The KI program for Personalised Cancer Medicine (PCM).
Task Force: Early Clinical Trials.

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Background

The PCM program requires a well-structured and affordable clinical trial constellation to translate preliminary discoveries into robust clinical wins for patients. The ‘one-size-fits-all' approach that delivers minimal benefit does not fit into a PCM concept. Molecular stratification strategies aiming at matching the trial to the patient rather than finding the right patient for the trial are to be pursued. In addition, the availability of new drugs with novel mechanism of action and toxicity profiles that are hard to predict and may occur far after the classical dose-limiting toxicity observation period introduces real challenges in trial design. Revolutionary statistical designs are currently being explored, but still lack broader validation. Hence, clinical trials must increasingly be more cooperative (bridging the academia-industry intersect) and deliver benefit from a health, innovation, economic and societal perspective. In order for this to be achieved, the integration and alignment of multiple stakeholders across the health care system must be established at en early stage to ensure that innovation and ‘real' benefit is rewarded.

Further issues which specifically apply to early clinical trials in a PCM context are that Early trials are often explorative, have as primary end-points feasibility and toxicity, may have an ancillary translational program based on the collection of samples that will be analyzed retrospectively, and enroll per definition few patients.

Aims

To outline the current status of early clinical trials in Stockholm, focusing on investigator-initiated studies. The purpose is to provide an overview on what are the challenges and possibilities to conduct trials with innovative designs and in depth translational components.
To integrate current results with the other PCM task Forces in order to provide a global action plan for the role of PCM within KI and Karolinska University Hospital.

Methods

1. Learn-by-doing: to challenge the system from inside, I designed and am presently coducting an investigator driven academic phase I trial

2. To explore the investigator experiences with academic trials, a questionnaire with few target questions was submitted to PIs of investigator-iniziated trials at Karolinska University Hospital.

Results

1. DURSAB I. Stereotactic Ablative Body Radiotherapy (SABR) followed by Durvalumab as maintenance treatment in patients with advanced non-small cell lung cancer not progressing after 4 to 6 cycles of first-line conventional chemotherapy: a phase I feasibility trial.

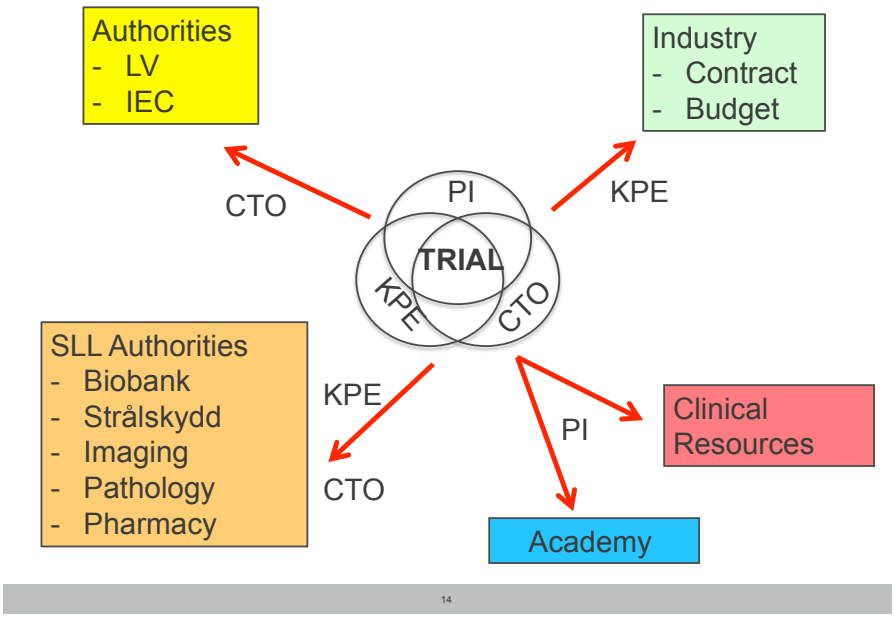
For the following reasons, this trial can be considered ideal to challenge the PCM approach:

