Novel Trial Designs in Oncology

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Why New Designs

- Rapid advances in biology
- Explosion of number of new treatments to be tested
- Increasing number of rare subsets
- Rising costs and shrinking funding
- Many large trial with inconclusive results
- Molecular heterogeneity challenges design
- Inter-patient heterogeneity of low frequency biological events
- Intra-patient heterogeneity through space and time
  - Serial molecular profiling.

✧ Next-Gen trial designs aimed to address heterogeneity.
✧ Novel ‘Exploratory’ and ‘Expansion’ Platform clinical trial designs.
Common reasons for failed trials

- Selecting the wrong patients
  - Selecting the wrong dosing
  - Selecting the wrong endpoint.
- Biological activity but wrong indication.
- Right indication but wrong subpopulations
- Wrong dose or dose interval
- Trial Design Not Giving Clear Answers
Evolving synergistic combinations of targeted immunotherapies to combat cancer

Ignacio Melero\textsuperscript{1}, David M. Berman\textsuperscript{2}, M. Angela Aznar\textsuperscript{1}, Alan J. Korman\textsuperscript{3}, José Luis Pérez Gracia\textsuperscript{1} and John Haanen\textsuperscript{4}
Multiple hypotheses = need for a platform trial
Basket Trials*

- Targeted drug
- Restrict to tumors expressing target
- Simultaneously develop across organ-specific tumors
- Sample sizes tiny, borrow; may be “pool”
- Formalizes “Gleevec phenomenon”


Master Protocol

• An overarching protocol that includes one or more of
  – Multiple diseases
  – Multiple treatments
  – Multiple molecular markers

• Other names
  – Umbrella trials
  – Cloud trials
  – Basket trials
AWAKEN THE FORCE WITHIN

Immunotherapy brings a new hope to cancer treatment
Immunotherapy Approaches

Immunotherapy is NOT one thing.

- Checkpoint Inhibitors ✔
- Oncolytic Viruses ✔
- Bi-specific Antibodies ✔
- Cancer Vaccines ✔
- CAR-T ✔
- Natural Killer Cell
- T-cell Receptors

- DART
- STING
- Cytotoxic T-cells
- Tumor Infiltrating Lymphocytes
- More...

✔ = FDA Approved
FDA approvals for immune checkpoint blockers, diagnostic tests, and treatment combinations

Melanoma
- Ipilimumab monotherapy
- Pembrolizumab 2nd-line
- Nivolumab 2nd-line
- Nivo 1st-line
- Pembrolizumab 1st-line
- Nivo/ipi combo

Non-Melanoma
- Nivo lung cancer squamous 2nd-line with biomarker
- Pembrol lung 2nd-line with biomarker
- Nivo lung cancer non-squamous 2nd-line with biomarker
- Nivo kidney 2nd-line
- Pembrol head/neck 2nd-line
- Nivo head/neck 2nd-line
- Nivo Hodgkin 4th-line
- Nivo bladder cancer 2nd-line with biomarker
- Atezo bladder cancer 2nd-line with biomarker
- Atezo lung cancer 2nd-line
- Pembrol cancer 1st-line with biomarker
- Nivo bladder 2nd-line
- Pembrol Hodgkin 4th-line

Pembro
- MSI-hi tumors 2nd-line with biomarker
- NSCLC combo 2nd-line
- Bladder 2nd-line with biomarker
- Merkel cell Ca 1st-line

Ipi
- Adjuvant

Nivo
- MSI-hi CRC 2nd-line with biomarker
- Mel biomarker

Courtesy of S. Topalian (JAMA 2017)
SEQUential ImmunoTherapy in Underserved Rare cancers (SEQUITUR)
<table>
<thead>
<tr>
<th></th>
<th>Tumour Type</th>
<th>Response Rate</th>
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<tbody>
<tr>
<td>1</td>
<td>Adrenocortical cancer</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>Carcinoma of the small bowel</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>Anal Cancer</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>Biliary Tract Cancer</td>
<td>7.7%</td>
</tr>
<tr>
<td>5</td>
<td>NECs</td>
<td>29%</td>
</tr>
<tr>
<td>6</td>
<td>NETs</td>
<td>29%</td>
</tr>
<tr>
<td>7</td>
<td>Uterine Sarcoma</td>
<td>20%</td>
</tr>
<tr>
<td>8</td>
<td>Vulvar Cancer</td>
<td>20%</td>
</tr>
<tr>
<td>9</td>
<td>SCC of the Cervix or Vagina</td>
<td>17%</td>
</tr>
<tr>
<td>10</td>
<td>Endometrial Cancer</td>
<td>27%</td>
</tr>
<tr>
<td>11</td>
<td>Rare Ovarian Cancers†</td>
<td>15%</td>
</tr>
<tr>
<td>12</td>
<td>Rare breast Cancers‡</td>
<td>18%</td>
</tr>
<tr>
<td>13</td>
<td>IDH mutated glioma</td>
<td>6%</td>
</tr>
<tr>
<td>14</td>
<td>IDH wild-type glioma</td>
<td>21%</td>
</tr>
<tr>
<td>15</td>
<td>Rare glial tumours§</td>
<td>20%</td>
</tr>
<tr>
<td>16</td>
<td>Thymic carcinoma</td>
<td>22%</td>
</tr>
</tbody>
</table>
Up to 15 Rare Cancer Baskets

