

Development Pipeline Progress Status

ONO PHARMACEUTICAL CO.,LTD.

May 11, 2018

Development status of OPDIVO (nivolumab) ①

Target disease	JAPAN	US/EU	KR/TW
Melanoma (1 st)	Approved	Approved	Approved
Melanoma (Adjuvant Therapy)	Filing	Approved (US) Filing(EU)	III
Non-small cell lung cancer (2 nd ~)	Approved	Approved	Approved *)
Non-small cell lung cancer (1 st)	III	III(US) Filing(EU)	III
Renal cell carcinoma (2 nd ~)	Approved	Approved	Approved (KR) Approved (TW)
Renal cell carcinoma (1 st)	Filing	Approved (US) Filing(EU)	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	Approved
Gastro-esophageal junction cancer and esophageal cancer	III	III	III
Small cell lung cancer	III	Filing (US) III (EU)	III
Hepatocellular carcinoma	III	Approved (US) III (EU)	III(KR) Approved (TW)
Esophageal cancer	III	III	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
Glioblastoma	III	III	-
Multiple myeloma	II	III	-
Malignant pleural mesothelioma	Filing	III	-
Ovarian cancer	III	I / II	-
Colorectal cancer	II / III	Approved (US) II / III (EU)	-
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	-
Prostate cancer	-	II	-
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	Filing	Approved (US) Filing (EU)	III
	Non-small cell lung cancer	III	III (US) Filing (EU)	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	-
	Esophageal cancer	III	III	III
	Urothelial cancer	III	III	III
	Colorectal cancer	-	Filing (US) II (EU)	-
	Ovarian cancer	-	I / II	-
	Virus positive/negative solid carcinoma	I / II	I / II	I / II

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-7701 (IDO1 inhibitor)	Solid tumor, Hematologic malignancy	I	I / II	-
ONO-4686 (Anti-TIGIT antibody)	Solid tumor	I / II	I / II	-
ONO-7807 (Anti-TIM-3 antibody)	Solid tumor	I / II	I / II	-
ONO-4482 / Relatlimab (Anti-LAG-3 antibody)	Melanoma	I / II	-	-
	Solid tumor	I	I / II	-
ONO-4483 / Lirilumab (Anti-KIR antibody)	Solid tumor	I	I / II	-
ONO-4481 / Urelumab (CD137 receptor agonist)	Solid tumor	I	I / II	-
Mogamulizumab (Anti-CCR4 antibody)	Solid tumor	I	I / II	-
ONO-4687 / Cabiralizumab (Anti-CSF-1R antibody)	Solid tumor, Hematologic malignancy	I	I	-

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
ONO-7702 (Encorafenib)	Melanoma	Filing
ONO-7703 (Binimetinib)	Melanoma	Filing
ONO-5371 (Metyrosine)	Pheochromocytoma	Filing
KYPROLIS (Additional dosage and administration)	Multiple myeloma	III
ONO-7643 (Anamorelin)	Cancer anorexia/cachexia (in all types of cancer)	III
ONO-7702 (Encorafenib)	Colorectal cancer	III
ONO-7703 (Binimetinib)	Colorectal cancer	III
ONO-4686 (BMS-986207)	Solid tumor	I / II
ONO-4059 (Tirabrutinib)	Central nervous system lymphoma	I / II
ONO-4482 (Relatlimab)	Melanoma	I / II
ONO-7807 (BMS-986258)	Solid tumor	I / II
ONO-7701 (BMS-986205)	Solid tumor	I
ONO-4481 (Urelumab)	Solid tumor	I
ONO-4687 (Cabiralizumab)	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	Approved
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 (SI-613)	Osteoarthritis	III
Onoact (Pediatric)	Tachyarrhythmia in low cardiac function	II / III
Onoact (Additional indication)	Ventricular arrhythmia	II / III
	Tachyarrhythmia upon sepsis	II / III
ONO-2370 (Opicapone)	Parkinson's disease	II
ONO-5704 (SI-613)	Enthesopathy	II
Opdivo (Additional indication)	Sepsis	I / II
ONO-4059 (Tirabrutinib)	Autoimmune disease	I