- It is based on direct collaborations between Clinical investigator, KI scientists and Industry → challenge with the design of the ancillary translational program, including mutiple strategies on how to analyze "limited" biological samples in order to obtain results robust enough to be both hypothesis generating and survive a validation step
- It requires extensive biopsy procedures → compliance issues for the patients
- It tests a novel not-yet approved drug → challenge with the TLV approval as well as the pharmacy procedures
- It explores a novel setting (the maintenance setting), not yet explored with immunotherapy strategies → lack of historic experience for an accurate statistical design for a following phase II trial where efficacy needs to be tested
- It tests a novel combination strategy, namely SABR and immunotherapy → hurdles in designing a study flow that can at the same time provide as much information as possible concerning several radiotherapy-immunotherapy issues (fractionation, timing, total dose, choice of site to irradiate in relation to expected immune response), without exposing the patients to unnecessary risks.
- The success of the trial is based on the extensive collaboration between several specialists at Karolinska (pneumologists, medical oncologists, radiation oncologists, radiologists, pathologists) → is our apparate strong enough not to collapse under these voluminous collaborative efforts?

Preliminary results of interest for the present report.
With extensive assistance from the Clinical Trial Office at the Clinical trial Unit, the journey has gone through, and been approved by, Support Company, TLV, EPN, Strålskyddskommitte. Biobank approval procedure is oingoing. Contracts (avtal) have been signed between the PI and the Support Company, the Radiology Department, the Pathology Department, the Oncology Department.

The first patient in is planned to be included in Q1 2017. However, to date (March 2017) we are still trying to understand which authority is going to perform the ”regulatory release” for a drug produced by a pharmaceutical company. Altough the same drug is being used in Sweden within another industry-sponsored clinical trial in lung cancer, for this academy-sponsored trial the same drug has to undergo again the process for ”regulatory release”, and at present it is still unclear how this is going to be solved.

2. During the years 2015 and 2016, approximately 25 trials are open for inclusion at the Clinical Trial Unit at the Department of Oncology, Karolinska University Hospital. The journey that a PI has to undergo to run an academic trial requires interaction with a number of diverse players, has depicted in the picture below.



The following questionnaire was submitted to 16 PIs. Thirteen (81%) have replied, and results are reported below.

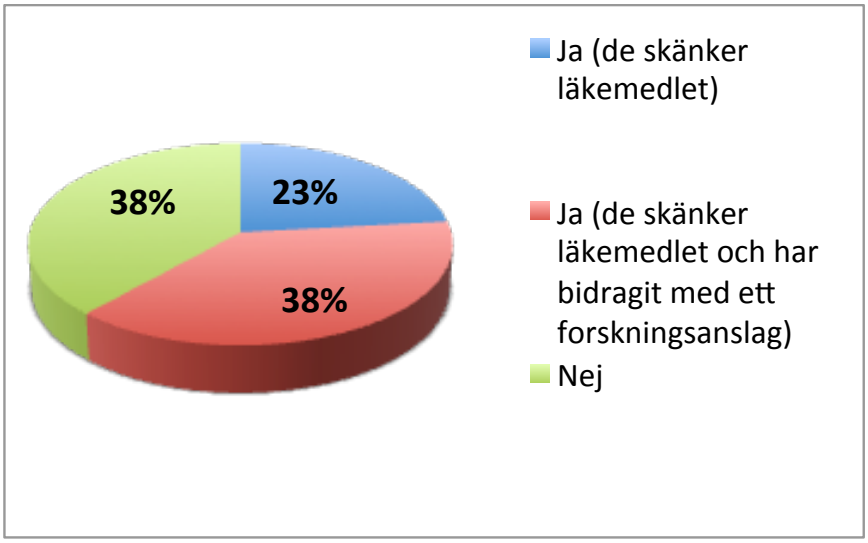
Jag skriver till Dig eftersom Du har en pågående tidigt prövning på KS som PI, dvs där Du är direkt engagerad i design, protokollskrivandet, ansökan till myndighet mm.

Jag skulle uppskatta om Du skulle kunna tänka Dig ta 5 minuter av Din tid och svara till följande 7 frågor med vändande post.

