# Strategic Plan SUBITO study (NKI 2014-7052)

## Preparatory phase (September 1, 2015 – January 1, 2015)

*Appointment of SUBITO study coordinator – physician researcher (MD)*
Upon approval of the strategic plan of the SUBITO study by the Dutch Cancer Society a physician researcher will be appointed as study coordinator, preferably in Q3 of 2015.

*Patient advocacy meeting*
In Q3 or early Q4 a patient advocacy meeting will be held at the Netherlands Cancer Institute (NKI) to discuss the concept final study protocol, patient information sheet, supportive care requirements, how patient awareness of the SUBITO study can be secured, how patients can obtain information from fellow patients, and other issues that may arise.

*Dutch automated pathology registry (PALGA) SUBITO patient identification system*
In Q3 a conference call will be scheduled with PALGA (Dr. Lucy Overbeek, Dr. Jelle Wesseling and Dr. Paul Seegers) to discuss how to customize the PALGA trial alert system to serve patient identification for the SUBITO study, taking into account privacy protection legislation.

*Study protocol approval, contracts and protocol submission to central ethics committee*
A concept of the final study protocol will be send around for approval by September 1, 2015. The study protocol will be finalized by October 15, 2015 and contracts will be signed by the NKI and participating centres before November 15, 2015 (contact person: Steven Vanhoutvin). Final protocol submission to the central medical ethics committee will take place before December 1, 2015.
To keep progress on track, conference calls with all SUBITO centres will be held every two weeks on a fixed time and day in the week, starting early September 2015.

*Determining the final SUBITO consortium*
*The Netherlands:* The following university medical centres in the Netherlands will be contacted whether their intention to join the SUBITO study can be formalized: University Medical Center Utrecht (UMCU), Leiden University Medical Center (LUMC), Free University Medical Center (VUMC), University Medical Center Nijmegen (UMCN), Maastricht University Medical Center (MUMC+), and University Medical Center Groningen (UMCG). In addition, a number of large teaching hospitals will be contacted, including Medisch Spectrum Twente (MST - Enschede), Reinier de Graaf Groep (RdGG - Delft), Isala Klinieken (IK – Zwolle), Medical Center Haaglanden (MCH – The Hague), Amphia Hospital (AH – Breda), Medical Center Leeuwarden (MCL – Leeuwarden) and Catharina Hospital (CH – Eindhoven). In total a maximum of 16 centres will be contacted.
*International:* The West German Study Group (WSG), represented by Prof. Dr. Ulrike Nitz at Mönchengladbach, Germany, will be contacted to formalize the WSG participation in the SUBITO study. Prof. Dr. Jean-Pierre Lotz, Hôpital Tenon (HT), Institut Universitaire de Cancérologie, Université Pierre et Marie Curie, Paris, France, and Prof. Dr. Anthony Gonçalves, Institut Paoli-Calmettes (IPC), Marseille, France will be contacted to formalize the French participation in the SUBITO study.

*Investigators' meeting Amsterdam Q4 2015 and yearly thereafter at ASCO annual meeting*
In Q4 2015 an investigators' meeting will be held in Amsterdam, The Netherlands, to discuss science, logistics (*e.g.* BRCA1-like testing) and strategy to guarantee feasibility of the SUBITO study (PALGA system, regional consultancy function university centres, etc).
Thereafter, yearly investigators' meetings will be held at the American Society of Clinical Oncology (ASCO) annual meetings in late May – early June.

*Strategic plan to create awareness of SUBITO study with professionals and lay public*

In late Q3 or early Q4 an appointment will be made with the public relation department of the NKI to develop a strategic plan to create awareness of the SUBITO study with the lay public. Proposals and suggestions from the patient advocacy meeting will be taken into account to optimize awareness among breast cancer patients.
Professional societies (NVMO (medical oncology), HOVON (haematology), BOOG/NABON (breast cancer – multidisciplinary) NVCO (surgical oncology), NVVP (surgical pathology), NVvR (radiology)) will be contacted to ask for advice to help creating awareness of the SUBITO study among professionals.

**SUBITO study (Q1 2016 – Q 3 2019)**

*Initiation visits*
Upon central medical ethics committee approval of the study protocol (expected Q1 2016) in all three countries initiation visits will be scheduled, after which the study can start. Local approvals in Dutch SUBITO centres are expected to be received by Q2 2016, after which initiation visits can be scheduled. Dutch centres (except for NKI) are expected to start patient accrual by July 1, 2016 at the latest.

