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JSMO Young Oncologist Preceptorship

BASICS OF LEADERSHIP IN CLINICAL RESEARCH WITH A FOCUS ON LUNG CANCER

Japanese Society of Medical Oncology (JSMO) Young Oncologist Preceptorship,
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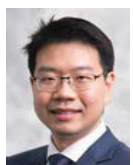
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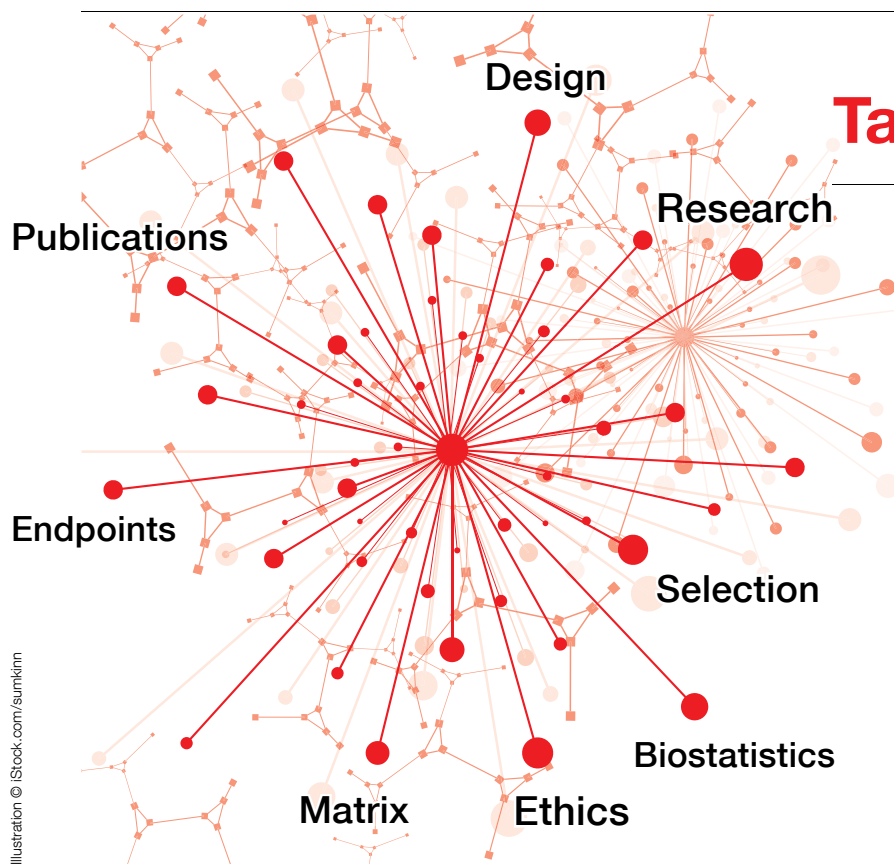


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Preface

Dear Colleagues

From 8th to 10th December, 2017, 15 young oncologists from Japan, Singapore, Taiwan, Korea and Vietnam convened in Singapore to participate in the Japanese Society of Medical Oncology (JSMO) Young Oncologist Preceptorship that was held under the guidance of a panel of renowned experts in the field of lung cancer. This Preceptorship, organized with the active support of the JSMO office, pursued a number of goals such as promoting the participants' research and refining their presentation skills. They learned to create a concept sheet for clinical trials and discussed evidence-based standard care decisions for non-small-cell lung cancer (NSCLC) patients.

For these purposes, the participants were divided into 4 groups of 3 to 4 students. Overall, 4 sessions in addition to lectures were dedicated to presentations, including the Journal Club, the Pros and Cons discussion, and the presentation of the concept sheet. Each student was required to give at least one talk. Winners of

the Pros and Cons discussion were determined based on the judgement of the panel. The agenda also contained a tour to the National Cancer Center Singapore that included visits to the histology and next-generation sequencing laboratories. This memo in Oncology special issue contains reports on the lectures given by 5 speakers that cover important aspects of the academic researcher's work, such as biostatistics, combination therapies, and principles of giving a talk in front of an audience.

Finally, an important goal of the conference was building relationships with other future opinion leaders in Asia. The participants were encouraged to socialize with each other, particularly across country borders, because internationality is a key to success in the modern scientific world. As was emphasized by the experts, the importance of relationships cannot be overestimated. Therefore, contact details were exchanged among the participants with the intention to stay in touch and to collaborate in future Asian clinical trials. Ideally, young oncologists receive mentors who promote their development, and later on they become mentors themselves, thus inducing a virtuous cycle.

With this Preceptorship, we hope to have contributed a little to enhancing patient care and scientific progress in the field of lung cancer care in Eastern Asia.



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How to approach translational research as a clinician

A career as a physician scientist can be extremely fulfilling, as it is an opportunity to make a difference in patient care by way of academic excellence. Clinical observations are explored in the translational setting based on experience and prior knowledge; eventually, the insights gained in this way can give rise to clinical innovation. For instance, a translational program is built around patients progressing on a particular targeted treatment, and new resistance mutations are identified based the analysis of repeated biopsies.

The drug development paradigms are constantly evolving. In the setting of targeted treatment, critical evaluation of the therapeutic effects of an investigational agent includes on-target and off-target effects, the therapeutic niche, and biomarker performance (**Figure 1**). Against the background of the enormous biological heterogeneity of cancer cells, there is no lack of issues worth assessing. If possible, issues should be explored that no one else is working on.