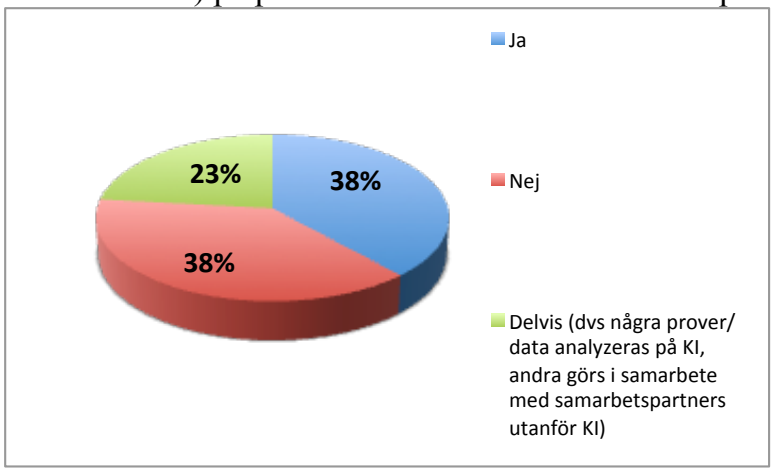
Syftet med min undersökning är att få en bild på vilka aspekter i design och genomgång av tidiga prövningar på KS/KI kan underlättas/stödjas av PCM programmet.

Svara gärna till följande frågor genom att kryssa på det svaret (eller dem svaren) som du tycker lämpar sig bäst till just Din kliniska prövning.

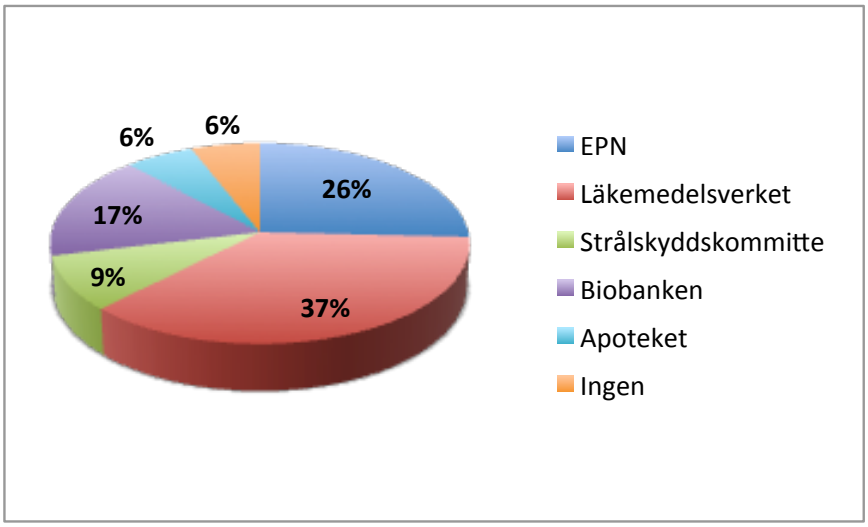
1. Har du samarbete med industri för din kliniska prövning?



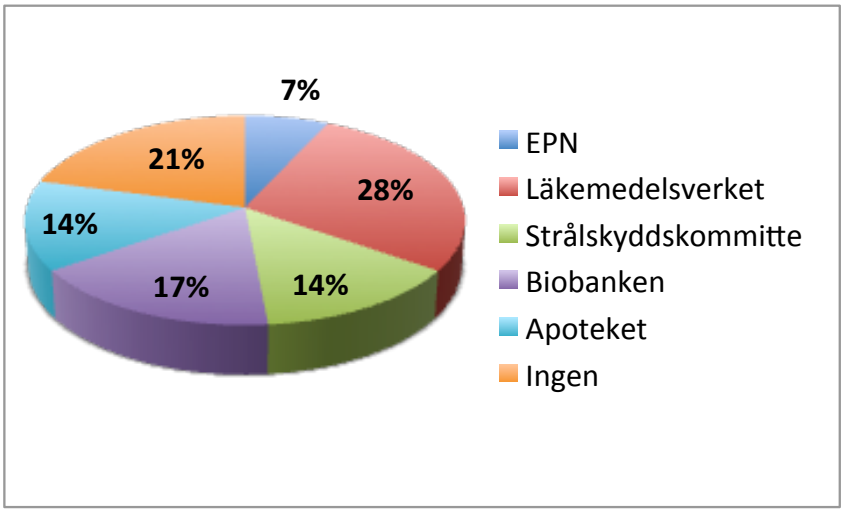
2. Har du samarbete med KI när det gäller molekylära analyser (inklusive bioinformatik) på prover som tas inom din kliniska prövning?



