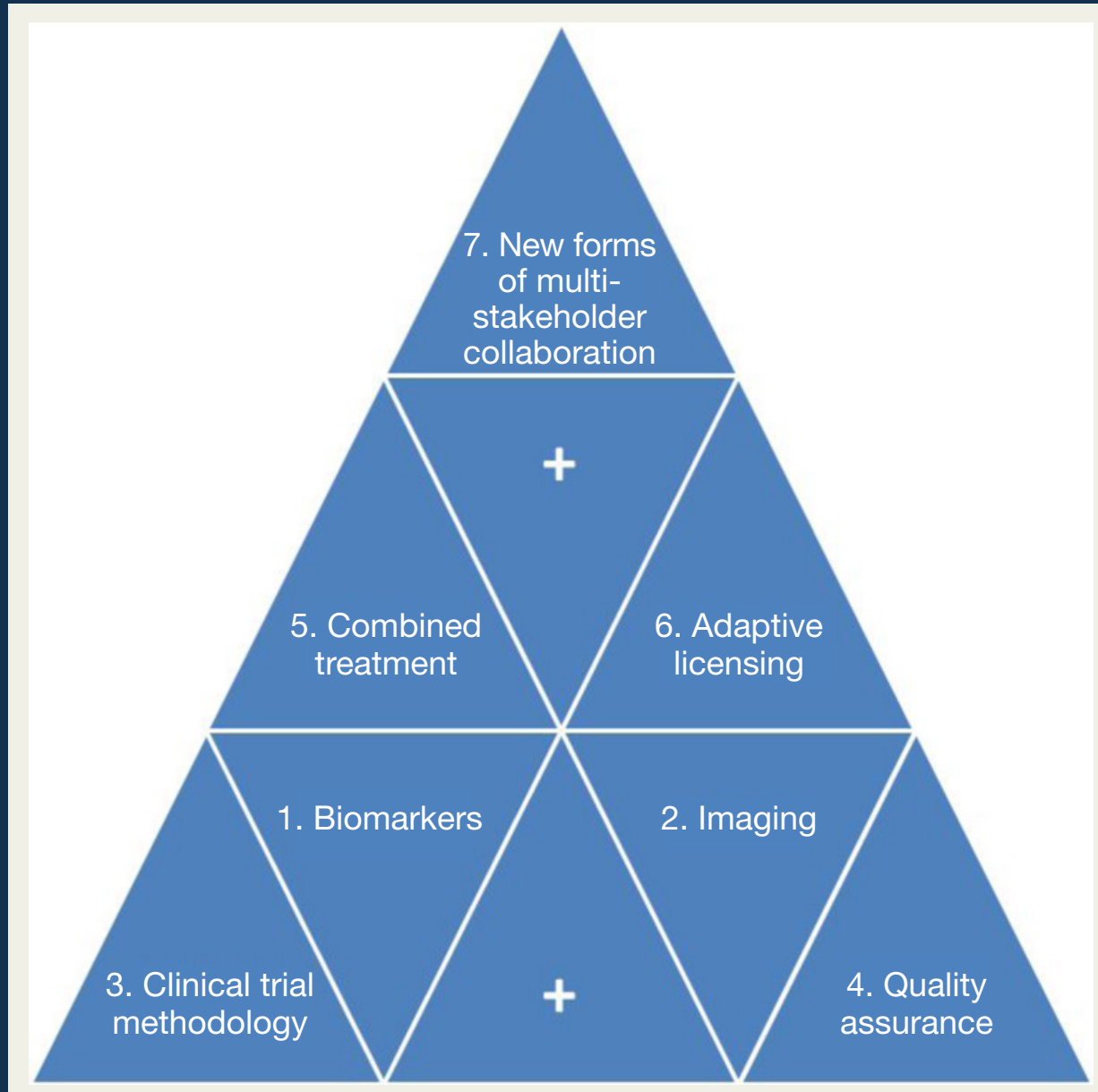# The "Seven Wonders" of the anticancer drug development

Drug developers are facing enormous challenges, including the productivity crisis of their own. Between 2002 and 2011, the pharmaceutical and biotech sector spent nearly 1.1 trillion dollars on research & development (R&D), and the United States Food and Drug Administration (FDA) approved 308 new molecular entities and biologics in the 10 years to 2011.

That means the average cost per approved molecule ranged from 2.3 to 4.9 billion dollars.