The pivotal roles of mentorship and the team

Young researchers benefit from mentors who open doors for grants or publications and provide opportunities to learn and grow. Ideally, mentorship creates a safe environment and facilitates autonomy as well as scientific independence. The mentor does not necessarily have to work at the researcher's institution.

Also, team collaboration is indispensable. It is important to find like-minded research partners. Challenging tasks such as the identification of a high-precision biomarker require dividing the research program into layers that are dealt with by different teams. For example, the Singapore-based Translational and Clinical Research Flagship Programme consists of three teams that are assessing cancer stem cell biology, genomics, and translational therapeutics. It was demonstrated that the number and distribution of driver aberrations in *EGFR*-mutant NSCLC shows great variety, which is also true for the

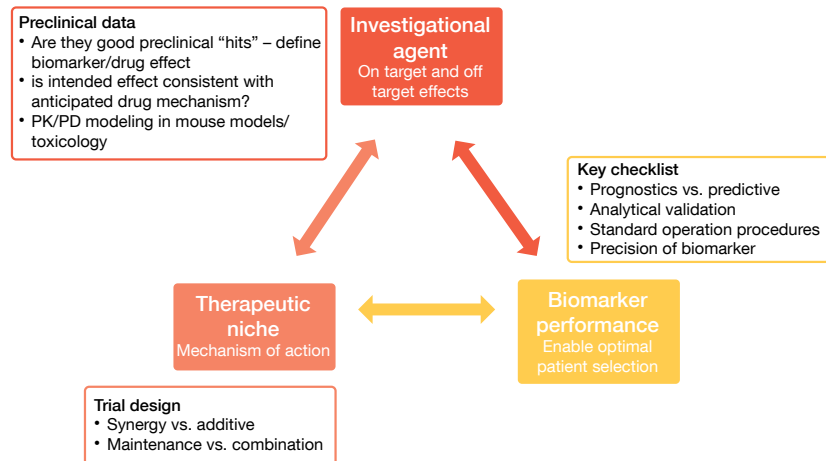


Figure 1: Critical evaluation of the therapeutic effect of a drug

same patient over time [1]. Co-drivers, which especially accumulate in smokers, can portend poor outcomes. According to these insights, the genomic landscape dictates clinical trajectories.

Learning from exceptional responders

Even negative trials can provide precious clues. In a study investigating gefitinib plus radiochemotherapy, two exceptional responders showed a silent mutation, which was a single nucleotide polymorphism Q787Q [2]. Other non-canonical mechanisms of EGFR addiction were therefore assessed in patient-derived cell lines. This analysis revealed that EGFR TKI sensitivity varies considerably according to Q787Q genotype [3]. The key experiment to prove this observation was single nucleotide editing, which indeed induced TKI sensitivity. Long non-coding RNA EGFR-AS1 that mediates EGFR addiction turned out to be sufficient to cause resistance. This new EGFR-mediated mechanism could be explored in the future.

Developing a strategy for a research career

The "research startup" calls for some basic traits, such as curiosity, creativity, and conviction. Formal education is always useful. Moreover, the research

track entails the acquisition of experience in translational research, manuscripts, and grants. Young researchers should not be picky but rather take any chance to publish a paper, even if it is for a less renowned journal. There is a need to differentiate between performing research on a professional level and on a hobbyist level; the former takes more time and requires continuous training, deep knowledge, high discipline and lifelong learning.

With regard to developing a scientific framework for clinical practice, the significance of relationships must not be underestimated. Managing relationships is crucial; this applies to the clinical team as well as to patients, departments, mentors, trial coordinators, scientific collaborators, journal editors, industry representatives and national/regional program representatives. International connections allow for being part of a broader community, e.g. JSMO or the International Association for the Study of Lung Cancer (IASLC). The "ripple" effect of research excellence includes the impact on clinical service, opportunities for mentorship and enhanced relationships with colleagues.

Challenges for the clinician-scientist

The worlds of clinicians and scientists differ in fundamental ways. Clinicians

think in a parallel manner and receive immediate gratification when the patient responds, although they are operating in uncertainty. On the other hand, scientists think sequentially, experience delayed gratification and engage in controlled experiments. There are synergies and common traits as well, but it is up to the individual to decide which part of the spectrum they find more appealing. Young physicians need to be aware of their traits, interests and motivations. Perspective is important, as getting tunnel-visioned should be avoided. Generally, the clinical-scientist should not be

overly focused on his or her work; it is necessary to take time off and to pursue hobbies and sports.

Overall, it is commendable to play to one's strengths and take some calculated risks, as there will be some uncertainty one operates under. Persistence and luck are necessary ingredients for the physician scientist's career. By setting up conditions that allow for good opportunities, it is possible to capitalize in the best possible way when luck comes round.

Take home message

Conducting translational research as a clinician can be highly rewarding as it accelerates the discovery of effective cancer therapeutics, but it is also demanding. It is of utmost importance to interact with the community and to engage in scientific societies. Manuscripts, grants and relationships with other experts constitute the currencies of academic medicine. Mentorship can open doors and support the "ripple" effect of research excellence.

