

CT Application(s) Summary Report

• Protocol title: A Phase III, Open-Label, Randomized Study of Atezolizumab with Lenvatinib or Sorafenib Versus Lenvatinib or Sorafenib alone in Hepatocellular Carcinoma Previously Treated with Atezolizumab and Bevacizumab • Protocol code number: MO42541 (Imbrave) • <u>Public Registry Number:</u> 2020-005231-78 • Version: 7 • Date: 23 Sep.2024			
• Investigational Medicinal Product being tested:			
Biological	☒	Pharmaceutical	☐
Innovative	☐		
Herbal medicine	☐	Medical device	☐
• Sponsor: F. Hoffmann-La Roche Ltd • Indication: Hepatocellular Carcinoma • Investigator's brochure (IB) Version: 22 Date: July 2025 • Name of all Sites: Air Force Specialized Hospital • Name of PI(s): Dr. Tarek Hashim			
• EDA approval date:			
1. Initial approval on Protocol Version 1.0 and IB Edition 17: 31/01/2022 2. Amendment approval on Protocol Version 4.0 and IB edition 18: 11/10/2023 3. Amendment approval on Protocol Version 5.0: 2/04/2024 4. Amendment approval on Protocol Version 6.0 and IB edition 20: 11/11/2024 5. Amendment approval on Protocol Version 7.0 and IB edition 21: 28/05/2025 6. Amendment approval on IB edition 22: 12/03/2026			
Summary of pre-clinical studies:			
1. Non-clinical Pharmacology: Atezolizumab binds with high affinity to PD-L1, effectively blocking its interaction with PD-1 and B7-1 receptors (Study 09-0426). It binds comparably to human and cynomolgus monkey T cells, supporting the use of cynomolgus monkeys for nonclinical toxicity and PK studies (Study 09-0426), and exhibits minimal Fcγ receptor binding (Study 09-0426). In vitro, atezolizumab and its chimeric derivatives (PRO304397,			

PRO314483) inhibit PD-L1 binding to human and murine PD-1 and B7-1 (Study 09-0426). In vivo, anti-PD-L1 treatment showed strong anti-tumor activity in murine colorectal and melanoma models: MC38.OVA tumors achieved complete, durable regression (Studies 08-1033 E, 08-1734 D, 09-2165 I, 10-1883), unmodified MC38 tumors had 76%–108% tumor growth inhibition, CT26 tumors showed 92% inhibition, and Cloudman S91 melanoma tumors had 78% inhibition. Combination studies with other agents, e.g., cobimetinib, were also conducted. No atezolizumab-related effects were observed in safety pharmacology assessments of CNS, cardiovascular, or respiratory systems.

2. Non-clinical Pharmacokinetics and Metabolism:

-The pharmacokinetics (PK) of atezolizumab and its chimeric derivative PRO304397 were studied in mice and cynomolgus monkeys to support toxicology and clinical development, and to demonstrate in vivo PD-L1 binding on peripheral blood lymphocytes. **Overall, the PK profile is consistent with that of a humanized IgG1 monoclonal antibody.**

□ Mice studies:

Single IV doses of 1–30 mg/kg of PRO304397 showed biphasic disposition in the first week, followed by a rapid decline in serum concentrations (Study 08-1946). Clearance ranged from 16.3–57.7 mL/day/kg, likely influenced by anti-drug antibodies (ADAs). Complete PD-L1 saturation on CD4+ and CD8+ T cells was achieved within 24 hours.

Repeated weekly IV doses of atezolizumab led to high immunogenicity; all animals developed ADAs, which increased clearance and reduced exposure over time (Study 08-0806).

□ Cynomolgus monkey studies:

Single IV doses of 0.5, 5, or 20 mg/kg demonstrated linear, dose-dependent PK through Day 7, with mean clearance 3.70 mL/day/kg, Vss ~59.8 mL/kg, and beta-phase half-life ~11.5 days (Study 08-0598).

Repeat-dose toxicology studies with weekly IV/SC doses (5–50 mg/kg) for up to 9 or 27 weeks confirmed linear dose-dependent exposures, with no significant sex differences (Studies 08-1148, 13-3278).

ADAs were detected in most animals after single or repeated dosing, but average exposure in ADA-positive and ADA-negative animals remained comparable (Studies 08-0598, 08-1148, 13-3278).

Atezolizumab exposure was maintained during chronic dosing, including after KLH administration and 50 mg/kg weekly doses (Study 16-1705).

--Cynomolgus monkeys are the most appropriate species for assessing general toxicity, and nonclinical PK data support clinical development of atezolizumab.

3. Toxicology and Safety Pharmacology:

The toxicology program included:

2-week non-GLP repeat-dose pilot study in mice (4-week recovery), 8- and 26-week GLP repeat-dose studies in cynomolgus monkeys (12- and 13-week recovery), Immunotoxicology study in cynomolgus monkeys (T cell and T cell-dependent antibody response to KLH), In vitro cytokine release assay, GLP in vitro hemolytic potential and blood compatibility assay, and GLP tissue cross-reactivity study using human and cynomolgus monkey tissues.

Mice studies:

Atezolizumab was well tolerated at up to 50 mg/kg weekly for 2 weeks (3 doses).

Minimal neuropathy was observed in C57BL/6 mice at ≥ 10 mg/kg (Study 08-0806).

No microscopic findings were observed in CD-1 mice.

Cynomolgus monkey studies:

Well tolerated at IV or SC doses up to 50 mg/kg for 8 weeks (9 doses) or 26 weeks (27 doses).

Minimal-to-mild arteritis/periarteritis in multiple organs observed at ≥ 15 mg/kg, which resolved after recovery; consistent with PD-L1 blockade pharmacology.

SC injection site lesions (minimal, mononuclear infiltrates) were reversible and non-adverse.

Irregular menstrual cycles at 50 mg/kg were reversible during recovery.

Chronic administration with KLH challenge did not produce unexpected toxicities; minor decreases in anti-KLH IgM/IgG responses were observed, of uncertain significance.

Other safety assays:

No hemolysis of human or cynomolgus erythrocytes at concentrations up to 125 mg/mL (Study 08-1172).

Tissue cross-reactivity: biotin-atezolizumab staining observed in human placenta, lymph node, tonsil, thymus, and in cynomolgus lymph node (Study 08-1174).

Cytokine release assay: no induction of cytokines from human PBMCs at 0.25–250 μ g/mL (Study 08-1827).

3.1 Genotoxicity and Carcinogenicity

Atezolizumab is a monoclonal antibody and is not expected to be directly genotoxic, as it does not interact with DNA or other chromosomal material. In accordance with ICH S6(R1) guidelines (2011) for biotechnology-derived pharmaceuticals, no genotoxicity or carcinogenicity studies have been conducted. Based on its mechanism of action and available preclinical data, atezolizumab is not anticipated to be genotoxic or teratogenic.

3.2 Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. The programmed death ligand-1 (PD-L1)/ programmed death 1 (PD-1) signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation .

Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality.

3.3 Additional Nonclinical Safety Findings:

Inhibition of the PD-1/PD-L1 pathway may modulate the host immune response to acute infections, which could result in immunopathology or dysregulated immune defenses. Preclinical studies using lymphocytic choriomeningitis virus (LCMV) CL-13 have demonstrated that the timing of PD-L1 blockade is critical in determining the outcome.

During the chronic phase of infection, PD-L1 blockade enhanced T-cell function and reduced viral load. In contrast, blockade at the peak of the acute T-cell response and concomitant peak viremia resulted in mortality rates of 80%–100%. This immunopathology was attributed to excessive systemic activation of CD8+ T-cells in the context of extremely high viral burden across multiple organs. These findings were consistent with those observed in PD-L1-deficient mice, where 100% of animals died within 8 days, underscoring the importance of the PD-1/PD-L1 pathway in controlling acute T-cell responses and preventing associated immunopathology.

Similar effects have been reported with independent antibodies targeting PD-L1 or PD-1 and in PD-L1 or PD-1 knockout mice (Study 10-1394). The mortality observed in the acute CL-13 model is likely mediated by enhanced CD8+ T-cell activity compromising vascular integrity, ultimately leading to circulatory collapse. These preclinical findings highlight a potential risk of immune dysregulation in patients who develop acute infections during PD-L1 blockade therapy.

• Summary of previous clinical studies:

❖ EFFECTS IN HUMANS

As of 17 May 2025, over 150 Sponsor studies are ongoing, and over 120 studies have been completed with atezolizumab as a single agent or in combination with other therapies

Protocol No.,	Study Design	Study Population	Objectives	Dosing Regimen, Duration, Formulation	No. of Patients	Study Status and Dates
BP40657 (IMscin001)	2-part, open-label, parallel Phase Ib/III dose-finding/confirmation study of atezolizumab subcutaneous	Patients with previously treated locally advanced or metastatic NSCLC	PK of atezolizumab SC compared with atezolizumab IV. Part 1: dose-finding Part 2: dose-confirmation (Part 2)	Part 1: Atezolizumab SC 1200-1800 mg q2w or q3w Part 2: Atezolizumab SC	Part 1: 67 a Part 2: 371 a	Completed; Final CSR May, 2025

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				1875 mg q3w vs Atezolizu mab IV 1200 mg q3w.		
MO43576 (IMscin002)	A randomized, multicenter, open-label cross-over Phase II study to evaluate patient preference of subcutaneous administration of atezolizumab (IMscin002)	Patients with resected Stage II or III, PD-L1 positive NSCLC (who have completed platinum-based adjuvant chemotherapy), and patients with previously untreated metastatic (Stage IV), PD-L1 high NSCLC	Participant preference for atezolizumab SC compared with atezolizumab IV, assessed using Question 1 of the Patient Preference Questionnaire (PPQ)	Atezolizu mab SC 1875 mg q3w, 3 cycles or Atezolizu mab IV 1200 mg q3w, 3 cycles	175	Complete , Final CSR February 2025.
CO39262	A Phase III, double-blinded, randomized, placebo-controlled study of atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib	Previously untreated BRAFV600 mutation-positive unresectable locally advanced or metastatic melanoma	Efficacy (Investigator-assessed PFS per RECIST 1.1) of atezolizumab in combination with cobimetinib and vemurafenib	Atezolizumab 840 mg q2w until investigator-determined disease progression	232	Completed, Final CSR December 2024
CO39385 (IMbassador250)	A Phase III, multicenter, randomized study of atezolizumab (anti-PD-L1 antibody) in combination with enzalutamide versus enzalutamide alone	Metastatic castration-resistant prostate cancer after failure of an androgen synthesis inhibitor and failure of, ineligibility for, or refusal	Efficacy of atezolizumab/enzalutamide compared with enzalutamide alone (OS)	Atezolizumab 1200 mg IV q3w	386	Completed Final CSR September 2023

