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Assessing the impact of digital patient monitoring on health outcomes and healthcare resource usage in addition to the feasibility of its combination with at-home treatment, in participants receiving systemic anticancer treatment in clinical practice: protocol for an interventional, open-label, multicountry platform study (ORIGAMA)

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ABSTRACT

Introduction Digital patient monitoring (DPM) tools can enable more effective clinical care and improved patient outcomes in cancer. However, their broad adoption requires ease of use and demonstration of real-world clinical utility/impact. ORIGAMA (MO42720) is an interventional, open-label, multicountry platform study investigating the clinical utility of DPM tools and specific treatments. ORIGAMA will begin with two cohorts that aim to assess the impact of the atezolizumab-specific Roche DPM Module (hosted on the Kaiku Health DPM platform (Helsinki, Finland)) on health outcomes and healthcare resource usage, and its feasibility to support at-home treatment administration, in participants receiving systemic anticancer treatment. Other digital health solutions may be added to future cohorts.

Methods and analysis In Cohort A, participants with metastatic non-small cell lung cancer (NSCLC), extensive-stage SCLC or Child Pugh A unresectable hepatocellular carcinoma will be randomised to a locally approved anticancer regimen containing intravenous atezolizumab (TECENTRIQ, F. Hoffmann-La Roche Ltd/Genentech) and local standard-of-care support, with/without the Roche DPM Module. Cohort B will assess the feasibility of the Roche DPM Module in supporting administration of three cycles of subcutaneous atezolizumab (1875 mg; Day 1 of each 21-day cycle) in the hospital, followed by 13 cycles at home by a healthcare professional (ie, flexible care), in participants with programmed cell-death ligand 1-positive, early-stage NSCLC. The primary endpoints are the mean difference in change of the participant-reported Total Symptom Interference Score at Week 12 from baseline (Cohort A) and flexible care adoption rate at Cycle 6 (Cohort B).

Ethics and dissemination This study will be conducted according to the Declaration of Helsinki, and/or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This platform study approach enables evaluation of digital health solutions (software as medical devices) in combination with specific treatments per cohort, for example, digital patient monitoring (DPM) and atezolizumab cancer treatment in Cohorts A and B.
⇒ New cohorts studying DPM or other digital health solutions in combination with specific treatments may be added in the future.
⇒ Multiple patient-reported outcome measures are used across cohorts to collect data for objectives/endpoints that are centred on real-world patient needs, interests and experiences.
⇒ Cohort designs and objectives/endpoints were chosen to qualify for digital health reimbursement pathways (eg, Digital Health Applications in Germany).
⇒ Cohorts A and B are focused on a single DPM platform, limiting generalisability of the results, with Cohort B only enrolling 40 patients in one arm; clinical evidence generation is therefore exploratory, with limited statistical power to enable subgroup analyses.

protection to the individual. The study received its first Ethics Committee approval in Spain in October 2022. Participants will provide written informed consent in a face-to-face setting. The results of this study will be presented at national and/or international congresses and disseminated via publication in peer-reviewed journals.

Trial registration number NCT05694013.

INTRODUCTION

In 2020, there were an estimated 19.3 million new cancer cases and 10 million cancer-related deaths worldwide.[1] By 2040, the global number of new cancer cases and deaths is expected to increase to 30.2 million and 16.3 million, respectively.[1] Despite this, studies have shown that overall cancer survival rates are increasing, mainly due to earlier diagnosis and advances in cancer treatment.[2 3]

Disease-related or treatment-related symptoms, some of them classified as adverse events (AEs), can affect an individual's quality of life (QoL) negatively and may even become life-threatening.[4] For example, nausea and vomiting, the most frequently reported symptoms from antineoplastic chemotherapy, can significantly impact patients' daily lives and consequently lead to the discontinuation of treatment.[5 6] Furthermore, treatment-related symptoms can be burdensome to patients, healthcare professionals and healthcare system resources. For instance, patients with urothelial carcinoma, renal cell carcinoma, non-small cell lung cancer (NSCLC) or Merkel cell carcinoma receiving immune checkpoint inhibitor therapy and experiencing treatment-related symptoms/AEs have an increased risk of unplanned hospitalisations and emergency room visits, and increased overall healthcare costs, compared with those without treatment-related symptoms/AEs.[7] In addition, the financial burden of using prescription medications and allied healthcare professionals (eg, physiotherapists, dieticians) to manage anticancer treatment-related symptoms/AEs can be a significant source of out-of-pocket patient expenses, which have not been well documented thus far.[8] Overall, there is a strong need for improved, patient-empowered management of cancer and anticancer treatment-related symptoms/AEs that may compromise improvements in patient outcomes or consume healthcare/financial resources. Improved understanding, prevention and mitigation of disease-related or treatment-related symptoms, and development of tools to facilitate long-term tracking of patient-reported outcomes (PROs) and self-management of such symptoms/AEs, are thus key research and cancer care priorities.[9]

Although some patients may prefer hospital care due to the desire to separate home life and place of care as well as to avoid the need to rely on relatives,[10] treatment in the hospital setting can be troublesome as a result of increased infection risks or the need to travel potentially long distances, subsequently disrupting daily activities.[11] Those administered outside of the oncology ward, outpatient clinic or office-based oncology setting (ie, in a 'flexible care' setting), have been shown to reduce the burden experienced by those living with cancer, improve overall outcomes and QoL, increase treatment satisfaction and adherence and reduce overall healthcare costs.[12–16]

At-home administration of subcutaneous (SC) forms of anticancer treatments are one example of flexible care; an SC combination of pertuzumab, trastuzumab and hyaluronidase (PHESGO, F. Hoffmann-La Roche Ltd (Basel, Switzerland)/Genentech (South San Francisco, California, USA]) has now been approved by the Food and Drug Administration and European Medicines Agency for the treatment of adults with HER2-positive early and metastatic breast cancer.[17 18] Studies have shown this combination, compared with sequential intravenous infusions of pertuzumab and trastuzumab, to be non-inferior with respects to safety and efficacy, to be preferred by patients (mainly due to reduced time in the clinic and increased comfort during administration) and to improve overall patient satisfaction.[19 20] Beyond breast cancer, use of SC bortezomib (VELCADE, Takeda, Cambridge, Massachusetts, USA) in patients with relapsed multiple myeloma has been shown to be better tolerated, preferred by patients and nurses, and associated with reduced chair time and overall clinic visit time, compared with its intravenous counterpart.[21–23] Comparisons of pharmacokinetics, safety, efficacy and participant preference of an SC formulation of atezolizumab (TECENTRIQ, F. Hoffmann-La Roche Ltd/Genentech) ± a recombinant human hyaluronidase with intravenous infusion in patients with locally advanced or metastatic NSCLC are also currently under clinical investigation in clinical trials (NCT03735121 and NCT05171777).

Alongside the growing availability of anticancer treatments outside the clinic, and the parallel improvements in cancer survival,[4 24–26] digital patient monitoring (DPM) tools are becoming increasingly important to support monitoring and symptom management of patients with cancer, through features such as online symptom and QoL reporting/monitoring,[27–29] healthcare professional–patient online communication[29–31] and disease-specific/treatment-specific educational services.[29 31] Patients with cancer require proactive self-management support as they are increasingly expected to recognise, report and manage mild or moderate side effects of treatment, attempt to adopt healthy lifestyle changes to reduce the risk of chronic treatment effects, manage comorbidities or co-medications and cope with implications of the disease and/or daily responsibilities.[26]

DPM tools have been shown to improve patient overall survival (OS), health-related QoL and symptom burden, increase adherence to chemotherapy treatment regimens, compliance with treatment dosing and duration of anticancer therapy, and enable earlier identification and more effective management of treatment-related symptoms/AEs, thereby reducing the rate and severity of severe or serious AEs, subsequent hospitalisations and healthcare resource usage.[27–45] Overall, using DPM tools to create more patient-centred and personalised treatment plans that encompass symptom monitoring and

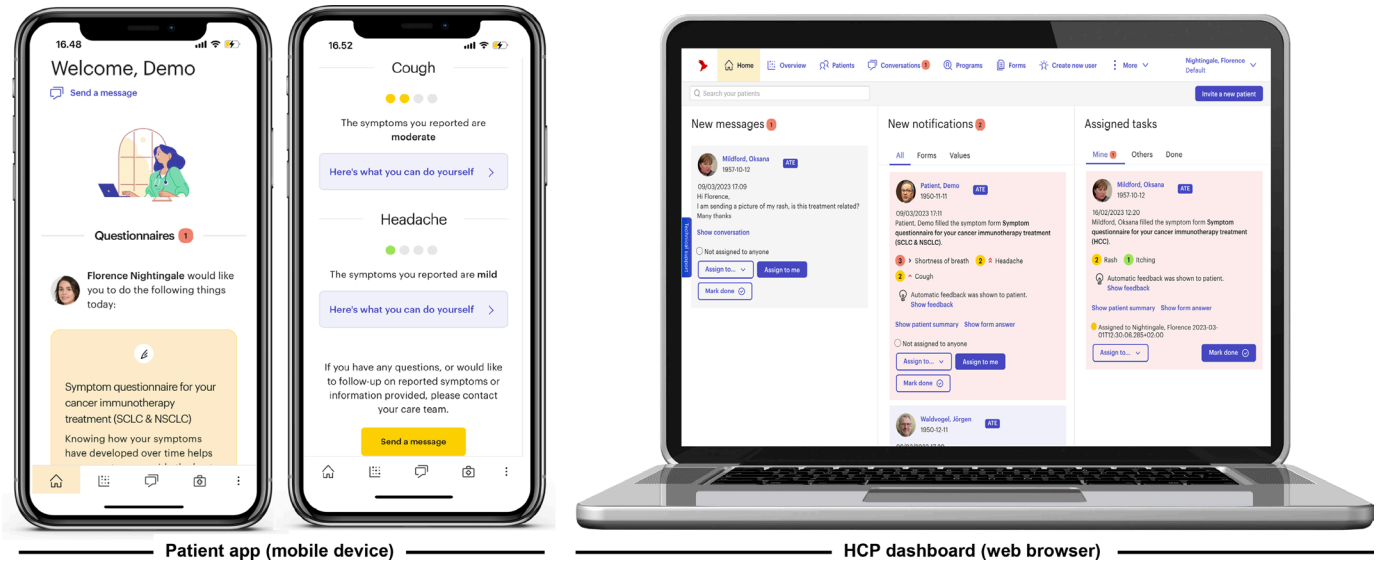

Figure 1 Example screenshots from the Roche DPM Module (hosted on the Kaiku Health DPM platform), mobile-enabled and accessible through a web browser or an application on devices such as personal computers, laptops, mobile phones and tablets. DPM, digital patient monitoring; HCC, hepatocellular carcinoma; HCP, healthcare professional; NSCLC, non-SCLC; SCLC, small cell lung cancer.

management can enable more effective clinical care and improved patient outcomes.[24]

The Roche DPM Module (F. Hoffmann-La RocheLtd) includes (but is not limited to): a participant-facing, tailored user interface; algorithms for symptom management and triaging; questionnaires; and content related to treatment-specific and disease-specific participant information and self-management instructions for mild/moderate symptoms. The Roche DPM Module is hosted on the Kaiku Health DPM platform (Helsinki, Finland) (figure 1). A proof-of-concept pilot study assessing user experience of the Module in patients with advanced/metastatic NSCLC treated with second-line, single-agent cancer immunotherapy demonstrated high satisfaction with and acceptance of the Module by both healthcare professionals and patients.[40] Ease of use and demonstration of the clinical value and impact of DPM tools in real-world practice is the key for their broad adoption.