Wei Yuan

Statistical considerations in randomized controlled trials

Basic statistical concepts

In the setting of a clinical study, sample data are used to make an inference for the entire population. Generally speaking, results from a randomized clinical trial (RCT) will be unlikely to be exactly the same as population parameters, which is the reason for bias involved. In addition, when a RCT were repeated 100 times, results obtained each time would not be identical, which is the reason for uncertainty involved. Statistics provides methods to deal with these uncertainties.

Prior to the start of a study, a research question needs to be established, followed by PICO (population, intervention, comparator, outcome) framework. Once these parameters are clearly defined, investigator can move on to issue of hypothesis testing.

Hypothesis testing

A study hypothesis is a statement concerning the value of one or more parameters of interest within the study population. It is difficult to prove that a study hypothesis is true using sample data, because the hypothesis is concerning the parameters at the population level and usually not all the data

from the population will be included as sample data in a trial. Therefore, a "falsificationist" approach is used: the original study hypothesis is turned into the opposite which has been termed as null hypothesis (H_0), and a researcher tries to reject the null hypothesis. The original study hypothesis has been termed as alternative hypothesis (H_1). In a study with a research question asking whether there are differences in a certain clinical outcome between new treatment and standard of care, the null hypothesis can be that there is no difference between two treatments with regard to the certain outcome. If the study provides enough evidence to reject the null hypothesis, a significant difference between two treatments is then demonstrated through the study. If not, there is no significant difference, which means that there is not enough evidence to conclude that there is a difference between two treatments. The insignificant

results can be due to many reasons, and insufficient sample size is one of the reasons.

One-sided hypothesis testing shows if one treatment is superior to the other. This gives rise to a hazard ratio (HR) below or above 1. In the examples below, progression-free survival (PFS) is the assessed outcome.

- + H_0 : $PFS_1 < PFS_0$, $HR > 1$.
- + H_1 : $PFS_1 > PFS_0$, $HR < 1$.

Two-sided testing establishes the difference between two treatments. In the example below, the null hypothesis says PFS does not differ across the treatments, whereas the alternative hypothesis says it does.

- + H_0 : $PFS_1 = PFS_0$, $HR = 1$
- + H_1 : $PFS_1 \neq PFS_0$, $HR \neq 1$

Type I and II errors, power and p value

In a clinical study, researchers need to make a decision whether the null hy-

TABLE 1
Type I and II errors

Decision	Null hypothesis is	
	True	False
Reject	Type I error (false positive)	Correct inference (true positive)
Not Reject	Correct inference (true negative)	Type II error (false negative)

pothesis can be rejected or not. The decision based on study results is one thing and the fact whether a null hypothesis is true is another. Here, the type I and type II errors come into play (Table 1). Type I error means that a false positive decision is made: the null hypothesis is rejected when it is actually true [4]. On the other hand, type II error relates to false negative decision: the null hypothesis is false, but the researcher fails to reject it. While conventionally type I error is defined at a level of 5 %, type II error has been set at 10 % or 20 %. The power of a study describes the probability of detecting effectiveness when the intervention is truly effective, leading to a true positive conclusion. By definition, the power amounts to 80 % or 90 %, as it is calculated as 1 minus type II error. Of course, the power of a study is the better the higher it is.

The p value describes the probability of observing the study result or a more extreme result if the treatment is ineffective. For example, if a targeted drug improves PFS compared to chemotherapy with a p value of < 0.0001, the probability of observing the study result or a more extreme result is 0.0001 if the targeted drug does not improve PFS. It is still possible to obtain an extremely small p value when the new intervention shows no activity and when this occurs the type I error is made. Notably, the p value does not reflect the probability of the treatment being ineffective.

Confidence intervals

The confidence interval (CI) is a statistical mean to address uncertainty of results from repeated sampling under the same conditions. A 95 % CI signifies that

in 95 times out of 100, the CI will contain the true value of the population parameter that was tested. If the CI for the HR crosses 1, this indicates insignificant result.

Sample size calculation

The sample size is usually calculated based on the primary outcome, which implies that a clearly defined primary objective and primary endpoint must be established. Moreover, the minimal clinically important difference/ proportion or width of the confidence interval are necessary for the calculation, as well as the choice between one-sided and two-sided hypothesis testing. Finally, the significant level and target power need to be considered.

Statistical issues of RCTs

From the onset of study conceptualization, statistical issues need to be dealt with. This involves protocol development and randomization as well as the interim and final analyses and reporting. Table 2 illustrates the biostatistician’s contribution along the way.

Endpoints

It is recommended to use only a single primary endpoint. Multiple primary outcomes are of course an option, but in this case, methods of multiplicity should be considered. The EMA guideline on multiplicity issues in clinical trials contains recommendations of different methods to adjust for multiplicity. When two or more primary variables are needed to describe clinically relevant treatment benefits [5], all of these must be significant to enable the researcher to claim clinical benefit. If two or more primary variables are ranked according to clinical relevance, the most clinically relevant outcome must be tested first. Only if this is significant, the second one would undergo evaluation.

