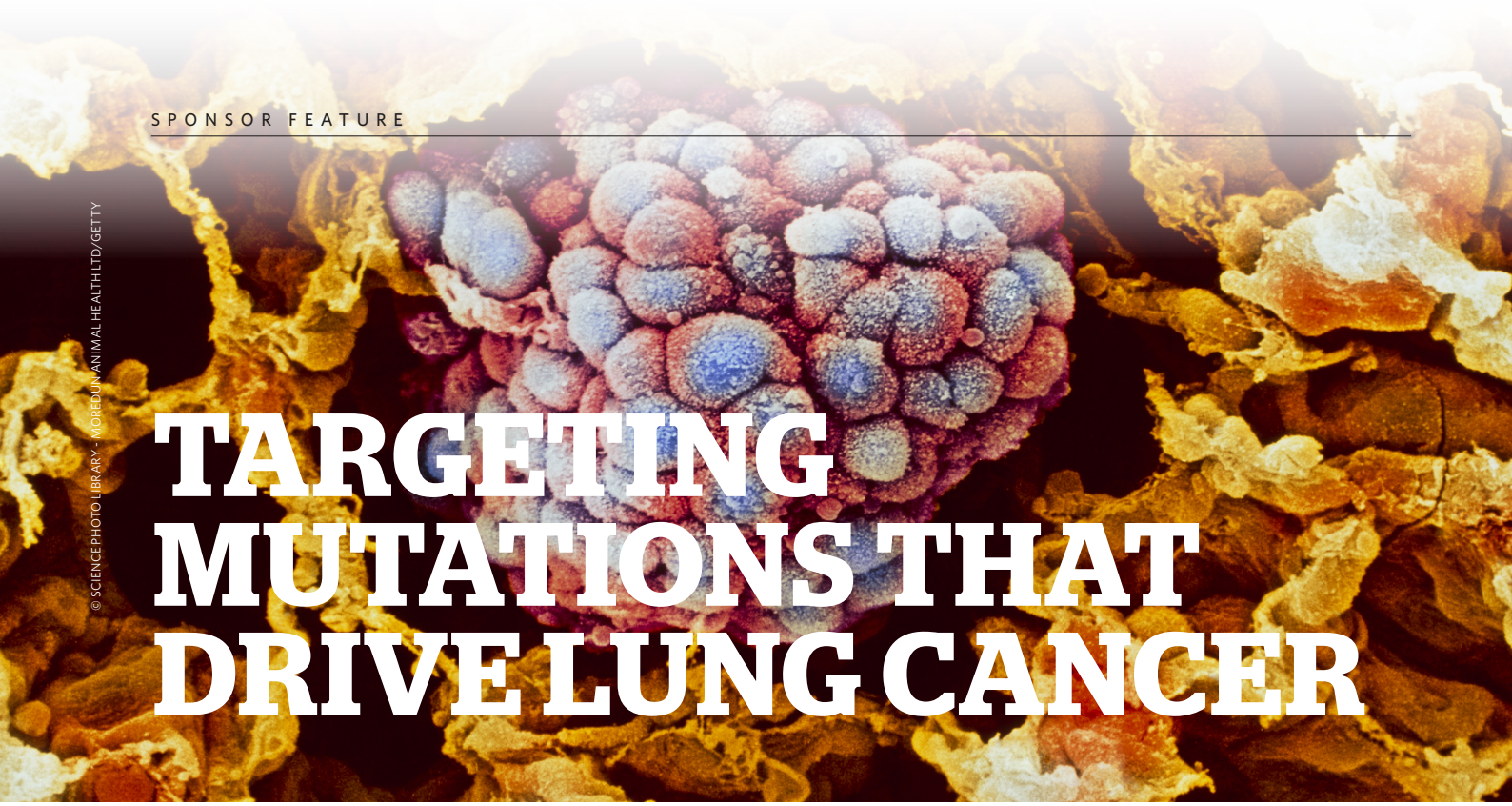


TARGETING MUTATIONS THAT DRIVE LUNG CANCER

A coloured scanning electron micrograph of a tumor in the lung.