ORIGAMA (MO42720; figure 2) is an interventional, open-label, multicountry platform study investigating the clinical utility of DPM tools in combination with specific treatments. The study will begin with two cohorts (figure 2) that aim to assess the tailored atezolizumab-specific Roche DPM Module's impact on health outcomes and healthcare resource usage, and the feasibility of using the Roche DPM Module to support at-home treatment administration, in participants receiving systemic anticancer treatment. Other digital health solutions may be added to additional cohorts in the future.

This study will provide key trial design insights related to the evaluation of a DPM tool in combination with anticancer treatments in one or more settings. In this study, 'participant' refers to the individual receiving anticancer treatment who is enrolled in this study.

METHODS AND ANALYSIS

The atezolizumab-specific Roche DPM Module on the Kaiku Health DPM platform

The atezolizumab-specific Roche DPM Module will be used in this study across cohorts to collect data on preselected disease-specific and treatment-specific symptoms, aid self-triaging of symptom severity and support self-management of mild and moderate symptoms (figure 3). Depending on the patient's indication, selected disease-related or treatment-related symptom questions, including a free-text symptom field, will be presented to the patient (online supplemental table 1). Relevant symptoms were selected based on the AE profile of the drug treatment and symptom profile of the disease. The selection was refined in a discussion process with physicians, nurses and patient groups. The coverage of symptoms experienced in clinical practice by patients and healthcare professionals was validated in a real-world evidence-based feasibility study.[46] The Module should be used in accordance with the provided training and as indicated in the accompanying user guide.

Participants will be invited every 7 days to report symptoms or can report symptoms ad hoc as needed. Notifications of symptom reports will be sent to the care team in order to prioritise review and management, based on the reported severity of the symptoms in line with the PROs version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[47] For selected mild or moderate symptoms, specific educational material will be provided, including additional symptom severity assessment and symptom self-management instructions (based on The Symptom Navi Programme).[48 49] Via a care team-user interface on the Kaiku Health DPM platform, the care team can track, across cohorts, participant symptom

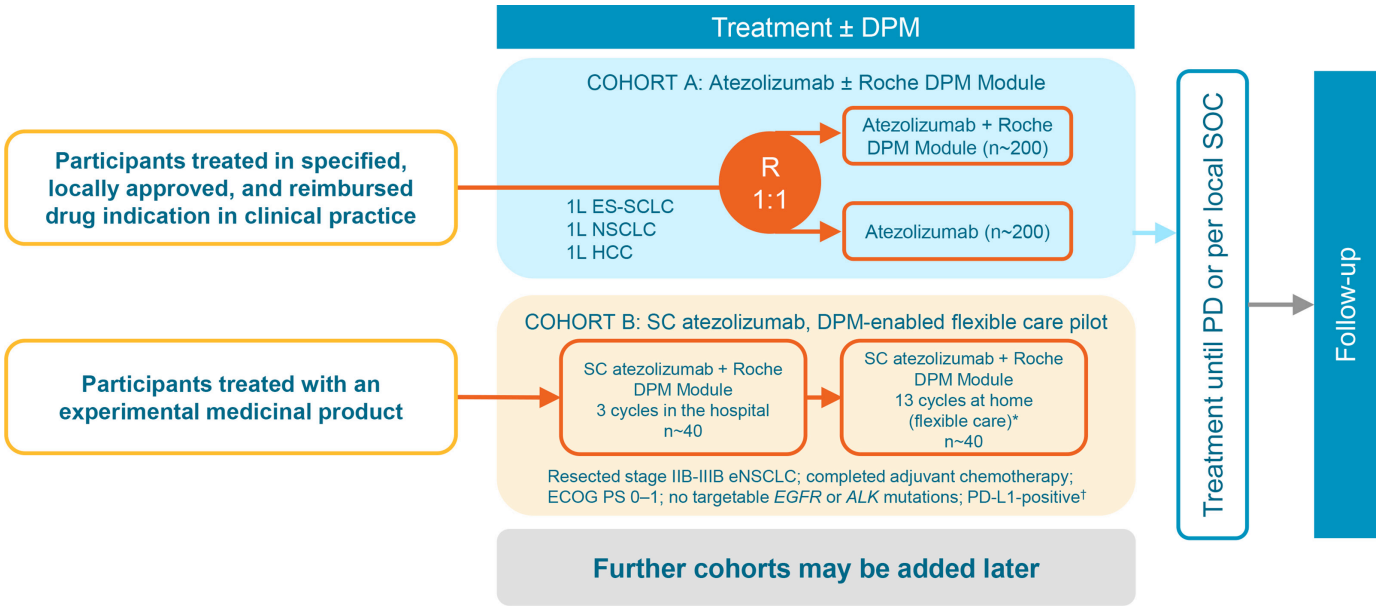

Figure 2 ORIGAMA study design. *Flexible care, or treatment administered outside of the oncology ward, outpatient clinic or office-based oncology setting, enables appropriate treatment at a time and location convenient for patients and HCPs. †PD-L1-positive tumours are defined as PD-L1-stained tumor-infiltrating immune cells covering ≥1% of the tumour area (Ventana PD-L1 (SP263) IHC assay, Ventana Medical Systems, Tucson, Arizona, USA]) or PD-L1 tumour proportion score ≥1% (Dako PD-L1 IHC 22C3 pharmDx, Agilent, Santa Clara, California, USA). The PD-L1 assay must be a health authority-approved test (ie, adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements. 1L, first line; DPM, digital patient monitoring; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ES-SCLC, extensive stage small-cell lung cancer; HCC, hepatocellular carcinoma; HCP, healthcare professional; IHC, immunohistochemistry; (e) NSCLC, (early) non-small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death-ligand 1; R, randomisation; SC, subcutaneous; SOC, standard of care.

reports between clinical appointments, in order to facilitate clinical decision-making. The care team is also able to exchange messages with the participant.

The atezolizumab-specific Roche DPM Module and Kaiku Health DPM platform is mobile-enabled and accessible through a web browser or an application on devices such as personal computers, laptops, mobile phones and tablets. Participants using the atezolizumab-specific Roche DPM Module will receive access to the DPM module on their own personal devices (ie, not devices provided during the study) and training on its use at their baseline study visit. Kaiku Health is a Class IIa active medical device both under the Medical Devices Directive (according to Rule 10; current at time of writing) and

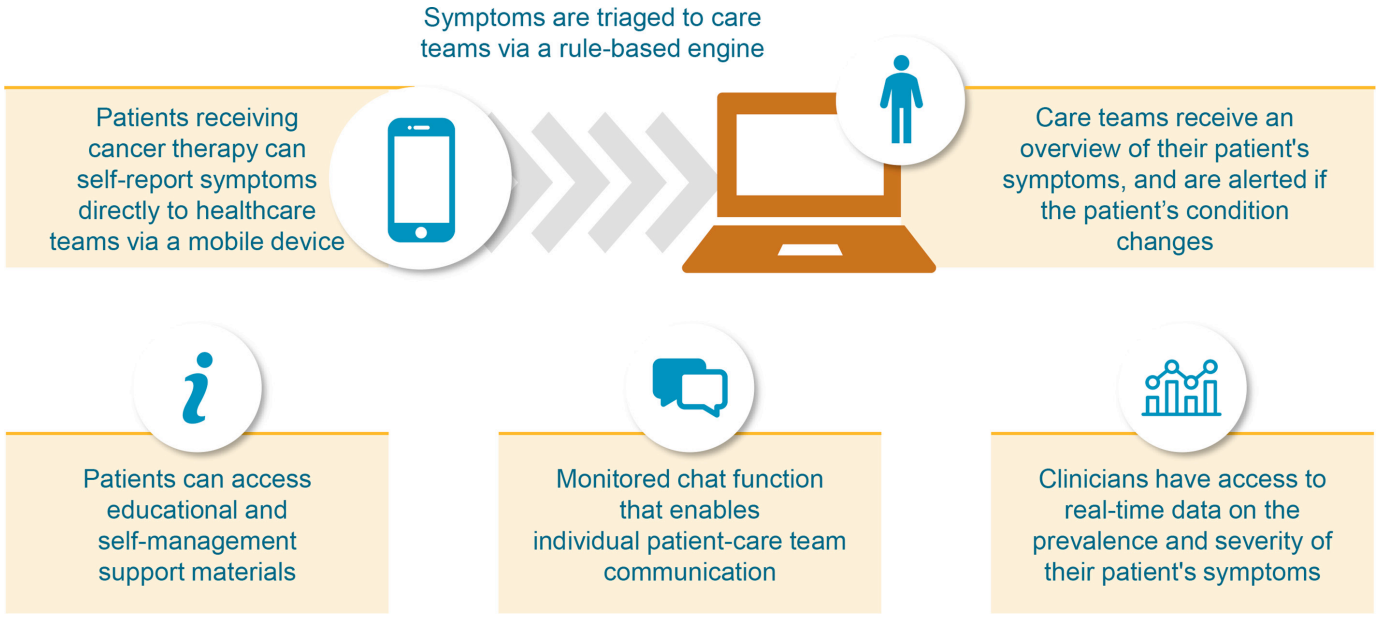

Figure 3 Overview of DPM tools. DPM, digital patient monitoring.

under the Medical Devices Regulation (according to Rule 11).[50 51]

All participants across both study cohorts will report symptom interference and burden, health-related QoL and treatment satisfaction using the validated questionnaires described below.

Study setting and participant recruitment

Approximately 40 sites, initially across 10 countries, will enrol approximately 400 participants in Cohort A and 40 participants in Cohort B (figure 2). Participants will provide written informed consent in a face-to-face setting (examples of the informed consent forms are provided as online supplemental materials) and will be enrolled and randomised (if applicable) through an interactive web-based response system. Ethics committees reviewed the protocol, the patient informed consent forms (Cohort A and B), the Roche modules and their content and the additional patient-facing material shared within the DPM solution. The study received its first Ethics Committee approval in Spain in October 2022 (received: 3 October 2022; health authority approval: 12 December 2022). Enrolment of patients is expected from December 2022 onwards, for a period of 18 months.