Green : Change from the announcement in May 2017

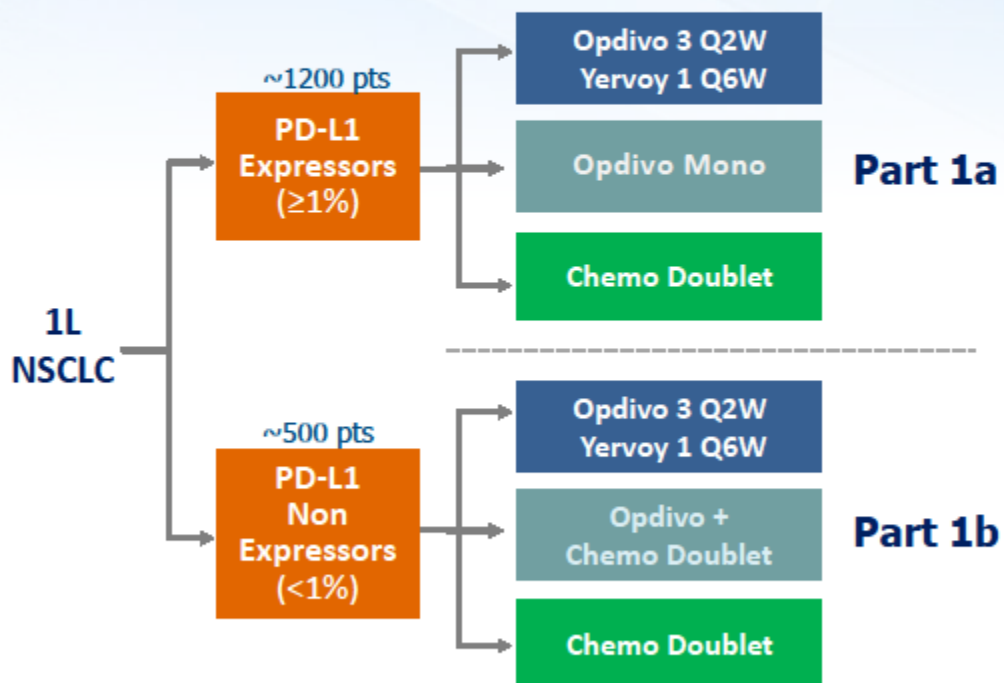
Global development projects (Other than OPDIVO)

Development code /Generic name	Target indication /Pharmacological Action	Phase	Area
ONO-7702 (Encorafenib)	Colorectal cancer /BRAF inhibitor	III	KR
	Melanoma /BRAF inhibitor	III	KR
ONO-7703 (Binimetinib)	Colorectal cancer /MEK inhibitor	III	KR
	Melanoma /MEK inhibitor	III	KR
ONO-4059 (Tirabrutinib)	B cell lymphoma /Btk inhibitor	II	EU
	Sjögrens syndrome /Btk inhibitor	II	US/EU
ONO-7579	Solid tumor /Trk inhibitor	I / II	US/EU
ONO-4059 (Tirabrutinib)	B cell lymphoma /Btk inhibitor	I	US
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

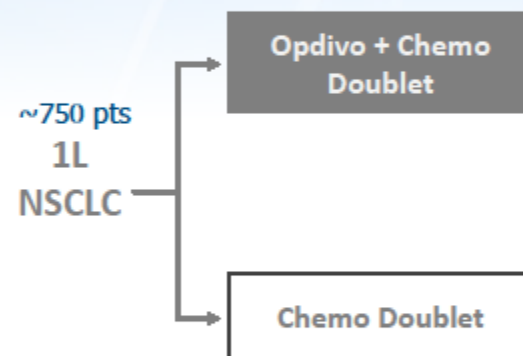
Today's Announcement is Focused on the Co-Primary Endpoints for Part 1 of CM-227

Part 1



Part 1 – Chemo doublet options include: NSQ: pem/cis, pem/carbo; SQ: gem/cis, gem/carbo.