Targeted treatments for non-small cell lung cancer: RECENT PROGRESS and FUTURE CHALLENGES

Despite advances in understanding lung cancer over the past two decades, it remains the number one cause of cancer-related deaths globally, claiming more than 1.7 million lives in 2018[1]. This exceeds the combined deaths for the next two top killing cancers, stomach and liver cancers[1].

One of the reasons for this high mortality is the early symptoms of lung cancer are fairly benign, often being little more than a persistent wheeze or cough, breathlessness and listlessness. Consequently, many patients are diagnosed late in the progression of the disease, when surgery is not an option and other treatments only slow the disease but do not bring complete recovery. With cancers often categorised into stages 0 to IV, statistics from the United States National Cancer Institute show 57% of lung cancer patients in the United States are diagnosed at stage IV, when the five-year survival rate is a little more than 5%.

But even an early diagnosis does not guarantee a successful outcome. The five-year recurrence rate after surgery to remove a tumour is high even for the early stages[2]. Therefore, complementary treatments, known as adjuvant and neoadjuvant therapies, have received a lot of attention. Studies have shown that these therapies, which include chemotherapy, reduce the risk of the disease reoccurring[3].

The targeted therapy revolution

Lung cancer was originally classified according to how tumour cells appeared under a microscope. Non-small cell lung cancer (NSCLC) is by far the most common form, representing about 85% of all lung cancer cases, with the remaining 15% of cases being small-cell lung cancer (SCLC)[4]. NSCLC can be further divided into three forms: adenocarcinoma (40% of lung cancer diagnoses), squamous cell carcinoma (30%) and large-cell carcinoma (15%).

The ability to analyse the genetics of tumour cells resulted in a much more diverse landscape for NSCLC. A plethora of driver genes for NSCLC has been identified, paving the path to the targeted therapy revolution, where the effects of cancer-causing mutations are countered with drugs.

For patients with early-stage NSCLC, targeted therapies can serve as an adjuvant therapy for primary treatments such as surgery[5]. For patients with late-stage NSCLC they can provide palliative care, offering patients more time and a better quality of life.

"We've made great advances in the lung-cancer space in the last couple of decades," says Mark Wildgust PhD, vice president of Global Medical Affairs at Janssen Research & Development, LLC. "A lot of that has been in understanding the biology of the disease, especially the genetics."

And an explosion of research is pushing targeted therapy for NSCLC forward today. Of the 481 NSCLC clinical trials currently registered with the National Cancer Institute in the United States, 70% (337) fall under the category of 'targeted therapy agent'.

Speaking in a webinar on NSCLC, Lecia Sequist, Landry Family Professor of Medicine at Harvard Medical School in Boston, Massachusetts, recently said: "This has been an unprecedented time for lung cancer in general. We've already this year in 2020 seen eight new [FDA] approvals for lung cancer, either new drugs or expanded indications and dosing of prior approved drugs, which is just record breaking."

Overcoming resistance

Currently, seven genes (*EGFR, ALK, ROS1, BRAF, NTRK, MET* and *RET*) have therapies that

have been approved by the United States Food and Drug Administration, with two of them being added in the first half of 2020. Several other genes are being targeted by drugs that are undergoing clinical trials.

Some of the most common driving mutations for NSCLC occur in *EGFR*, the gene that encodes for the protein epidermal growth factor receptor. These *EGFR* mutations can be classified as common (also known as classic) mutations and rare mutations[6].

The prevalence of *EGFR* mutations varies with racial background and is much higher in Asia than in Europe and the United States. One study found that 38% of NSCLC patients in Asia had *EGFR* mutations, 24% of North and South American patients had them, while only 14% of patients in Europe had them[3].

In the process of translating DNA to messenger RNA, introns are dropped from the code and exons retained. However, in one common *EGFR* mutation, there is a deletion in exon 19, while in another a single amino acid is substituted at L858R in exon 21. With these mutations, which account for about 85% of observed *EGFR* mutations in NSCLC, an excess of active *EGFR* promotes the growth of tumours[6].