		of a taxane regimen				
GC207JG	Phase I, open-label, multicenter, dose-escalation study of codrituzumab (anti-glypican-3 monoclonal antibody), in combination with atezolizumab	Patients with locally advanced or metastatic HCC	MTD, safety, tolerability, anti-tumor activity and PK of codrituzumab in combination with atezolizumab		20 b	Ongoing; 30 Aug 2016 (FPI)
GO29293 (IMvigor210)	Open-label, non-randomized, non-controlled, single-arm Phase II study of atezolizumab	Locally advanced or metastatic urothelial carcinoma after failure of platinum-containing chemotherapy and 1L cisplatin-ineligible patients	IRF-assessed ORR per RECIST v1.1 and investigator-assessed ORR per modified RECIST	Atezolizumab IV 1200 mg q3w	438 a	Completed Final CSR November 2023
GO29438 (IMpower132)	Randomized, open-label Phase III study of atezolizumab in combination with carboplatin or cisplatin, pemetrexed compared with carboplatin or cisplatin, pemetrexed	Chemotherapy-naïve Stage IV non-squamous NSCLC	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizumab IV 1200 mg q3w for 4 or 6 cycles	370 a	Completed; Final CSR July 2023
GO29527 (IMpower010)	Randomized, open-label Phase III study of atezolizumab compared with best supportive care following adjuvant cisplatin-based chemotherapy	Completely resected Stage IB to IIIA NSCLC	Investigator-assessed disease-free survival	Atezolizumab IV 1200 mg q3w	495 a	Ongoing; Oct 2015 (FPI)
GO30103	Phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of MTIG7192A as a single agent and in combination with atezolizumab	Locally advanced or metastatic tumors.	Safety, PK, pharmacodynamics, and preliminary anti-tumor activity of MTIG7192A as a single agent or in combination with atezolizumab	Atezolizumab IV 1200 mg q3w	198 a	Ongoing; May 2016 (FPI)
JO39363	Japanese version compassionate use study of atezolizumab	Locally advanced or metastatic urothelial cancer after failure with	ORR, DCR, DOR, and PFS Confirmation of safety profile per AEs	Atezolizumab IV 1200 mg q3w	18 a	Ongoing; Mar 2017 (FPI)

		platinum-containing chemotherapy				
ML28897	MY PATHWAY: an open-label Phase IIa study evaluating trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib and atezolizumab	Patients with advanced solid tumors with mutations or gene expression abnormalities predictive of response to one of these agents	Efficacy (determined by investigator-assessed OR)	Atezolizumab IV 1200 mg q3w	174 a	Completed Final CSR May 2024
ML29725	Open-label, multicenter, expanded access program for atezolizumab	Patients with PD-L1-positive locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy	Provide access to atezolizumab as treatment for patients with locally advanced or metastatic UC	Atezolizumab IV 1200 mg q3w	214 a	Completed; Aug 2016 (FPI)
ML39236	Phase II, open-label, multicenter, single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant and adjuvant therapy	Patients with Stage Ib, II, IIIa respectable and untreated NSCLC	Efficacy of atezolizumab as neoadjuvant treatment for Stage IB, II, and IIIA NSCLC, defined by major pathologic response	Atezolizumab IV 1200 mg q3w for 2cycles (neoadjuvant treatment) or maximum 12 months (adjuvant treatment)	181 a	Completed, Final CSR June 2024
ML39345	Open-label, single-arm, Phase II study of atezolizumab in patients with advanced ASPS	Adult patients -18 years of age and in pediatric/adolescent subjects- 2 years of age	Response rate using RECIST v 1.1	Atezolizumab IV 1200 mg q3w for adults and 15 mg/kg for	54 a	Completed, Final CSR May 2022

				pediatric patients		
MO29983 (SAUL)	Open-label, single-arm, multicenter, safety study of atezolizumab	Locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract	Nature, severity, duration, frequency, and timing of adverse events	Atezolizumab IV 1200 mg q3w	1004 a	Completed Final CSR June 2023
MO29872 (IPSOS)	Phase III, open-label, multicenter, randomized study	Advanced, recurrent, (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC who are deemed unsuitable for platinum-containing therapy	Efficacy, safety, tolerability, and PROs of atezolizumab compared with single agent chemotherapy with respect to antitumor effects	Atezolizumab IV 1200 mg q3w	300 a	Completed, Final CSR September 2024.
MO39193 (IMpassion 132)	Phase III, randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of atezolizumab plus chemotherapy	Patients with early relapsing recurrent (inoperable locally advanced or metastatic) triple-negative breast cancer	Efficacy, safety, PK, and ADAs of atezolizumab plus chemotherapy compared with placebo plus chemotherapy	Atezolizumab IV 1200 mg q3w	298 (blinded) a	Completed, Final CSR March 2025
MO39196 (IMpassion 131)	Phase III, multicenter, randomized double-blind, placebo-controlled study of atezolizumab in combination with paclitaxel compared with placebo with paclitaxel	Previously untreated inoperably locally advanced or metastatic triple-negative breast cancer	Efficacy, safety, and PK of atezolizumab plus paclitaxel compared with placebo plus paclitaxel	Atezolizumab IV 840 mg q2w	434 (blinded) a	Completed Final CSR August 2023
WO30070 (IMvigor130)	Phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti-PDL1 antibody) as monotherapy and	Untreated locally advanced or metastatic urothelial carcinoma	PFS and OS	Atezolizumab IV 1200 mg q3w	1197 a	Completed Final CSR August 2024

	in combination with platinum-based chemotherapy					
WO39391 (IMpassion 030)	Phase III, multicenter, randomized, open-label study comparing atezolizumab in combination with anthracycline/taxane-based chemotherapy versus chemotherapy alone	Operable triple-negative breast cancer	Efficacy, safety, and PK	Atezolizumab IV 840 mg q2w for 1 year	1093 a	Completed Final CSR June 2024
WO40242 (IMvove010)	Phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy after definitive local therapy	High-risk locally advanced squamous cell carcinoma of the head and neck	PFS, OS, safety, and PK	Atezolizumab IV 840 mg q2w	203 (blinded) a	Completed Final CSR July 2024
YO29232 (IMpower210)	Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with docetaxel	Non-small cell lung cancer after failure with platinum-containing chemotherapy	OS, PFS, ORR, DOR, and safety	Atezolizumab IV 1200 mg q3w	377 (blinded) a	Completed Final CSR July 2023
YO40245 (IMbrave150)	Phase III, randomized, multicenter, open-label, two-arm study evaluating the efficacy and safety of atezolizumab □ bevacizumab versus sorafenib	Locally advanced or metastatic HCC who have not received prior systemic treatment.	OS and IRF-assessed PFS by RECIST v1.1	Atezolizumab IV 1200 mg q3w	372 a	Completed Final CSR May 2023
WO42633	Phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of adjuvant atezolizumab or placebo and trastuzumab emtansine	HER2-positive breast cancer at high risk of recurrence following preoperative therapy	Invasive disease-free survival (IDFS)	Atezolizumab IV 1200 mg q3w for 14 cycles	397 (blinded) a	Ongoing; May 2021 (FPI)
MO42319	Phase III, randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of trastuzumab emtansine in combination with atezolizumab or placebo	Patients with HER2-positive and PD-L1-positive locally advanced or metastatic breast cancer	PFS, ORR, DOR, safety	Atezolizumab IV 1200 mg q3w	48 (blinded) a	Completed Final CSR December 2024

		who have received prior trastuzumab (± pertuzumab) and taxane-based therapy				
ML42612	Phase III, open-label, randomized study of on-demand TACE combined with Atezolizumab plus Bevacizumab (atezo/bev) or on-demand TACE alone	Patients with untreated hepatocellular carcinoma patient	Transarterial chemoembolization (TACE) PFS as determined by IRC; OS	Atezolizumab IV 1200 mg q3w	128 a	Ongoing; Mar 2021 (FPI)
MO42541 (IMbrave251)	Phase III, open-label, randomized study of atezolizumab with Lenvatinib or sorafenib versus lenvatinib or sorafenib alone	Hepatocellular carcinoma previously treated with atezolizumab and bevacizumab	OS	Atezolizumab IV 1200 mg q3w	147 a	Ongoing; Apr 2021 (FPI)
ML41256	Phase II, single-arm study of atezolizumab in combination with bevacizumab	Patients with EGFR mutation-positive Stage IIIB-IV non-squamous NSCLC pretreated with epidermal growth factor receptor tyrosine kinase inhibitors	Investigator-assessed PFS according to RECIST v1.1	Atezolizumab IV 1200 mg q3w	23 a	Completed, Final CSR September 2023
BO41932 (TAPISTRY)	Phase II, tumor-agnostic precision immune-oncology and somatic targeting rational for you platform trial	Solid tumor	Cohort D (atezolizumab): IRC-assessed ORR	Atezolizumab IV 1200 mg q3w for patients ≥ 18 years or 15 mg/kg for patients < 18 years	485 b	Ongoing; Jan 2021 (FPI)

BO42843 (IMvigor011)	Phase III, double-blind, multicenter, randomized study to evaluate efficacy, safety, and pharmacokinetics of atezolizumab versus placebo as adjuvant therapy	Muscle-invasive bladder cancer patients who are at risk of recurrence after cystectomy and are ctDNA-MRD-positive	Independent Review Facility (IRF)-assessed DFS in patients who are ctDNA-positive within 20 weeks of cystectomy	Atezolizumab IV 1680 mg q4w	153 (blinded) a	Ongoing; May 2021 (FPI)
CO41792	Phase Ib, open-label, multicenter study evaluating the safety, efficacy, and pharmacokinetics of ipatasertib in combination with atezolizumab and docetaxel	Metastatic castration-resistant prostate cancer	In all patients: confirmed Prostate Specific Antigen response. In patients presenting with measurable visceral disease or measurable extrapelvic adenopathy at baseline: investigator-assessed ORR according to RECIST v1.1	Atezolizumab IV 1200 mg q3w	6 a	Completed, Final CSR July 2023
GO42144	Phase Ia/Ib dose-escalation and dose expansion study evaluating the safety, pharmacokinetics, and activity of GDC-6036 as a single agent and in combination with other anti-cancer therapies	Advanced or metastatic solid tumors with a KRAS G12C mutation	Safety of GDC-6036 as a single agent and in combination: AEs; DLTs, vital signs, clinical laboratory test results, ECG parameters	Atezolizumab IV 1200 mg q3w	248 a	Ongoing; Jul 2020 (FPI)
GO42661	Phase II, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine	Untreated, advanced biliary tract cancer	Investigator-assessed PFS according to RECIST v1.1	Atezolizumab IV 1200 mg q3w	162 (blinded) a	Completed Final CSR April 2024
ML41253	Phase II, open-label, single-arm, multicenter study to investigate the efficacy and safety of atezolizumab	Previously treated patients with thymic carcinoma	Investigator-assessed ORR according to RECIST v1.1, PFS, DOR, DCR	Atezolizumab IV 1200 mg q3w	30 a	Ongoing; Aug 2020 (FPI)
ML42439 (MyTACTIC)	Phase II, open-label study evaluating efficacy and safety of targeted therapies	Patients who have advanced solid tumors with genomic alterations or	Confirmed ORR by investigator according to RECIST v1.1 (solid tumors) or RANO	Atezolizumab IV 1200 mg q3w	252 b	Completed Final CSR October 2024