When multiple secondary outcomes have been defined, there are three different settings. If all of the variables are intended to provide only supportive evidence, no confirmatory claim can be made. The second scenario relates to secondary variables which may become the basis for additional claims; here, a hierarchical approach can be consid-

TABLE 2
Involvement of the biostatistician at different times during a clinical study

Early discussion	+ Formulate a research question
	+ Conceptualize a study design
	+ Define study endpoints
	+ Calculate the sample size
	+ Research grant application
Protocol development	+ Analysis of preclinical experiments
	+ Write study endpoints, sample size calculation, statistical methods
	+ Review the full protocol
Randomization	+ Provide randomization list for treatment allocation for web randomization
	+ Prepare back-up randomization envelopes
	+ Prepare emergency code break envelopes
CRF and database design	+ Review CRF and CRF annotation
	+ Review database design
Interim analysis	+ Provide interim analysis report
	+ Provide both open and closed section reports
	+ Communicate with DMC members
Final analysis	+ Prepare statistical analysis plan
	+ Perform data analysis
	+ Output control and QA
	+ Data interpretation
Reporting	+ Write analysis report
	+ Write statistical method and results section of manuscript
	+ Review the full manuscript
	+ HA response analysis and writing
Secondary analyses	+ Formulate, conduct and report secondary analysis

Abbreviations:
CRF: Case report form; DMC: Data monitoring committee; QA: quality assurance; HA: Health authority

ered. The primary outcome needs to be significant prior to testing the secondary outcomes. Finally, if the variables are indicative of a clinical benefit but were not planned as primary outcomes, further studies are called for.

Randomization

Block-stratified randomization has become increasingly popular. Patients are allocated to treatment within a subgroup of a certain size; this implies that allocation is balanced within each block and offers an obvious advantage if the study has to be terminated prematurely. In a setting of simple randomization without blocks, the first 50 patients might be randomized to placebo and the next 50 patients to the intervention, which creates a problem of severe imbalance when the study is prematurely stopped, such as at 25 patients. The stratified randomization approach guarantees allocation balance within each stratification factor. The use of a block size of only 2 patients should be avoided due to high risk of guessing the treatment allocations

Allocation concealment means that the person taking care of the randomization is unaware of what the next treatment allocation will be. This prevents manipulation of the allocation.

Analyses

Interim analyses need to be pre-planned. Aspects to consider in this context include the number of patients and the time of the analysis. Both safety data and efficacy data can be analyzed. An important topic is early stopping criteria, which must be defined in advance.

The final analysis requires a statistical analysis plan detailing the type of analysis, the study population (intent-to-treat, per-protocol, treated), the statistical method, and mock Tables/ Figures/ listings that give an idea of the appearance of the final Tables and Figures. Ideally, most of the analyses are pre-planned before database lock or breaking the blind. The same methods should be used for the primary efficacy analysis as the methods used for sample size calculation. Exploratory analyses are possible, but researchers should state clearly in their final report that these were not pre-planned.

Subgroup analyses have become a prominent part of many cancer studies. However, their reliability is questionable, as RCTs are usually not powered to support subgroup analysis. Sun et al. published criteria for the assessment of the credibility of subgroup analyses including factors such as design and context [6]. Essential aspects relate to the

question of whether the direction of the subgroup effect was specified a priori, and its consistency with other results. A significant subgroup effect should be independent. For example, the analysis might show that males benefit to a greater extent from a certain treatment than females, but this observation loses its value when it is found that patients in the male group are generally younger than those in the female group. Lagakos et al. demonstrated a positive correlation between the number of subgroup analyses run in a trial and the likelihood of false positive results [7].

Reporting

Certain standards have been defined for the reporting of RCTs. The Consort Statement provides a list of items that need to be included [8].

Take home message

The PICO framework is used to frame a clinical question. From the start of a randomized controlled trial, issues arising from the choice of endpoints, randomization and various types of analyses including interim and subgroup analyses need to be dealt with.

James Chih-Hsin Yang

Combination of molecularly targeted drugs in lung cancer

Most of the targeted agents currently recommended for the treatment of lung cancer are administered as single agents. However, there is a rationale for combinations, as two drugs might act in an additive or synergistic manner and may control different populations of tumor cells. Tumor heterogeneity plays a major role here, especially in patients who have already developed resistance to their first treatment.

Principles of evaluating combination regimens

Generally speaking, research into dual targeted inhibition in NSCLC patients has not yielded very successful results yet. If researchers plan to assess such an approach, it is important to create a strong scientific background portending the utility of a certain combination in order to avoid wasting time, money

and effort. Pharmacological interactions must be kept in mind, as multiple pathways contribute to cell survival. Moreover, pharmacokinetic aspects (e.g., dose adjustments) deserve attention. The phase I is dedicated to working out the dose and feasibility of the combination. Here, the tests should demonstrate that the plasma level that is expected to inhibit the pathways is indeed achieved. Also, both drugs have to be