Participants and study design

For all cohorts, participants must be aged ≥18 years old, have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2, and have an email address, access to an internet-capable device (smartphone, tablet or personal computer) and access to an internet connection.

Key exclusion criteria for Cohorts A and B are: (1) any physical or cognitive condition preventing use of the Kaiku Health DPM platform; (2) lack of proficiency with any of the available Roche DPM Module language translations or presence of psychiatric/neurological disorders or any condition that may impact the participant's ability to use the DPM platform; (3) current use of another DPM or electronic PRO tool for symptom management and/or reporting; (4) current participation in another interventional trial; (5) receiving an atezolizumab biosimilar or non-comparable biologic; and (6) history of other malignancy within 5 years prior to initiation of study treatment (excluding malignancies with a negligible risk of metastases or death).

Cohort A will investigate the impact of the atezolizumab-specific Roche DPM Module on health outcomes in participants prescribed locally approved anticancer regimens containing intravenous atezolizumab for metastatic NSCLC, extensive-stage SCLC or Child Pugh A unresectable hepatocellular carcinoma, according to Barcelona Clinic Liver Cancer staging.[52] Participants in Cohort A must have a confirmed diagnosis from their treating physician for the relevant indication (via local laboratory or radiological report), have a life expectancy of ≥12 weeks and be systemic therapy-naïve (except for participants with *EGFR*-mutant or *ALK*-positive NSCLC who may have received prior systemic therapy with prior tyrosine kinase inhibitors). Participants receiving concomitant anticancer treatment not part of a locally approved combination at the time of starting intravenous atezolizumab will be excluded.

In Cohort A, participants will be randomised 1:1, through a permuted-block randomisation method to ensure a balanced assignment, to a locally approved, anticancer regimen containing intravenous atezolizumab and local standard-of-care support ± the atezolizumab-specific Roche DPM Module (table 1). Randomisation will be stratified by disease indication and baseline ECOG

Table 1 Schedule of atezolizumab anticancer treatment in Cohort A and B

Population	Atezolizumab anticancer treatment schedule (regimen as per local label)
Cohort A	
Metastatic NSCLC	Atezolizumab monotherapy 840 mg intravenously Q2W or 1200 mg Q3W or 1680 mg Q4W.*
Metastatic NSCLC (non-squamous)	Four to six 21-day cycles of atezolizumab 1200 mg intravenously and chemotherapy (bevacizumab, carboplatin and paclitaxel; or carboplatin and nab-paclitaxel) induction therapy, followed by atezolizumab 1200 mg Q3W and bevacizumab maintenance therapy.*
Extensive-stage SCLC	Four 21-day cycles of atezolizumab 1200 mg intravenously and chemotherapy (carboplatin and etoposide) induction therapy, followed by atezolizumab 840 mg intravenously Q2W or 1200 mg Q3W or 1680 mg Q4W maintenance therapy, including bevacizumab where locally approved.*
Child Pugh A advanced or unresectable hepatocellular carcinoma, according to BCLC staging[52]	Atezolizumab 1200 mg intravenously Q3W+bevacizumab 15 mg/kg intravenously Q3W.*†
Cohort B	
PD-L1-positive, early-stage NSCLC	Atezolizumab 1875 mg SC Q3W for three cycles (Day 1 of each 21-day cycle) in the hospital setting, followed by 13 cycles at home (administered by a healthcare professional).

*Treatment continued until disease progression/loss of clinical benefit or unmanageable toxicity; treatment beyond disease progression may be considered at the discretion of the physician.
†If bevacizumab is discontinued due to toxicity, atezolizumab regimen may continue until loss of clinical benefit or unmanageable toxicity.
BCLC, Barcelona Clinic Liver Cancer; (N)SCLC, (non-)small cell lung cancer; PD-L1, programmed cell death-ligand 1; QXW, every X weeks; SC, subcutaneous.

PS (0/1 vs 2). Following the study baseline visit to receive access to and training on the atezolizumab-specific Roche DPM Module, participants will return for visits per their routine anticancer treatment administration schedule. No extra visits are mandated by this protocol, but additional clinical visits may occur at the discretion of both the care team and participant, based on symptom reports via the DPM Module.

Cohort B will assess the feasibility of using the Roche DPM Module to support SC atezolizumab administration by a qualified healthcare professional at the participant's home, as part of symptom management support in between treatment administration visits, in patients with programmed cell-death ligand 1 (PD-L1)-positive, early-stage NSCLC. Participants who have had a complete resection of histologically/cytologically confirmed Stage IIB–IIIB NSCLC (T3–N2 for stage IIIB per the Union for International Cancer Control/American Joint Commission on Cancer staging system),[53] have locally confirmed PD-L1-positive tumours, and have completed adjuvant chemotherapy at 4–12 weeks prior to randomisation and are adequately recovered from this (per the investigator's decision), are eligible. PD-L1-positive tumours are defined as PD-L1 expression on ≥1% of tumour cells, as documented through locally approved, pre-existing local testing of a representative tumour tissue specimen. The PD-L1 assay must be a health authority-approved assay (ie, adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements. Participants with *EGFR* mutation-positive or *ALK* rearrangement-positive tumours, as determined by local testing, will be excluded from Cohort B.

In Cohort B, eligible participants will use the atezolizumab-specific Roche DPM Module and will receive three cycles of SC atezolizumab (1875 mg; Day 1 of each 21-day cycle) in the hospital setting, before receiving up to 13 cycles at home by a healthcare professional (ie, in the flexible care setting) (table 1). Participants will continue to receive SC atezolizumab until Cycle 16 or loss of clinical benefit. Monitoring of participants beyond the atezolizumab-specific Roche DPM Module is supported by vital sign assessment and collection of laboratory samples at every administration visit, phone/video calls to the clinic healthcare professional during or on the day before administration and participant hospital visits every 3 months. In addition to the standard 7-day interval for symptom reporting, participants in Cohort B are also invited to report symptoms on the day after administration.

Objectives and endpoints

In Cohort A, the primary efficacy endpoint is the mean difference in change of the participant-reported Total Symptom Interference Score from the MD Anderson Symptom Inventory (MDASI) Core Items at Week 12 from baseline (table 2).[54] This will be measured in participants receiving a locally approved, anticancer regimen containing intravenous atezolizumab and local standard-of-care support ± the atezolizumab-specific Roche DPM Module. MDASI is a 19-item questionnaire to assess symptom burden defined as the sum of symptom severity and impact of symptoms (interference).[54] Overall symptom distress is defined as the mean of the ratings of the interference questions in MDASI.[54] This primary endpoint was selected based on multiple previous studies, some of which used MDASI, demonstrating the potential of DPM tools to significantly reduce overall symptom burden, severity and distress in patients with cancer, compared with the standard of care alone.[29 40–45]

Secondary efficacy endpoints include number of hospitalisations and cumulative days hospitalised due to serious AEs, number of unscheduled visits to the emergency room or clinical visits for symptom management, changes from baseline in global health status (GHS)/QoL score from the European Organisation for Research and Treatment of Cancer (EORTC) Item Library 6 (EORTC IL6) GHS/QoL (from the EORTC Quality of Life Questionnaire (QLQ-C30)),[55] change from baseline in the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)[56] and change from baseline in the mean symptom severity score from the MDASI Core Items (table 2). The EORTC QLQ-C30 is a validated, reliable self-reported measure that will be used to assess GHS and QoL.[55 57] The EuroQol EQ-5D-5L is a validated, self-reported health status questionnaire that will be used to calculate a health status utility score for use in health economic analyses. There are two components: a five-item health state profile and a Visual Analogue Scale.[56]

Participants will be assessed for the primary endpoint and health-related QoL data at baseline and every 6 weeks until Week 24, regardless of whether they have discontinued anticancer therapy or started a new line of therapy. Safety and tolerability, including incidence and severity of device-associated AEs and adverse device effects, and incidence, nature and severity of anticancer treatment-associated AEs, will also be assessed, graded according to the National Cancer Institute's CTCAE V.5.0.[58] Safety data related to anticancer treatment will continue to be collected for 90 days following the last dose of atezolizumab, and for 30 days following the last dose of an alternative cancer therapy that has started prior to the 24-week time point and where the patient has continued to be followed up beyond this time point. Safety data related to adverse device effects will continue to be collected for 30 days following study end. A number of exploratory efficacy endpoints will also be assessed in Cohort A, as detailed in table 2. After 24 weeks, participants will continue to be followed up until 18 months after randomisation for OS.

In Cohort B, the primary endpoint is the flexible care adoption rate at Cycle 6 in participants using the atezolizumab-specific Roche DPM Module and receiving an SC atezolizumab anticancer treatment regimen (table 2). Adoption is defined as a joint decision by the investigator and the participant to continue to receive SC atezolizumab at home rather than in the hospital setting; if a participant or investigator decides to terminate

Table 2 Summary of endpoints/objectives in Cohort A and B

Cohort A	Cohort B
Primary endpoint or objective	
The mean difference in change of the Week 12 value from baseline of the participant-reported Total Symptom Interference Score from the MDASI Core Items.*	Flexible care-adoption rate at Cycle 6 in participants using the atezolizumab-specific Roche DPM Module and receiving an SC atezolizumab anticancer treatment regimen.
Secondary/exploratory endpoints or objectives	
Number of hospitalisations and cumulative days hospitalised due to serious AEs (according to the NCI-CTCAE V.5.0).[58]	Number of hospitalisations within 1 day of SC atezolizumab administration due to serious AEs (according to the NCI-CTCAE V.5.0).[58]
Number of unscheduled visits to the emergency room or clinical visits for symptom management.	Number of unscheduled visits to the emergency room or clinical visits for symptom management within 1 day of SC atezolizumab administration.
Changes from baseline in GHS/QoL score from the EORTC IL6 GHS/QoL (from the EORTC QLQ-C30 questionnaire)† every 6 weeks until Week 24.	Changes from baseline in GHS/QoL score from the EORTC IL6 GHS/QoL (from the EORTC QLQ-C30 questionnaire) at Cycles 3, 6, 9 and 12.†
Change from baseline in the EQ-5D-5L‡ every 6 weeks until Week 24.	Change from baseline in EQ-5D-5L at Cycles 3, 6, 9 and 12.‡
Change from baseline in the mean symptom severity score from the MDASI Core Items every 6 weeks until Week 24.	Change from baseline in the mean symptom severity score from the MDASI Core Items at Cycles 3, 6, 9 and 12.
Incidence and severity of device-associated AEs and adverse device effects and incidence, nature and severity of anticancer treatment-associated AEs (according to the NCI-CTCAE V.5.0),[58] with additional analyses of: ► Grade ≥3 AEs. ► Serious AEs. ► Selected immune-related AEs (pneumonitis, thyroid disorders, diarrhoea or colitis, nephritis, rash and hepatitis). ► Weighted toxicity score.[61] ► Interruption, modification or discontinuation of atezolizumab regimen due to AEs.	Incidence, nature and severity of SC atezolizumab-related AEs (according to the NCI-CTCAE V.5.0),[58] with additional analyses of: ► Grade ≥3 AEs. ► Serious AEs.
Participant-reported satisfaction of healthcare treatment (using the EORTC QLQ-OUT-PATSAT7 questionnaire)§ every 6 weeks until Week 24.	Participant acceptability of care and perception of safety culture at Cycles 4, 6 and 8.
Time to discontinuation of any prescribed anticancer treatment.	Interruption, modification, or discontinuation of SC atezolizumab regimen due to AEs occurring within 1 day of SC atezolizumab administration
Usage (eg, adherence) of the atezolizumab-specific Roche DPM Module.	Usage (eg, adherence) of the atezolizumab-specific Roche DPM Module.
Others:	**Others:**
Time to clinical progression or death (progression-free survival).	Time from first signs/symptoms to unscheduled clinical visit or hospitalisation.
Overall survival at 12 months.¶	Safety of SC atezolizumab administration in the hospital and flexible care settings on the basis of the incidence of AEs (of any grade, according to the NCI-CTCAE V.5.0),[58] within 1 day of SC atezolizumab administration in a hospital or flexible care setting.
Usage of concomitant medication of special interest for management of AEs (eg, steroids for immune-related AEs, diarrhoea medication, pain medication).	Flexible care adoption rate at Cycles 9, 12 and 15.
Drug dose intensity and exposure of locally approved, anticancer regimen containing intravenous atezolizumab and local standard-of-care support.	Reasons for not continuing in flexible care setting (questionnaire for participants/healthcare professionals).
Care team satisfaction with workflow efficiency.	