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		protein expression patterns predictive of response	Criteria (primary CNS tumors)			
WO41535 (IMbrave050)	Phase III, Multicenter, randomized, open-label study of atezolizumab (anti-PD-L1 antibody) plus bevacizumab versus active surveillance as adjuvant therapy	Hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation	RFS after randomization, defined as the time from randomization to the first documented occurrence of local, regional, or metastatic HCC as determined by an IRF, or death from any cause (whichever occurs first)	Atezolizumab IV 1200 mg q3w	334 a	Ongoing; Dec 2019 (FPI)
WO41994	Phase III, randomized, open-label study to evaluate the efficacy and safety of atezolizumab given in combination with cabozantinib versus cabozantinib alone	Inoperable, locally advanced, or metastatic renal cell carcinoma who experienced radiographic tumor progression during or after immune checkpoint inhibitor treatment	IRF-assessed PFS; OS	Atezolizumab IV 1200 mg q3w	258 a	Ongoing; Jul 2020 (FPI)
YO42138	Phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of atezolizumab plus tiragolumab in combination with paclitaxel and cisplatin compared with paclitaxel and cisplatin as first-line treatment	Unresectable locally advanced, unresectable recurrent, or metastatic esophageal squamous cell carcinoma	OS; IRF-assessed PFS according to RECIST v1.1	Atezolizumab IV 1200 mg q3w	231 (blinded) a	Ongoing; Oct 2020 (FPI)
BO40747 (IMpassion 050)	Phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of atezolizumab or placebo in combination with	Early HER2-positive breast cancer	pCR in the ITT and PD-L1-positive populations	Atezolizumab IV 840 mg q2w (Cycles 1	227 (blinded) a	Completed Final CSR March 2024

	neoadjuvant dose-dense doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab			to 4), followed by Atezolizumab IV 1200 mg q3w (Cycles 5 to 8)		
CO40115 (MORPHEUS -panBC)	Phase Ib/II, open-label, multicenter, randomized umbrella study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations	Metastatic triple-negative breast cancer	Investigator-assessed ORR according to RECIST v1.1	Atezolizumab IV 1200 mg q3w	133 b	Completed Final CSR December 2023
CO39611	Phase Ib/II, open-label, multicenter, randomized umbrella study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations	Patients with hormone receptor-positive HER2-negative breast cancer	OR, PFS, CBR, OS, DOR	Atezolizumab IV 1200 mg q3w	144 b	Ongoing; Dec 2017 (FPI)
WO39608 (MORPHEUS-pancreatic cancer)	Phase Ib/II, open-label, multicenter, randomized umbrella study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations	Patients with metastatic pancreatic ductal adenocarcinoma	Investigator-assessed objective response according to RECIST v1.1	Atezolizumab IV 840 mg q2w	237 a	Ongoing; Jul 2017 (FPI)
BO44157	Phase II, randomized, multicenter, open-label, controlled study evaluating to bemstomig (RO7247669) alone or in combination with tiragolumab versus atezolizumab.	Adult patients with previously untreated locally advanced or metastatic urothelial cancer who are ineligible for platinum-containing chemotherapy ECOG £ 2	Investigator-assessed ORR according to RECIST v1.1	Atezolizumab 1200 mg IV q3w	2 b	Ongoing; Apr 2023 (FPI)
ML43138	Phase II, single-arm study of tiragolumab plus atezolizumab and bevacizumab	Patients with previously untreated locally	ORR, PFS, OS, DOR	Atezolizumab 1200 mg IV q3w	4 a	Ongoing; Mar 2023 (FPI)

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		advanced unresectable or metastatic PD-L1-selected non-squamous NSCLC				
YO30157 (IMpower151)	Phase III, randomized, double-blind study of bevacizumab, carboplatin, and paclitaxel or pemetrexed with or without atezolizumab	Chemotherapy-naïve adults patients with Stage IV non-squamous NSCLC	Investigator-assessed PFS according to RECIST v1.1	Atezolizumab 1200 mg IV q3w	306	Completed, Final CSR February 2025
BO29561	Non-randomized, open-label, non-controlled parallel Phase Ib/II study evaluating the safety and efficacy of obinutuzumab in combination with atezolizumab plus polatuzumab vedotin.	Patients with relapsed or refractory follicular lymphoma and/or rituximab in combination with atezolizumab plus polatuzumab vedotin in patients with relapsed or refractory diffuse large B-cell lymphoma	RP2D, safety and tolerability for polatuzumab vedotin in combination with fixed doses of obinutuzumab and atezolizumab (DLTs, AEs, and changes in clinical laboratory results)	Atezolizumab 1200 mg IV q3w (induction treatment) or Atezolizumab 1680 mg IV q4w (maintenance treatment)	36 a	Completed Final CSR March 2020
BO29562	Non-randomized, open-label, non-controlled parallel Phase Ib/II study of atezolizumab in combination with obinutuzumab plus lenalidomide	Patients with relapsed or refractory follicular lymphoma	Proportion of patients achieving a complete response at end of induction as assessed by the IRC on the basis of PET-CT scans	Atezolizumab 840 mg IV q2w (induction treatment) or Atezolizumab 1680 mg IV q4w (maintenance treatment)	38 a	Completed Final CSR May 2021

BO29563	Non-randomized, open-label, non-controlled parallel Phase Ib/II study of atezolizumab in combination with either obinutuzumab plus bendamustine or obinutuzumab plus CHOP	Patients with follicular lymphoma or diffuse large B-cell lymphoma	Proportion of patients achieving a complete response at end of induction as assessed by the IRC using Lugano 2014 criteria	Atezolizumab 1200 mg IV q2w (induction or consolidation treatment) or 840 mg IV q2w (induction treatment) or 1680 mg IV q4w (maintenance treatment)	91 a	Completed Final CSR Sep 2020
BO29561	Non-randomized, open-label, non-controlled parallel Phase Ib/II study evaluating the safety and efficacy of obinutuzumab in combination with atezolizumab plus polatuzumab vedotin in patients with relapsed or refractory follicular lymphoma and/or rituximab in combination with atezolizumab plus polatuzumab vedotin	Patients with relapsed or refractory diffuse large B-cell lymphoma	RP2D, safety and tolerability for polatuzumab vedotin in combination with fixed doses of obinutuzumab and atezolizumab (DLTs, AEs, and changes in clinical laboratory results)	Atezolizumab 1200 mg IV q3w	34 a	Completed Final CSR Mar 2020
BO30013	Randomized open-label active-controlled parallel Phase Ib, open-label study of the safety and tolerability of atezolizumab in combination with radium-223 dichloride	Patients with castration-resistant prostate cancer who have progressed following treatment with an androgen pathway inhibitor	Safety and tolerability of atezolizumab when given in combination with radium-223 dichloride	Atezolizumab 840 mg IV on Days 1 and 15 q4w	44 a	Completed Final CSR Mar 2020
BP28179	Non-randomized, open-label, non-controlled, dose-escalation Phase I study of atezolizumab	Patients with locally advanced or	To determine the MTD and/or RP2D of vanucizumab; to	Atezolizumab	17 a	Completed Final CSR Nov 2018

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	in combination with vanucizumab	metastatic solid tumors	investigate anti-tumor activity of vanucizumab; to evaluate safety/tolerability of the combination; to evaluate anti-tumor activity of the combination	840 mg IV q2w		
BP29392	Open-label, non-randomized, non-controlled, Phase Ib study of RO7009789 in combination with atezolizumab	Patients with locally advanced and/or metastatic solid tumors	Safety/tolerability, MTD, RP2D, and clinical activity (as assessed by RECIST v1.1 and irRC) of RO7009789 in combination with atezolizumab	Atezolizu mab 1200 mg IV q3w	140 a	Completed Final CSR Jun 2020
BP29428	Open-label, non-randomized, non-controlled, dose-escalation Phase Ib study of emactuzumab and atezolizumab administered in combination	Patients with advanced solid tumors	Safety/tolerability and MTD of emactuzumab in combination with atezolizumab	Atezolizu mab 1200 mg IV q3w	221 a	Completed Final CSR Mar 2021
BP29435	Non-randomized, open-label, non-controlled, dose-escalation Phase Ib study of cergutuzumab amunaleukin (CEA-IL2v) and atezolizumab administered in combination	Patients with locally advanced and/or metastatic solid tumors	Safety/tolerability, MTD, and RP2D of cergutuzumab amunaleukin in combination with atezolizumab	Atezolizu mab 1200 mg IV q3w	69 a	Completed Final CSR Aug 2020
BP39365	Open-label, multicenter, randomized, dose-escalation, Phase Ib study to evaluate safety, PK and therapeutic activity of RO6874281, in combination with atezolizumab, bevacizumab, following obinutuzumab pre-treatment	Patients with unresectable advanced and/or metastatic renal cell carcinoma	MTD, dosing, and ORR for RO6874281 in combination with atezolizumab and bevacizumab	Atezolizu mab 1200 mg IV q3w or Atezolizu mab 840 mg IV fixed flat dose on days 1, 15, and 29	66 a	Completed Final CSR Jan 2022
GO29436 (IMpower150)	Randomized, open-label Phase III study of atezolizumab , carboplatin , paclitaxel with or without bevacizumab compared with	Chemotherapy -naïve patients with Stage IV non-squamous NSCLC	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizu mab 1200 mg IV q3w	793 a	Completed Final CSR Jul 2021

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	carboplatin , paclitaxel, bevacizumab					
BP29435	Non-randomized, open-label, non-controlled, dose-escalation Phase Ib study of cergutuzumab amunaleukin (CEA-IL2v) and atezolizumab administered in combination	Patients with locally advanced and/or metastatic solid tumors	Safety/tolerability, MTD, and RP2D of cergutuzumab amunaleukin in combination with atezolizumab	Atezolizumab 1200 mg IV q3w or 840 mg q2w	69 a	Completed Final CSR Aug 2020
GO29437 (IMpower131)	A Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of atezolizumab (MPDL3280A, anti-PD-L1 antibody) in combination with carboplatin , paclitaxel or atezolizumab in combination with carboplatin , nab-paclitaxel versus carboplatin, nab-paclitaxel	Chemotherapy-naïve patients with Stage IV squamous NSCLC	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizumab 1200 mg IV q3w	666 a	Completed Final CSR Nov 2021
GO29537 (IMpower130)	Randomized, open-label Phase III study of atezolizumab, carboplatin □ nab-paclitaxel compared with carboplatin □ nab-paclitaxel	Chemotherapy-naïve patients with Stage IV non-squamous NSCLC	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizumab 1200 mg IV q3w	473 a	Completed Final CSR Jun 2021
GO29695	Open-label, non-randomized Phase Ib study of atezolizumab alone or in combination with an immunomodulatory drug and/or daratumumab	Patients with multiple myeloma	Safety and tolerability, RP2D, and ORR as defined as a best overall response of sCR, CR, VGPR, or PR by IMWG criteria	Atezolizumab 1200 mg IV q3w	79 a	Completed Final CSR Jul 2021
CO39083	Phase Ib open-label study evaluating the safety, tolerability, and pharmacokinetics of cobimetinib with atezolizumab and bevacizumab when administered	Patients with colorectal cancer	Safety, tolerability and proposed dosing regimen	Atezolizumab 840 mg IV q2w	49 a	Completed Final CSR Mar 2020
CO39721	Phase Ib, open-label, multicenter study designed to evaluate the preliminary efficacy, safety, and pharmacokinetics of cobimetinib and atezolizumab and to evaluate efficacy, safety, and pharmacokinetics of atezolizumab monotherapy	Patients with BRAF V600 WT metastatic or unresectable locally advanced melanoma who have progressed on	Investigator-assessed ORR per RECIST v1.1 and DCR.	Atezolizumab 840 mg IV q2w	155 a	Completed Final CSR Mar 2021