A class of drugs known as tyrosine kinase inhibitors (TKIs) block the phosphorylation of *EGFR*, retarding the growth of tumours. TKIs are now the standard care for treating common *EGFR* mutations. However, for most patients with late-stage NSCLC, targeted therapies buy them time, but don't eradicate the disease. That's because while a drug is usually effective against tumours initially, over time tumours acquire resistance, rendering the drug increasingly ineffective.

This problem has a very human face. "*EGFR*-positive disease is more commonly seen in females, non-smokers and in patients of Asian descent," says Wildgust. "And so imagine a 45-year-old Japanese mother with a diagnosis of *EGFR*-positive lung cancer. The oncologist says, 'I've got good news — there's a TKI therapy for you.' But the only good news is that she's going to get 18 months before her disease comes back. After that, all she's got is chemotherapy. She's probably only got two to three years in total; the outcomes for these patients are still quite poor."

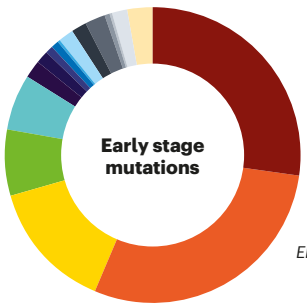
Three generations of TKIs have now been developed. "First-generation TKIs gave about 6–12 months of benefit before resistance set in," says Huang, leader of the Molecular and Systems Oncology Team of The Institute of Cancer Research in London. "The most common resistance mechanism is a secondary mutation, T790M; therefore, third-generation TKIs were developed to tackle this mutation, giving patients a further 6–12 months of benefit and dealing with both the primary sensitivity and the resistance mechanism simultaneously." The success of third-generation TKIs for NSCLC and have "become the poster child of targeted therapy in oncology," according to Vyse and Huang, writing in *Signal Transduction and Targeted Therapy* in 2020. "In many cases, these third-generation TKIs have superseded the first- and second-generation drugs and are generally offered as the first line of treatment," says Huang.

However, Joshua Bauml, assistant professor of medicine at the Perelman School of

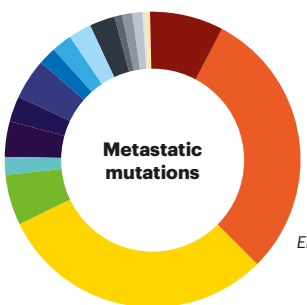
PREVELANCE OF MUTATIONS THAT DRIVE NON-SMALL-CELL LUNG CANCER

The prevalence of mutations that drive non-small-cell lung cancer depend on many factors, including racial background, the stage of disease and treatments received.

These pie charts show how the incidences of driving mutations vary between early stage non-small-cell lung cancer (NSCLC) and metastatic NSCLC. *KRAS* varies very little, whereas *EGFR* doubles by the time the disease becomes metastatic.[13]



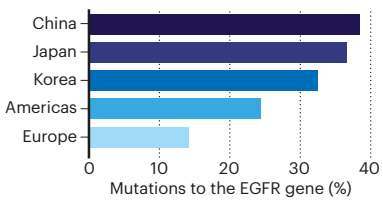
Other genes **27.3%**
KRAS **29.1%**
EGFR **14.2%**
BRAF **7.2%**
NF1 truncation **6.3%**
ERBB2 **1.8%**
MET splice **1.4%**
ALK fusion **0.8%**
ROS1 fusion **0.9%**
RET fusion **0.3%**
MET amplification **1.7%**
ERBB2 amplification **1.6%**
MAP2K1 **2.2%**
NRAS **0.5%**
HRAS **0.5%**
RIT1 **1.6%**
FGFR1 or *FGFR2* **2.6%**