Only about two of every ten marketed drugs generate sufficient revenues to cover their associated R&D cost. Compared to other clinical medicine, oncology has the highest attrition rate for late stage clinical trials, and overall success rate from first-in-man to approval is about 5%.
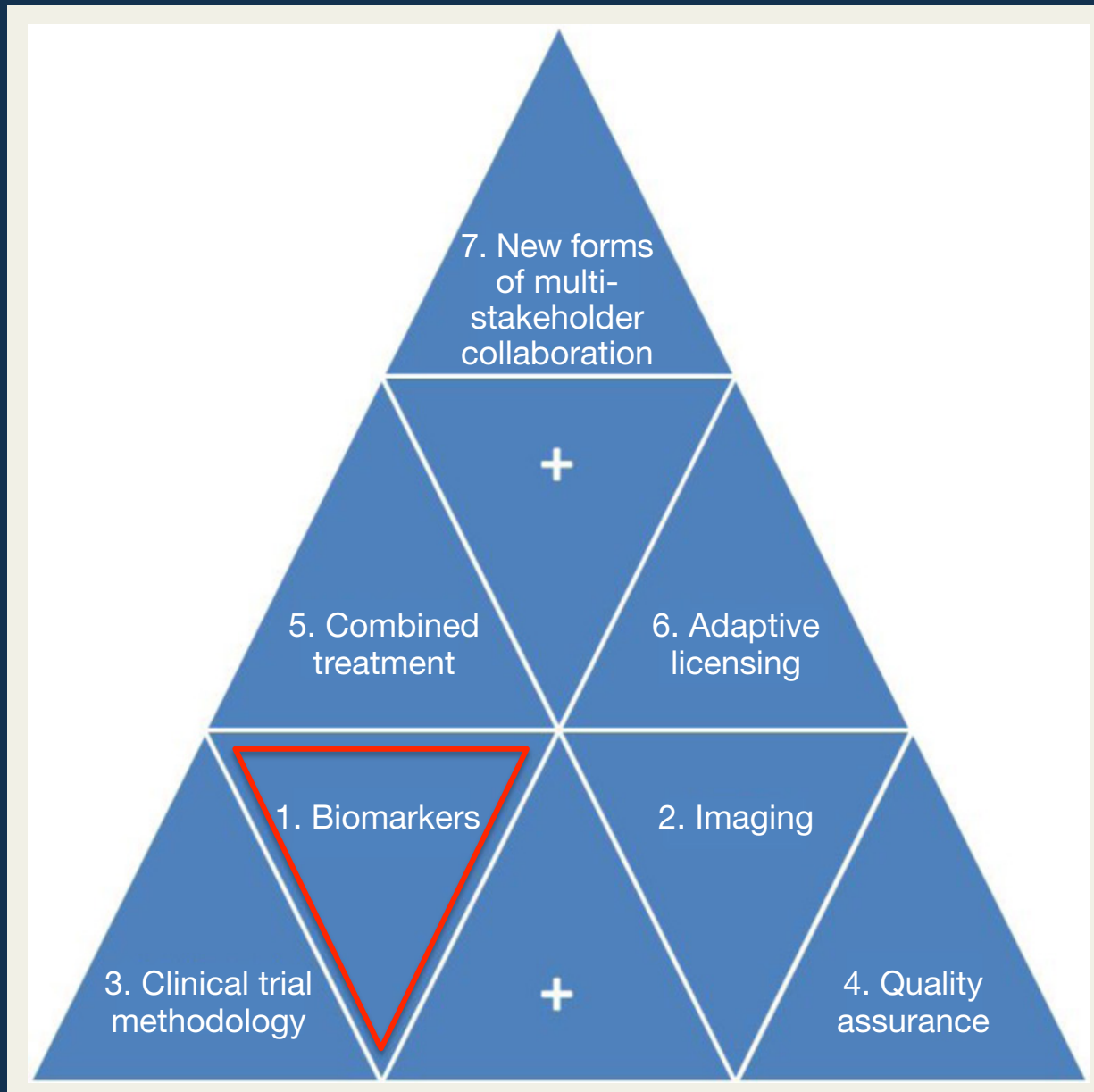
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasa
Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson,
Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

➢ Identificati **5 cluster di pazienti** in base a diverse caratteristiche (es. progressione della malattia, diverse caratteristiche, rischi di complicazioni..).

➢ Questa nuova stratificazione potrebbe essere utile **per definire nuovi trattamenti di medicina di precisione**, ovvero disegnati sulle caratteristiche dei cluster.

Lancet Diabetes Endocrinol 2018, Published Online March 1, 2018
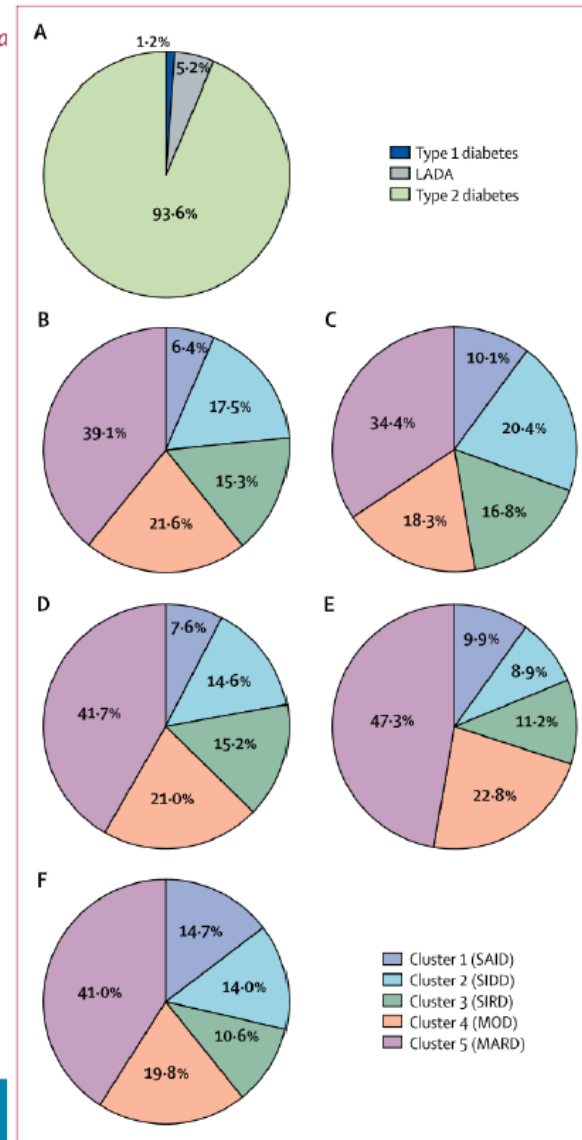
Next – generation sequencing