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		a prior anti-PD-1 therapy OR patients with BRAF V600 WT metastatic or unresectable locally advanced melanoma who have not been previously treated				
ML41186	Phase II, open-label, multicenter, single-arm study designed to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab	Patients with unresectable locally advanced or metastatic mucosal melanoma	Investigator-assessed ORR according to RECIST v1.1	Atezolizumab 1200 mg IV q3w	43 b	Completed Final CSR December 2023
CO39722	Phase III, open-label, multicenter, two-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab versus pembrolizumab	Patients with previously untreated advanced BRAF wild-type melanoma	IRC-assessed PFS	Atezolizumab 840 mg IV on days 1 and 15 q4w	220 a	Completed Final CSR Jul 2021
GO27831 (PCD4989g)	First-in-human, open-label Phase Ia study of atezolizumab	Patients with locally advanced or metastatic solid tumors or hematologic malignancies	Safety and tolerability, including MTD, DLTs, and RP2D	Atezolizumab 1200 mg IV q3w	658 a	Completed Final CSR Jul 2019
GO28625 (FIR)	Open-label, non-controlled, single-arm Phase II study of atezolizumab	PD-L1 positive patients with locally advanced or metastatic NSCLC	Investigator-assessed ORR per modified RECIST	Atezolizumab 1200 mg IV q3w	137 a	Completed Final CSR Nov 2015
GO28753 (POPLAR)	Open-label, randomized Phase II study of atezolizumab compared with docetaxel	Patients with locally advanced or metastatic NSCLC	OS for atezolizumab vs. Docetaxel	Atezolizumab 1200 mg IV q3w	144 a	Completed Final CSR May 2019

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		following progression on a platinum-containing regimen				
GO28754 (BIRCH)	Open-label, non-controlled, single-arm Phase II study of atezolizumab	PD-L1 positive patients with locally advanced or metastatic NSCLC	IRF-assessed ORR per RECIST v1.1	Atezolizumab 1200 mg IV q3w	659 a	Completed Final CSR Oct 2019
GO28915 (OAK)	Open-label, randomized, Phase III study of atezolizumab compared with docetaxel	Patients with locally advanced or metastatic NSCLC after failure with platinum-containing chemotherapy	OS for atezolizumab vs. Docetaxel	Atezolizumab 1200 mg IV q3w	621	Completed Final CSR Oct 2019
GO29294 (IMvigor211)	A Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with chemotherapy	Patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy (IMvigor211)	Efficacy of compared with chemotherapy patients (OS, ORR, PFS, DOR)	Atezolizumab 1200 mg IV q3w	459 a	Completed Final CSR Mar 2019
GO29322	Open-label, non-randomized Phase Ib study of atezolizumab administered with ipilimumab (Arm A), IFN alfa-2b (Arm B), pegylated IFN alfa-2a (Arm C), pegylated IFN alfa-2a + bevacizumab (Arm D), or obinutuzumab (Arm E)	Patients with locally advanced or metastatic solid tumors	Safety and tolerability of atezolizumab + ipilimumab or atezolizumab, IFN alfa-2b or atezolizumab, pegylated IFN alfa-2a or atezolizumab, pegylated IFN alfa-2a, bevacizumab or obinutuzumab, and atezolizumab	Atezolizumab 600 mg IV q3w increased to 1200 mg q2w	155 a	Completed Final CSR Jul 2020
GO29383	Open-label, non-randomized Phase Ib study of atezolizumab	Patients with relapsed/refractory	Safety and tolerability and RP2D of	Atezolizumab	92 a	Completed

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	administered with obinutuzumab or tazemetostat	tory follicular lymphoma and diffuse large B-cell lymphoma	atezolizumab in combination with obinutuzumab or tazemetostat	1200 mg IV q3w		Final CSR Nov 2020
GO29432 (IMpower111)	Randomized, open-label Phase III study of atezolizumab compared with cisplatin/carboplatin , gemcitabine	PD-L1,selected chemotherapy-naïve patients with Stage IV squamous NSCLC	Investigator-assessed PFS per RECIST v1.1	Atezolizumab 1200 mg IV q3w	4 a	Completed Final CSR May 2018
GO29664	Open-label, non-controlled Phase I/II study of atezolizumab	Pediatric and young adult patients with relapsed/refractory solid tumors	Safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab	Atezolizumab 1200 mg IV q3w	87 a	Completed Final CSR Nov 2019
GO29674	Phase Ib, open-label, dose-escalation study of the safety, tolerability, and pharmacokinetics of MOXR0916 and atezolizumab	Patients with locally advanced or metastatic solid tumors	Safety and tolerability	Atezolizumab 1200 mg IV q3w	298 a	Completed Final CSR Jun 2020
GO29754	A Phase Ib study of the safety and pharmacology of atezolizumab administered alone or in combination with azacitidine	Patients with myelodysplastic syndromes	Safety and tolerability	Atezolizumab 1200 mg IV q3w or 840 mg IV q2w	46 a	Completed Final CSR Feb 2020
GO29779	Open-label, non-randomized Phase Ib study of GDC-0919 administered with atezolizumab	Patients with locally advanced or metastatic solid tumors	Safety and tolerability	Atezolizumab 1200 mg IV q3w	157 a	Completed Final CSR Mar 2020
GO29831	Open-label, non-randomized Phase Ib study of atezolizumab □ trastuzumab emtansine/trastuzumab and pertuzumab	Patients with HER2 □ breast cancer	Safety and tolerability	Atezolizumab 1200 mg IV q3w or 840 mg IV q2w	76 a	Completed Final CSR Jul 2020
GO30139	Phase Ib study evaluating the safety and pharmacology of atezolizumab (anti-PD-L1 antibody) administered in combination with immunomodulatory agents	Patients with acute myeloid leukemia	Safety, preliminary efficacy, pharmacokinetics, and immunogenicity	Atezolizumab 840 mg IV q2w	16 a	Completed Final CSR Jul 2020

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GO30140	Open-label Phase Ib study of atezolizumab administered with bevacizumab (Arm A), with bevacizumab plus FOLFOX (Arm B), with gemcitabine and nab-paclitaxel (Arm C), and with vanucizumab (Arm D)	Patients with solid tumors	Safety and tolerability	Atezolizu mab 1200 mg IV q3w or 840 mg IV q2w	287 a	Completed Final CSR Feb 2022
GO30182 (IMblaze370)	Phase III, open-label, multicenter, 3 arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib	Patients with unresectable locally advanced or metastatic colorectal adenocarcinoma	Efficacy, safety, and pharmacokinetics	Atezolizu mab 1200 mg IV q3w or 840 mg IV q2w	269 a	Completed Final CSR Sep 2019
GO39590	Phase II, multicenter, randomized, placebo-controlled, double-blind study of MOXR0916 in combination with atezolizumab versus atezolizumab alone	Patients with untreated locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-based therapy	Efficacy and safety of MOXR0916 plus atezolizumab (PFS & OS)	Atezolizu mab 1200 mg IV q3w	5 a	Completed Final CSR Dec 2018
GO40828	Phase Ib, open-label study evaluating the safety and pharmacokinetics of atezolizumab (anti-PD-L1 antibody) administered in combination with Hu5F9-G4	Patients with relapsed and/or refractory acute myeloid leukemia	Safety and tolerability and, pharmacokinetics of atezolizumab given in combination with magrolimab	Atezolizu mab 840 mg IV q2w	11 a	Completed Final CSR May 2021
GP28328	Open-label, non-controlled Phase Ib study of atezolizumab administered with bevacizumab alone (Arm A), with bevacizumab plus mFOLFOX-6 (Arm B), with carboplatin and paclitaxel (Arm C), with carboplatin and pemetrexed (Arm D), with carboplatin and nab-paclitaxel (Arm E), or with nab-paclitaxel (Arm F)	Patients with advanced solid tumors	Safety and tolerability	Atezolizu mab 1200 mg IV q3w	235 a	Completed Final CSR Sep 2020

GP28363	Open-label, non-randomized Phase Ib study of atezolizumab and cobimetinib	Patients with locally advanced or metastatic solid tumors	Safety and tolerability, DLTs, MTD, and RP2D	Atezolizu mab 800 mg IV q2w	151 a	Completed Final CSR Sep 2020
GP28384	Open, Phase Ib study of atezolizumab administered with vemurafenib or with vemurafenib and cobimetinib	Metastatic melanoma patients with previously untreated BRAFV600 mutation-positive	Safety and tolerability and future dose and schedule	Atezolizu mab 1200 mg IV q3w	67 a	Completed Final CSR Dec 2020
JO28944	Open-label Phase I study of atezolizumab	Advanced solid tumors	Adverse events and DLT profile	10 mg/kg or 20 mg/kg	6 a	Completed Final CSR May 2015
JO39184	Phase I study of GDC-0919 as a single agent and in combination with other anticancer drugs	Patients with advanced solid tumors	Safety, tolerability, PK, DLT, and MTD of GDC-0919 as a single agent and in combination with other anti-tumor drugs		10 a	Completed Final CSR Aug 2018
ML39237	Phase II single-arm study of atezolizumab monotherapy in locally advanced or metastatic NSCLC: clinical evaluation of novel blood-based diagnostics	Locally advanced or metastatic NSCLC	Clinical efficacy per investigator-assessed ORR according to RECIST v1.1	Atezolizu mab 1200 mg IV q3w	152 a	Completed Final CSR Mar 2020
MO29112	Open-label, randomized Phase II study of biomarker-driven maintenance treatment	first-line metastatic colorectal cancer	20% reduction in tumor size after 2 months of treatment, PFS, and safety	Atezolizu mab 800 mg or 840 mg IV q2w	362 a	Completed Final CSR Nov 2021
MO29518	Phase II, open-label, non-controlled study of atezolizumab	Advanced solid tumors	Investigator-assessed non-progression rate at 18 weeks	Atezolizu mab 1200 mg IV q3w	474 a	Completed Final CSR Apr 2021
WO29074 (IMmotion150)	Open-label, randomized Phase II study of atezolizumab in combination with bevacizumab or alone versus sunitinib	Previously untreated RCC	PFS per RECIST v1.1 via an independent central radiologic review	Atezolizu mab 1200 mg IV q3w	267 a	Completed Final CSR Jul 2019
WO29479	Multistage, Phase II study evaluating the safety and efficacy of cobimetinib plus paclitaxel, cobimetinib plus atezolizumab plus paclitaxel, or cobimetinib plus	Patients with metastatic, triple-negative breast cancer	Clinical benefit as measured by investigator-assessed PFS, safety, of atezolizumab based on nature, severity,	Atezolizu mab 840 mg IV q2w	62 a	Completed Final CSR Mar 2022