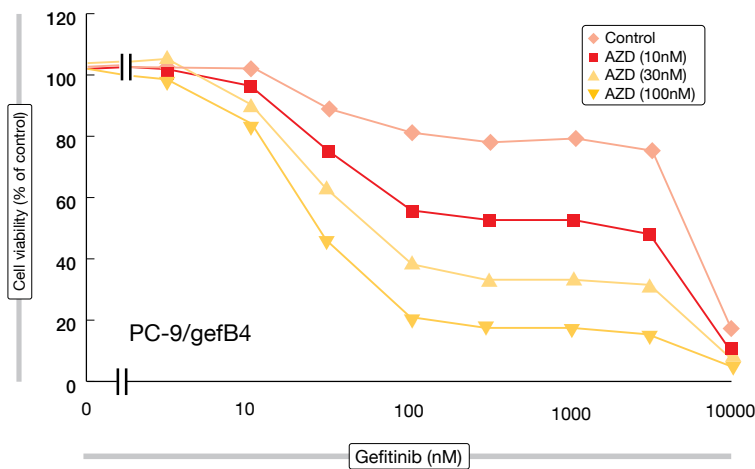


Figure 2: Reversal of gefitinib resistance in PC-9 cells using the MEK inhibitor AZD6244. Modified from Huang MH et al. [9]

shown to reach effective plasma concentrations. The phase II focuses on proving the clinical efficacy of the combination.

For phase III, there is a number of possibilities to evaluate dual targeted inhibition. Academic cancer groups need to work out if comparing A plus B to A or B is more useful than evaluating sequences of the two drugs. The focus of pharmaceutical companies will solely be on investigating the combination compared to the single agents. However, there is a rationale for sequences, as drugs can change the clonality and the tumor microenvironment, which might affect the activity of the subsequent treatment.

Resistance mechanisms in EGFR-mutant NSCLC

On the preclinical level, Huang et al. provided evidence that a two-drug combination with gefitinib and a MEK inhibitor might be used in acquired gefitinib resistance [9]. The MEK inhibitors AZD6244 (**Figure 2**) and CI1040 were shown to reverse resistance in cells harboring EGFR mutations. These cells, as opposed to those with PC-9 wild type, have developed EGFR exon 19 deletion and thus have become anti-EGFR-resistant.

In addition, the NRAS Q61K mutation was identified in the gefitinib-resistant cells but not in those with PC-9 wild type. Although there are currently no NRAS-targeted agents available, MEK inhibition can be used as MEK is located downstream in the RAS/RAF/MEK path-

way. A phase I/II study testing gefitinib plus the MEK 1/2 inhibitor selumetinib is ongoing in EGFR-TKI-resistant patients with EGFR T790M mutation.

cMET plus EGFR inhibition

EGFR inhibition combined with MEK inhibition is an example of a vertical blockade. The horizontal blockade, on the other hand, relates to the inhibition of two pathways that both independently trigger the same signal transduction cascade. An example of a horizontal blockade is MET inhibition in combination with EGFR inhibition in acquired EGFR TKI resistance. MET amplification occurs in approximately 20% of erlotinib- or gefitinib-treated NSCLC patients, and in approximately 5% of erlotinib/ gefitinib-naïve patients [10]. In gefitinib-resistant HCC827 cells, both EGFR and MET inhibition are required to induce apoptosis.

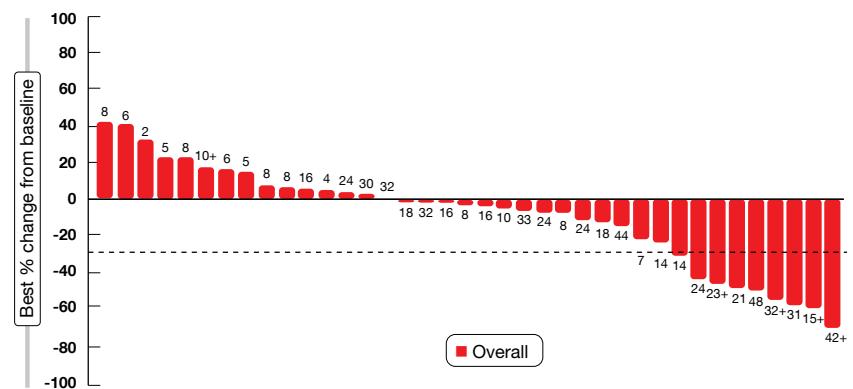


Figure 3: Tumor responses to INC280 plus gefitinib in patients with EGFR-mutant, gefitinib-resistant, MET-positive NSCLC. Modified from Wu Y-L et al. [14]

Another study confirmed that resistance does not come alone. Patients with EGFR T790M mutation sometimes also display MET amplification and vice versa, which complicates the picture [11]. Patients with the T790M mutation will not respond if gefitinib is added to a MET inhibitor. Overexpression of the hepatocyte growth factor, which is a MET ligand, also contributes to EGFR TKI resistance. These patients might benefit from a MET inhibitor that is administered along with EGFR TKI therapy.

Preliminary clinical data from the phase Ib expansion cohort of the TATTON trial suggest encouraging activity of the EGFR TKI osimertinib combined with the MET inhibitor savolitinib in patients with EGFR-mutation-positive, MET-positive NSCLC [12]. The response rates ranged from 33% to 61%. However, the possibility of adverse events must be kept in mind. Another arm of the TATTON trial evaluated osimertinib in combination with the checkpoint inhibitor durvalumab, and this regimen led to unacceptable rates of interstitial lung fibrosis [13]. The lung changes occurred with a considerable delay after the end of the study, and the phase III trial that was already ongoing had to be terminated.