Nivolumab 240-mg Q2 weeks + IDOi
BMS-986205, 100mg PO daily

Disease Progression

Nivolumab 240-mg + LAG-3i (BMS-986016; Relatlimab) 80 mg IV Q 2 weeks
SPECIFIC AIMS of SEQUITUR

• Conduct simulation studies to evaluate the performance of the analysis under various assumptions for the distribution of true underlying RR across the tumour types and assess operating characteristics including power and type I error.

• A model will be developed prospectively by evaluating its performance from simulated trials allowing for the controlling of the false positive rate assessment of statistical power.
SPECIFIC AIMS of SEQUITUR

• Answer economic questions about the cost-effectiveness of the research from the perspective of research funders (government, funders, industry, and charity)
  – What are the costs and benefits of a basket trial approach for adults with rare cancers versus a standard trial approach?
  – Are expected resource efficiencies realised?
Bayesian response adaptive randomization (BRAR) designs

• Increase patient allocation to treatment arms that are performing well during the course of the trial. In this paper,
• BRAR and flexible MAMS designs have comparable power and type 1 error rate under varying
• Simulated scenarios, allowing for addition of flexible treatment selection. BRAR outperforms flexible MAMS
• When there is a single effective treatment, flexible MAMS designs are more efficient compared to BRAR when there are no effective treatments.
• BRAR performance increases as the probability of a treatment arm being dropped increases.
Cancer Trial Landscape

Platform trials
- I-SPY 2,
- GBM-AGILE,
- Etc.

Basket trials
- Lung-MAP,
- NCI MATCH, Etc.
- Novartis’s Signature, Etc.
**I-SPY 2 TRIAL:**

Learn, Drop, Graduate, and Replace Agents Over Time

- Paclitaxel + Trastuzumab
- Paclitaxel + Trastuzumab + New Agent A
- Paclitaxel + Trastuzumab + New Agent B

**HER 2**

**Drug:** Neratinib
**Drug:** ABT-888
**Drug:** Standard Therapy
**Drug:** AMG 386 (Trabancanib)
**Drug:** AMG 479 (Ganitumab) plus Metformin
**Drug:** MK-2206 with or without Trastuzumab
**Drug:** AMG 386 and Trastuzumab
**Drug:** T-DM1 and Pertuzumab
**Drug:** Pertuzumab and Trastuzumab

**Targets key pathways/molecules in breast cancer**

**AC**

Surgery

Learn and adapt from each patient as we go along
Adaptive Randomization of Neratinib in Early Breast Cancer


N ENGL J MED 375:1  NEJM.ORG  JULY 7, 2016

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

EDITORIAL

I-SPY 2 — Toward More Rapid Progress in Breast Cancer Treatment

Lisa A. Carey, M.D., and Eric P. Winer, M.D.

PERSPECTIVE

I-SPY 2 — The Future of Phase 2 Drug Development?

STATISTICS IN MEDICINE

I-SPY 2 — A Glimpse of the Future of Phase 2 Drug Development?

David Harrington, Ph.D., and Giovanni Parmigiani, Ph.D.