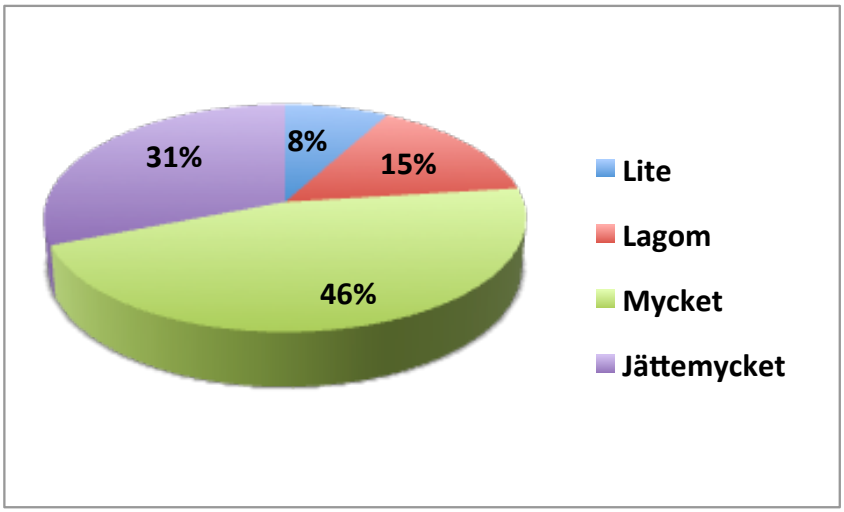
3. Med vilken/vilka av följande ”myndigheter” har Du haft svårast att interagera när det gäller: ansökningsblankett? (Du kan sätta ett kryss vid det svåraste, och 2 kryss vid det näst svåraste)



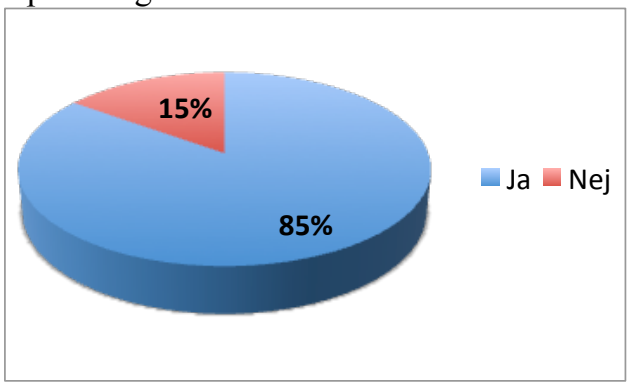
4. Med vilken/vilka av följande lokala ”myndigheter” har Du haft svårast att interagera när det gäller: vägen från inskickandet av ansökan till själva godkännande? (Du kan sätta ett kryss vid det svåraste, och 2 kryss vid det näst svåraste)



