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 (M042720) 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).

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.

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
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.2-5 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.3-6 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 (e.g. 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 (i.e. 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,124-26 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,7-28 healthcare professional-patient online communication29-31 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...


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

The Roche DPM Module (F. Hoffmann-La Roche Ltd) 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
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 the EU medical device regulation (MDR). The therapeutic area is defined as 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.

**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.

**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 intervention or experimental treatment not part of a locally approved anticancer regimen containing intravenous atezolizumab (bevacizumab, carboplatin and paclitaxel); or carboplatin and nab-paclitaxel) induction therapy, followed by atezolizumab 1200 mg Q3W and bevacizumab maintenance therapy.*

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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Atezolizumab anticancer treatment schedule (regimen as per local label)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td></td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>Atezolizumab monotherapy 840 mg intravenously Q2W or 1200 mg Q3W or 1680 mg Q4W,*</td>
</tr>
<tr>
<td>Metastatic NSCLC (non-squamous)</td>
<td>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.*</td>
</tr>
<tr>
<td>Extensive-stage SCLC</td>
<td>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.*</td>
</tr>
<tr>
<td>Child Pugh A advanced or unresectable hepatocellular carcinoma, according to BCLC staging52</td>
<td>Atezolizumab 1200 mg intravenously Q3W+bevacizumab 15 mg/kg intravenously Q3W.†</td>
</tr>
<tr>
<td><strong>Cohort B</strong></td>
<td></td>
</tr>
<tr>
<td>PD-L1-positive, early-stage NSCLC</td>
<td>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).</td>
</tr>
</tbody>
</table>

* 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), 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 Inteference Score from the MD Anderson Symptom Inventory (MDASI) Core Items at Week 12 from baseline (table 2). 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). Overall symptom distress is defined as the mean of the ratings of the interference questions in MDASI. 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.

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)), change from baseline in the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) 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. 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.

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 V5.0. 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

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

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.80
¶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 and analyses of historical data from pivotal trials of the GHS scale from EORTC QLQ-C30. 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. Via prior publications (eg, the first pilot study and the real-world evidence-based feasibility study), 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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Supplemental material
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