Other genes **7.8%**
KRAS **29.9%**
EGFR **30.3%**
BRAF **5.5%**
NF1 truncation **1.9%**
ERBB2 **3.8%**
MET splice **3%**
ALK fusion **4.4%**
ROS1 fusion **1.9%**
RET fusion **2.3%**
MET amplification **2.5%**
ERBB2 amplification **2.7%**
MAP2K1 **0.7%**
NRAS **1.2%**
HRAS **1.2%**
RIT1 **0.2%**
FGFR1 or *FGFR2* **0.7%**

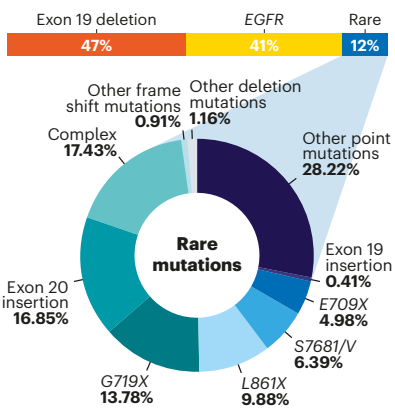
Mutations to the *EGFR* gene

Mutations to the *EGFR* gene (China: 38.4%; Japan: 36.6%; Korea: 32.4%) are much more prevelant in Asia than they are the Americas (24.4%) and Europe (14.1%). This makes targeting *EGFR* onocogenes even more attractive in Asian countries.[3]



Percentage of mutations

About 12% of *EGFR* mutations are rare and do not respond to TKIs. Of these rare mutations, exon 20 insertion has the highest abundance, making it an attractive target for new drugs.[6]



Chest X-rays and computer tomography (CT) scans can be used to detect non-small-cell lung cancer, but often tumours are only picked up quite late in the development of the cancer.

Medicine at the University of Pennsylvania in Philadelphia, says the development of resistance to targeted therapies is a huge issue that demands addressing. "Over the next five to ten years, I believe it is critical that we not only explore new drugs to target these molecularly driven cancers, but also gain a better understanding of resistance to therapy. This research is critical to improving long-term outcomes for our patients."

Rare *EGFR* mutations make up the remaining 12% of *EGFR* mutations in NSCLC. Of these, exon 20 insertion is the most prevalent (approximately 2% of all *EFGR* mutations)[6]. There are currently no approved targeted therapies for these rare mutations, and thus chemotherapy is often the only choice for patients with them.

A vote of confidence

Some have questioned the huge investment that has been made in targeted therapies, pointing out that they are very expensive and help only a limited subset of patients, to whom they offer only modest benefits while causing side effects. But a recent assessment of the mortality rates in the United States from NSCLC and SCLC has provided some validation for the investment[7]. Previous analyses had found a decline in mortality rates, but it was unclear how much of this decline was due to factors such as lower rates of smoking and improved diagnosis and how much was due to better treatments. The study observed declines in mortality rates for both NSCLC and SCLC between 2006 and 2016[7]. However, the decline nearly doubled after 2013, the year when targeted therapies for NSCLC became available. For men living in the United States with NSCLC, mortality decreased 3.2% annually for 2006–2013 and decreased 6.3% per year for 2013–2016; a similar trend was observed for women. Researchers did not observe a similar increase in the decline of mortality for SCLC, for which targeted therapies have not been widely introduced[7]. Thus, they suggest that targeted therapies are making a real difference. "Our analysis suggests that a reduction in incidence along with treatment advances — particularly approvals for and use of targeted therapies — is likely to explain the reduction in mortality observed during this period," the study's authors concluded.

Reducing toxicity

One promise of targeted therapies is that because they target specific mutations, they should have fewer and milder side effects than broader treatments such as chemotherapy[8]. But some targeted-therapy drugs do not exhibit a high specificity between the mutant genes they are targeting and their wild-type counterparts. This can result in severe side effects, which limit the dose that can be given to patients.

"It's a bit controversial, but I understand from oncologists that a big challenge is overcoming the narrow therapeutic window of some drugs," says Huang, "And so we're not seeing the long-lasting benefits for TKIs for rare mutations that we see for the classical inhibitors and first- and third-generation TKIs and we're nowhere near a 12-month response. They're not working at the same potency as you would expect from this class of drugs."