The following shading applies to this table: orange (primary endpoint), grey (secondary endpoint) and blue (exploratory endpoint).
*MDASI is a 19-item questionnaire to assess symptom burden defined as the sum of symptom severity and impact of symptoms (interference).[54] Overall symptom distress is defined as the mean of the ratings of the interference questions in MDASI.[54]
†The EORTC QLQ-C30 is a validated, reliable self-report measure that will be used to assess GHS and QoL.[55 57]
‡The EuroQol EQ-5D-5L is a validated, self-reported health status questionnaire that will be used to calculate a health status utility score for use in health economic analyses. There are two components: a five-item health state profile and a visual analogue scale.[56]
§The EORTC QLQ OUT-PATSAT7 is a seven-item complementary module from QLQ PATSAT-33, a core questionnaire to assess participant satisfaction with cancer care.[62]
¶All participants will be followed for overall survival until death, withdrawal of consent, loss to follow-up, or 18 months after the last participant has been randomised, whichever occurs earliest.
AE, adverse event; DPM, digital patient monitoring; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimension, 5-Level Questionnaire; GHS, Global Health Status; IL6, Item Library 6; MDASI, MD Anderson Symptom Inventory; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; QLQ-C30, Quality of Life Questionnaire; QLQ-OUT-PATSAT7, Quality of Life Questionnaire - Satisfaction with Out-Patient Cancer Care; QoL, quality of life; SC, subcutaneous.

administration of SC atezolizumab at home before Cycle 6, but continue in the hospital setting, this will be classified as 'not adopting'. Exploratory endpoints for Cohort B are detailed in table 2.

Data collection methods

An electronic case report form will be used by care teams to collect and report participant clinical data across all cohorts at each scheduled anticancer treatment visit and unscheduled study-related visits. Across cohorts, electronic PRO measures that collect symptom interference/burden and health-related QoL data (ie, MDASI, EORTC IL6, EQ-5D-5L) will be completed through an application separate to the DPM Module downloaded on an electronic device, or a web link. In both cohorts, safety data on the Module will also be collected.

Across both cohorts, the atezolizumab-specific Roche DPM Module will be used by participants to report symptoms and communicate with care teams. Participants will be required to report their symptoms as they occur and at least once weekly. Additional qualitative data may also be collected via interviews with the participants and/or care teams.

Statistical analysis

For Cohort A, the full analysis population will consist of all randomised participants, that is, the intention-to-treat population. The safety analysis population is defined as all participants who received at least one dose of the anticancer intravenous atezolizumab treatment regimen and/or used the atezolizumab-specific Roche DPM Module. All participants who were given access to the atezolizumab-specific Roche DPM Module will be included in the DPM arm.

Hypothesis tests will be two-sided (significance level: 5%). The focus of ORIGAMA is hypothesis testing, and the primary endpoint for Cohort A was used to determine the sample size of the study. A sample size of 400 randomised participants (200 participants per arm) provides 90% power to detect a difference between study arms in the mean change from baseline at Week 12 in the MDASI Total Interference Score of at least 8 points, assuming a two-sided 5% significance level and an SD of approximately 25 points. The assumption for mean change and SD is based on both the responsiveness of the MDASI Total Interference Score reported by Shi *et al*[59] and analyses of historical data from pivotal trials of the GHS scale from EORTC QLQ-C30.[57] In order to ensure that there is a representation of participants across the three indications included, enrolment will be capped for any one indication at 40% of the total sample size.

The clinical cut-off date for the primary analysis of Cohort A will take place when all randomised participants have been followed for ≥12 weeks, unless they withdraw from the study before this. If less than 50% of participants have been followed up for 12 months at the time of the primary analysis, an OS follow-up secondary analysis may take place. The study is not powered to demonstrate a statistically significant difference in OS.

For Cohort B, 40 participants will be enrolled. Since this cohort is exploratory, no sample size was calculated, and no formal hypothesis testing will be performed on the primary endpoint.

In Cohort B, the full analysis population will consist of all enrolled participants who completed three cycles of SC atezolizumab administered in the hospital setting. The safety analysis population is defined as all participants who received at least one dose of SC atezolizumab and/or used the atezolizumab-specific Roche DPM Module. The clinical cut-off date for the primary analysis will take place when all participants have completed 16 cycles, unless they withdraw from the study prior to this.

Across all cohorts assessing the same digital health solution, solution use (such as patient module adoption and adherence to weekly symptom reporting) and workflow efficiency data will be collected and analysed.

Study oversight and safety reporting

The study will be sponsored and managed by F. Hoffmann-La Roche Ltd. The sponsor will provide clinical operations management, data management and medical monitoring. The investigator is responsible for ensuring that all safety events are recorded on the electronic case report form and reported to the sponsor.

Patient and public involvement

Patients were systematically involved in the development and testing of the symptom self-management recommendations that are included in The Symptom Navi Programme.[48 49] Via prior publications (eg, the first pilot study and the real-world evidence-based feasibility study),[40 60] patients have been involved in the development of the atezolizumab-specific Roche symptom questionnaire and the Kaiku Health DPM tool.

Anne-Marie Baird is president of Lung Cancer Europe (LuCE), an umbrella patient organisation, and was involved in study concept and protocol development (since the first comprehensive protocol draft). Furthermore, she advised on patient-focused educational materials and study documents.

In collaboration with multiple stakeholders, research objectives and questions were developed with a focus on patient needs. The primary endpoint and several secondary endpoints are PROs using well validated measures. The impact or clinical utility of DPM for patients is the primary focus of this research.

It is planned that study findings will be discussed with patient representatives and presented at medical congresses and patient forums.

Ethics and dissemination

This study will be conducted in full conformance with the principles of the Declaration of Helsinki, and/or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater

protection to the individual. The study received its first Ethics Committee approval in Spain in October 2022. The results of this study will be presented at national and/or international congresses and disseminated via publication in peer-reviewed journals.

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Competing interests SI has acted in a consultancy and advisory role for Bristol-Myers Squibb, Roche and Merck Sharp & Dohme; has participated in a speaker bureau or provided expert testimony for Boehringer Ingelheim; is an employee at an institution that has received a research grant or funding from Roche; and has received travel and accommodation expenses from Boehringer Ingelheim, Merck Sharp & Dohme, Roche, Novartis and Kaiku Health. A-MB: has received honoraria for participation in an advisory board for Roche (Ireland), has received institutional research funding to Lung Cancer Europe (LuCE) from Amgen, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Merck, MSD, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda and Thermo Fisher, has received institutional honoraria to LuCE from Janssen, and has participated in various meetings, presentations and advisory boards, on behalf of LuCE. BB, AB, and AYCS are employees of and have stocks/other ownership in F. Hoffmann-La Roche Ltd. ME has acted in a consultancy and advisory role for Roche, is an employee at an institution that has received research grants from Novartis, Roche, BMS and Kaiku Health, and has received travel and accommodation expenses from Vifor. SG and MM-O are employees of and have stocks/other ownership in F. Hoffmann-La Roche Ltd. MR has received grants or contracts from Bayer and Ipsen, has received consulting fees from Bayer, BMS, Roche, Ipsen, AstraZeneca, Eli Lilly, BTG and Universal DX, and has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, from Bayer, BMS, Gilead Sciences, Eli Lilly, Roche and Eisai. MW has received research funding from Roche for conduct of the study. JA is an employee of and has stocks/other ownership in F. Hoffmann-La Roche Ltd.

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MASTER INFORMED CONSENT FORM (COHORT A)

TITLE:	**INTERVENTIONAL PLATFORM STUDY INVESTIGATING THE IMPACT OF DIGITAL HEALTH SOLUTIONS ON HEALTH OUTCOMESAND HEALTH-CARE RESOURCE UTILIZATIONIN PARTICIPANTS RECEIVING SYSTEMIC TREATMENT IN CLINICAL PRACTICE (ORIGAMA)**
STUDY NUMBER:	MO42720
SPONSOR:	F. Hoffmann-La Roche Ltd
STUDY DOCTOR:	{Name} {Phone number}
NAME OF INSTITUTION:	{Name}
INSTITUTION ADDRESS:	{Address} **NAME**
OF IRB/EC:	{Name}
IRB/EC APPROVAL DATE:	_____

SECTION 1: STUDY OVERVIEW

1.1 INTRODUCTION

- This study is testing digital patient monitoring software (the Roche Digital Patient Monitoring (DPM) atezolizumab Module, hereafter referred to as the patient monitoring app) that is designed to track symptoms for people receiving anti-cancertreatment containing atezolizumab.

- You are being asked to take part in this research study (also known as a clinical study) because you have one of the following types of cancer: lung cancer (metastatic non-small cell lung carcinoma (mNSCLC) or extensive-stage small-celllung carcinoma (ES-SCLC)) or liver cancer (advanced or unresectable hepatocellular carcinoma (HCC)).
- F. Hoffmann-La Roche Ltd (hereafter referred to as Roche is the sponsor of thisstudy and is paying {Name of Study Site} to cover the costs of this study.
- This consent form tells you what will happen if you take part. It also tells you aboutthe possible benefits and risks of being in the study.
- Taking part in this study is your choice. Please read the information carefully and feel free to ask questions. It may be helpful for you to discuss this information withyour family and friends.
- Instead of participating in this study, you may choose to
  - Get treatment for your cancer without being in this study
  - Join a different study
- Talk to your doctor about all of your choices, and the risks and benefits of each choice. If you choose not to take part, you will not lose the regular care you receivefrom your doctors.
- If you decide to take part, you will be asked to sign this consent form. You will begiven a copy of your signed consent form.