*Monitoring of study progress*
The study coordinator will be the central person to monitor study progress. He/she shall keep close contact with PALGA to approach Dutch hospitals with potential SUBITO patients. In addition, he/she will keep close contact with the principle investigators of the study centres abroad. In case of less than five patients accrued per month, the study coordinator will contact all SUBITO study sites to explore whether there are any problems that should be addressed.
To facilitate patient accrual, the study will run in both the adjuvant as well as the neoadjuvant setting. Monthly SUBITO newsletters will be sent around.
Depending on the outcome of the neo-TN study (NCT01057069), and accrual in the SUBITO study, inclusion criteria may be broadened to include also stage II, BRCA1-like breast cancer patients.

*Annual investigators' meetings*
From 2016 until 2021 annual investigators' meetings will be planned at the annual meetings of the American Society of Clinical Oncology (ASCO), which take place in late May – early June each year. During these meetings study progress, logistics, science and other issues will be discussed.

**Principal SUBITO study analyses (Q3 2020 – Q3 2021)**

The interim analysis of the SUBITO study has been scheduled for Q3 2020. Data on the quality of life sub-study will be presented in Q3 2021. The main analysis of the SUBITO study will be carried out in Q3 2021. The health economics analysis will take place around the same time.

**Secondary SUBITO study analyses (Q3 2022 – Q3 2027)**

5- and 10-years analyses will be due around Q3 2022, and Q3 2027, respectively.

**Milestones**

M1. Approved trial protocol by central ethics committee (February 1, 2016)
M2. SUBITO study open for accrual (NKI, WSG, HT, IPC) (February 1, 2016)
M3. Accrual of 174 patients in SUBITO study completed (September 1, 2019)
M4. Interim analysis SUBITO study (September 1, 2020 – beyond timelines of this project)
M5. Quality of life sub-study results (July 1, 2021 – beyond timelines of this project)
M6. Principal analysis of SUBITO study (September 1, 2021 – beyond timelines of this project)
M7. Health Economics analysis SUBITO study (September 1, 2021 – beyond timelines of this project)

M8. 5-years analysis of SUBITO study (± Q3 2022 - beyond timelines of this project)
M9. 10-years analysis of SUBITO study (± Q3 2027 - beyond timelines of this project)

**Go/no go moments**

July 1, 2016 if study has not started, project revision required
January 1, 2017 if less than 10 patients accrued onto study, project revision required
January 1, 2018 if less than 40 patients accrued onto study, project revision required
January 1, 2019 if less than 80 patients accrued onto study, project revision required
January 1, 2020 if less than 130 patients accrued onto study, project revision required
January 1, 2021 if less than 174 patients accrued onto study, project revision required

**Deliverables (annually) (see also table)**

*2015 – Q3*
D1. Appointment study coordinator
D2. Concept study protocol and patient information sheet (PIS) written, conference calls with all SUBITO sites every 2 weeks initiated
D3. Patient advocacy meeting for advice, including awareness SUBITO study
D4. Strategic plan to create awareness of SUBITO study with professionals and patients

*2015 – Q4*
D5. Formalization of final SUBITO consortium and contracts signed
D6. Start-up investigators' meeting
D7. Final study protocol and PIS ready
D8. NKI trial-center meeting to develop e-CRF and randomization system
D9. PALGA SUBITO candidate patient identification system up and running

*2016 – Q1*
D10. Approved SUBITO protocol by central ethics committee in The Netherlands, France and Germany
D11. Initiation visits NKI, HT, IPC, WSG

*2016 – Q2*
D12. Local approval Dutch SUBITO centers
D13. Initiation visits Dutch SUBITO centres
D14. Annual investigators's meeting 2016

*2017 – Q1*
D15. Patient accrual 5 pts/month = 15 pts/Q = 60 pts / year
D16. Annual progress report

*2017 – Q2*
D17. Annual investigators's meeting 2017

*2018 – Q1*
D18. Patient accrual 5 pts/month = 15 pts/Q = 60 pts / year
D19. Annual progress report