Results obtained with INC280

The investigational oral MET inhibitor INC280 was tested together with gefitinib in patients with EGFR-mutant, MET-amplified NSCLC progressing on EGFR TKI treatment [14]. In this phase Ib/II, open-label, multicenter study, molecular pre-screening identified patients with MET dysregulation who had

developed resistance to gefitinib or erlotinib. Thirty-eight patients were included in the phase II of the trial; they responded well to the treatment with INC280 plus gefitinib (**Figure 3**).

These patients had not been tested for the *EGFR* T790M mutation, but it can be assumed that they were not T790M-positive, as otherwise they would not have responded. Pronounced *MET* amplification or high *MET* protein expression might preclude the presence of T790M, although further study into this is required.

BRAF alterations

Although BRAF inhibition works well in patients with melanoma, single-agent dabrafenib therapy gave rise to a surprisingly low response rate (RR) of 33 % in patients with BRAF^{V600E}-mutant metastatic NSCLC participating in a multicenter, open-label phase II trial [15]. RRs achieved with the blockage of a genuine driver mutation are expected to range between 50 % and 70 %.

As for patients with melanoma, the combined approach using both BRAF and MEK inhibition, which induces vertical blockade, was shown to yield improved results in the NSCLC setting. A phase II trial investigating dabrafenib plus trametinib revealed an RR of 63 %, and disease control occurred in 79 % [16]. Also, PFS was longer with the combination than with dabrafenib alone (9.7 vs. 5.5 months). The rationale behind the addition of a MEK inhibitor is based on

the observation that compensatory over-activation of downstream MEK ensues when a BRAF inhibitor is administered [17-21]. Early resistance and skin cancer can occur. These effects are prevented by the use of the combination.

Unexplained phenomena

Not all of the targeted agents can be combined, however, and the analysis of combinations does not always reveal predictable results. For instance, erlotinib plus cetuximab evoked no responses whatsoever in a trial setting aimed to overcome acquired resistance to anti-EGFR treatment [22]. On the other hand, data obtained in the mouse model showed activity of afatinib plus cetuximab regardless of the presence of the *EGFR* T790M mutation [23]. A variety of anticancer agents was tested here, but only this combination induced dramatic shrinkage of erlotinib-resistant tumors. The authors noted that afatinib and cetuximab jointly depleted both phosphorylated and total EGFR in an efficient manner.

These observations are actually unexplained against the background of the current knowledge of molecular pathways. The synergistic effect of a TKI and an antibody cannot be due to vertical or horizontal blockade. One of the hypotheses relating to this phenomenon states that once the extracellular domain binds to the antibody, the tyrosine kinase conformation will change. However, there is currently no way to assess

conformational changes. Another theory refers to the fact that homodimerisation is not symmetric but rather asymmetric. TKIs only exert their effects by binding to one part of the EGFR, which means that binding must occur at the correct side of the tyrosine kinase [24]. If the drug binds at the inactive site, it will not show any activity.

Nevertheless, the interest in combination therapy has been renewed due to the issue of osimertinib resistance, as there is no targeted therapy available for these patients. The experiences described above illustrate how little is actually known at present.

Take home message

Potential additive or synergistic effects provide the rationale for combinations of targeted agents in the treatment of NSCLC, particularly in the setting of resistance, as different populations of tumor cells might be controlled using this approach. Combinations work by either vertical or horizontal blockade. Overall, studies have yielded somewhat contradictory results, although some findings are promising. EGFR inhibition appears to be active together with MET or MEK inhibition, which also applies to the combination of BRAF and MEK inhibitors. The risk of unacceptable adverse events must be kept in mind.

Yuichiro Ohe

Precision medicine in the field of lung cancer in Japan

In 2013, Japanese researchers launched a nationwide, prospective, observational study for patients with lung cancer and genomic alterations, called Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM-Japan). The number of participating institutions has risen greatly over time, and today 241 institu-

tions from almost all regions across the country are part of the project.

The tumors of patients with locally advanced or metastatic NSCLC who participate in LC-SCRUM are tested centrally for genomic alterations. Testing is based on fresh frozen samples plus formalin-fixed, paraffin-embedded (FFPE) tissue, or pleural effusion. Until

2015, real-time PCR (RT-PCR) and fluorescence in situ hybridization (FISH) have been the technique of choice for non-squamous NSCLC, but it has been replaced by multiplex genome analysis using next-generation sequencing (NGS). If testing reveals an actionable aberration, the patient enters a trial. These studies can be either investigator-

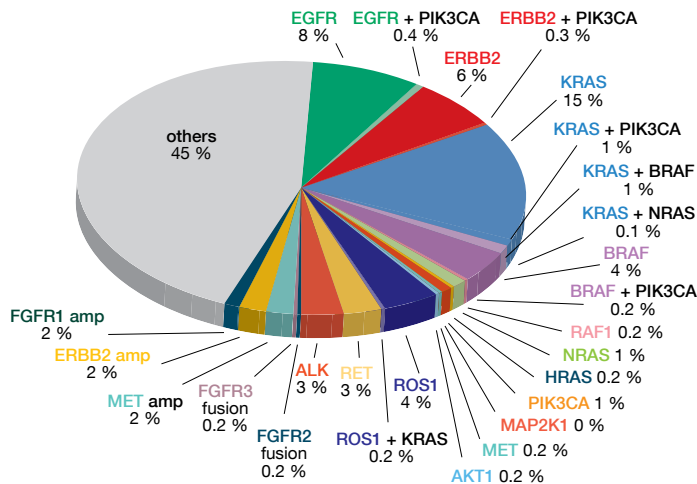


Figure 4: Screening results obtained in 1,688 non-squamous NSCLC samples collected in LC-SCRUM-Japan

initiated or company-initiated. The program has expanded greatly; initially, it only covered patients with non-squamous, *EGFR*-mutation-negative NSCLC, but today there are also distinct projects for squamous NSCLC, small-cell tumors, and for biomarker assessment in the immuno-oncological setting (LC-SCRUM-Japan IBIS). Also, patients with unknown *EGFR* mutation status started to be accepted into the screening program.