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	atezolizumab plus nab-paclitaxel, as first-line treatment		duration, frequency and timing of adverse events			
WO29522 (IMpassion 130)	Randomized, double-blind Phase III study of atezolizumab □ nab-paclitaxel compared with placebo □ nab-paclitaxel	Patients with previously untreated metastatic triple-negative breast cancer	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizu mab 840 mg IV q2w	460 a	Completed Final CSR Dec 2021
WO29635	Phase Ib/II, open-label study of the safety and pharmacology of atezolizumab administered with or without Bacille Calmette–Guérin	Patients with high-risk non–muscle-invasive bladder cancer	Safety, PK, immunogenicity, patient-reported outcomes (PROs), and preliminary anti-tumor activity	Atezolizu mab 1200 mg IV q3w	24 a	Completed Final CSR Jun 2021
WO30085 (KATE2)	Randomized, multicenter, double-blind, placebo-controlled Phase II study of the efficacy and safety of trastuzumab emtansine in combination with atezolizumab or placebo	Patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab and taxane-based therapy	Efficacy in combination with trastuzumab emtansine in comparison with placebo, assessed by PFS, determined by investigator assessment using RECIST v1.1	Atezolizu mab 1200 mg IV q3w	133 a	Completed Final CSR Aug 2020
WO39409 (CO-338-050)	Phase Ib combination study of rucaparib (CO-338) and atezolizumab (MPDL3280A)	Patients with advanced gynecologic cancer, with a focus on ovarian cancer	Safety, anti-tumor activity, PK, and definition of RP2D of combined rucaparib and atezolizumab	Atezolizu mab 1200 mg IV q3w	28 a	Completed Final CSR Apr 2021
WO39760	Phase II, open-label, multicenter, multicohort study to investigate the efficacy and safety of cobimetinib plus atezolizumab	Patients with solid tumors	Investigator-assessed ORR according to RECIST v1.1	Atezolizu mab 840 mg IV q2w	86 a	Completed Final CSR Nov 2020
WP29158	Open-label, non-randomized Phase Ib study of atezolizumab plus erlotinib/alectinib	Patients with advanced or NSCLC	Safety and tolerability, DLTs, and RP2D	Atezolizu mab 1200 mg IV q3w	49 a	Completed Final CSR Aug 2020
WP29945	Open-label, non-randomized Phase Ib study of RO6958688 in combination with atezolizumab	Patients with locally advanced and/or metastatic	Safety and tolerability, DLTs, and RP2D	Atezolizu mab 1200 mg IV q3w	228 a	Completed Final CSR Dec 2020

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		CEA-positive solid tumors				
IMmotion151 (WO29637)	Phase III, open-label, randomized study of atezolizumab (anti-PD-L1 antibody) in combination with bevacizumab versus sunitinib.	Adult patients with histologically confirmed, inoperable, locally advanced or metastatic RCC who had not received prior systemic active or experimental therapy, in the adjuvant or metastatic setting	Efficacy of atezolizumab _ bevacizumab compared with sunitinib with respect to investigator-assessed PFS per RECIST v1.1 and OS	Atezolizumab 1200 mg IV q3w	451 a	Completed Final CSR Aug 2022
WO39392 (IMpassion 031)	Phase III randomized study to investigate the efficacy and safety of atezolizumab in combination with neoadjuvant anthracycline-based chemotherapy compared with placebo and chemotherapy	Patients with primary invasive triple-negative breast cancer	Efficacy, safety, and PK of atezolizumab in combination with neoadjuvant anthracycline-based chemotherapy compared with placebo and chemotherapy	Atezolizumab 840 mg IV q2w	164 a	Completed Final CSR May 2023
GO30081 (IMpower133)	A Phase III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody)	Patients with untreated extensive-stage small cell lung cancer	Efficacy as measured by investigator-assessed PFS according to RECIST v1.1 and by OS	Atezolizumab 1200 mg IV q3w	250 a	Completed Final CSR Feb 2023
GO29431 (IMpower110)	Randomized, open-label Phase III study of atezolizumab compared with cisplatin/carboplatin, pemetrexed or cisplatin/carboplatin, gemcitabine	PD-L1, selected chemotherapy-naïve patients with Stage IV non-squamous NSCLC	Investigator-assessed PFS per RECIST v1.1 and OS	Atezolizumab 1200 mg IV q3w	286 a	Completed Final CSR Sep 2022
WO29636 (IMvigor010)	Randomized, open-label Phase III study of atezolizumab versus observation as adjuvant therapy	Patients with high-risk muscle-invasive bladder cancer	Disease-free survival	Atezolizumab 1200 mg IV q3w	390 a	Completed Final CSR Apr 2023

		after cystectomy				
WO39210 (IMmotion010)	Phase III, multicenter, randomized, placebo-controlled, double-blind study of atezolizumab (anti-PD-L1 antibody) as adjuvant therapy	Adult patients with RCC, post-nephrectomy and classified as high risk for RCC recurrence. ECOG PS of 1	Efficacy of adjuvant treatment with atezolizumab by IRF-assessed DFS, defined as the time from randomization to the earliest death from any cause or first documented recurrence event assessed by IRF.	Atezolizumab 1200 mg IV q3w for 16 cycles or 1 year (whichever occurs first)	390 (blinded) a	Completed Final CSR May 2023
MO39107 (TEGAR)	Phase II study in combination with obinutuzumab or rituximab	Adult patients with relapsed/refractory mantle cell lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia ECOG PS 0, 1, or 2	Efficacy, safety, tolerability, and PK of atezolizumab in combination with obinutuzumab	Atezolizumab 1200 mg IV q3w	55 a	Completed Final CSR Oct 2022
YO29233	Phase I, open-label study to assess the pharmacokinetics, efficacy and safety of atezolizumab administered intravenously as a single agent	Chinese patients with locally advanced or metastatic solid tumors	PK of atezolizumab, gemcitabine and cisplatin following multiple-dose administration	Atezolizumab 1200 mg IV q3w	120 a	Completed Final CSR May 2023
YO39523 (IMagyn050)	Phase III, multicenter, randomized, study of atezolizumab versus placebo administered in combination with paclitaxel, carboplatin, and bevacizumab	Patients with newly-diagnosed Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer	Investigator-assessed PFS by RECIST v1.1 and OS	Atezolizumab 1200 mg IV q3w	642 a	Completed Final CSR Mar 2023
MO39171 (TAIL)	Phase III/IV, single-arm, multicenter study	Previously treated patients with locally advanced or	Adverse events	Atezolizumab 1200 mg IV q3w	615 a	Completed Final CSR Jun 2022

		metastatic NSCLC				
CO40151	Phase Ib, open-label, multicenter study	Patients with locally advanced or metastatic triple-negative breast cancer	Safety and feasibility of combination of ipasertib + atezolizumab + chemotherapy	Atezolizumab 840 mg IV q2w	114 a	Completed Final CSR Sep 2022
AMY205JP	Phase I, open-label study to assess the pharmacokinetics, tolerability, efficacy and safety of AMY109 in combination with antineoplastic drugs	Patients with advanced solid tumors	Tolerability, safety PK of AMY109 in combination with atezolizumab	Atezolizumab 1200 mg IV q3w	38 a	Completed Final CSR August 2024
JO44110	Phase I/II, single-arm, open-label study	Patients with solid tumors	DLTs, PK, and safety of atezolizumab	1680 mg IV q4w	21 a	Ongoing; Sep 2022 (FPI)
JO41492	A Phase III, randomized, double-blind, placebo-controlled study of carboplatin or cisplatin, etoposide plus atezolizumab (anti-PD-L1 antibody) with or without bevacizumab	Patients with untreated extensive-stage small cell lung cancer	Efficacy as measured by investigator-assessed PFS according to RECIST v1.1 and by OS	Atezolizumab 1200 mg IV q3w for 4 cycles	333 a	Ongoing Jan 2020 (FPI)
ERY103JG	Phase I study of ERY974 in combination with atezolizumab and bevacizumab	Patients with locally advanced or metastatic hepatocellular carcinoma	Safety, tolerability, PK, DLT, and MTD of ERY974 in combination with atezolizumab and bevacizumab	Atezolizumab 1200 mg IV q3w	8 a	Ongoing Jun 2021 (FPI)
JO39792	Phase I study of cobimetinib as a single agent or in combination with other anticancer agents	Patients with Advanced Solid Tumors	Safety, tolerability, PK, DLT, and MTD of cobimetinib in combination with other antitumor drugs	Atezolizumab 840 mg IV q2w	37 b	Ongoing Jul 2017 (FPI)
JO41178	Phase I study of RO6874281	Patients with advanced solid tumors	Safety, tolerability, PK, DLT, and MTD of RO6874281 in combination with other anti-tumor drugs	Atezolizumab 840 mg IV q2w	11 b	Completed ; Final CSR October 2023
SOF101JP	Phase I study of SOF10 in combination with antineoplastic agents in	Patients with advanced solid tumors	Safety, tolerability, PK, DLT, and MTD	Atezolizumab 1200 mg IV q3w	31	Ongoing May 2021 (FPI)
STA101JG	Phase Ia/b, open-label, dose-escalation study of the safety and PK of STA551 as a single	Patients with locally advanced or	Safety, tolerability, PK, DLT, and MTD	Atezolizumab	60 a	Ongoing Jun 2021 (FPI)

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	agent and in combination with atezolizumab	metastatic solid tumors		1200 mg IV q3w		
OBP304JP	Phase I, non-randomized, open-label, single-arm, multicenter study to evaluate the safety and efficacy of combination therapy with OBP-301, atezolizumab and bevacizumab	Patients with hepatocellular carcinoma	Safety and tolerability	Atezolizu mab 1200 mg IV q3w	4 a	Completed Final CSR Aug 2022
GC207JG	Phase I, open-label, multicenter, dose-escalation study of codrituzumab, an anti-glypican-3 monoclonal antibody, in combination with atezolizumab	Patients with locally advanced or metastatic hepatocellular carcinoma	Safety, tolerability, PK, and anti-tumor activity	Atezolizu mab 1200 mg IV q3w	20 a	Completed Final CSR; March 2025
JO41789	Phase I study of tiragolumab	Patients with advanced solid tumors	Safety, tolerability	Atezolizu mab 1200 mg IV q3w	3 a	Completed Final CSR Jun 2021
CO42177	Phase Ib, open-label, multicohort study of the safety, efficacy, and PK of tiragolumab in combination with atezolizumab and chemotherapy	Patients with triple-negative breast cancer	Safety, efficacy, PK	Atezolizu mab 1680 mg IV q4w or 840 mg q2w	83 b	Complete, Final CSR November 2023
GO40241 (IMpower030)	Phase III, double-blinded, multicenter, randomized study of neoadjuvant treatment with atezolizumab or placebo in combination with platinum-based chemotherapy	Patients with resectable stage IB-III A NSCLC	Safety, efficacy	Atezolizum ab 1200 mg IV q3w for 4 cycles during the neoadjuvant treatment phase Atezolizu mab 1200 mg IV q3w for 16 cycles during the post-operative adjuvant phase	452	Ongoing; April 2018 (FPI)

MX39795	Phase II, randomized, active-controlled, multicenter study comparing targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy	Patients with cancer of unknown primary site who have received three cycles of platinum doublet chemotherapy	Safety, efficacy	Atezolizumab 1200 mg IV q3w, alone or in combination with chemotherapy, until loss of clinical benefit or unacceptable toxicity, through the end of the study (approx. 70 months).	636	Completed Final CSR March 2025
GO43104, (IMforte)	Phase III, randomized, open-label, multicenter study of lurbinectedin in combination with atezolizumab or atezolizumab as maintenance therapy following first-line induction therapy with carboplatin, etoposide and atezolizumab	Participants with extensive-stage SCLC	Safety, efficacy	Atezolizumab 1200 mg IV q3w, alone or in combination with lurbinectedin until unacceptable toxicity, disease progression per RECIST v1.1	660 b	Ongoing November 2021 (FPI)

1. Clinical pharmacokinetics:

-No dedicated clinical pharmacology studies have been conducted for atezolizumab. Available pharmacokinetic (PK) data are derived from monotherapy studies (**PCD4989g**, **JO28944**, **IMvigor210**, **IMvigor211**, **BIRCH**, **POPLAR**, **FIR**, **OAK**, **IMpower010**) and SC studies (**IMscin001**, co-formulated with **rHuPH20**), as well as combination therapy studies (**IMmotion150**, **IMpower150**, **IMbrave150**, **IMbrave050**).