1.2 WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to find out whether the patient monitoring app impacts health, symptoms, and quality of life in people with mNSCLC, ES-SCLC, or HCC. Thisstudy will also assess whether the patient monitoring app can be used safely in peoplewith mNSCLC, ES-SCLC, or HCC. In this study, you may or may not get to use the patient monitoring app.

About 400 people will take part in Cohort A of this study.

The patient monitoring app to be used in this study is intended to allow people with cancer who are being treated with atezolizumab as part of their anti-cancer treatment to:

- Report their symptoms and quality of life to their care team
- Receive reminders and instructions related to their symptoms
- Obtain information related to their disease and treatment
- Send non-urgent messages to their care team.

The patient monitoring app can be accessed via an app on an internet-capable device (smartphone, tablet, or PC). It is also possible to access the app through a web browser.You will be trained how to use the patient monitoring app by your doctor or a nurse. Theinformation that you enter into the patient monitoring app is visible to your care team in

real-time. The patient monitoring app is used by the care team to track and manageparticipant symptoms.

1.3 WHAT WILL HAPPEN IF I PARTICIPATE?

This study has four parts:

1. Screening (to see if you are eligible for the study)
2. Randomization
3. Treatment
4. Follow-up (to check on you after treatment is finished)

If you participate in this study, you will be required to install up to two apps on your owninternet-capable device (smartphone, tablet, or PC): the patient monitoring app and an app to complete questionnaires about your health and quality of life. All participants willbe required to install the questionnaire app, whereas only some participants will be required to install the patient monitoring app.

The study procedures are described in detail in Section 2.2. Some procedures will be the same as your regular care for your cancer, and some procedures will be just for thisstudy.

1.3.1 Screening

During the screening visit, the following will occur:

- The study doctor or one of his/her colleagues will discuss this study with you andyou will read and sign this Informed Consent Form together

  If you agree to participate in this study, you will sign this consent form beforeany study-related procedures are performed.

  Once you have signed this consent form, your personal physician will be informed of your participation in this study.
- If you decide you want to participate in this study, you will undergo assessments to see if this study is right for you. These assessments will be performed in the hospitalby your doctor.

1.3.2 Randomization

If the screening tests show you can be in the study, you will be enrolled into the study.

You will be placed in one of the following treatment groups:

- Group 1 will receive their anti-cancer treatment and support from their care teamplus the patient monitoring app
- Group 2 will only receive their anti-cancer treatment and support from their careteam (no patient monitoring app)

Your group will be decided by chance (like tossing a coin). You will have an equalchance of being placed in either group.

1.3.3 Treatment

During this study you will receive anti-cancer treatment containing atezolizumab according to normal practices in the area where you live. You will have visits approximately every 2–4 weeks to receive your anti-cancer treatment, depending on your type of cancer. After you finish your anti-cancer treatment, you will be asked to return to the clinic approximately 28 days after your last treatment so that your doctorcan check up on your well-being (safety follow-up visit).

Throughout the study treatment period, you will be asked to complete questionnaires about your health and quality of life via an app installed on your internet-capable device.

If you are placed in the group that receives the patient monitoring app, you can report symptoms throughout the course of the study. You will also receive weekly messages toremind you that you must report symptoms at least every 7 days.

If you are placed in the group that does not receive the patient monitoring app, you will be able to report symptoms according to normal practice in your local area and can still contact your care team.

Your total time in the study will be about 12 months.

1.3.4 Follow-up

Your care team will check on you by telephone call 90 days after your last dose of atezolizumab. You will also be asked to complete questionnaires about your health andquality of life.

1.4 ARE THERE ANY BENEFITS?

Your health may or may not improve in this study, but the information that is learned mayhelp other people who have a similar medical condition in the future.

1.5 ARE THERE ANY RISKS?

You may have side effects from the device or procedures used in this study, as described in Sections 2.1 and 2.2. Side effects can be mild to severe and even life threatening, and they can vary from person to person. Talk to your study doctor rightaway if you have any of the following during the study:

- Symptoms that are new or have worsened

  New or worsened symptoms should be reported directly to your study doctor. This includes symptoms reported in the patient monitoring app because your study doctor might not see those symptoms right away.

- Changes in your prescribed or over-the-counter medications (including herbal therapies)
- Visits to the doctor or hospital for any reason, including urgent care or emergencyroom visits

1.6 ARE THERE ANY SPECIAL REQUIREMENTS?

While participating in this study, there are certain requirements, as listed below:

- You should not join another research study
- You will need to install up to two apps on your own internet-capable device (smartphone, tablet, or PC). For this, you will need an email address and access to an internet connection. You will also need to accept the terms and conditions for useof the apps. You are solely responsible for all actions taken under your account (i.e.,using your username and password), except in the event that the security of your account is compromised due to a security breach caused by the provider (Kaiku Health). Do not give your username or password to a third party.

1.7 WILL I BE PAID TO PARTICIPATE?

- You will not be paid for taking part in this study.

Information from this study, may lead to discoveries, inventions, or development of commercial products. You and your family will not receive any benefits or payment ifthis happens.

1.8 WILL IT COST ME ANYTHING?

While participating in this study, you will not have to pay for the apps, drugs or procedures that are required only for this study and are not part of your regular medical care. {Responsible party [e.g., "You or your health plan"]} will have to pay for medicinesand clinic, hospital, and doctors' services that are part of your regular medical care.

Roche will not reimburse any additional costs caused by the use of your internet-capable device or any costs for your internet connection. Roche will also not reimburse any costs incurred as a result of device malfunction.

1.9 WHAT HAPPENS IF I AM INJURED OR HAVE A SIDE EFFECT?

If you get injured or have a side effect because you took part in this study, contact your study doctor as soon as possible at {telephone number}. Your study doctor will explain your options and tell you where to get treatment.

Roche will pay for reasonable costs of immediate care for any physical injury that resultsfrom the investigational device but only if all of the following are true:

- Roche and the study doctor agree that your injury resulted from the investigationaldevice and not from a preexisting medical condition
- The costs are not paid for by your medical insurance
- Your injury was not because you or the study team did not follow instructionsYou will

not receive any other kind of payment.

If you get injured in this study, you will not lose any of your legal rights to seek paymentby signing this form.

1.10 CAN I STOP BEING IN THE STUDY?

You can leave this study at any time. Tell your study doctor if you are thinking about stopping, and your study doctor will tell you how to stop safely. If you leave this study,you will not lose access to any of your regular care.

If you are placed in the group that receives the patient monitoring app, you will loseaccess to the app 90 days after you leave the study.

If there are important new findings or changes in this study that may affect your health or willingness to continue, your study doctor will let you or your legally authorized representative know as soon as possible.

You may be required to stop participating in the study, even if you wish to continue.Below are some of the reasons why you may be asked to stop:

- Your safety would be at risk if you continued
- You were unable to or did not follow study instructions or procedures
- You need medical care that is not allowed by this study
- This study has been stopped by Roche or a health authority

SECTION 2: STUDY DETAILS

2.1 STUDY RISKS

Risks associated with the patient monitoring app

The patient monitoring app will be provided by a digital platform called Kaiku Health. TheKaiku Health platform is a medical device that has been approved for use in use in cancer care. Potential risks associated with the use of the patient monitoring app are listed in the table below.

Potential Risks
• Information is not received or cannot be viewed in a timely manner • Incorrect self-management instructions provided • Incorrect reporting of symptoms in the free text field, meaning that self-management instructions for the symptoms will not be received • Risks associated with the confidentiality of personal data

2.2 STUDY PROCEDURES AND POTENTIAL RISKS

Procedures with associated risks are listed below. The study doctor will provide moredetailed information about the risks and their frequency.

Procedures with Associated Risks		
Procedure	**Approximate Timing**	**Potential Risks**
Blood sample (about 20 mL [1.5 tablespoons] at each visit)	• Screening • At any visit, if requested by your doctor • According to normal practice in your local area • At the safety follow-up visit	Drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn.

Non-invasive procedures with minimal risks are listed below.

Non-Invasive Procedures with Minimal Risks	
Procedure	**Approximate Timing**
Review of medical history, including medications and cancer treatment history	• Screening
Recording of demographic information, such as age, sex, race/ethnicity	• Screening
Questionnaires about your health-related quality of life, symptoms, and satisfaction with care	• Day 1 • Weeks 6, 9, 12, 18, and 24 • Follow-up telephone call (90 days after last dose of atezolizumab)
Vital signs: temperature, pulse rate, blood pressure, breathing rate	• Screening • According to normal practice in your local area
Complete or limited physical examination (may include height or weight)	• Screening • Every anti-cancer treatment visit, if needed • Safety follow-up visit
Review changes in your health or medications	• Screening • Every anti-cancer treatment visit • Safety follow-up visit
Urine sample	• At any visit, if requested by your doctor

2.3 USE AND HANDLING OF LABORATORY SAMPLES

Sample use

Blood and urine samples will be collected according to normal practice in your localarea. Blood and urine samples will be collected for reasons such as the following:

- Check your health through standard laboratory tests
- Check how quickly your blood clots
- Check on your thyroid function

Sample storage

Samples will be securely stored at the study site for a defined period (as describedbelow) and will then be destroyed.

Samples will be stored for up to 5 years after the final study results have been reported.

2.4 PROTECTION, USE, AND SHARING OF INFORMATION

During this study, health and personal information ("information") about you will be collected. This section describes the protection, use, and sharing of your information,which consists of the following:

- Information in your medical record, which is held by {Study Site} ("study site")
- Information (including symptom data) that is collected or produced during this study ("study data"), which is held by the study site, Roche, Roche affiliates, and Roche's representatives (people and companies who work for Roche)

Your privacy is very important, and Roche uses many safeguards to protect your privacy, in accordance with applicable data privacy laws and laws related to the conductof clinical trials.

Your study data and samples will be labeled with a participant identification (ID) numberthat is unique to you and not related to or derived from information that identifies you (such as your name, your picture, or any other personally identifying information).
Roche, Roche affiliates, and Roche's representatives will only have access to study dataand samples labeled with a participant ID number, except when accessing your medical record under certain circumstances, as described below:

Your information (including your medical record, which contains personal information that can identify you) may need to be reviewed to make sure the studyis being done properly or to check the quality of the information. This information will be kept private. The following people and groups of people may review this information:

- Authorized individuals (such as study monitors and auditors) representing Roche and Roche's collaborators and licensees (people and companies whopartner with Roche)

- The Institutional Review Board or Ethics Committee (people responsible for protecting the rights and safety of people who take part in research studies)
- Regulatory authorities (government agencies involved in keeping research safefor people)

Roche, Roche affiliates, and Roche's collaborators and licensees may use study data labeled with your participant ID number. Your study data may also be shared with independent researchers or government agencies, but only after personal information that can identify you has been removed. Your study data may be combined with otherpeople's data and/or linked to other data collected from you. Your study data may be used to help better understand why people get diseases and how to best prevent, diagnose, and treat diseases, and to develop and provide access to new medicines, medical devices, and health care solutions.