Screening results

As of 30th September 2017, 4,820 patients have been tested in the LC-SCRUM-Japan project. Fresh frozen samples plus FFPE constituted the majority of samples. More than 90 % of these were adequate for both RT-PCR and NGS. Out of 3,394 samples that were tested using RT-PCR or NGS until the end of August 2017, 4 %, 3 % and 2 % tested positive for *ROS1*, *RET*, and *ALK* fusion, respectively. Ninety-one percent of the other samples were negative for these three fusion genes as well as for *EGFR* mutation.

Testing of non-squamous NSCLC by means of either the OncoPrint™ Cancer Research Panel (OCP) (**Figure 4**) or the OncoPrint™ Comprehensive Assay (OCA) showed a range of established aberrations, such as *EGFR* mutation, *HER2* mutation, *BRAF* mutation, *ALK* fusion, and *FGFR1* amplification. Three percent of patients included in LC-SCRUM-Japan were positive for *MET* exon 14 skipping mutation.

Screening results for squamous cell lung cancer using OCP revealed that *FGFR* and *PIK3CA* aberrations were

prevalent here, as well as *KRAS* mutations. For tumors with small-cell histology, the proportion of identifiable aberrations was quite low. Alterations included *PIK3CA* mutation, *PTEN* mutation, *MYC*, *MYCL1* and *MYCN* amplification, *EGFR* mutation, *FGFR1* gain, *KRAS* mutation, and *TSC2* mutation. Eight percent of the patients showed PI3K/AKT/mTOR pathway mutations.

LURET and other trials

Patients who tested positive for *RET* rearrangement according to both RT-PCR and FISH were included in the phase II LURET study that assessed the efficacy of the oral *RET* inhibitor vandetanib at a dose of 300 mg/d after at least one prior chemotherapy. Among 1,433 screened patients, 34 patients tested *RET*-posi-

tive, and 19 entered the trial including 2 ineligible patients [25]. Objective response rate (ORR) constituted the primary endpoint. The study was positive, with an ORR of 53 % (90 % CI: 31-74 %) (**Figure 5**).

To date, a total of 653 NSCLC patients with actionable gene alterations have been screened for clinical trials. Among these, 174 had *HER2* amplification/mutation, 135 had *ROS1* fusion, and 96 were shown to harbor *RET* fusion. *ALK* fusion was present in 78 patients, *MET* amplification/exon 14 skipping mutation in 76, *PIK3CA* mutation in 52, and *NTRK3* fusion in 1 patient. Overall, 128 patients have entered clinical trials. Both well-known agents (e.g., crizotinib, alectinib) and experimental drugs are evaluated. For some alterations, multiple treatment approaches exist; patients with *RET* fusion, for instance, have entered studies testing vandetanib, lenvatinib, and alectinib. Twenty-five clinical trials targeting genomic alterations that have been identified in LC-SCRUM-Japan are ongoing or have been conducted to date.

SCRUM-Japan

The next step after the inception of LC-SCRUM-Japan was the implementation of SCRUM-Japan, a nationwide cancer genome screening project which covers entities beyond lung cancer. It is based on collaborations between academic institutions, the industry and the government; funding is provided by 16 pharmaceutical companies as well as

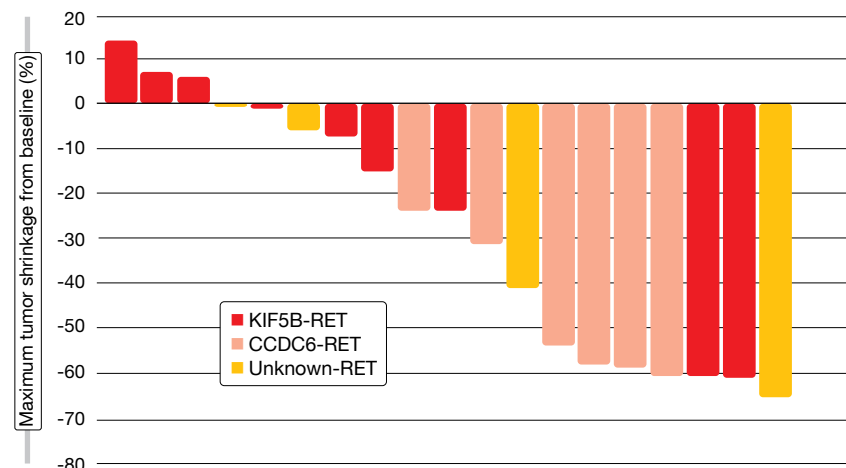


Figure 5: LURET trial: responses to vandetanib in patients with *RET*-rearranged NSCLC. Modified from Yoh K et al. [25]

through grants from the Japanese Agency for Medical Research and Development (AMED) and the National Cancer Center. Public databases can be used to conduct research.