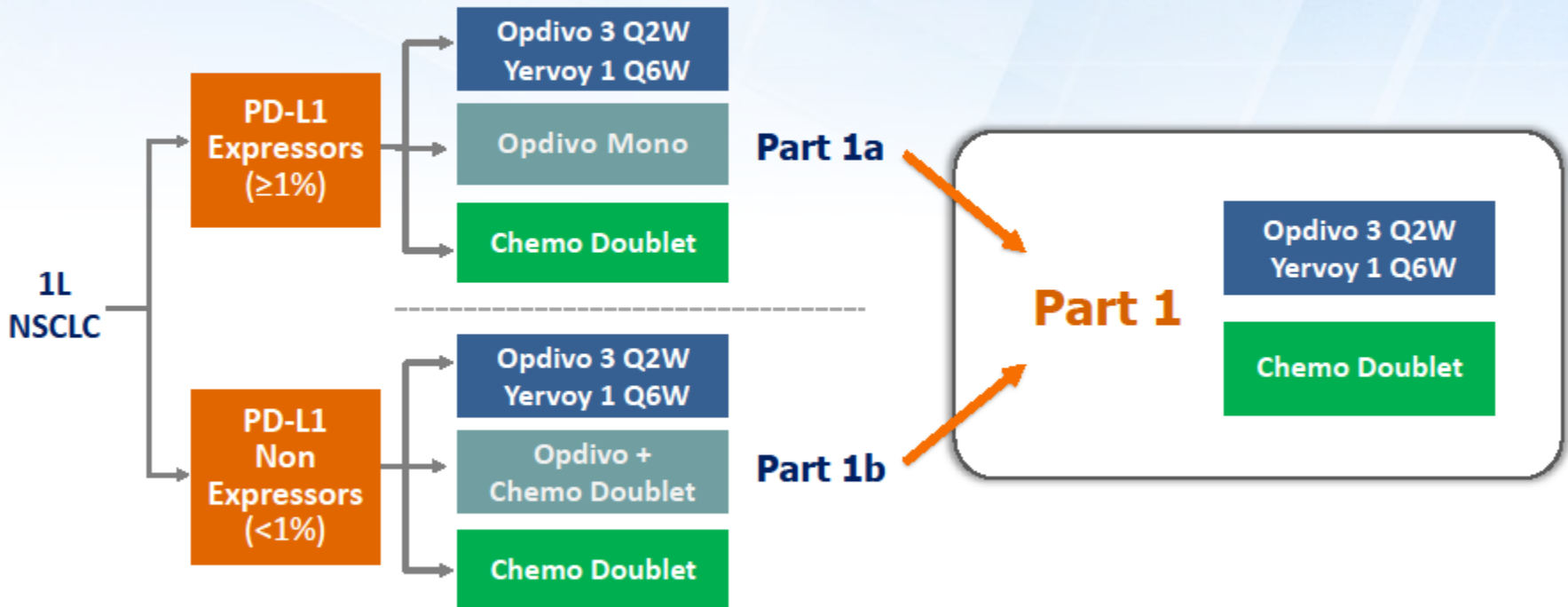
Part 2:



Fully Enrolled since October 2017

Part 2 – Chemo doublet options include NSQ: pem/carbo, pem/cis; SQ: carbo/taxol.

Integrated Analysis Plan Across Part 1



Part 1 – Chemo doublet options include: NSQ: pem/cis, pem/carbo; SQ: gem/cis, gem/carbo.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

Melanoma

Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238).

Epacadostat plus nivolumab for advanced melanoma: Updated phase 2 results of the ECHO-204 study.

Phase 1 study to evaluate safety and efficacy of nivolumab (nivo) + ipilimumab (ipi) + external beam radiotherapy (RT) in patients with metastatic melanoma.

Characterization of complete responders to combination nivolumab (nivo) and ipilimumab (ipi) in patients (pts) with advanced unresectable melanoma.

Safety and preliminary activity data from a single center phase II study of triplet combination of nivolumab (N) with dabrafenib (D) and trametinib (T) [trident] in patients (Pts) with BRAF-mutated metastatic melanoma (MM).

Indirect treatment comparison of nivolumab versus placebo as an adjuvant therapy for resected melanoma.

Assessing the value of nivolumab (NIVO) versus placebo (PBO) and ipilimumab (IPI) as adjuvant therapy for resected melanoma.

Combining ipilimumab (ipi) and nivolumab (nivo) in advanced melanoma following progression on a PD-1 inhibitor (SWOG S1616).

Multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO) (OpACIN-neo).

NSCLC

Association of baseline body mass index (BMI) with overall survival (OS) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with nivolumab (N) and pembrolizumab (P).

ALT-803, an IL-15 superagonist, in combination with nivolumab in metastatic non-small cell lung cancer: Ongoing experience and biomarker development from a non-randomized, open-label, phase Ib/II trial.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

NSCLC

Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-RT regimen in unresectable locally advanced NSCLC: The ETOP NICOLAS phase II trial.

Nivolumab (Nivo) + Ipilimumab (Ipi) vs Platinum-Doublet Chemotherapy (Chemo) as First-line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Safety Analysis and Patient-Reported Outcomes (PROs) From CheckMate 227.

Exome analysis to reveal genomic markers associated with better efficacy of nivolumab in lung cancer patients.

Correlation between nivolumab exposure and treatment outcome in NSCLC.

Immune-related adverse events and nivolumab outcomes in non-small cell lung cancer patients: A multi-institutional, retrospective cohort study.

Immune-related adverse events to predict survival in patients with advanced non-small cell lung cancer treated with nivolumab: A multicenter analysis.

Veliparib in combination with nivolumab and platinum doublet chemotherapy (CT) in metastatic/advanced NSCLC.

