenotucirev (EnAd), an oncolytic Ad11/Ad3 chimeric group B adenovirus, in combination with nivolumab in tumors of epithelial origin.
An open-label, phase Ib study of NEO-PV-01 + adjuvant with nivolumab in patients with melanoma, non-small cell lung carcinoma, or transitional cell carcinoma of the bladder.
Epacadostat plus nivolumab in patients with advanced solid tumors: Preliminary phase I/II results of ECHO-204.
Clinical results with combination of anti-CD27 agonist antibody, varlilumab, with anti-PD1 antibody nivolumab in advanced cancer patients.

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