Your information will not be given to your insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, you will not be identified.

Information from this study will be retained by the study site for 15 years after the end ofthe study or for the length of time required by applicable laws, whichever is longer. In addition, Roche will retain the study data for 25 years after the final study results have been reported or for the length of time required by applicable laws, whichever is longer.

2.5 STUDY RESULTS

A clinical study report containing the results of this trial will be made available to anyonewho requests a copy. Before this report is provided, additional steps will be taken to protect your information from being linked to you.

A description of this clinical study will be available at http://www.ClinicalTrials.gov, and/oranother study register. These websites will not include information that can identify you. At most, the websites will include a summary of the results. You can search these websites at any time.

2.6 CONTACT INFORMATION

If you have any questions, contact your study team, listed below:

	Study Doctor	Study Coordinator
Name:		
Address:		
Telephone number:		
Email address:		

If you have any questions about your rights while taking part in this study, call {Study Site}'s Institutional Review Board or Ethics Committee (a group of people who review theresearch to protect your rights) at {telephone number}:

You will receive a card with the name and phone number of the study doctor. Pleasekeep this card with you at all times, for as long as you remain in the study.

Signature

I confirm that I have read this consent form, or it has been read to me. I understand the information presented and have had my questions answered. I understand that I will be given a copy of all {total number of pages} pages of this form after it has been signed and dated. I agree to take part in this research studyas described above and authorize {Study Site} to use and share my information asdescribed in this form.

Participant name (print)

If applicable – Name of participant's legally authorized representative (print) | Relationship to participant

Participant signature or signature of participant's legally authorized representative | Date

I, the undersigned, have fully explained this informed consent to the participantnamed above and/or the participant's legally authorized representative.

Name of person conducting informed consent discussion (print)

Signature of person conducting informed consent discussion | Date

Witness name [a] (print)

Witness signature [a] | Date

[a] If the investigator or Institutional Review Board or Ethics Committee deems a witness signature is necessary.

MASTER INFORMED CONSENT FORM (COHORT B)

TITLE:	**INTERVENTIONAL PLATFORM STUDY INVESTIGATING THE IMPACT OF DIGITAL HEALTH SOLUTIONS ON HEALTH OUTCOMESAND HEALTH-CARE RESOURCE UTILIZATIONIN PARTICIPANTS RECEIVING SYSTEMIC TREATMENT IN CLINICAL PRACTICE (ORIGAMA)**
STUDY NUMBER:	MO42720
SPONSOR:	F. Hoffmann-La Roche Ltd
STUDY DOCTOR:	{Name}
	{Phone number}
NAME OF INSTITUTION:	{Name}
INSTITUTION ADDRESS:	{Address} **NAME**
OF IRB/EC:	{Name}
IRB/EC APPROVAL DATE:	_____

SECTION 1: STUDY OVERVIEW

1.1 INTRODUCTION

- This study is testing a new formulation of a drug called atezolizumab, which will be given as an injection into the tissue under the skin (called subcutaneous, or SC administration) initially in the hospital and later at your home, as well as digital patient monitoring software (the Roche Digital Patient Monitoring atezolizumab Module, hereafter referred to as the patient monitoring app) that is designed to tracksymptoms for people receiving subcutaneous atezolizumab.

- You are being asked to take part in this research study (also known as a clinicalstudy) because you have non-small cell lung cancer (NSCLC).
- F. Hoffmann-La Roche Ltd (hereafter referred to as Roche is the sponsor of thisstudy and is paying {Name of Study Site} to cover the costs of this study.
- This consent form tells you what will happen if you take part. It also tells you aboutthe possible benefits and risks of being in the study.
- Taking part in this study is your choice. Please read the information carefully and feel free to ask questions. It may be helpful for you to discuss this information withyour family and friends.
- Instead of participating in this study, you may choose to
  - Get treatment for your lung cancer without being in this study
  - Join a different study
- Talk to your doctor about all of your choices, and the risks and benefits of each choice. If you choose not to take part, you will not lose the regular care you receivefrom your doctors.
- If you decide to take part, you will be asked to sign this consent form. You will begiven a copy of your signed consent form.

1.2 WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to investigate the potential benefits of atezolizumab given asan injection under the skin (called subcutaneous administration) given at home in combination with the patient monitoring app. In this study, all participants will receive access to subcutaneous atezolizumab and the patient monitoring app.

About 40 people will take part in Cohort B of this study.

Atezolizumab given as an injection under the skin is an experimental drug, which meanshealth authorities have not approved atezolizumab given as an injection under the skin for the treatment of lung cancer. Atezolizumab given as an infusion into the vein is approved by health authorities for the treatment of people with certain types of lung cancer and other cancers. Atezolizumab given as an injection under the skin is administered at a higher dose than atezolizumab given as an infusion into the vein in order to achieve the right amount of atezolizumab in your blood. Other anti-cancer drugsfor other kinds of cancer, such as trastuzumab and rituximab, have already been approved by several health authorities around the world to be administered as injections under the skin.

Atezolizumab is an antibody (a large, Y-shaped protein used by your body's immune system to identify and neutralize foreign objects such as bacteria, viruses, and tumor cells) that affects your immune system by blocking the PD-L1 pathway. The PD-L1 pathway is involved in decreasing your body's natural immune response to fight cancer.

By blocking the PD-L1 pathway, atezolizumab may help your immune system stop orreverse the growth of tumors.

The subcutaneous formulation of atezolizumab includes an enzyme called rHuPH20. This enzyme is a manufactured human enzyme that helps certain drugs move into the bloodstream following injection under the skin. The enzyme has already been tested andapproved in some countries for other cancer treatments given subcutaneously.

People with NSCLC who's tumors express enough of the PD-L1 biomarker might be able to take part in this study. If any of the specimens you provide for testing in a local laboratory (i.e., a previously taken archival tumor specimen, or a newly taken tumor biopsy) are sufficiently positive for the PD-L1 biomarker, you may be able to participatein Study MO42720. If none of the specimens you provide for testing locally or centrally are positive for the PD-L1 biomarker, you cannot participate in Study MO42720.

The patient monitoring app to be used in this study is intended to allow people with cancer who are being treated with atezolizumab as part of their anti-cancer treatment to:

- Report their symptoms and quality of life to their care team
- Receive reminders and instructions related to their symptoms
- Obtain information related to their disease and treatment
- Send non-urgent messages to their care team.

The patient monitoring app can be accessed via an app on an internet-capable device (smartphone, tablet, or PC). It is also possible to access the app through a web browser.You will be trained how to use the patient monitoring app by your doctor or a nurse. Theinformation that you enter into the patient monitoring app is visible to your care team in real-time. The patient monitoring app is used by the care team to track and manage participant symptoms.

1.3 WHAT WILL HAPPEN IF I PARTICIPATE?

This study has four parts:

1. Screening (to see if you are eligible for the study)
2. Hospital treatment period
3. At home treatment period
4. Follow-up (to check on you after treatment is finished)

During this study, you will visit the site approximately every three weeks for the first nineweeks to receive atezolizumab treatment during the hospital treatment period. You will then have visits at home approximately every three weeks during the at home treatmentperiod. Visits may last approximately 2 hours.

If you participate in this study, you will be required to install two apps on your own internet-capable device (smartphone, tablet, or PC): the patient monitoring app and anapp to complete questionnaires about your health and quality of life.

Your total time in the study will be about 15 months.

The study procedures are described in detail in Section 2.2. Some procedures will be the same as your regular care for lung cancer, and some procedures will be just for thisstudy.

1.3.1 Screening

During the screening visit, the following will occur:

- The study doctor or one of his/her colleagues will discuss this study with you andyou will read and sign this Informed Consent Form together

  If you agree to participate in this study, you will sign this consent form beforeany study-related procedures are performed.

  Once you have signed this consent form, your personal physician will be informed of your participation in this study.

- If you decide you want to participate in this study, you will undergo assessments to see if this study is right for you. These assessments will be performed in the hospitalby your doctor.

1.3.2 Hospital treatment period

All the treatments for this study are given in what are called cycles. A cycle is a period of treatment that lasts 3 weeks and consists of drug injections and a recovery time before the next injection. You will receive the first three cycles of atezolizumab treatment (as injections under the skin) at the hospital. If your doctor decides that you are eligible, youwill then receive up to 13 cycles of atezolizumab treatment in your home. If your doctor decides you are not eligible for treatment in your home, you will continue to receive atezolizumab treatment in the hospital.

1.3.3 At home treatment period

During the at home treatment period, subcutaneous injections of atezolizumab will be given in your home by a qualified healthcare professional. The qualified healthcare professional company hired by Roche will arrange a qualified healthcare professional to visit you at your home, and Roche will pay for the costs. Your personal information (suchas your name, address, and contact information) will be shared with the qualified healthcare professional company and the qualified healthcare professional to allow themto plan the visits. Your health information related to home visits will be kept under the same level of privacy used for the main study. The qualified healthcare professional will be trained on the program procedures, and will contact you before the visit, to confirm

the time and place of the visit. The qualified healthcare professional will contact yourdoctor during the visit.

You will continue to receive atezolizumab every 3 weeks at home for a further 13 cycles(for a total of 16 cycles of atezolizumab treatment).

During the at home treatment period, you will visit the hospital every 3 months so thatyour doctor can check up on your well-being.

Throughout the study treatment periods, both in the hospital and at your home, you will be asked to complete questionnaires about your health and quality of life via an app installed on your internet-capable device. You will also be able to report symptoms throughout the course of the study using the patient monitoring app. You will also receive weekly messages to remind you that you must report symptoms at least every 7days as well as 24 hours after each subcutaneous atezolizumab administration in your home.

1.3.4 Follow-up

After you finish your atezolizumab treatment, you will be asked to return to the clinic approximately 30 days after your last study treatment so that your doctor can check up on your well-being. You will also be asked to complete questionnaires about your healthand quality of life. Your study doctor or their colleague will also contact you by telephoneapproximately 90 days after your last study treatment to check up on you again.

1.4 ARE THERE ANY BENEFITS?

Your health may or may not improve in this study, but the information that is learned mayhelp other people who have a similar medical condition in the future.