L'identificazione dei **biomarcatori predittivi** di risposta alla terapia hanno permesso l'**arruolamento** solo di pazienti che potevano trarre **maggiore beneficio** dalle nuove terapie.
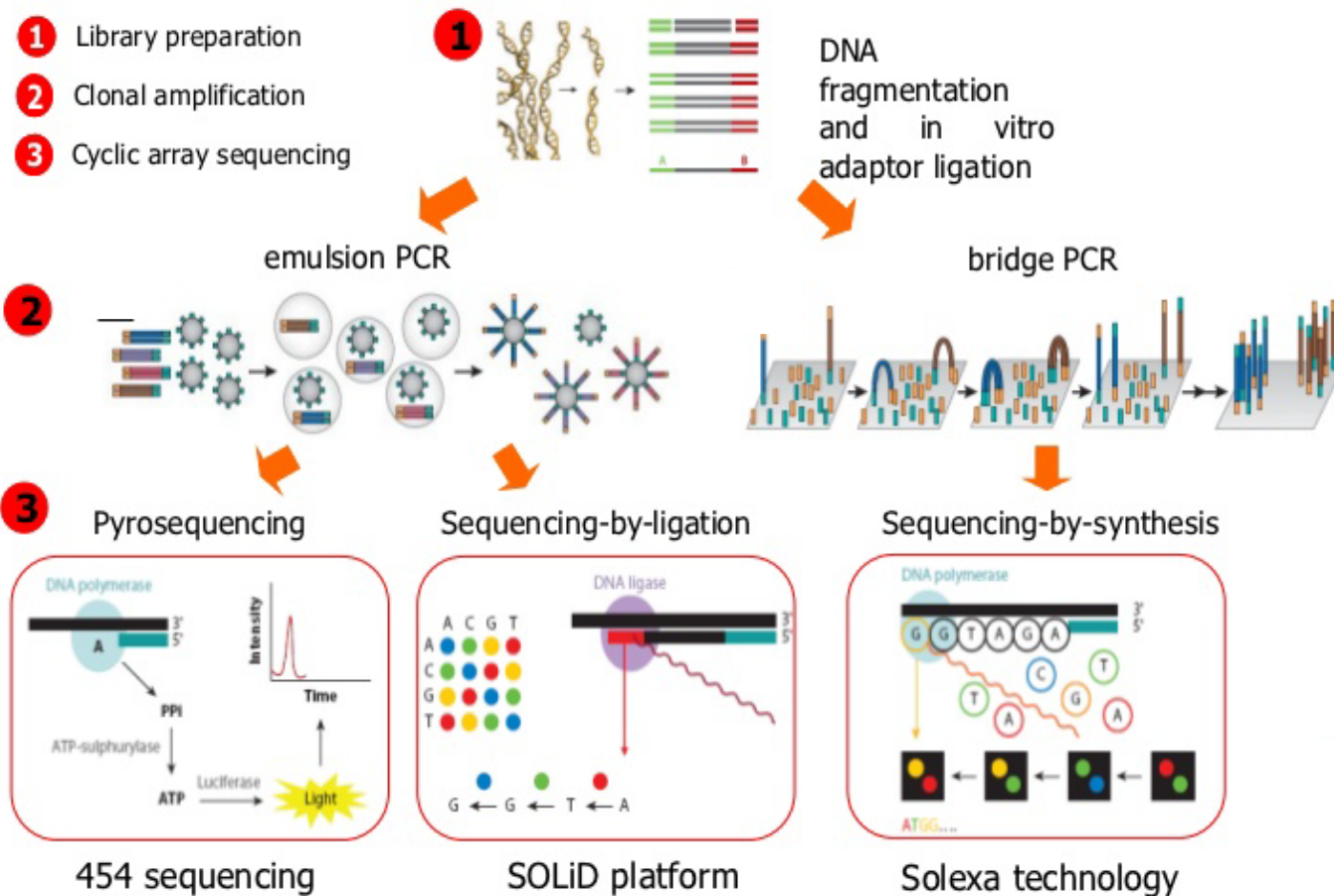
Vantaggi
- Alta sensibilità
- Alta specificità
- Rapporto costo – beneficio vantaggioso

Biomarkers

Effective integration of biomarkers into clinical drug development programs has been identified as a key prospect in the FDA's Critical Path document.

In novel drug development, the predictive value of validated biomarkers could inform crucial go/no go decisions around safety and efficacy.

Effective integration of biomarkers into drug development may facilitate and accelerate drug approval and promote personalized medicine.

Biomarkers require the development of companion diagnostic tests able to select patients who are likely to respond to a given molecule, a "preselected" or "enriched" patient population.

For example, panitumumab is a human monoclonal antibody to epidermal growth factor receptor (EGFR), approved for the treatment of patients with metastatic colorectal cancer, however the efficacy of panitumumab was restricted to patients with wild-type KRAS genes, while patients with mutated KRAS did not benefit.

It is challenging to develop an exact dose intervention that fits all patients due to the inter-individual variability. It may be possible to have a dose adjustment based on the genetic polymorphisms of drug-metabolizing enzymes or drug transporter proteins.