Rare mutations

If the prospects for patients with common *EGFR* mutations are limited, those for patients with rare *EGFR* mutations and mutations to other genes are currently much bleaker. "For a patient who has an uncommon mutation, the outcome is much worse, maybe 12 to 18 months from diagnosis," says Wildgust. "So it's a place where we definitely need to make headway."

The challenge for oncology researchers is finding enough patients to enroll in clinical trials for drugs that counteract rare mutations. Thus, work on rare mutations necessitates collaboration among many medical centres and even between countries.

One such programme is the Lung Cancer Genomic Screening Project for Individualized Medicine (LC-SCRUM-Asia). As mentioned earlier, the proportion of Asian patients with *EGFR*-mutated NSCLC is much higher than for patients in the United States and Europe[3]. This provides Asian researchers with extra incentive to find therapies that target *EGFR* mutations. Koichi Goto, chief of the Department of Thoracic Oncology at the National Cancer Center Hospital East, Chiba, Japan, and principal investigator of LC-SCRUM-Asia says: "Since these rare mutations occur in less than 5% of lung

adenocarcinoma, it's very difficult to detect these rare diseases and to conduct clinical trials of molecular targeting agents. Therefore, large-scale genomic screening platforms to identify patients with rare driver alterations are vital to enable precision medicine and to support the development of novel targeted therapies."

LC-SCRUM-Asia started genomic screening in 2013 and since then, more than 10,000 patients have been enrolled in the study. Currently, 14 pharmaceutical and diagnostic companies and more than 200 medical centres in Japan and Taiwan are participating, and other Southeast Asian countries including Vietnam, Thailand, Malaysia and Singapore, will be included in the programme in the future. "We have identified various targetable rare genomic alterations, including *EGFR, KRAS, HER2* and *BRAF* mutations, *ALK, RET, ROS1, NTRK* fusions, and *MET* ex14skip in non-squamous NSCLC," says Goto. "Through this genomic screening, more than 300 patients with rare driver oncogenes have been enrolled into various clinical trials, which have contributed to the development of new molecular targeting agents."

Of the rare *EGFR* mutations, exon 20 insertion is the most promising to attack by future targeted therapies since it is the most common of the rare *EGFR* mutations. "From a pharmaceutical company's point of view, exon 20 insertion is a real window of opportunity," says Huang. "The *EGFR* inhibitor space for common mutations is highly competitive and crowded, and one could argue that pushing out another inhibitor for a common mutation is not going to make a huge difference. Whereas with exon 20 insertion, you can help a patient population that has no options. So a lot of companies are joining the race to find inhibitors for exon 20 insertion."

In many ways, the current situation for targeting exon 20 insertion resembles that for the common *EGFR* mutations about 15 years ago. "We're pretty much where the common mutations were in 2004," says Huang. "New drugs will be developed, some of them will get approved, and then we will deal with their resistance mechanisms. So we're repeating the whole process with these rarer mutations."