-In **Study PCD4989g**, atezolizumab doses ranging from 0.01 to 20 mg/kg q3w (including a fixed 1200 mg dose) showed dose-proportional exposure between 1–20 mg/kg. ADA-positive patients at lower doses

experienced reductions in C_{min} below assay limits, whereas higher doses-maintained serum concentrations above both the LOQ and target therapeutic level (6 µg/mL).

-Population PK analysis in 472 patients (Studies **PCD4989g** and **JO28944**) supported a linear two-compartment model with first-order elimination, V₁ of 3.28 L, V_{ss} of 6.91 L, CL of 0.20 L/day, and a half-life of 27 days, with steady state achieved after 6–9 weeks. Repeated 1200 mg q3w IV administration led to AUC, C_{max}, and C_{min} accumulation of 1.91-, 1.46-, and 2.75-fold, respectively.

-Covariate analysis indicated that body weight, albumin, positive ADA, tumor burden, and gender had minor effects on PK parameters, none exceeding 27% change from typical values. Factors such as age (2–89 years), sex, albumin, tumor burden, race, renal or mild-to-moderate hepatic impairment, PD-L1 expression, and ECOG status had no clinically relevant impact on PK. The effect of severe hepatic impairment remains unknown.

-Across combination studies (**IMmotion150**, **IMpower150**, **IMpower010**, **IMbrave150**, **IMbrave050**), atezolizumab PK was consistent with monotherapy, and co-administration with bevacizumab or chemotherapy did not appear to influence exposure. Serum concentrations remained stable over prolonged periods (up to 295 days in **IMmotion150**), and covariate effects were consistent with the Phase I model.

-SC administration was investigated in Study **IMscin001**, with Part 1 identifying 1875 mg SC q3w in the thigh as comparable to 1200 mg IV q3w. In Part 2, 371 patients received SC or IV atezolizumab, demonstrating non-inferior exposure based on serum C_{trough} at Cycle 1 (GMR 1.05, 90% CI 0.88–1.24) and model-predicted AUC_{0–21 d} (GMR 0.87, 90% CI 0.83–0.92). SC bioavailability was estimated at 71.8% with inter-individual variability of 83.0%

❖ Absorption, Bioavailability, Distribution, Metabolism, and Elimination

a validated ELISA with an LOQ of 0.06 µg/mL was used to determine serum atezolizumab concentrations in patients taking part in clinical studies. Atezolizumab is approved for intravenous administration. Atezolizumab subcutaneous absorption was characterized by a first-order absorption with a bioavailability (F₁) of 71.8% and an absorption rate constant (K_A) of 0.304 per day (Roche Report No. 1116054). The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism to inactive metabolites.

Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 GM (%CV)			
	C _{max} (µg/mL)	C _{min} (µg/mL)	AUC _{0-inf} ^a (day • µg/mL)	t _{1/2} ^b (Days)
0.03 mg/kg (n = 1)	0.37	NA	NA	NA
0.1 mg/kg (n = 1)	0.96	NA	1.62	NA
0.3 mg/kg (n = 3)	6.49 (19) n = 3	NA	33.0 (7.9) n = 2	NA
1 mg/kg (n = 3)	25.8 (17) n = 3	3.80 (160) n = 3	225 (2.8) n = 2	26.6 n = 1
3 mg/kg (n = 3)	75.6 (26) n = 3	12.2 (62) n = 3	651 (22) n = 2	21.8 n = 1
10 mg/kg (n = 36)	265 (16) n = 36	54.1 (25) n = 34	2780 (22) n = 9	22.7 (56) n = 10
15 mg/kg (n = 235)	332 (53) n = 232	67.1 (73) n = 214	3280 (35) n = 17	18.0 (39) n = 29
20 mg/kg (n = 145)	472 (35) n = 145	91.1 (36) n = 132	4860 (23) n = 10	23.7 (36) n = 28
Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 GM (%CV)			
	C _{max} (µg/mL)	C _{min} (µg/mL)	AUC _{0-inf} ^a (day • µg/mL)	t _{1/2} ^b (Days)
1200 mg (n = 45)	405 (50) n = 40	95.5 (51) n = 30	NA	NA

• **Effect of ADA on Atezolizumab Monotherapy Pharmacokinetics:**

A summary of the C_{max} and C_{min} of atezolizumab following multiple doses of atezolizumab (10 to 20 mg/kg and 1200 mg q3w) by ADA status in Study **PCD4989g**. A subset of ADA-positive patients in the lower dose groups (i.e., 0.3, 1, and 3 mg/kg) experienced a reduction of atezolizumab C_{min} to below the PK assay LOQ following multiple atezolizumab q3w dosing. However, the vast majority of patients receiving 15 to 20 mg/kg atezolizumab, including the fixed 1200 mg dose of atezolizumab, maintained an average C_{min} that was in excess of both the LOQ and the target serum concentration of 6 µg/mL, regardless of the ADA status. The similar C_{min} concentrations observed in ADA-positive and ADA-negative patients at doses ≥ 10 mg/kg suggest ADA positivity has little effect on atezolizumab exposure at these doses.

• **Atezolizumab Monotherapy – Other Studies (IMvigor210, IMvigor211, BIRCH, POPLAR, OAK, and IMpower010)**

Atezolizumab PK data obtained in mUC patients from **IMvigor210** and **IMvigor211** and in NSCLC patients from **BIRCH**, **POPLAR**, **OAK**, and **IMpower010** were consistent with the Phase Ia Study **PCD4989g** popPK model estimates. These results suggest that atezolizumab PK characteristics are similar across a range of tumor types and studies.

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- **Atezolizumab for Subcutaneous Administration-Study IMscin001 (BP40657)**
- **IMscin001 (BP40657): Part I**

Part 1 of Study IMscin001 enrolled 67 patients with locally advanced or metastatic NSCLC who were naïve to checkpoint inhibitor therapy and had progressed after prior platinum-based therapy. Patients received atezolizumab subcutaneously as monotherapy in three cohorts with different dosing schedules, followed by IV administration of 1200 mg q3w for subsequent cycles.

- **Cohort 1 (n=13):** Single SC dose of 1800 mg in the thigh for one cycle (21 days), then 1200 mg IV q3w.
- **Cohort 2 (n=15):** SC dose of 1200 mg q2w in the thigh for 3 cycles (14-day interval), then 1200 mg IV q3w.
- **Cohort 3 (n=39):** SC dose of 1800 mg q3w (first cycle in abdomen, subsequent 2 cycles in thigh) for 3 cycles, then 1200 mg IV q3w.

PK analysis included 57 of 67 patients with adequate data following SC dosing, which was used for non-compartmental pharmacokinetic evaluation.

- **IMscin001 (BP40657): Part 2**

Part 2 of Study IMscin001 enrolled 371 patients with locally advanced or metastatic NSCLC who were naïve to checkpoint inhibitor therapy and had progressed after prior platinum-based therapy. Patients were randomized 2:1 to receive either 1875 mg of atezolizumab SC administered in the thigh q3w or 1200 mg IV q3w. The primary objective was to demonstrate non-inferiority of SC versus IV administration based on co-primary PK endpoints: observed serum Ctrough at Cycle 1 (predose Cycle 2) and model-predicted AUC_{0-21 d}. Secondary PK endpoints included descriptive comparisons of model-predicted Ctrough at Cycle 1, Ctrough,ss, and AUC_{ss} between the two arms.

Results showed that SC administration of 1875 mg q3w achieved non-inferior exposure relative to 1200 mg IV q3w, with observed Cycle 1 Ctrough (GMR 1.05; 90% CI: 0.88–1.24) and model-predicted AUC_{0-21 d} (GMR 0.87; 90% CI: 0.83–0.92) meeting non-inferiority criteria. Steady-state exposure metrics (Ctrough,ss and model-predicted AUC_{ss}) were similar between SC and IV arms. Sensitivity analysis of model-predicted AUC_{ss} confirmed comparability (GMR 1.01; 90% CI: 0.94–1.08), supporting the SC formulation as an alternative to IV administration.

❖ Special Patient Populations:

- **Children:** The pharmacokinetics of atezolizumab were evaluated in 53 children and adolescents aged (2 to < 16 years, 12 to 89.4 kg) within Study GO29664 using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of atezolizumab were comparable between pediatric patients receiving 15 mg/kg and young adult patients receiving 1200 mg of atezolizumab q3w when normalized by body weight, with exposure trending lower in pediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure, as all pediatric patients (2 to <16 years) achieved C_{min} above the therapeutic target exposure.

• **Elderly:** No dedicated studies of atezolizumab have been conducted specifically in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a popPK analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on a patient age range of 21–89 years (n= 472) and a median age of 62 years. No clinically important differences were observed in the pharmacokinetics of atezolizumab among patients aged < 65 years (n= 274), between 65–75 years (n= 152), and > 75 years (n= 46).

• **Renal Impairment:** No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In a popPK analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60–89 mL/min/1.73 m² ; n= 208) or moderate (eGFR 30–59 mL/min/1.73 m² ; n=116) renal impairment compared with patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m² ; n= 140). Only a few patients had severe renal impairment (eGFR 15–29 mL/min/1.73 m² ; n= 8)

• **Hepatic Impairment:** No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In a popPK analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST [n= 71]) and normal hepatic function (bilirubin and AST ≤ ULN [n= 401]). No data were available in patients with either moderate or severe hepatic impairment. The effect of moderate (bilirubin > 1.5 to 3 × ULN and any AST) or severe (bilirubin > 3 × ULN and any AST) hepatic impairment on the pharmacokinetics of atezolizumab is unknown.