The articles by Rugo et al. (pages 23–34) and Park et al. (pages 11–22) in this issue of the NEJM describe the I-SPY 2 trial, which aims to detect good responses and, equally important, may be useful in allowing patients to avoid treatments that are ineffective or toxic.
A HER2+ HR−

Predictive probability in phase 3 testing, 79%

Estimated Response Rate

Density of Probability Distribution

Control, 33%
Neratinib, 56%
<table>
<thead>
<tr>
<th>Biomarker Signature</th>
<th>Estimated Rate of Pathological Complete Response (95% Probability Interval)</th>
<th>Probability of Neratinib Being Superior to Control</th>
<th>Predictive Probability of Success in Phase 3 Trial</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Neratinib</td>
<td>Control</td>
<td>percent</td>
</tr>
<tr>
<td>Any</td>
<td>33 (24–40)</td>
<td>23 (14–33)</td>
<td>93</td>
</tr>
<tr>
<td>Hormone-receptor positive</td>
<td>23 (13–33)</td>
<td>16 (6–28)</td>
<td>81</td>
</tr>
<tr>
<td>Hormone-receptor negative</td>
<td>44 (30–55)</td>
<td>31 (17–45)</td>
<td>92</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>39 (28–51)</td>
<td>23 (8–38)</td>
<td>95</td>
</tr>
<tr>
<td>HER2 negative</td>
<td>28 (15–37)</td>
<td>24 (13–35)</td>
<td>69</td>
</tr>
<tr>
<td>High-risk category 2 on 70-gene profile*</td>
<td>48 (30–60)</td>
<td>29 (11–48)</td>
<td>93</td>
</tr>
<tr>
<td>HER2 positive, hormone-receptor positive</td>
<td>30 (18–44)</td>
<td>17 (3–32)</td>
<td>91</td>
</tr>
<tr>
<td>HER2 positive, hormone-receptor negative</td>
<td><strong>56 (37–73)</strong></td>
<td><strong>33 (11–54)</strong></td>
<td><strong>95</strong></td>
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<tr>
<td>HER2 negative, hormone-receptor positive</td>
<td>14 (3–25)</td>
<td>16 (5–27)</td>
<td>42</td>
</tr>
<tr>
<td>HER2 negative, hormone-receptor negative</td>
<td>38 (22–50)</td>
<td>31 (15–46)</td>
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</table>
Pancreatic Cancer

Conroy et al NEJM 2011; Goldstein et al JNCI 2015
Emerging Molecular Taxonomy
Prevalence of Phenotypes

Courtesy Lorraine Chantril and Andrew Biankin
The precision-oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says Vinay Prasad.

Precision oncology promises to pair individuals with cancer with drugs that target the specific mutations in their tumour, in the hope of producing long-lasting remission and extending their survival. The basic idea is to use genetic testing to link patients with the drugs that will work best for them, irrespective of the tissue of origin of their tumour. Enthusiasm has been fuelled by reports of exceptional or super responders — individuals for whom experimental therapies seem to work spectacularly well.

In one such example, an individual with metastatic bladder cancer showed a dramatic response to the drug everolimus. Sequencing later revealed that the patient had a mutation that affects the mTOR pathway, which is the mechanism of action of everolimus. Yet despite the hype surrounding rare cases such as these, most people with cancer do not benefit from the precision strategy, nor has this approach been shown to improve outcomes in controlled trials. Precision oncology remains a hypothesis in need of verification.

Few patients benefit from precision oncology. Data from some 2,600 people enrolled in a sequencing programme at the MD Anderson Cancer Center in Houston, Texas, showed that just 6.6% were paired with a targeted drug for identified mutations. Similarly, the Molecular Analysis for Therapy Choice (NCI-MATCH) trial at the US National Cancer Institute has enrolled 795 people who have relapsed solid tumours and lymphoma, but as of May 2016 it had only been able to pair 2% of patients with a targeted therapy.

When considered objectively, the prospects and potential of precision oncology are sobering. At best, we may expect short-lived responses in a tiny fraction of patients, with the inevitable toxicity of targeted therapies and inflated cost that this approach guarantees.

Precision Oncology on Trial

In medical science, the ultimate judge of a therapeutic strategy is the randomized controlled trial. So far, precision oncology has been tested in only one such published study. The SHIVA trial assigned 99 patients with cancer to therapies based on an identified mutation or mutations, and 96 patients to the treatment selected by their physicians. Median progression-free survival, the primary endpoint, was almost equally poor in both cases (2.3 and 2.0 months, respectively).