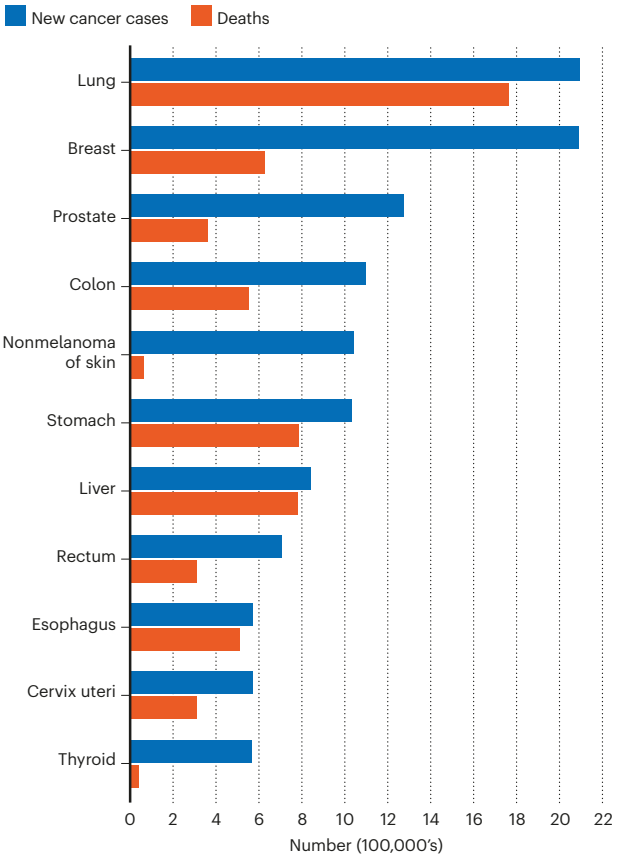
Addressing the complexity of cancer

The more researchers learn about NLSCLC, the more aware they become of its complexity. It is this complexity that makes the disease so difficult to treat effectively in the long term, even with the latest targeted therapies. Tumours are heterogeneous mixes of cancer cells that are constantly evolving. The current targeted therapies are based on the assumption that there is a single, dominant mutation that is driving the disease. And while this model has resulted in effective therapies, there is an increasing awareness that it is an oversimplification. Often several mutations are present in a tumour, particularly knocking out tumour-suppressor genes, that assist it to survive and grow. In their review of the topic, Skoulidis and Heymach call for a "next-generation, dynamic model for the molecular classification of NSCLC that encompasses the molecular and clinical diversity affected by co-mutations." This will require cataloguing all the mutations that co-occur in NSCLC and assessing how to tailor therapies to the suite of mutations that are present.

Another reminder of the complexity of NSCLC was provided by a recent umbrella study conducted in the United Kingdom. Of the nearly 5,500 NSCLC patients screened

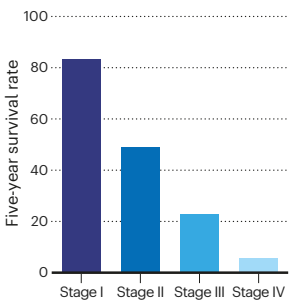
WHY LUNG CANCER CLAIMS SO MANY LIVES

Global estimated numbers of new cancer cases and deaths

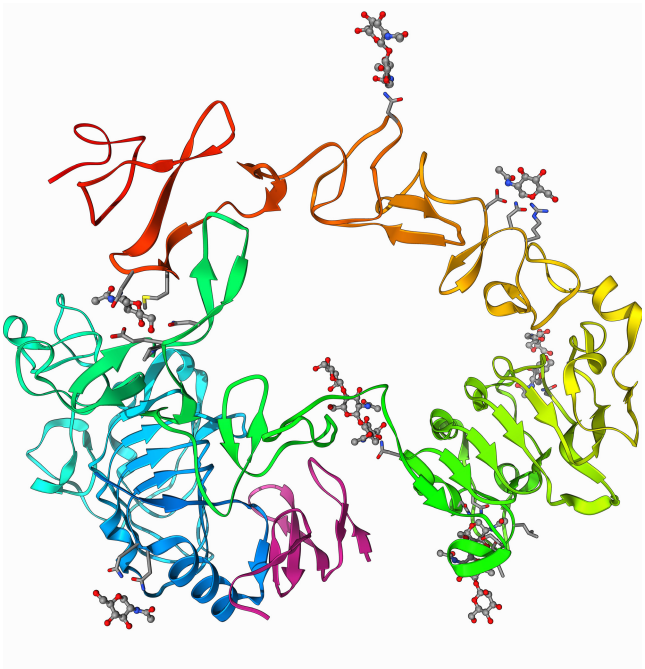


This graph shows the global estimated numbers of new cancer cases and the numbers of deaths according to cancer location for 2018 for the ten cancers that have the most cases[1]. It shows two reasons why lung cancer is the number one cause of cancer-related deaths globally: it has the highest number of cases globally (almost 2,094,000) and it has a high number of deaths relative to the number of cases (84.1%). The low survival rate contrasts with other common cancers such as breast, prostate and skin cancers, which have much better outcomes in general. It is due in part to the late diagnoses of the disease.