Delivering appropriate therapeutic agents to each cancer patient is at the heart of SCRUM-Japan. This includes the nationwide cancer genome screening for orphan-fractionated cancers, the clinical development of corresponding therapeutic products based on cancer genome alterations, and a strong support for the clinical development of companion diagnostics such as NGS multiplex genomic diagnostics.

Take home message

LC-SCRUM-Japan, a nationwide, prospective, observational study, is providing the basis for a number of trials investigating targeted agents in patients with lung cancer carrying rare driver oncogenes. This project has expanded considerably after its launch in 2013. Meanwhile, SCRUM-Japan has been established. This is the first nationwide genome screening network that is conducted in collaboration with industries and the academic world with the aim of developing precision medicine in Japan.

Tony Mok

Behind the magic of giving academic lectures

According to a Wikipedia definition, a presentation is the act of giving something to someone in a formal way. This should not just be a narration of information or data; ideally, a presentation should contain a story, which means that a plot, characters and a narrative point of view need to be included. All of the established types of presentation, i.e., oral abstract presentations, abstract discussions and education symposia, can be created to match this requirement.

Oral abstract

Oral abstracts follow a formal pattern. The mandatory framework consists of background, method, results, and conclusion. Still, a story can be made out of it by highlighting the idea underlying the study, the way it was investigated, the findings, and the impact these will make on clinical practice. It is commendable to define one key point for each of these areas and to highlight it accordingly. The rest of the talk is of limited importance.

Abstract discussion

Compared to abstract presentations, abstract discussions leave the presenter

more space for creativity. This is not a presentation of data; rather, data should be used to present the story. A catchy title and teaser is likely to attract the attention of the audience. Ideally, the plot should be as controversial as possible, but yet balanced, to make it interesting. As data can always be interpreted in different ways, the controversial area within a given trial setting needs to be identified. The narrative can lead from opposing views to a common view, showing how diverse opinions converge into one. Final words expressing the presenter's opinion are mandatory.

The rule of three, which relates to confining the number of items listed on a single power-point slide to three, facilitates memorizing the facts. Whereas it is hard to put an entertaining note to oral abstract presentations, it is not a bad idea to make abstract discussions entertaining.

Education symposium

When preparing a talk for an education symposium, it is necessary to look at the meeting agenda to ensure that the presentation fits into the overall context, and to avoid overlaps with other talks. There are three types of story styles to choose from:

- The chronological story (e.g., the development of a certain drug in the treatment of NSCLC)
- The argumentative story (e.g., use of a certain drug as first-line therapy in a certain patient group)
- The explanatory story (e.g., the role of a certain test for the detection of genetic aberrations: how to test, what is the accuracy, why is it better than other methods?)

As for writing, the presenter has to create a specific format. Starting from a proposal, one would present the evidence to support the story line, until finally coming to a conclusion. Basically, the same set of data can be interpreted in opposing directions, and the presenter is expected to express his or her point of view. Importantly, it should be kept in mind that only the relevant data need to be summarized, rather than all of the available data. This will make for a more compact and impactful story, and it will prevent delays. The plot should be planned in a way that enables the audience to take home 2 or 3 key messages.

The setup and the audience

It is essential to know the stage and the technical equipment, including panel control, microphone and sound system,

as well as the brightness and clarity of the projection screen. The podium should have an appropriate height, and nothing should block the view of the presenter from the floor. Depending on where the presenter stands on the stage, it might be difficult to get into contact with part of the audience. Moreover, the presenter should know the chairperson and have an idea about which questions to expect. It is advisable to arrive early at the lecture hall to familiarize oneself with the surroundings.

With regard to the audience, several aspects are of relevance: Who are they? How many people? What is their background? What is their country of origin? How good is their English? What are they looking for in this presentation? The answers to all of these questions will help to prepare the presentation. If one has already given a presentation in front of a certain audience, a subsequent talk should contain new information.

Trying to interact is important, even when speaking to a huge audience. At large meetings, the presenter is primar-

ily facing the camera, which implies that he or she should actually talk to the camera rather than look down at the computer screen. If necessary, one should ask the technical staff where the camera is, as it can be at the far end of the hall.

The presenter

It is important not to talk in a monotonous way but to modulate the tone and volume of one's speech. Generally, the presenter should talk slowly. Writing a script can be helpful.

Body language is vital. The presenter should stand tall and straight and avoid swaying from side to side, as this indicates a lack of confidence. Likewise, touching one's face signifies insecurity. Hands should be used well; they are among the most powerful tools of communication. If the presenter is not certain how to use them, he or she should hide them instead of gesturing too much. It is important to make eye contact with the audience.

Even though power-point slides are helpful, they should not be relied on completely. The presenter should never read from a slide, but rather point out and highlight essential aspects. Here, animations are preferable to using the pointer. Building oneself up to become a competent communicator is a crucial goal that can require much practice.

Take home message

The presentation of oral abstracts, abstract discussions and education symposia alike should follow a story line containing key messages that the audience can remember. Before the talk, presenters should familiarize themselves with the stage and technical equipment. Interaction with the audience is important, as well as adequate body language and speech. Power-point presentations should not be relied on too heavily.

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