No single trial can prove that a therapy does not work in any circumstances, and SHIVA is no exception. It paired patients with drugs for ‘pathway’ mutations, not just for mutations that can be targeted with drugs, allowing those running the trial to enrol more than a quarter of screened patients. But further randomized controlled trials are needed to test alternative hypotheses, and the use of different medications and alternative pathways. These trials will have to balance applicability and generalizability (the percentage of screened patients that can be enrolled) against the strength of the biological rationale. Several
Precision and The Person

- Precision Medicine
- Personalized Medicine

*The Premise, The Promise and The Hype!*
Precision Promise

- Pancreatic cancer is an area of great need

- Two standard chemo regimens available but the outcome is still very dismal

- PanCAN is sponsoring Precision Promise and providing funding to support its goal to change patient outcomes for those suffering from pancreatic cancer

- The statistical design of Precision Promise is based on the I-SPY breast cancer trial, in collaboration with PanCAN and with guidance from the U.S. Food and Drug Administration (FDA)
The Precision Promise’s design

- Adaptive Phase II/III platform of first- and second-line pancreatic cancer
  Primary end point is OS
- Adaptive randomization
- Re-randomization for second-line if they progress on first-line treatment
- Two control arms (mFOLFIRINOX and gemcitabine/nab-paclitaxel)

- Minimizes numbers needed to achieve statistically significant data

- Expected to launch 2019 at 14 high-volume pancreatic cancer centers (US)
Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RT n = 286</th>
<th>RT+TMZ n = 287</th>
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<tbody>
<tr>
<td>2 years (%)</td>
<td>10.9</td>
<td>27.2</td>
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<tr>
<td>3 years (%)</td>
<td>4.4</td>
<td>16.4</td>
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<tr>
<td>4 years (%)</td>
<td>3.0</td>
<td>12.1</td>
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<tr>
<td>Hazard ratio</td>
<td>0.63 [0.53 - 0.75]</td>
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</tr>
<tr>
<td>P &lt; 0.0001</td>
<td></td>
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Patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>RT</th>
<th>RT+TMZ</th>
</tr>
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<tr>
<td>278</td>
<td>286</td>
<td>144</td>
<td>175</td>
</tr>
<tr>
<td>254</td>
<td>287</td>
<td>31</td>
<td>76</td>
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</table>
The Study of Glioblastoma in an Adaptive, Global, Innovative Learning Environment GBM – AGILE

Clinical Development: Standard Early to Late Stage Development in Neuro-Oncology

**Early Stage**
- **Dose escalation phase**
  - Cohort 5: N = 7
  - Cohort 4: N = 6
  - Cohort 3: N = 3
  - Cohort 2: N = 6
  - Cohort 1 qd: N = 3

**Dose confirmation phase**
- Pt enrollment: N = 20

**Late Stage**
- **Phase II/III evaluations**
  - Single arm Phase II: N = 40-60
  - ORR
  - PFS
  - OS
  - Randomized Phase II
  - Randomized Phase II/III
  - Randomized Phase III

**MTD**
GBM Development has many lengthy, costly (knowable?) failures

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Indication</th>
<th>Phase II-phase III time</th>
<th>Phase III N</th>
<th>Phase II N</th>
<th>Phase II endpoint</th>
<th>Phase II RCT?</th>
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<tr>
<td>Cilengitide</td>
<td>Newly Diagnosed</td>
<td>7.6</td>
<td>545</td>
<td>112</td>
<td>OS</td>
<td>No</td>
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<tr>
<td>Intraoperative RT</td>
<td>Newly Diagnosed</td>
<td>6.3</td>
<td>314</td>
<td>12</td>
<td>MTD</td>
<td>No</td>
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<tr>
<td>ICT-107</td>
<td>Newly Diagnosed</td>
<td>8.9</td>
<td>414</td>
<td>124</td>
<td>OS</td>
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<tr>
<td>NovoTTF</td>
<td>Newly Diagnosed</td>
<td></td>
<td>700</td>
<td></td>
<td></td>
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<tr>
<td>Bevacizumab</td>
<td>Newly Diagnosed</td>
<td>5.8</td>
<td>921</td>
<td>70</td>
<td>OS</td>
<td>No</td>
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<td>Bevacizumab</td>
<td>Newly Diagnosed</td>
<td>6.8</td>
<td>637</td>
<td>70</td>
<td>OS</td>
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<tr>
<td>Rindoepimut</td>
<td>Newly Diagnosed</td>
<td>9.3</td>
<td>745</td>
<td>82</td>
<td>PFS</td>
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<td>ddTMZ</td>
<td>Newly Diagnosed</td>
<td></td>
<td>1173</td>
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<td></td>
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<td>Nivolumab</td>
<td>Newly Diagnosed</td>
<td></td>
<td>550</td>
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<tr>
<td>DCVax</td>
<td>Newly Diagnosed</td>
<td>9.9</td>
<td>348</td>
<td>240</td>
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<td>VB-111</td>
<td>Recurrent</td>
<td>7.0</td>
<td>252</td>
<td>75</td>
<td>OS</td>
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<td>Enzastaurin</td>
<td>Recurrent</td>
<td>4.8</td>
<td>397</td>
<td>120</td>
<td>Activity</td>
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<tr>
<td>Cediranib</td>
<td>Recurrent</td>
<td>4.3</td>
<td>423</td>
<td>31</td>
<td>PFS</td>
<td>No</td>
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<tr>
<td>Nivolumab</td>
<td>Recurrent</td>
<td></td>
<td>626</td>
<td></td>
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<tr>
<td>NovoTTF</td>
<td>Recurrent</td>
<td></td>
<td>236</td>
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<tr>
<td>AP 12009</td>
<td>Recurrent</td>
<td>8.8</td>
<td>27 (term)</td>
<td>141</td>
<td>ORR</td>
<td>Yes</td>
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Courtesy of Brian Alexander
MGMT methylation