1.5 ARE THERE ANY RISKS?

You may have side effects from the device or procedures used in this study, as described in Sections 2.1 and 2.2. Side effects can be mild to severe and even life threatening, and they can vary from person to person. Talk to your study doctor rightaway if you have any of the following during the study:

- Symptoms that are new or have worsened

  New or worsened symptoms should be reported directly to your study doctor. This includes symptoms reported in the patient monitoring app because your study doctor might not see those symptoms right away.
- Changes in your prescribed or over-the-counter medications (including herbal therapies)
- Visits to the doctor or hospital for any reason, including urgent care or emergencyroom visits

1.6 ARE THERE ANY SPECIAL REQUIREMENTS?

While participating in this study, there are certain requirements, as listed below:

- You should not join another research study that involves an intervention. An intervention may be a drug, medical device, procedure, vaccine, or other product.
- For women: If you can become pregnant, you must use a reliable birth control method during the study and for 5 months after your final dose of atezolizumab. Talkwith your study doctor about what method may be best for you. Tell your study doctor right away if you get pregnant during this period. If you get pregnant, the study doctor will want to follow up with you on the outcome of the pregnancy and willask for your permission to collect information on the baby.
- You should not use certain medications during this study. Your study doctor will talkto you about these medications.
- You will need to install two apps on your own internet-capable device (smartphone, tablet, or PC). For this, you will need an email address and access to an internet connection. You will also need to accept the terms and conditions for use of the apps. You are solely responsible for all actions taken under your account (i.e., usingyour username and password), except in the event that the security of your accountis compromised due to a security breach caused by the provider (Kaiku Health). Donot give your username or password to a third party.

There are additional requirements for the at home treatment period, as listed below:

- You must not open the drug package or other supply packages.
- You must have a place where you can store the drug package (out of reach ofchildren or pets).
- The drug package should be stored in the refrigerator, preferably in the main compartment away from the door or the cooling vent area.
- The qualified healthcare professional will be responsible for inspecting the packagesand opening them.
- The qualified healthcare professional will also be responsible for removing any usedand unused drugs and program supplies and returning them.
- You will receive a lock box that will be used in between your treatment visits to storethe medications used to treat allergic reactions. Only the qualified healthcare professional will be able to access the contents within the lock box. The lock box should be stored in a secure location away from children and pets. The lock box must be provided to the qualified healthcare professional at the start of each visit.

1.7 WILL I BE PAID TO PARTICIPATE?

You will not be paid for taking part in this study.

Information from this study, may lead to discoveries, inventions, or development of commercial products. You and your family will not receive any benefits or payment ifthis happens.

1.8 WILL IT COST ME ANYTHING?

While participating in this study, you will not have to pay for the apps, drugs or procedures that are required only for this study and are not part of your regular medical care. {Responsible party [e.g., "You or your health plan"]} will have to pay for medicinesand clinic, hospital, and doctors' services that are part of your regular medical care.

Roche will not reimburse any additional costs caused by the use of your internet-capabledevice or any costs for your internet connection. Roche will also not reimburse any costs incurred as a result of device malfunction.

Roche will pay for the costs of the qualified healthcare professional services. There areno costs to {Responsible party [e.g., "You or your health plan"]} for at home visits.

1.9 WHAT HAPPENS IF I AM INJURED OR HAVE A SIDE EFFECT?

If you get injured or have a side effect because you took part in this study, contact your study doctor as soon as possible at {telephone number}. Your study doctor will explain your options and tell you where to get treatment.

Roche will pay for reasonable costs of immediate care for any physical injury that resultsfrom the investigational device but only if all of the following are true:

- Roche and the study doctor agree that your injury resulted from the investigationaldevice and not from a preexisting medical condition
- The costs are not paid for by your medical insurance
- Your injury was not because you or the study team did not follow instructionsYou will

not receive any other kind of payment.

To request payment for treatment costs, contact your study doctor, who will make sure Roche takes appropriate action. Roche maintains a contract with {Insurance Company}to ensure Roche can pay for treatment costs.

If you get injured in this study, you will not lose any of your legal rights to seek payment by signing this form.

1.10 CAN I STOP BEING IN THE STUDY?

You can leave this study at any time. Tell your study doctor if you are thinking about stopping, and your study doctor will tell you how to stop safely. If you leave this study,you will not lose access to any of your regular care.

You will lose access to the patient monitoring app 90 days after you leave the study.

If there are important new findings or changes in this study that may affect your health or willingness to continue, your study doctor will let you or your legally authorized representative know as soon as possible.

You may be required to stop participating in the study, even if you wish to continue.Below are some of the reasons why you may be asked to stop:

- Your safety would be at risk if you continued
- You were unable to or did not follow study instructions or procedures
- You need medical care that is not allowed by this study
- This study has been stopped by Roche or a health authority

SECTION 2: STUDY DETAILS

2.1 STUDY RISKS

Risks associated with the patient monitoring app

The patient monitoring app will be provided by a digital platform called Kaiku Health. TheKaiku Health platform is a medical device that has been approved for use in cancer care.Potential risks associated with the use of the patient monitoring app are listed in the table below.

Potential Risks
• Information is not received or cannot be viewed in a timely manner • Incorrect self-care instructions provided • Incorrect reporting of symptoms in the free text field, meaning that self-management instructions for the symptoms will not be received • Risks associated with the confidentiality of personal data

Risks associated with atezolizumab

Atezolizumab is designed to increase the number of immune system cells in your body that can fight cancer. These cells may cause inflammation within the tumor, as well as in normal tissue. Therefore, by taking atezolizumab, you may develop a condition wherethere is inflammation against a part of your own body (an autoimmune condition).

The qualified healthcare professional is trained to monitor for, and respond to, any sideeffects and will have immediate access to emergency equipment. During or after the atezolizumab injection, inform the qualified healthcare professional or your doctor immediately if you experience any severe symptoms. Mild or moderate symptoms can be reported using the patient monitoring app. Atezolizumab stays in the body for manyweeks after stopping treatment. Therefore, be sure to tell your doctor or your qualified healthcare professional if you think you have experienced any late side effects even some time after stopping study treatment.

Side effects known to be associated with atezolizumab

The side effects described in this section are known to be associated with atezolizumab.

Side Effects Known to Be Associated with Atezolizumab		
Very common (occurs in more than 10% of people treated with atezolizumab)	• Back pain • Cough • Decreased appetite • Diarrhea • Fatigue • Fever • Headache • Itching of the skin (pruritus) • Joint pain (arthralgia)	• Lack of energy (asthenia) • Muscle and bone pain (myalgia, musculoskeletal pain and bone pain) • Nausea • Rash • Shortness of breath (dyspnea) • Urinary tract infection • Vomiting
Common (occurs in 1%–10% of people treated with atezolizumab)	• Allergic reaction or intolerance to medication (hypersensitivity) • Chills • Decreased level of potassium in blood (hypokalemia) • Decreased level of sodium in blood (hyponatremia) • Decreased oxygen supply in body resulting in shortness of breath (hypoxia) • Difficulty swallowing (dysphagia) • Dry skin • Flu-like illness • Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine • Increased blood sugar level (hyperglycemia)	• Increase in certain liver enzymes, which may indicate inflammation of the liver (ALT/AST increased) • Inflammation of the intestines (colitis) • Inflammation of the liver (hepatitis) • Inflammation of the lungs (pneumonitis) • Infusion-related reaction • Low blood pressure (hypotension) • Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia) • Mouth and throat pain (oropharyngeal pain) • Inflammation of the nose and throat (nasopharyngitis) • Stomach area pain (abdominal pain) • Underactive thyroid gland (hypothyroidism)

Less common but important (occurs in less than 1% of people treated with atezolizumab)	• Decreased production of hormones by the adrenal glands (adrenal insufficiency) • Diabetes mellitus • Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis) • Inflammation of the heart muscle (myocarditis) • Inflammation of the kidneys (nephritis) • Inflammation of the pancreas (pancreatitis), including increase in pancreatic enzymes (such as amylase and lipase)	• Inflammation of the pituitary gland (hypophysitis) • Inflammation or damage of the muscles (myositis)Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis) • Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome) • Overactive thyroid gland (hyperthyroidism) • Red, dry, scaly patches of thickened skin (psoriasis) • Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis) • Severe skin or mucosal reactions (severe cutaneous adverse reactions)

Among the side effects known to be associated with atezolizumab, Roche and yourstudy doctors would like you to pay more attention to the following:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood instool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptomsmay include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- Inflammation of the pituitary gland (hypophysitis); symptoms may include fatigueand headaches that will not go away, increased thirst, increased urination, and changes in vision

  Side effects that may occur at the same time include hypothyroidism andadrenal insufficiency (see above for details).
- Inflammation of the liver (hepatitis); symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin,and dark urine
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light

- Nerve damage resulting in muscle weakness (myasthenic syndrome/myastheniagravis); symptoms may include weakness in the arm and leg muscles, double vision, and difficulties with speech and chewing
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficultywalking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worseningcough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness ofbreath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain,nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure ofthe kidneys
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis); symptoms may include muscle pain and weakness, urine with adark brown or reddish color, nausea, and vomiting
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptomsmay include itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being giveninto your vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure.

These reactions could be mild or severe and might lead to death or permanent disability.If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

Side effects potentially associated with atezolizumab

The following are side effects that may be associated with atezolizumab:

- Development of special antibodies to atezolizumab (proteins made in the body thatrespond to a substance that is foreign to the body) by your immune system

If you develop these special antibodies, it may affect your body's ability to respond to atezolizumab in the future. Blood samples will be drawn to monitorfor the development of these antibodies during study treatment and at your treatment discontinuation visit.

- Potential to cause harm to a developing fetus
- Inflammation of the eye (uveitis); symptoms may include eye pain and redness,vision problems, and blurry vision
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss, weakness, generalaches and pains, rash, headache, lightheadedness, shortness of breath, and numbness
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skinand/or eyes, weakness, and inability to do physical activity

Immune reaction

In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example, liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may includevery low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or intubation, severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately, as you may need immediate treatment and hospitalization. Your study doctor may give youdrugs to treat these symptoms.

Risks associated with rHuPH20

Important side effects associated with rHuPH20 are listed below. The study doctor will provide information about these and other side effects. There may be side effects that are not known at this time.

Most side effects include mild and transient injection-site reactions, as shown in the tablebelow.

Important Side Effects Known to Be Associated with rHuPH20	
• Redness • Pain • Bruising • Itching • Burning • Tenderness • Swelling	• Induration • Irritation • Tingling • Numbness • Rash • Headache

2.2 STUDY PROCEDURES AND POTENTIAL RISKS

Procedures with associated risks are listed below. The study doctor will provide moredetailed information about the risks and their frequency.