• **Population Pharmacokinetics:** Overall, females had a moderately higher exposure compared with males. Patients with low albumin tended to have a lower exposure with a larger effect on C_{min,ss}. The following factors have no clinically relevant effect on atezolizumab pharmacokinetics: age (2–89 years), body weight, sex, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild or moderate hepatic impairment, level of PD-L1 expression, or ECOG status.

2. **Clinical pharmacodynamics:** N/A (No pharmacodynamic data relevant to the clinical development of atezolizumab are available.)

3. Clinical Efficacy:

Overall, atezolizumab demonstrated anti-tumor activity across multiple tumor types when used as monotherapy or in combination, with efficacy observed across treatment lines and PD-L1 expression subgroups. The magnitude of benefit varied by indication, with the most consistent improvements seen in lung cancer and hepatocellular carcinoma, while more limited or inconsistent efficacy was observed in other tumor types.

3.1. Non-Small Cell Lung Cancer

Across multiple studies (IMpower150, IMpower130, IMpower132, IMpower110, IPSOS [MO29872], OAK [GO28915], POPLAR, BIRCH, PCD4989g, IMpower010 [GO29527]), atezolizumab demonstrated consistent efficacy. Combination regimens (IMpower150, IMpower130, IMpower132) improved OS and PFS, while monotherapy (IMpower110, IPSOS) showed survival

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benefit or favorable trends. In previously treated settings (**OAK**, **POPLAR**), atezolizumab improved OS versus docetaxel across PD-L1 subgroups. In the adjuvant setting (**IMpower010**), DFS benefit was observed, although OS benefit remains immature.

3.1.1 1L First-Line (1L) Metastatic NSCLC

In first-line NSCLC, atezolizumab demonstrated clinically meaningful efficacy across multiple studies. Monotherapy studies **IMpower110 (GO29431)** and **IPSOS (MO29872)** showed overall survival (OS) benefit or favorable trends compared with chemotherapy. Combination studies **IMpower150 (GO29436)**, **IMpower130 (GO29537)**, and **IMpower132 (GO29438)** demonstrated statistically significant improvements in progression-free survival (PFS) and/or OS, including in patients with EGFR or ALK alterations, supporting the benefit of atezolizumab-based regimens in the first-line setting.

3.1.2. Second-Line and Later (2L+) Metastatic NSCLC

In previously treated NSCLC, atezolizumab monotherapy demonstrated a consistent survival benefit. In **OAK (GO28915)** and **POPLAR**, atezolizumab significantly improved OS compared with docetaxel across PD-L1 subgroups, including patients with low or negative PD-L1 expression. In **IMscin001 (BP40657)**, subcutaneous and intravenous formulations showed comparable efficacy outcomes.

3.1.3. Early-Stage NSCLC

In the adjuvant setting, **IMpower010 (GO29527)** demonstrated improvement in disease-free survival (DFS) with atezolizumab compared with best supportive care, particularly in PD-L1–positive populations, although overall survival benefit has not yet been confirmed and remains immature.

3.2. Small Cell Lung Cancer

In **IMpower133 (GO30081)**, atezolizumab + chemotherapy improved OS (12.3 vs. 10.3 months; HR 0.755) and PFS. **BEAT-SC (JO41492)** showed improved PFS with bevacizumab (HR 0.70), and **IMforte (GO43104)** demonstrated significant PFS (HR 0.54) and OS (HR 0.73) benefits.

3.3. Urothelial Carcinoma

❖ **IMvigor130 (WO30070)**: Atezolizumab Monotherapy and Atezolizumab + Platinum-based Chemotherapy in 1L Muc. A total of 1,213 patients were enrolled and randomized in IMvigor130: 451 patients received atezolizumab plus chemotherapy, 362 patients received atezolizumab monotherapy, and 400 patients received placebo plus chemotherapy.

--Atezolizumab + Chemotherapy vs. Placebo + Chemotherapy

In **IMvigor130 (WO30070)**, atezolizumab in combination with chemotherapy demonstrated a statistically significant improvement in PFS compared with chemotherapy alone, with consistent results across analyses and subgroups; although OS did not reach statistical significance, a numerical improvement was observed.

❖ -Atezolizumab Monotherapy vs. Placebo + Chemotherapy

In **IMvigor130 (WO30070)**, atezolizumab monotherapy showed similar OS outcomes compared with chemotherapy (median OS 15.2 vs. 13.3 months; HR 0.98), with Kaplan–Meier curves favoring atezolizumab over time.

Other Studies

In **IMvigor211 (GO29294)**, atezolizumab demonstrated OS improvement trends (ITT HR 0.82), and in the **SAUL study (MO29983)**, clinically meaningful activity was observed (ORR 16%, median OS 8.6 months, median DOR 27.8 months).

3.4. Muscle-Invasive Urothelial Carcinoma

In **IMvigor010 (WO29636)**, no OS benefit was observed (175 vs. 171 deaths), and median OS was not reached.

3.5. High-Risk Non-Muscle-Invasive Bladder Cancer

In **WO29635**, atezolizumab demonstrated clinically meaningful CR rates (37.5%), with higher and more durable responses observed in combination with BCG (41.7%).

3.6. Renal Cell Carcinoma

In **IMmotion151 (WO29637)**, PFS benefit was observed (HR 0.74), but OS was not significant (HR 0.93). In **IMmotion010 (WO39210)**, no DFS benefit was demonstrated (HR 0.93).

3.7. Breast Cancer

In **IMpassion130 (WO29522)**, OS was not significant in ITT (HR 0.87) but improved in PD-L1–positive patients (HR 0.67). **IMpassion131 (MO39196)** showed no benefit (HR 1.11), while **IMpassion031 (WO39392)** showed improved pCR and favorable trends. **KATE2 (WO30085)** and **IMpassion050 (BO40747)** showed limited or subgroup benefit.

3.8. Metastatic Colorectal Cancer

In **IMblaze370 (GO30182)** and **GP28363**, no meaningful clinical benefit was observed.

3.9. Hepatocellular Carcinoma

In **IMbrave150 (YO40245)**, atezolizumab + bevacizumab improved OS (19.2 vs. 13.4 months; HR 0.66) and PFS (6.9 vs. 4.3 months; HR 0.65). **IMbrave050 (WO41535)** showed improved RFS (HR 0.72).

3.10. Biliary Tract Cancer

In **IMbrave151 (GO42661)**, no significant improvement in PFS (HR 0.76) or OS (HR 0.97) was observed.

3.11. Metastatic Melanoma

In **IMspire150 (CO39262)**, OS was not significant (HR 0.84), though DOR improved (21.0 vs. 12.6 months). **CO39721** showed no efficacy, while **ML41186** showed ORR up to 42.9%.

3.12. Pediatric Solid Tumors

In **GO29664**, atezolizumab demonstrated exploratory activity across multiple tumor types (n=87).

3.13. Hematological Malignancies

Across **GO29383**, **GO29754**, **GO29695**, **GO30139**, **GO40828**, and **MO39107**, no favorable benefit–risk profile was demonstrated.

Ovarian Cancer

In **IMagyn050 (YO39523)**, no OS benefit was observed (39.0% vs. 42.8%).

3.14. Other Solid Tumors

In **ML39345**, atezolizumab showed clinically meaningful activity in ASPS (ORR 24.5–34.7%) with durable responses.

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Clinical Safety

➤ Overall Safety Profile

Pooled safety data for atezolizumab monotherapy included 3178 patients across eight studies (**IMvigor210**, **IMvigor211**, **OAK**, **BIRCH**, **POPLAR**, **FIR**, **IMmotion150**, and **PCD4989g**), with the majority receiving 1200 mg every 3 weeks. Patients included those with urothelial carcinoma (n=983), NSCLC (n=1636), RCC (n=175), and other tumor types (n=384). Overall, atezolizumab demonstrated a consistent and manageable safety profile across studies and indications, with no new safety signals identified.

➤ Common Adverse Events

The majority of patients (**96.0%**) experienced at least one adverse event (AE). Treatment-related AEs occurred in **68.2%** of patients, with the most common ($\geq 20\%$) including **fatigue**, **decreased appetite**, **nausea**, **cough**, **constipation**, **dyspnea**, and **pyrexia**, consistent with the known safety profile of atezolizumab.

➤ Adverse Events by Intensity

Grade 3–4 AEs were reported in **46.5%** of patients, with the most frequent ($>3\%$) being **anemia (5.0%)**, **dyspnea (3.7%)**, **fatigue (3.4%)**, **hyponatremia (3.1%)**, and **pneumonia (3.0%)**. Grade 5 AEs occurring within 30 days of last treatment or prior to new therapy were reported in **3.8% (122/3178)** of patients, reflecting the severity profile in a heavily pretreated oncology population.

➤ Serious Adverse Events (SAEs)

Serious adverse events were reported in **41.2%** of patients. The most common SAEs included **pneumonia (3.1%)**, **dyspnea (2.8%)**, **pyrexia (2.5%)**, **urinary tract infection (1.9%)**, and **pleural effusion, pulmonary embolism, and sepsis (each 1.3%)**. These findings are consistent with the underlying disease and treatment context.

➤ Fatal Adverse Events

Fatal adverse events (Grade 5) occurred in a small proportion of patients (3.8%), generally within 30 days of last dose or before initiation of subsequent therapy, and should be interpreted in the context of advanced disease and comorbidities.

Overall Safety Conclusion

Across monotherapy and combination studies, atezolizumab demonstrated a **well-characterized and predictable safety profile**, with adverse events consistent with its mechanism of action and underlying disease. The safety profile remained **consistent across tumor types, treatment settings, and combinations**, supporting its continued clinical use.

4. Immunogenicity

	Monotherapy Pooled Population Atezolizumab IV (N= 3460)	Combination Pooled Population Atezolizumab IV (N = 3319)	IMscin001 Atezolizumab SC (N = 221)

Total number of patients with:	ADA-negative n = 2241	ADA-positive n= 1219	ADA-negative n =2564	ADA-positive n =755	ADA-negative n =178	ADA-positive n = 43
At least one AE	2145 (95.7%)	1174 (96.3%)	2539 (99.0%)	749 (99.2%)	73 (41.0%)	18 (41.9%)
Grade 3-4 AE	884 (39.4%)	563 (46.2%)	1636 (63.8%)	507 (67.2%)	31 (17.4%)	9 (20.9%)
Grade 5 AE	61 (2.7%)	36 (3.0%)	78 (3.0%)	29 (3.8%)	5 (2.8%)	2 (4.7%)
Serious AE	747 (33.3%)	483 (39.6%)	945 (36.9%)	346 (45.8%)	25 (14.0%)	6 (14.0%)
AE leading to treatment withdrawal ^a	174 (7.8%)	104 (8.5%)	523 (20.4%)	194 (25.7%)	2 (1.1%)	0
AE leading to dose interruption ^a	626 (27.9%)	379 (31.1%)	1615 (63.0%)	519 (68.7%)	45 (25.3%)	11 (25.6%)

□ Available data indicate that the presence of anti-drug antibodies (ADAs) did not have a clinically relevant impact on the safety profile of atezolizumab. Patient safety management was not affected by ADA status, and no consistent patterns of adverse drug reactions attributable to ADAs were identified. However, the available data are limited and do not allow firm conclusions regarding potential causal relationships.