For example, the azathioprine label added information related to thiopurine methyltransferase, and recommends that patients with thiopurine methyltransferase deficiency or lower activity are at increased risk for myelotoxicity.
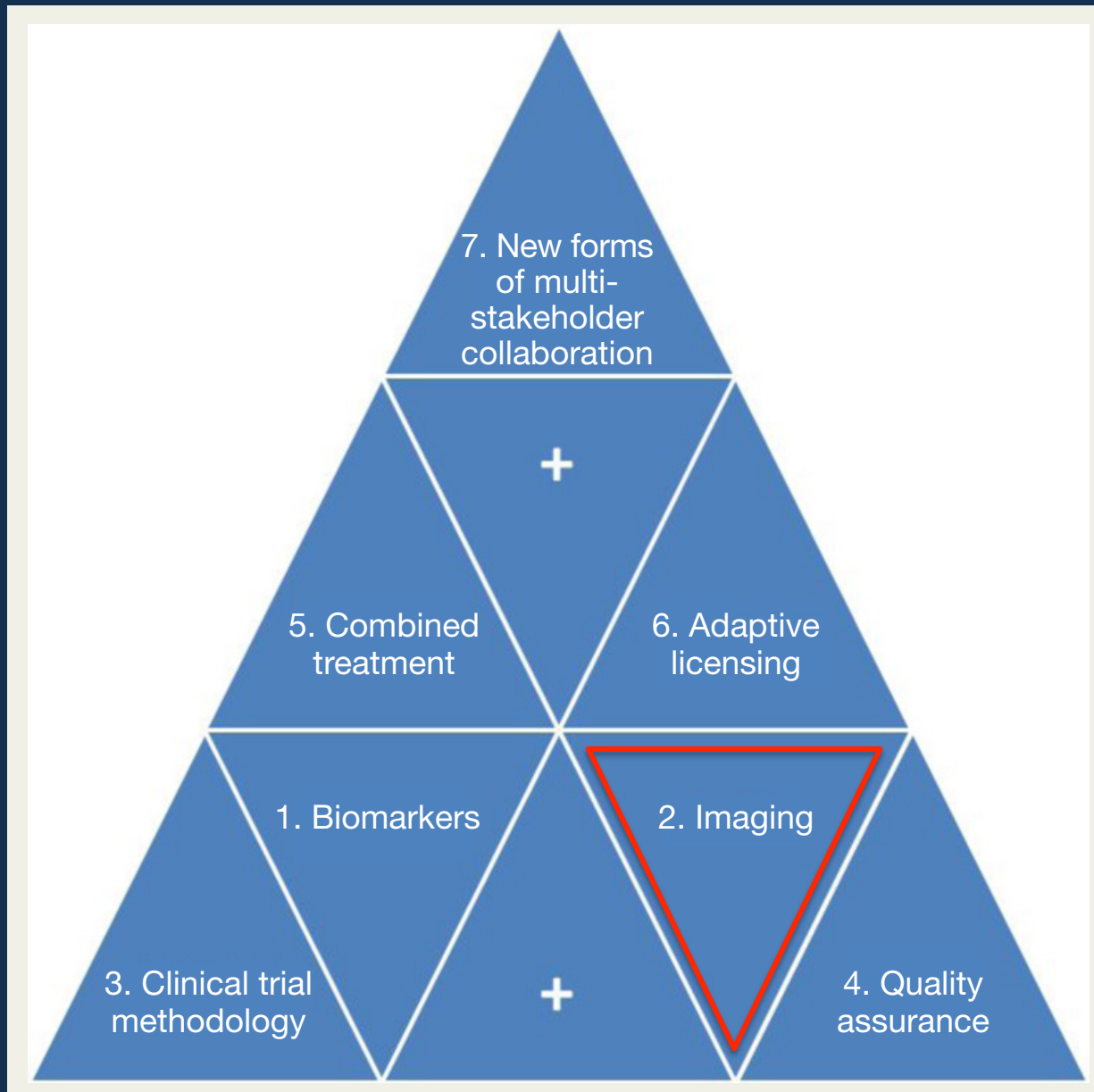
Imaging

Non-invasive imaging methods are widely used in cancer research for staging, diagnosis, response assessment, monitoring.

Some molecular imaging techniques provide an insight to tumor microenvironment in vivo and predict response or non-response at very early stage.

A reliable early identification of non-responding patients will be extremely valuable in guiding management and treatment, and to avoid that non-responsive patients are receiving unnecessary toxicity related to therapy.

These advanced imaging technologies will allow for earlier selection of candidates for new drugs, and thereby reducing the large attrition rate in the pharmaceutical development process.

The quality and the comparability of images collected within international multi-center clinical trials are not optimal.

Clinical research involving imaging can only be achieved within robust, quality assured, multi-site clinical trials supported by robust methodology and operational infrastructures allowing the processing, storage, and analysis of imaging data, which should be fully integrated with clinical and biological data.
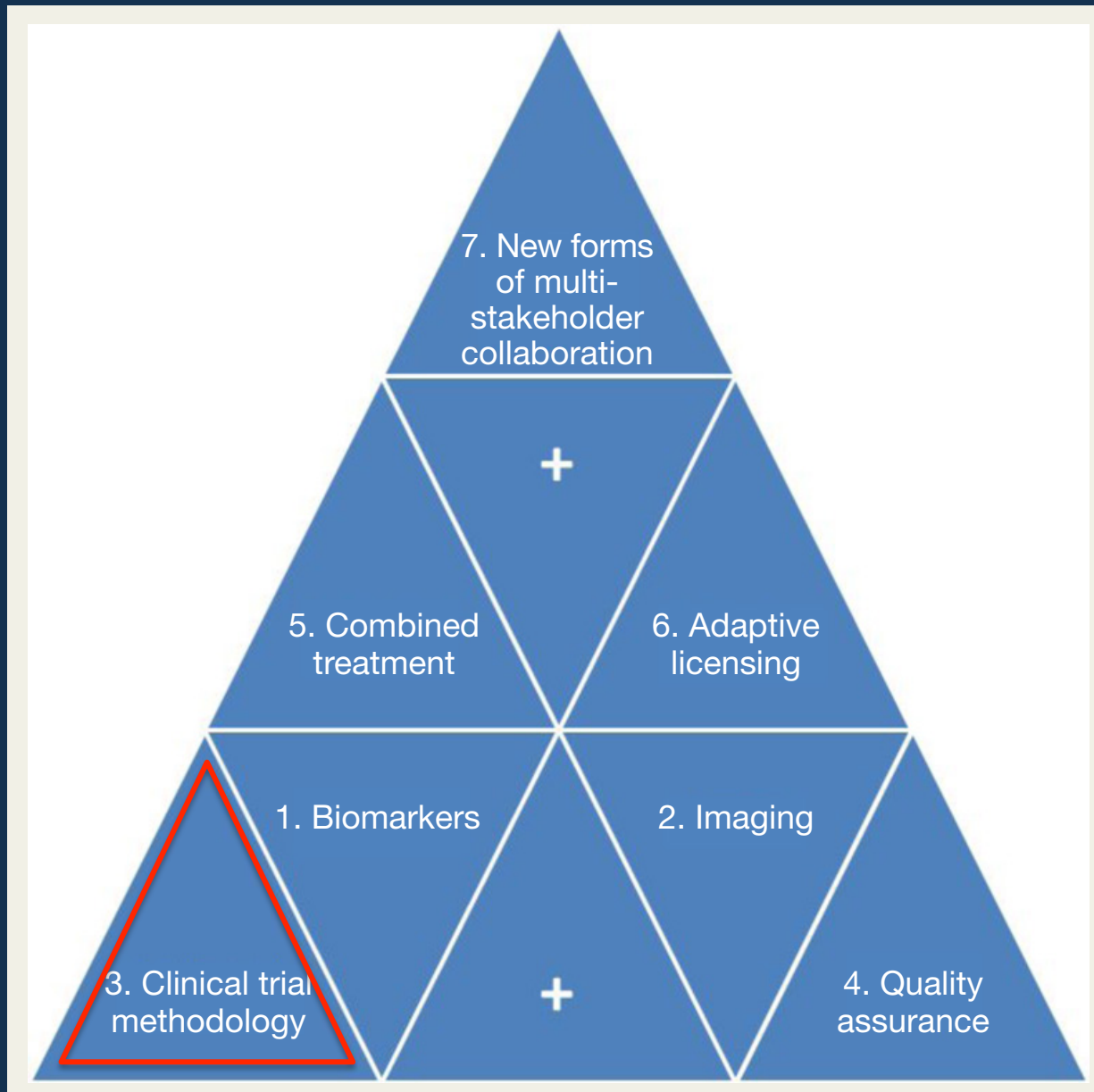
Clinical trial methodology