Computer extracted features of cancer nuclei from H&E stained tissues of tumor predicts response to nivolumab in non-small cell lung cancer.

Computer-extracted features relating to spatial arrangement of tumor infiltrating lymphocytes to predict response to nivolumab in non-small cell lung cancer (NSCLC).

Nivolumab (Nivo) + platinum-doublet chemotherapy (Chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: Results from CheckMate 227.

EA5142 adjuvant nivolumab in resected lung cancers (ANVIL).

Nivolumab plus cisplatin/pemetrexed or cisplatin/gemcitabine as induction in resectable NSCLC.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

NSCLC

Phase I/II study of nivolumab and ipilimumab combined with nintedanib in advanced NSCLC.

Trial in progress: Multicenter observational study to evaluate the relationship between gut bacterial flora and their therapeutic or adverse effects in advanced non-small cell lung cancer patients treated with nivolumab.

SCLC

Phase I/II trial of anti-PD-1 checkpoint inhibitor nivolumab and 177Lu-DOTA0- yr3-Octreotate for patients with extensive-stage small cell lung cancer.

Malignant Mesothelioma

A real-world experience of nivolumab in advanced malignant mesothelioma (MM).

CONFIRM: A phase III randomized trial to evaluate the efficacy of nivolumab versus placebo in relapsed mesothelioma.

Gastric Cancer / Esophageal Cancer

Preliminary result of phase 1/2 study of ramucirumab plus nivolumab in patients with previously treated advanced gastric adenocarcinoma (NivoRam study).

An investigator initiated multicenter phase I/II study of paclitaxel, ramucirumab with nivolumab as the second-line treatment in patients with metastatic gastric cancer.

Induction nivolumab or nivolumab/ipilimumab prior to concurrent chemoradiation plus nivolumab in patients with operable stage II/III esophageal/gastroesophageal junction cancer.

Head and neck carcinoma

A phase II randomized trial of nivolumab with stereotactic body radiotherapy (SBRT) versus nivolumab alone in metastatic (M1) head and neck squamous cell carcinoma (HNSCC).

Safety evaluation of nivolumab (Nivo) concomitant with cetuximab radiotherapy for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG 3504.

Nivolumab (nivo) vs investigator's choice (IC) in patients (pts) with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Analysis of CheckMate 141 by age.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

Head and neck carcinoma

ECHO-310: A phase 3, randomized trial of epacadostat + nivolumab + chemo vs EXTREME as first-line treatment of recurrent/metastatic SCCHN.

Renal cell carcinoma

Pegilodecakin with nivolumab (nivo) or pembrolizumab (pembro) in patients (pts) with metastatic renal cell carcinoma (RCC).

Gut microbiome composition to predict resistance in renal cell carcinoma (RCC) patients on nivolumab.

A pilot randomized study evaluating nivolumab (nivo) or nivo + bevacizumab (bev) or nivo + ipilimumab (ipi) in patients with metastatic renal cell carcinoma (MRCC) eligible for cytoreductive nephrectomy (CN), metastasectomy (MS) or post-treatment biopsy (Bx).

Real world experience and biomarkers of nivolumab in dutch advanced renal-cell carcinoma patients.

Pilot trial of ibrutinib plus nivolumab in patients with metastatic renal cell cancer (mRCC): results from a dose-finding cohort.

Nivolumab (nivo) for patients (pts) with metastatic non-clear cell renal cell carcinoma (nccRCC): A single-institution experience.

PROSPER: A phase III randomized study comparing perioperative nivolumab (nivo) vs. observation in patients with localized renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN 8143).

A phase 3, randomized, open-label study of nivolumab combined with cabozantinib vs sunitinib in patients with previously untreated advanced or metastatic renal cell carcinoma (RCC; CheckMate 9ER).

Optimized management of nivolumab (NIVO) and ipilimumab (IPI) in advanced renal cell carcinoma (OMNIVORE): A response-based phase II study.

NIVES study: A phase II trial of nivolumab (NIVO) plus stereotactic body radiotherapy (SBRT) in II and III line of patients (pts) with metastatic renal cell carcinoma (mRCC).

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

breast cancer

Adaptive phase II randomized trial of nivolumab after induction treatment in triple negative breast cancer (TONIC trial): Final response data stage I and first translational data.

Phase II study of a combination therapy of nivolumab, bevacizumab and paclitaxel in patients with HER2-negative metastatic breast cancer as a first-line treatment (WJOG9917B, NEWBEAT trial).

A randomized phase II trial of carboplatin with or without nivolumab in first- or second-line metastatic TNBC.

A phase II study of nivolumab in combination with cabozantinib for metastatic triple-negative breast cancer (mTNBC).