□ With respect to efficacy, although some variability was observed across studies, ADA status did not appear to have a clinically meaningful impact on treatment efficacy.

5. Post-Marketing safety experience

□ Atezolizumab was first approved in the United States in May 2016 for patients with locally advanced or metastatic urothelial carcinoma (UC) following platinum-containing chemotherapy, and subsequently in the European Union in September 2017 for UC and non-small cell lung cancer (NSCLC). Since then, the intravenous formulation has been approved in approximately 125 countries across multiple indications.

□ Post-marketing safety data indicate that the safety profile of atezolizumab remains consistent with that observed in clinical trials, with no new or unexpected safety signals identified.

• **Protocol:** A Phase III, Open-Label, Randomized Study of Atezolizumab with Lenvatinib or Sorafenib Versus Lenvatinib or Sorafenib alone in Hepatocellular Carcinoma Previously Treated with Atezolizumab and Bevacizumab

- **Atezolizumab** is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1, and B7-1 (also known as CD8), both of which function as inhibitory

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receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity. Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

- **Lenvatinib** is another multikinase-inhibitor targeting the VEGF receptors 1–3, fibroblast growth factor receptor (FGFR) 1–4, and platelet-derived growth factor (PDGF) receptors α and β , as well as the proto-oncogenes KIT and RET (Baxter et al. 2018). Lenvatinib specifically also inhibits FGFR-1.

- **Sorafenib** is a multikinase inhibitor suppressing the activity of several tyrosine kinases involved in tumor angiogenesis and progression. It has been described to target VEGFR–2/3, PDGF receptor (PDGF-R), receptor tyrosine kinase Flt3 and cell surface marker c-Kit, and also targets rapidly accelerated fibrosarcoma (Raf) kinases involved in the mitogen activated protein kinase (MAPK; originally called extracellular signal–regulated kinases [ERK]) pathway). Sorafenib was the first systemic substance globally available, approved in 2007 in the United States by the FDA for patients with unresectable HCC.

Phase: III

Objective(s):

Primary Efficacy Objective	Corresponding Primary Endpoint
To evaluate the efficacy of atezolizumab plus lenvatinib or sorafenib compared with lenvatinib or sorafenib alone	OS, defined as the time from randomization into the study to death from any cause
Secondary Efficacy Objective	Corresponding Endpoints
To evaluate the efficacy of atezolizumab plus lenvatinib or sorafenib compared to lenvatinib or sorafenib alone	Assessments per investigator according to RECIST v1.1: • PFS, defined as the time from randomization into the study to the first occurrence of disease progression or death from any cause (whichever occurs first) • Confirmed ORR, defined as the proportion of patients with a best response of either complete or partial response • TTP, defined as the time from randomization to the first occurrence of disease progression • DOR, defined as the time from the first occurrence of a documented confirmed objective response to disease progression or death from any cause (whichever occurs first)

To evaluate patient-reported function and GHS/QoL experienced by patients receiving atezolizumab plus lenvatinib or sorafenib versus lenvatinib or sorafenib alone	TTCD, of HRQoL, defined as the time from randomization to first confirmed deterioration (decrease from baseline of ≥ 10 points) maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks (if Cycle 1–6) or 6 weeks (if after Cycle 6) in the following EORTC QLQ-C30 scales (separately): physical function, role function, and GHS/QoL
Safety Objective	Corresponding Endpoints
To evaluate the safety of atezolizumab plus lenvatinib or sorafenib compared with lenvatinib or sorafenib alone	Incidence and severity of adverse events, including adverse events for combination treatment, adverse events related to atezolizumab, and TKI-related adverse events with severity determined according to NCI CTCAE v5.0 • Vital signs • Clinical laboratory test results
Immunogenicity Objective	Corresponding Endpoints
To evaluate the immune response to atezolizumab	Prevalence of ADAs to atezolizumab at time of study entry and incidence of ADAs to atezolizumab during the study
Pharmacokinetic Objective	Corresponding Endpoints
To characterize the PK profile of atezolizumab when given in combination with lenvatinib or sorafenib	Serum concentration of atezolizumab at specified timepoints

Rationale:

This study will evaluate the efficacy and safety of atezolizumab plus lenvatinib or sorafenib compared with lenvatinib or sorafenib alone in patients with hepatocellular carcinoma (HCC) who progressed on prior HCC treatment with atezolizumab and bevacizumab.

Benefit-Risk:

Combination therapy with atezolizumab and VEGF-targeting agents has demonstrated superior efficacy over standard treatment (e.g., sorafenib) in first-line advanced hepatocellular carcinoma (HCC). Continuing immunotherapy beyond progression and combining it with TKIs (lenvatinib or sorafenib) may enhance clinical outcomes, including overall survival, by overcoming resistance mechanisms and improving antitumor immune response. This approach is particularly relevant given the lack of established second-line standard of care.

Atezolizumab and TKIs are associated with known and generally manageable toxicities, including immune-related adverse events (e.g., hepatitis, pneumonitis, endocrinopathies) and TKI-related effects (e.g., hypertension, gastrointestinal and hepatic toxicities). Combination therapy may lead to overlapping toxicities; however, available evidence suggests these are predictable, manageable, and consistent with known safety profiles.

The overall benefit-risk profile of atezolizumab combined with lenvatinib or sorafenib is considered favorable, offering potential efficacy advantages with an acceptable and manageable safety profile in patients with advanced HCC.

Design:

This is a Phase III, open-label, multicenter, randomized, two-arm study designed to evaluate the efficacy and safety of atezolizumab plus either lenvatinib or sorafenib versus lenvatinib or sorafenib alone in patients with locally advanced or metastatic HCC who have progressed on prior systemic treatment with atezolizumab plus bevacizumab.

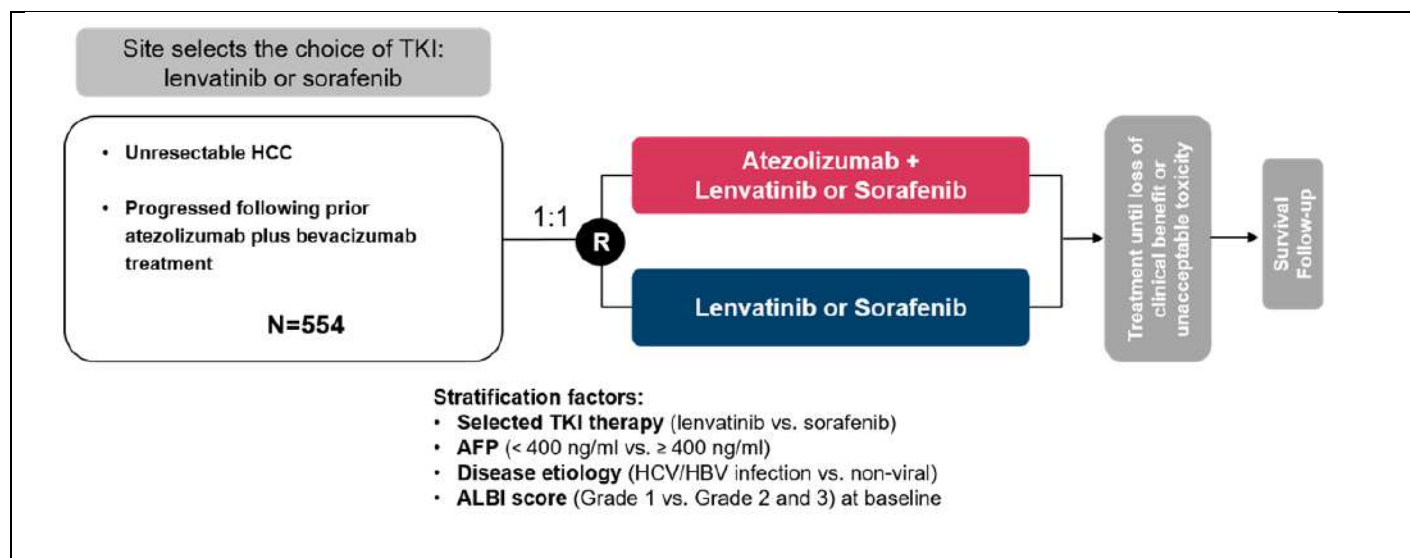
This study will enroll approximately 554 patients randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (experimental arm): atezolizumab 1200 mg IV infusions dosed in 3-week cycles (Q3W) plus either oral lenvatinib 12 mg once a day (QD) for patients with baseline body weight of 60 kg and above, and 8 mg for patients with baseline body weight below 60 kg, or oral sorafenib 400 mg twice a day (BID)
- Arm B (control arm): lenvatinib 12 mg QD, by mouth (PO) for patients with baseline body weight of 60 kg and above, and 8 mg for patients with baseline body weight below 60 kg, or sorafenib 400 mg PO BID, continuously

Randomization will be stratified according to the following stratification factors:

- Selected TKI therapy (lenvatinib vs. sorafenib)
- AFP (< 400 ng/ml vs. ≥ 400 ng/ml)
- Disease etiology (HCV/HBV infection vs. non-viral)
- ALBI score (Grade 1 vs. Grade 2 and 3) at baseline

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log . Patients who withdraw from the study will not be replaced.



• **Recommendation &/ or Questions & Answers:** NA

• **Abbreviation:**

ADA	Anti-Drug Antibody
AE(s)	Adverse Event(s)
AUC	Area Under the Curve
BRAFV600	BRAF Mutation at V600
CA	Central Administration
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CL	Clearance
CNS	Central Nervous System
CNS	Central Nervous System
CR	Complete Response
CSR	Clinical Study Report
CT	Clinical Trial
DCR	Disease Control Rate
DFS	Disease-Free Survival
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response

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ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDA	Egyptian Drug Authority
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked Immunosorbent Assay
Fcγ	Fc gamma receptor
FPI	First Patient In
GA	General Administration
GLP	Good Laboratory Practice
HCC	Hepatocellular Carcinoma
HER2	Human Epidermal Growth Factor Receptor 2
IB	Investigator's Brochure
IDFS	Invasive Disease-Free Survival
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
IRF	Independent Review Facility
ITT	Intent-To-Treat
IV	Intravenous
KLH	Keyhole Limpet Hemocyanin
KRAS	Kirsten Rat Sarcoma Viral Oncogene
LCMV	Lymphocytic Choriomeningitis Virus
mFOLFOX	Modified FOLFOX regimen
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathological Complete Response
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1

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PET-CT	Positron Emission Tomography – Computed Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PPQ	Patient Preference Questionnaire
PR	Partial Response
PRO(s)	Patient-Reported Outcome(s)
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-Free Survival
RP2D	Recommended Phase 2 Dose
SC	Subcutaneous
sCR	Stringent Complete Response
TACE	Transarterial Chemoembolization
TK	Toxicokinetics
VGPR	Very Good Partial Response
Vss	Volume of Distribution at Steady State
WT	Wild Type