Optimized phase II trial design with reasonable endpoints based on a strong biological rationale, will help to facilitate smaller, faster, and less expensive confirmatory phase III trials, or even give enough data to draw the necessary conclusion after phase II study and lead to successful drug approval.

Imatinib (Glivec®, Gleevec®, Novartis), was developed rationally targeting bcr-abl protein. The results of imatinib's preliminary studies were dramatic: nearly every CML patients responded and only minimal side effects were reported. Before imatinib, prognosis was dismal and only 3 out of 10 patients survived 5 years, today the 5-year survival rates are up to 90%. The first phase I study began in June 1998, and the drug received the FDA approval in May 2001, only 10 weeks after the new drug application was submitted.

A conventional design to find optimal dose-response might use multiple fixed-size randomized groups to ensure that an optimal dose level is included, but including several groups with sub-optimal doses will decrease the study efficiency.

An adaptive design can ascertain when further data collection for a particular group is not useful, and stop data collection, decreasing the cost and time while, when planned upfront and adequately, allows keeping the study's integrity.

Smart but robust clinical research methodology using adaptive design can shorten the trial duration, the size of the studied population and ultimately the trial costs.
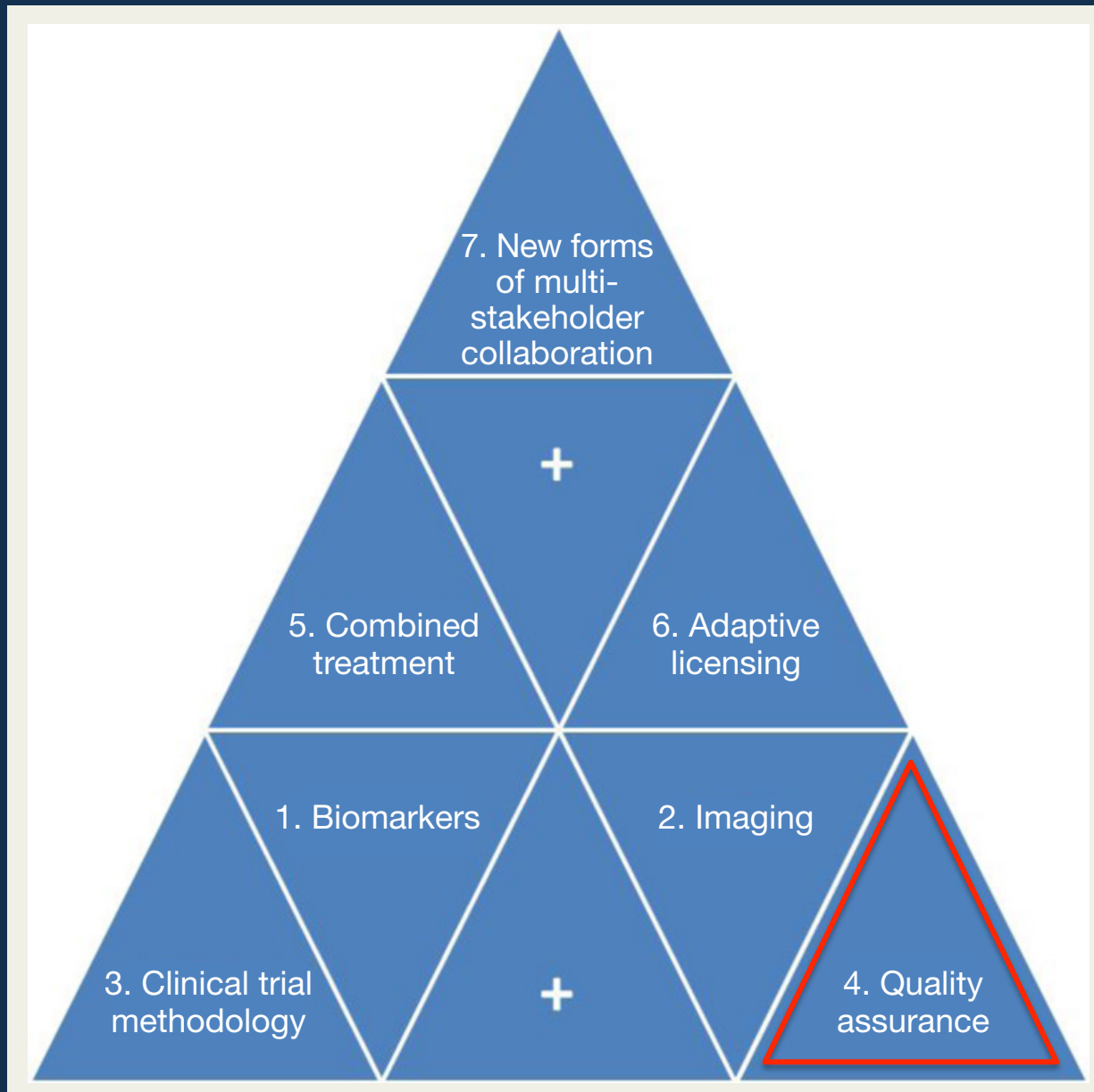
Quality assurance