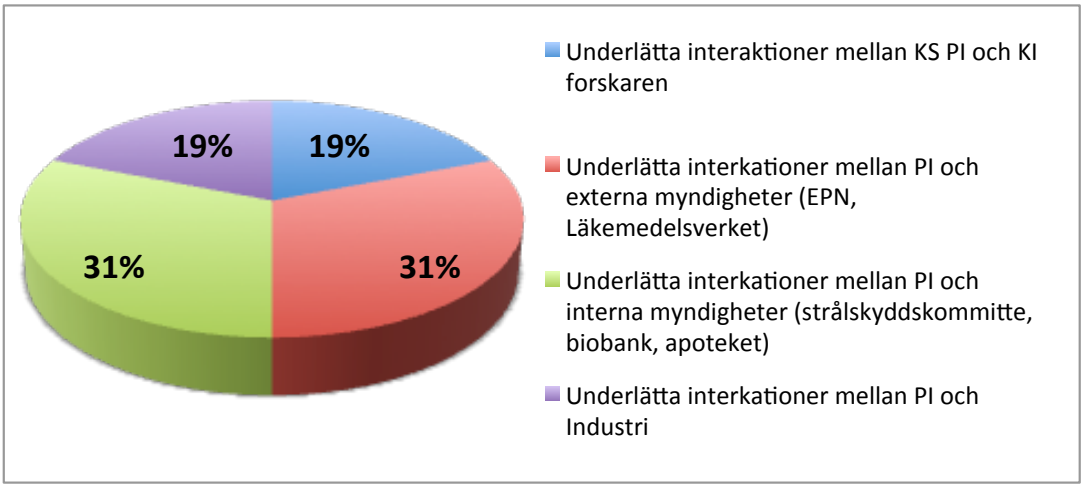
5. Hur mycket stöd har du fått av KPE och CTO (Clinical Trial Organization) genom hela processen?



6. Tycker du att en KI organisation som PCM skulle kunna vara av hjälp för en klinisk PI i just planeringen och genomförandet av akademiska kliniska prövningar?



7. Om du svarat ja till fråga 6, på vilket sätt?



Interpretation

The results from the PI questionnaire are extremely interesting, because they indicate how important a PCM effort can be in order to further implement clinical investigations at KI/KS.
Firstly, it looks like that the majority of the PIs currently driving academic trials do not have a collaboration with the industry, nor with investigators at KI (Questions 1 and 2). This may be interpreted as if these collaborations are too difficult to pursue, and in order to be able to perform a trial you need to make it simple and exclude from your design both industry and basic science/facilities.
When it comes to the single experiences with stakeholders (Questions 3 and 4), diverse PIs may have encountered diverse hurdles, and this may be explained by the heterogeneity of the research projects.
It is worth noting that 77% of PIs have received a lot of support from the Clinical Trial Unit. A functional, effective and professional Clinical trial unit is the key to the success of clinical trials.
Finally, when it comes to PCM-specific items, it looks like the highly majority of interviewed PIs do believe that PCM may play an important role to implement clinical trials at KI/KS. However, again different opinions have been expressed, and the majority point towards PCM as facilitator in the relationship between PIs and stakeholders, reflecting how these steps do represent significant hurdles for the conduction of academic driven trials. This is particularly relevant when one wants to integrate the present investigation in the context of the other PCM task forces. In other words, how can we aim at integrating basic science and KI facilities with clinical science, if the major issues are still regulatory?

Action plan: Proposal for a role of PCM within KI.

Clinical trials are based on a complex and high cost workflow, which can be developed and sustained only though adequate funding. Such funding can mainly be obtained from industry. Academy can provide enough funding for a trial, but not to sustain a system. Inclusion of more patients in industry-driven trials would make Karolinska attractive for the companies and thereby increase their willingness to invest resources. A cooperation, which in turn will create better conditions for academic initiatives.

In my opinion PCM should focus on facilitating and supporting the integration between KS PIs and KI investigators, although this was not the major opinion of the interviewed PIs.

This could be done through:

- Harmonization of application forms and of other documentation through data sharing may facilitate the flow of the trial through the diverse stakeholders. This for example could be obtained through the

standardization of informed consent and EPN text in order to be able to easily share data and material within diverse consortia (for example Cancer Core Europe).
- Creating platforms for clinical and molecular data sharing (IT-task force)
- Providing a platform where clinical PIs and KI investigators can interact early during the design of the trials in order to be able to define personalized cancer medicine questions to be answered with the proper clinical and experimental design

Conclusions.

To effectively conduct academic early clinical trials at Karolinska requires enormous resources and efforts. The diverse steps thorough authority approval represent significant bottlenecks in the entire process. Unfortunately, independently of the quality of the scientific approaches and the novelty of the clinical questions to be answered, the utmost major problem for the investigators is still the hassles emerging from the bureaucratic machinery. In order for this to be improved, the PCM program should work together with Tema Cancer and its FoU chief to establish a comprehensive cancer center.