Urothelial cancer

BMS-986205, an indoleamine 2,3-dioxygenase 1 inhibitor (IDO1i), in combination with nivolumab (NIVO): Updated safety across all tumor cohorts and efficacy in pts with advanced bladder cancer (advBC).

Clinical efficacy of cabozantinib plus nivolumab (CaboNivo) and CaboNivo plus ipilimumab (CaboNivoIpi) in patients (pts) with chemotherapy-refractory metastatic urothelial carcinoma (mUC) either naïve (n) or refractory (r) to checkpoint inhibitor (CPI).

A phase 3, open-label, randomized study of nivolumab plus ipilimumab or standard of care (SoC) vs SoC alone in patients (pts) with previously untreated unresectable or metastatic urothelial carcinoma (mUC; CheckMate 901).

Hepatocellular carcinoma

A multicenter pilot study of nivolumab (NIVO) with drug eluting bead transarterial chemoembolization (deb-TACE) in patients (pts) with liver limited hepatocellular carcinoma (HCC).

Glioblastoma

A phase II, open label, single arm study of nivolumab for recurrent or progressive IDH mutant gliomas with prior exposure to alkylating agents.

sarcoma

IMMUNOSARC: A collaborative Spanish (GEIS) and Italian (ISG) Sarcoma Groups phase I/II trial of sunitinib plus nivolumab in selected bone and soft tissue sarcoma subtypes—Results of the phase I part.

Phase 1/2 study of safety/efficacy using trabectedin, ipilimumab and nivolumab triple therapy as first line treatment of advanced soft tissue sarcoma.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

Prostate cancer

An open-label, phase 2 study of nivolumab in combination with either rucaparib, docetaxel, or enzalutamide in men with castration-resistant metastatic prostate cancer (mCRPC; CheckMate 9KD).

Biliary tract cancer

A multi-center randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first line therapy for patients with advanced unresectable biliary tract cancer.

Cervix carcinoma

A phase II evaluation of nivolumab, a fully human antibody against PD-1, in the treatment of persistent or recurrent cervical cancer.

Ovarian cancer

A phase I study of concomitant galinpepimut-s (GPS) in combination with nivolumab (nivo) in patients (pts) with WT1+ ovarian cancer (OC) in second or third remission.

Merkel cell carcinoma

Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358.

Acute myeloid leukemia

Nivolumab (Nivo) maintenance (maint) in high-risk (HR) acute myeloid leukemia (AML) patients.

Other

ICONIC: Biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in patients (pts) with advanced cancers.

ASCO 2018 Annual meeting — OPDIVO(Nivolumab) –related Subjects

Other

Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results.

NKTR-214 (CD122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT.

Association of pre-existing thyroid autoimmunity with the development of thyroid dysfunction induced by nivolumab.

Initial results from first-in-human study of IPI-549, a tumor macrophage-targeting agent, combined with nivolumab in advanced solid tumors.

Pharmacodynamics (PD) and genomic profiling of pts treated with cabiralizumab (cabira) + nivolumab (NIVO) provide evidence of ontarget tumor immune modulations and support future clinical applications.

Clinical and pharmacological parameters associated with nivolumab toxicity.

Efficacy and safety of nivolumab (Nivo) in patients (pts) with advanced or recurrent uterine cervical or corpus cancers.

Entinostat in combination with nivolumab for patients with advanced holangiocarcinoma and pancreatic adenocarcinoma.

Phase 1b/2 study of nivolumab in combination with an anti-IL-8 monoclonal antibody, BMS-986253, in a biomarker-enriched population of patients with advanced cancer.

Phase 1b trial of nivolumab combined with metformin for refractory/recurrent solid tumors.

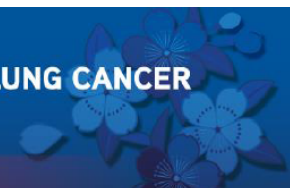
A multicenter phase 2 study of nivolumab combined with ipilimumab in patients with pediatric solid tumors in adulthood (GETHI021).

Regorafenib and nivolumab combination therapy for advanced and metastatic solid tumors: Phase I clinical trial (EPOC1603).

Phase I study of recombinant interleukin-15 in combination with checkpoint inhibitors nivolumab and ipilimumab in subjects with refractory cancers.

AMC 095 (AIDS Malignancy Consortium): A phase I study of ipilimumab (IPI) and nivolumab (NIVO) in advanced HIV associated solid tumors (ST) with expansion cohorts in HIV associated solid tumors and classical Hodgkin lymphoma (cHL).

A Phase II Study of Nivolumab in Malignant Pleural Mesothelioma



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]