Access to good quality biosamples or imaging data for translational research is fundamental to personalized cancer treatment. New skills are required to build on new platforms to integrate clinical, biological, and imaging data in the decision making process to control attrition rate of new drugs and/or decide on molecular sub-entities that will ultimately benefit new therapeutic strategies.

Screening Patients for Efficient Clinical Trial Access (SPECTA) colorectal cancer platform (SPECTAcolor) is the first prospective tumor tissue biobank and centralized biomarker analysis infrastructure for genetic profiling aiming at easy and targeted clinical trial access.

An infrastructure should implement common principles and guidelines for appropriate levels of quality assurance for biosample collection (e.g., centralized biobanking) with a sample tracking system, appropriate assay methods, and accredited laboratories to perform biomarker testing, supporting data management with biostatistics and bioinformatics experts for molecular data analysis and reporting.

The Quantitative Imaging in Oncology: Connecting Cellular Processes to Therapy (QuIC-ConCePT) consortium, created and resourced by the Innovative Medicines Initiative, aims to qualify three specific imaging biomarkers of tumor cell proliferation, apoptosis, and necrosis, to allow drug developers to demonstrate reliably the modulation of these pathologic processes in tumors of patients in future trials. The qualified imaging biomarkers will help drug developers in decision-making during phase I trials of investigational therapies, confident that the biomarkers are robust, consistent in multiple cancer centers, and reflective of the desired change in the underling tumor pathology.
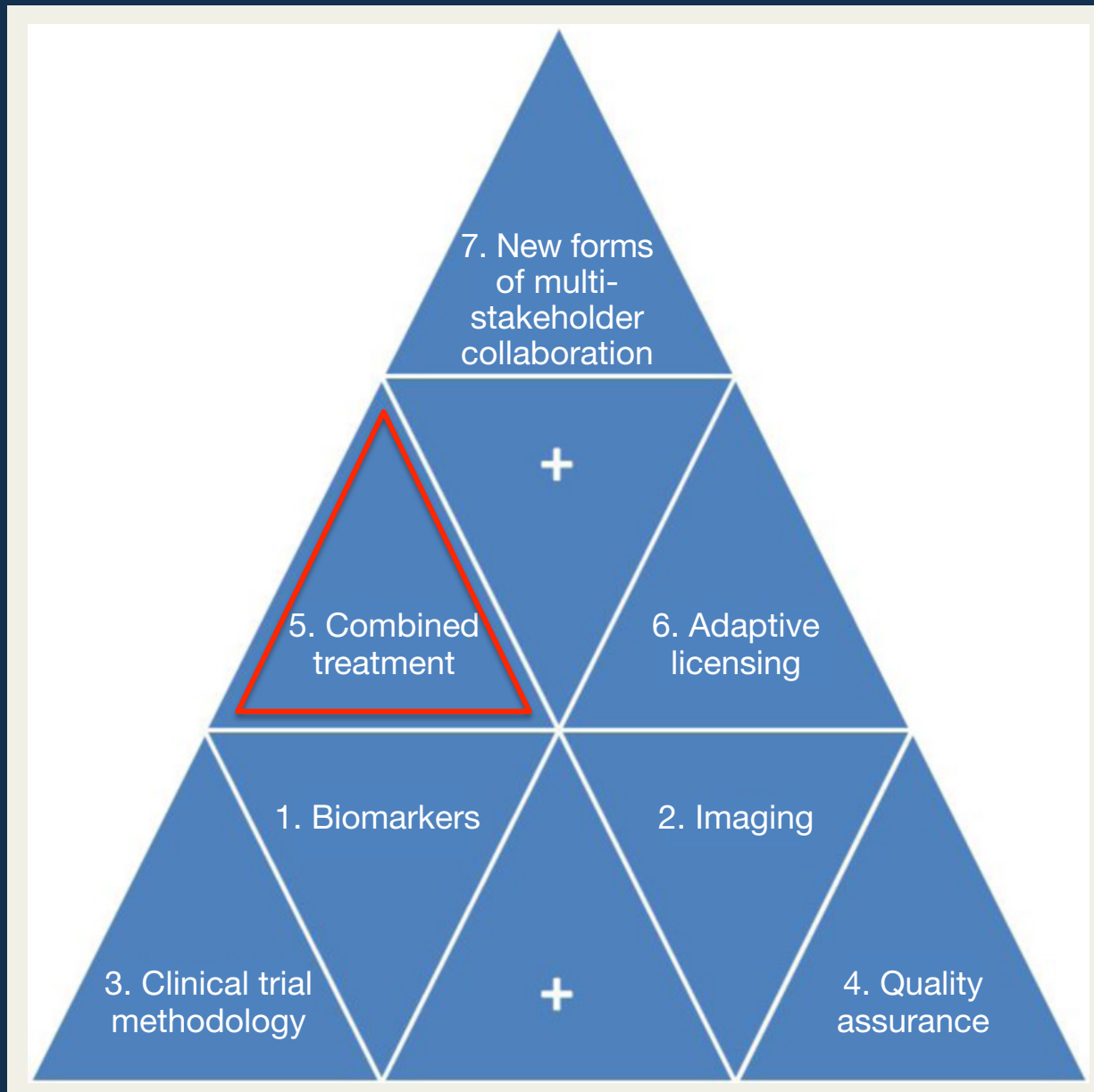
Combined treatment

Combination therapy whether it is combination of drugs, inhibition of multiple pathways or combination of modalities (e.g., combined chemo-radiotherapy) is of great importance in oncology.