Prospective marker for patients who would benefit from chemo
2 × 2 Biomarkers → 3 Signatures

- Newly diagnosed MGMT-unmethylated
- Newly diagnosed MGMT-methylated
- Recurrent GBM MGMT-unmethylated
- Recurrent GBM MGMT-methylated
Drug Signature

• Combination of biomarker subsets
• Examples:
  – All GBM
  – Target A
  – Target B
  – A + B
  – Etc.
• Each drug is continuously evaluated within each candidate signature
GBM AGILE
Arm 2 graduates to small focused Phase 3 trial
Population of patients

Arm 3 drops for futility

GBM AGILE

Experimental arm 1
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Arm 5 graduates to small focused Phase 3 trial

GBM AGILE
GBM AGILE: Value to Drug Makers

- De-Risk (faster, cheaper)
  - Create a Master protocol with shared control and shared infrastructure
  - Infrastructure designed to shorten timelines
  - Use Bayesian statistics to right size trial (Fail early, Win Early)
  - Used for variety of development opportunities (1st to market, expanding indications)
  - Cost savings encourages involvement in orphan disease

- Innovate
  - Regulatory interest in these endeavors: seen as the future of clinical trials
  - Borrow across multiple signatures (possible indications) to increase power
  - Empower ability to ask biomarker questions (CDx)
  - For significant effect size allow for NDA with regulators

- Capitalize on a Win
  - Evaluate Multiple possible indications
  - Evaluate in multiple countries simultaneously
  - Establishing New controls
  - Opportunity for Rational Combinations

- International regulatory alignment
GBM AGILE: Value to Patients and Advocates

- **Access**
  - Multiple therapies available
  - Offered at many sites, potentially reducing travel distance

- **Opportunity for continuous improvement**
  - Trial becomes Standard of Care

- **Precision Medicine**
  - More likely to get most beneficial treatment for patient subtype today

- **Design informed by patients and advocates**
  - Disease centric not drug centric
  - Patient-centric trial design informed by patient and caregiver input
  - Shared control group
  - Faster to fail and faster to market
GBM AGILE: Value to Academics and Physicians

- Provides Late Stage Clinical Trial Portfolio
  - Less bias toward what is thought to be better drug
- Leadership Opportunities
  - Lead late stage development of therapy
  - Broader international community interactions/engagement
- Opportunities for Continuous learning
  - Massive, longitudinal, highly annotated data set (imaging, outcomes, biomarkers) available to community of investigators
Clinical Development: Early to Late Stage Development in Neuro-Oncology

Early Stage
- Dose escalation phase
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- Cohort 2: N = 6
- Cohort 1 qd: N = 3

Late Stage
- Dose confirmation phase
- Pt enrollment: N = 20
- Pt enrollment: N = 40
- Disease specific expansion cohort
- ORR
- PFS
- OS

Phase II/III evaluations

GBM AGILE
Adaptive Global Innovative Learning Environment

GLOBAL COALITION FOR ADAPTIVE RESEARCH™
Complexity

Traditional Monitoring

Start up → Close out

Adaptive Monitoring

Continuous monitoring by Central Monitoring and CAF → KRI Trigger or Central Monitoring triggers → "Targeted" → Onsite visits → Decision to move back to a traditional model: Y/N → Traditional Model → Close out

- FM decision to transition to Adaptive Monitoring
- Adaptive Monitoring Report: Central monitoring: Continuous
- Adaptive Monitoring Model: Onsite visit: twice per year
- Traditional Model: On-site visit: Once every 4 to 6 weeks
- Knowledge-based remote monitoring: Once every 4 to 6 weeks

NOVARTIS
Challenges & Opportunities
Questions?