Procedures with Associated Risks		
Procedure	**Approximate Timing**	**Potential Risks**
Tumor tissue sample (biopsy)	• Screening • Note: A biopsy will not be needed at screening if a previously collected sample is available and meets study requirements.	Biopsies can cause pain, redness, swelling, excessive bleeding, bruising, or draining at the needle site. Abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site can also occur. Your doctor will explain the details and risks of the procedure, which may vary depending on how the biopsy will be obtained.
Test for PD-L1, EGFR, and/or ALK in tumor tissue to see if you are eligible for the study	• Screening • Note: these tests will not be needed if they have already been conducted prior to screening	Although measures are in place to ensure tests are accurate, there is a risk of an incorrect test result. If your enrollment in the study is based on an incorrect test result, you may be less likely to respond to study treatment. If you are excluded from the study because of an incorrect test result, you will not receive treatment with a potential benefit.
Blood sample (about 20 mL [1.5 tablespoons] at each visit or about 31.5 tablespoons for the whole study period [approximately 15 months])	• Screening • Day 1 of every treatment cycle • Every hospital visit during the at home treatment period • At the safety follow-up visit	Drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn.

Procedures with Associated Risks		
Procedure	**Approximate Timing**	**Potential Risks**
Tumor assessments: scans of your internal organs and bones, such as the following: • Computed tomography (CT) scan: X-ray test that gives off radiation at a dose similar to natural radiation people are exposed to over 3□6 years • Positron emission tomography (PET)/CT scan: imaging test that requires a radioactive tracer to be swallowed, injected, or inhaled and gives off radiation at a dose similar to natural radiation people are exposed to over 4□5 years • Magnetic resonance imaging (MRI) scan: imaging test that uses magnets and radio signals but does not give off radiation • Bone scan: imaging test that gives off radiation at a dose similar to natural radiation people are exposed to over 2 years To increase visibility, a contrast agent may be swallowed, injected, or inserted into the rectum (enema). You cannot have an MRI scan if you have any metal or electronic devices in your body or if your kidneys are not working properly. Study staff will ask questions and (if needed) run tests to make sure the scans are safe for you.	• Screening If you have had a suitable tumor assessment within the 28 days before the start of this study, you may not need to have this assessment repeated at screening.	• You may have an allergic reaction to a tracer or contrast agent. • Oral and rectal contrast agents may cause nausea, constipation, diarrhea, and abdominal bloating. • Injected contrast agents may cause nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. There may be pain, bruising, or infection at the injection site. • CT, PET, and MRI scanners may cause some anxiety and claustrophobia (fear of being in small places). You may be given a mild sedative or anti-anxiety drug to help manage your symptoms. • Although there are no known long-term harmful effects from the radiation of a single scan, the risk of harmful effects from multiple scans over a period of time is not known. Talk to your doctor if you are concerned about your radiation exposure prior to or during this study.

Non-invasive procedures with minimal risks are listed below.

Non-Invasive Procedures with Minimal Risks	
Procedure	**Approximate Timing**
Review of medical history, including medications and cancer treatment history	• Screening
Recording of demographic information, such as age, sex, race/ethnicity	• Screening
Questionnaires about your health-related quality of life, symptoms, and satisfaction with care	• Cycles 1, 3, 4, 6, 8, 9, and 12 • Safety follow-up visit
Vital signs: temperature, pulse rate, blood pressure, breathing rate	• Day 1 of every treatment cycle • Every hospital visit during the at home treatment period • At the safety follow-up visit
Complete or limited physical examination (may include height or weight)	• Screening • Day 1 of every treatment cycle • Every hospital visit during the at home treatment period • At the safety follow-up visit
Review changes in your health or medications	• Screening • At every treatment visit
Urine sample	• Day 1 of every treatment cycle

2.3 ACCESS TO STUDY DRUG AFTER COMPLETING THE STUDY You will be eligible to receive the Roche study drug (atezolizumab) for free after youcomplete the study if all of the following are true:

- You have a life-threatening or severe medical condition and require continuedRoche study drug treatment for your well-being
- There are no appropriate alternative treatments available to you
- You and your study doctor meet any legal or regulatory requirements that apply

You will not be eligible to receive the Roche study drug (atezolizumab) after you complete the study if any of the following are true:

- The Roche study drug is available in your country and is reasonably accessible toyou (for example, it is covered by your insurance or would not create a financial burden for you)
- Roche has discontinued development of the drug or information suggests that thedrug is not effective for NSCLC
- Roche has safety concerns about the drug as a treatment for NSCLC

- Provision of the Roche study drug is not permitted under the laws and regulations ofyour country

2.4 USE AND HANDLING OF LABORATORY SAMPLES

Sample use

Blood, urine, and tumor tissue samples will be collected for reasons such as thefollowing:

- Check your health through standard laboratory tests
- Find out if you are pregnant
- Check how quickly your blood clots
- Check for an infection with hepatitis B or C
- Check on your thyroid function
- Test for PD-L1 protein, EGFR, and/or ALK on your tumor tissue sample to see if you are eligible for the study, if required

Sample storage

Samples will be securely stored for a defined period (as described below) and will then be destroyed, with one exception: Tumor tissue from a previous biopsy will be returnedto your doctor upon request or after all study information has been collected.

Samples will be stored for up to 5 years after the final study results have been reported.

2.5 PROTECTION, USE, AND SHARING OF INFORMATION

During this study, health and personal information ("information") about you will be collected. This section describes the protection, use, and sharing of your information,which consists of the following:

- Information in your medical record, which is held by {Study Site} ("study site")
- Information (including symptom data) that is collected or produced during this study ("study data"), which is held by the study site, Roche, Roche affiliates, and Roche's representatives (people and companies who work for Roche)

Your privacy is very important, and Roche uses many safeguards to protect your privacy, in accordance with applicable data privacy laws and laws related to the conductof clinical trials.

Your study data and samples will be labeled with a participant identification (ID) numberthat is unique to you and not related to or derived from information that identifies you (such as your name, your picture, or any other personally identifying information).
Roche, Roche affiliates, and Roche's representatives will only have access to study dataand samples labeled with a participant ID number, except when accessing your medical record under certain circumstances, as described below:

Your information (including your medical record, which contains personal information that can identify you) may need to be reviewed to make sure the studyis being done properly or to check the quality of the information. This information will be kept private. The following people and groups of people may review this information:

- Authorized individuals (such as study monitors and auditors) representing Roche and Roche's collaborators and licensees (people and companies whopartner with Roche)
- The Institutional Review Board or Ethics Committee (people responsible for protecting the rights and safety of people who take part in research studies)
- Regulatory authorities (government agencies involved in keeping research safefor people)

Roche, Roche affiliates, and Roche's collaborators and licensees may use study data labeled with your participant ID number. Your study data may also be shared with independent researchers or government agencies, but only after personal information that can identify you has been removed. Your study data may be combined with otherpeople's data and/or linked to other data collected from you. Your study data may be used to help better understand why people get diseases and how to best prevent, diagnose, and treat diseases, and to develop and provide access to new medicines, medical devices, and health care solutions.

Your information will not be given to your insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, you will not be identified.

Information from this study will be retained by the study site for 15 years after the end ofthe study or for the length of time required by applicable laws, whichever is longer. In addition, Roche will retain the study data for 25 years after the final study results have been reported or for the length of time required by applicable laws, whichever is longer.

2.6 STUDY RESULTS

A clinical study report containing the results of this trial will be made available to anyonewho requests a copy. Before this report is provided, additional steps will be taken to protect your information from being linked to you.

A description of this clinical study will be available at http://www.ClinicalTrials.gov, and/oranother study register. These websites will not include information that can identify you. At most, the websites will include a summary of the results. You can search these websites at any time.

2.7 CONTACT INFORMATION

If you have any questions, contact your study team, listed below:

	Study Doctor	Study Coordinator
Name:		
Address:		
Telephone number:		
Email address:		

If you have any questions about your rights while taking part in this study, call {Study Site}'s Institutional Review Board or Ethics Committee (a group of people who review theresearch to protect your rights) at {telephone number}:

Signature

I confirm that I have read this consent form, or it has been read to me. I understand the information presented and have had my questions answered. I understand that I will be given a copy of all {total number of pages} pages of this form after it has been signed and dated. I agree to take part in this research studyas described above and authorize {Study Site} to use and share my information asdescribed in this form.

Participant name (print)

If applicable – Name of participant's legally authorized representative (print) | Relationship to participant

Participant signature or signature of participant's legally authorized representative | Date

I, the undersigned, have fully explained this informed consent to the participantnamed above and/or the participant's legally authorized representative.

Name of person conducting informed consent discussion (print)

Signature of person conducting informed consent discussion | Date

Witness name [a] (print)

Witness signature [a] | Date

[a] If the investigator or Institutional Review Board or Ethics Committee deems a witness signature is necessary.

Supplementary Table

Prespecified disease- or treatment-related symptom questions, displayed per indication.

Category(s)	Symptom/AE	Cohort A: metastatic NSCLC/ extensive stage SCLC	Cohort B: PD-L1-positive, early NSCLC	Cohort A: Child Pugh advanced or unresectable hepatocellular carcinoma
Generic symptoms/mind and neurological	Fatigue/tiredness/ asthenia	X	X	X
Pain/gastrointestinal	Abdominal pain	X	X	X
Pain	Chest pain	X	X	
Pain/head, eyes, and vision, mouth, and throat	Headache	X	X	
Pain	Musculoskeletal pain, bone/joint pain	X	X	X
Generic symptoms/head, eyes, and vision, mouth, and throat	Cough	X	X	
Generic symptoms	Shortness of breath (dyspnea)	X	X	
Generic symptoms/pain	Pounding or racing heartbeat (palpitations)	X	X	
Generic symptoms	Swelling of arms and legs		X	X
Skin, nails, and hair	Itching (pruritus)	X	X	X
Skin, nails, and hair	Rash, urticaria	X	X	X
Skin, nails, and hair	Pain and swelling at injection site (infusion or injection site reaction)	X	X	
Gastrointestinal	Decreased appetite (anorexia)	X	X	X
Gastrointestinal	Diarrhea	X	X	X
Gastrointestinal	Nausea	X	X	X
Gastrointestinal	Vomiting	X	X	
Gastrointestinal	Constipation			X
Head, eyes, and vision, mouth, and throat	Taste changes (eg, bad taste in mouth)	X	X	
Mind and neurological	Cognitive or psychological (anxiety, fear, and depression)	X	X	
Skin, nails, and hair/mind and neurological/generic symptoms	Numbness and tingling (peripheral neuropathy)	X	X	
Generic symptoms	Fever	X	X	X
Generic symptoms	Hemorrhage/bleeds (blood in urine,	X	X	X

Iivanainen S, *et al. BMJ Open* 2023; 13:e063242. doi: 10.1136/bmjopen-2022-063242

	nosebleed, or blood in cough)			
Generic symptoms	Weight loss	X	X	X
Generic symptoms	High blood pressure (hypertension)			X
Other symptoms	Free text field for other symptoms not listed	X	X	X
No symptoms	Button to report "no symptoms" with one click	X	X	X

AE, adverse event; (N)SCLC, (non-)small cell lung cancer; PD-L1, programmed cell death-ligand 1.