New therapeutic approaches using combinations of drugs (multiple therapeutic targeted agents, or targeted agents + chemotherapy) can help to improve treatment response, minimize development of resistance, or minimize adverse events.

Combinations of two or more new therapeutic entities may be required to achieve measurable clinical benefit.

Parallel co-development in combination of two new agents has its own challenges:
- it will generally not provide sufficient information about safety and effectiveness of each of the individual new investigational drug;
- ethical concerns and low efficacy when used alone may prevent conducting parallel-group comparison with each individual compound;
- for pharmaceutical companies, the combination of new compounds in the early development increases the risk of failure, since knowledge about drug interactions may be missing;
- the involvement of several companies within one trial creates challenges to data sharing, intellectual property and marketing concerns.

The FDA has provided guidelines on the standard for licensing of new-new combination: the combination should be based on a strong biological rationale and promising preclinical data, proving that the combination is superior to existing treatments or to the individual agents alone.
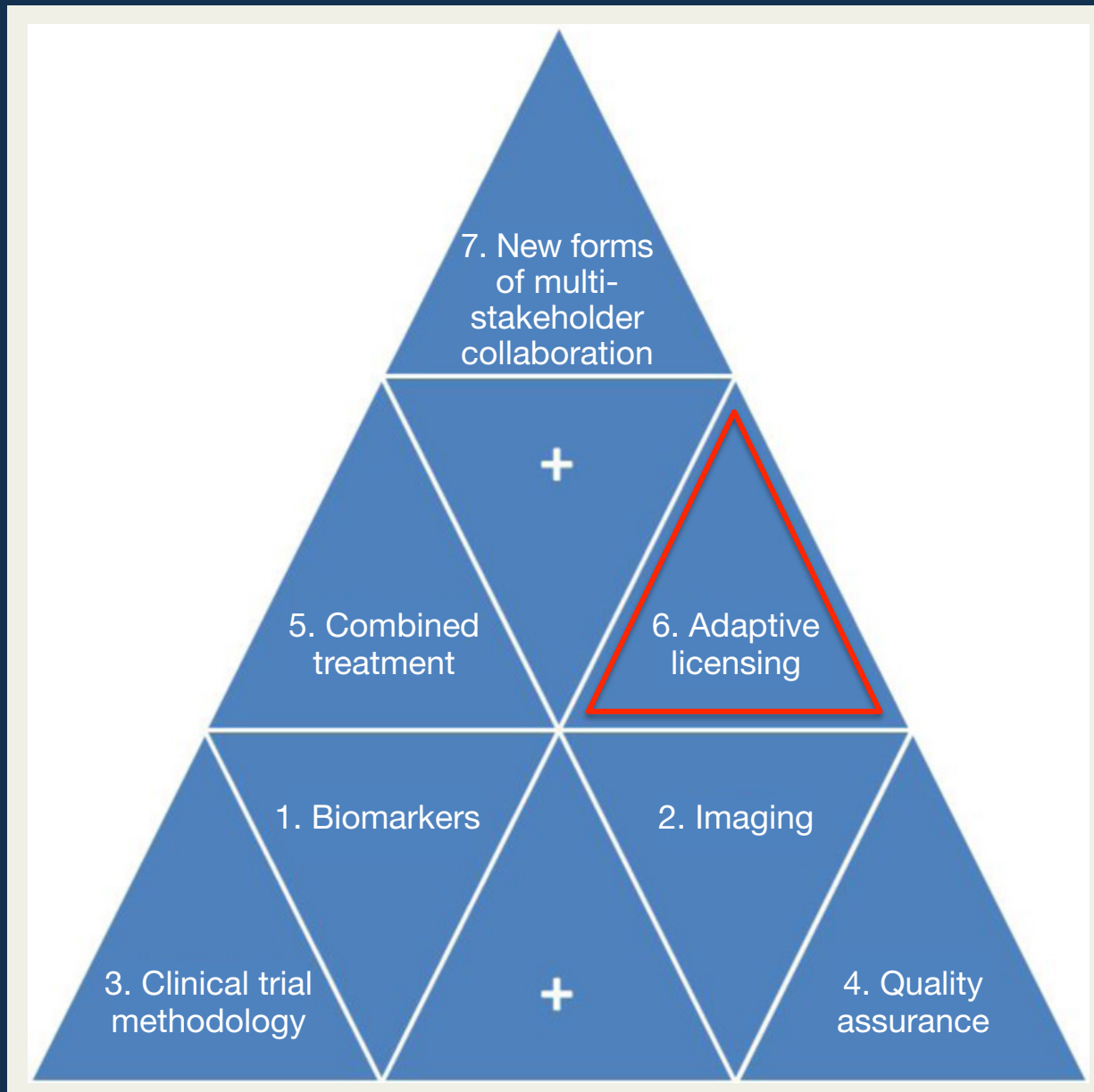
Adaptive licensing

Adaptive licensing, based on stepwise learning, progressive management and reduction of uncertainty, allows earlier access to patients with unmet medication needs, and patients, doctors, and regulators are all willing to take greater risks, including unknown efficacy and safety.

Adaptive licensing is not binary but a continuum: pre- vs. post-licensing stages will be replaced by graded, more timely and cost-effective market entry, leading to greater market stability.