*2018 – Q2*
D20. Annual investigators's meeting 2018

*2019 – Q1*

D21. Patient accrual 5 pts/month = 15 pts/Q = 60 pts / year

D22. Annual progress report

*2019 – Q2*

D23. Annual investigators's meeting 2019

*2019 – Q3*

D24. 174 patients included

*2020 – Q1*

D25. Annual progress report

*2020 – Q2*

D26. Annual investigators's meeting 2020

*2020 – Q3*

D27. interim analysis SUBITO study

*2021 – Q1*

D28. Annual progress report

*2021 – Q2*

D29. Annual investigators's meeting 2021

*2021 – Q3*

D30. Quality of life sub-study results

D31. Primary analysis SUBITO study

D32. Health economics analysis SUBITO study

**Table.** Deliverables and timelines

| Deliverables | Prepa-ratory phase | Start SUBITO project (NKI 2014-7052) | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2015 | | 2016 | | | | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | | 2021 | | | |
| | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Appointment study coordinator | D1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concept study protocol and PIS written | D2 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Patient advocacy meeting for advice, including awareness SUBITO study | D3 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Strategic plan to create awareness of SUBITO study with professionals and patients | D4 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Formalization of final SUBITO consortium and contracts signed | | D5 | | | | | | | | | | | | | | | | | | | | | | | | |
| Start-up investigators' meeting | | D6 | | | | | | | | | | | | | | | | | | | | | | | | |
| Final study protocol and PIS | | D7 | | | | | | | | | | | | | | | | | | | | | | | | |
| NKI trialcenter meeting to develop e-CRF and randomization system | | D8 | | | | | | | | | | | | | | | | | | | | | | | | |
| PALGA SUBITO candidate patient identification system up and running | | D9 | | | | | | | | | | | | | | | | | | | | | | | | |
| Approved SUBITO protocol by central ethics committee in The Netherlands, France and Germany | | | D10 | | | | | | | | | | | | | | | | | | | | | | | |
| Initiation visits NKI, HT, IPC, WSG | | | D11 | | | | | | | | | | | | | | | | | | | | | | | |
| local approval Dutch SUBITO centres | | | | D12 | | | | | | | | | | | | | | | | | | | | | | |
| Initiation visits Dutch SUBITO centres | | | | D13 | | | | | | | | | | | | | | | | | | | | | | |
| Annual investigators's meeting | | | | D14 | | | | D17 | | | | D20 | | | | D23 | | | | D26 | | | | D29 | | |
| Patient accrual 5 pts/month = 15 pts/Q = 60 pts / year | | | | | | | D15 | | | | D18 | | | | D21 | | | | | | | | | | | |
| Annual progress report | | | | | | | D16 | | | | D19 | | | | D22 | | | | D25 | | | | D28 | | | |
| 174 pts included | | | | | | | | | | | | | | | | | D24 | | | | | | | | | |
| interim analysis SUBITO study | | | | | | | | | | | | | | | | | | | | | D27 | | | | | |
| Quality of life substudy results | | | | | | | | | | | | | | | | | | | | | | | | | D30 | |
| Principal analysis SUBITO study | | | | | | | | | | | | | | | | | | | | | | | | | D31 | |
| Health economics analysis SUBITO study | | | | | | | | | | | | | | | | | | | | | | | | | D32 | |

**Update on parallel track of conditional approval through ZiN and ZonMw**

On June 5, 2015 it was announced that high-dose chemotherapy with autologous stem cell rescue had been approved as a candidate for conditional approval to health care insurance coverage: http://www.rijksoverheid.nl/ministeries/vws/nieuws/2015/06/05/ook-in-2016-vergroting-van-het-basispakket-kopie.html

The second phase of this trajectory has started and will take approximately 6 months. During this phase a covenant will be put together with all involved parties that secures a successful realization of the SUBITO study. Involved parties include health care professionals, health care insurance organization the Netherlands (Zorgverzekeraar Nederland), patient advocacy groups, and ZiN (Zorginstituut Nederland). The final covenant will be send to the Ministry of Health before May 1, 2016. A final decision on whether or not the high-dose treatment for stage III, BRCA1-like breast cancer patients aged 59 years or younger will be accepted for conditional approval to health care insurance coverage will be given before July 1, 2016. In case of endorsement for conditional approval costs for BRCA1-like testing, leukapheresis and high-dose CTC with autologous stem cell rescue will be covered by health care insurance in the Netherlands, starting from July 1, 2016 onwards. Recalculation afterwards will then result in partial reimbursement of the Dutch Cancer Society grant NKI 2014-7052 to KWF.