Adaptive licensing (EMA), progressive licensing (Canada) accelerated approval (USA), adaptive approval (Singapore): a possible solution for earlier approval of drugs to reduce barriers to innovation, and provide timely access for patient with unmet medication needs.

For a product used to treat a life-threatening disease, the quantity of data required for an initial authorization might be considerably less than that for a product used to treat a disease for which many treatments are available.

Major concerns:
- the willingness of patients, doctors, payers, and regulators to accept a great level of uncertainty in term of safety and efficacy;
- all stakeholders will need to accept that initial approval is not just early but also conditional;
- a clear commitment is required from developers to continue conducting studies to collect data after initial licensing;
- the appropriate regulatory action to take in the event that promised studies are not performed or expected data do not become available.

Restrictions of the license due only to lack of new data will, in the case of a potential lifesaving drug, be difficult to accept for patients and doctors.
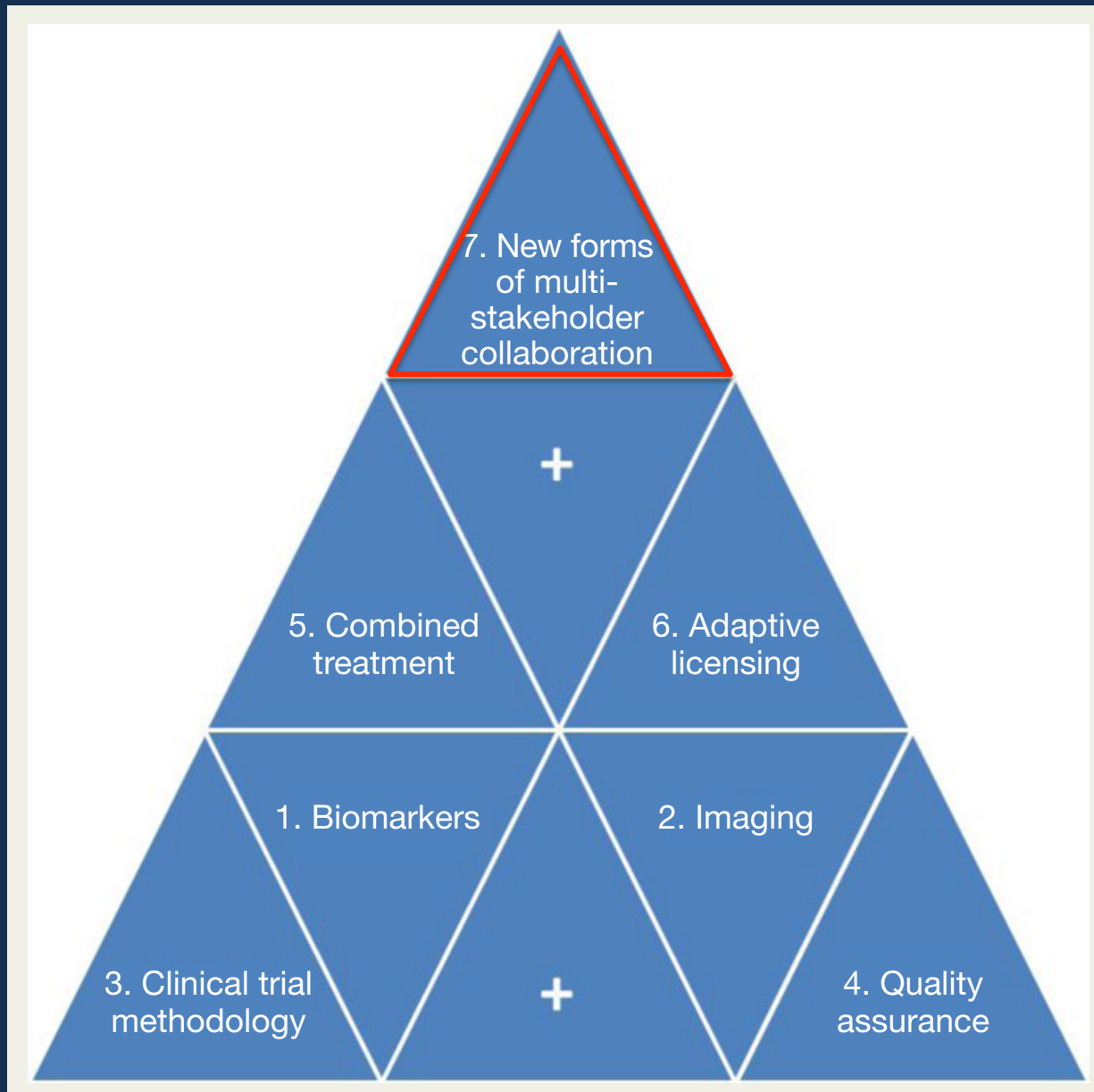
New forms of multi stakeholder collaboration

Pharmaceutical companies are collaborating in co-development of their individual products, offering a double-team approach to fight cancer.

Target Selection validation	Lab/animal studies	phase I	phase II	phaseIII	Approval
7.1	21.5	9.2	17.4	39.8	5.0 %

Academic research organizations can provide scientific advice and clinical trial methodology, and also incorporate additional translational research projects. Commercial research organizations can support site monitoring and operational management. Industry can provide new agents as well as input for regulatory aspects. The responsibility split could maximize the strengths of each stakeholder.

One of the success stories between AstraZeneca and Merck involves their capitalizing on the synergies of two different drug mechanisms, a MEK inhibitor (AZD6244) and a protein kinase B inhibitor (MK-22060) in non-small cell lung cancer, and speeded the development time (19).

Similarly, Bristol-Myers Squibb and Roche are collaborating on a melanoma product (vemurafenib).

In September 2012, ten leading biopharmaceutical companies formed a non-profit organization, TransCelerate BioPharma, with the mission to share research and solutions that will simplify and accelerate the delivery of exciting new medicines for patients.