Five-year survival rate



This plot shows the five-year survival rate for 33 cancer hospitals in Japan. Patients diagnosed in stage I have a five-year survival rate of 83.3%, but this drops rapidly for later stages (stage II: 48.8%; stage III: 22.7; stage IV: 5.8%).[11]



Molecular model of epidermal growth factor (EGF) bound to a receptor. EGF plays an important role in the regulation of cell growth, proliferation and differentiation. Mutations to the gene that encodes for EGFR can drive lung cancer. Therapies that target these mutations are helping to prolong patients' lives.

for the National Lung Matrix Trial, 302 received one of 22 targeted therapies for specific mutations — effectively multiple trials running in parallel[9]. The results were mixed. Some mutation–drug combinations resulted in high response rates, whereas other combinations gave low responses rates. In particular, they found poor results for patients who had had high exposure to tobacco smoke because their tumours tended to more complex than those in patients with light exposure to tobacco.

The results of the umbrella study highlight the fact that various factors are at play. In a commentary on the study, Drilon and Hellmann[10] caution against throwing out "the 'genome-driven care' baby … with the proverbial bathwater, even if this approach failed to identify a strong match for every genomic alteration tested." They note that "Ultimately, the success of each paired treatment depends on multiple factors — such as the right science to guide the approach, the right genomic alteration to identify those who are likely to respond, the right test to identify these alterations, and the right therapy — and these inputs might improve over time through gradual iterations."

The researchers who did the study say that the current models are overly simplistic. "They don't represent the genomic complexity of the tumour, or the trajectory of how they rapidly evolve. We need models that take into account the complexity and trajectory of a human tumour to decide if a drug is going to work," said Gary Middleton, professor at the University of Birmingham, who led the National Lung Matrix Trial, in a press release.

Future challenges

Meanwhile, the rise of resistance has resulted in a shift in thinking about cancer treatment. "There's this school of thought that maybe we shouldn't be thinking about curing cancer, maybe we should be thinking about managing the disease and giving patients the best quality of life, in the same way that you might manage diabetes or heart disease," said Paul Huang, at the Institute of Cancer Research, "I think that's something that's frankly achievable, and it's really a shift in how we think about the disease."

The patient-advocacy group EGFR Resistors (egfrcancer.org) has adopted this approach, describing itself on its website as a "grassroots patient-driven community, dedicated exclusively to changing *EGFR*-positive lung cancer into a manageable, chronic disease." With more than 1,700 members in more than 30 countries, it seeks to provide a community for survivors and caregivers to share knowledge, provide support and collect data.

Such groups will become increasingly important, because as the number of treatment options expands, so does the need to ensure that patients are well informed about them. The Internet is a source of both information and misinformation, and it can be challenging for patients to distinguish between them. It is crucial to manage patient expectations by making them aware of the limitations as well as the advantages of targeted therapies.

Arguably, the greatest gains to be had in combating lung cancer are in the areas of prevention (for example, by continuing to curtail smoking rates) and early diagnosis. "From the point of view of the general public and patients, prevention and early detection are top priorities," says Reiko Akizuki, director of the Oncology Department of Medical Affairs at Janssen Pharmaceutical K.K. "If we can detect lung cancer in stage two or three, there is the possibility of curing it with a combination of surgery and drugs or radiotherapy and drugs." ■

REFERENCES

1. Bray, F. *et al. CA: A Cancer J. Clin.* **68**, 394–424 (2018).
2. Uramoto, H. & Tanaka, F. *Transl. Lung Cancer Res.* **3**, 242–249 (2014).
3. Zhang, Y.-L. *et al. Oncotarget* **7**, 48 (2016).
4. Vyse, S. & Huang, P. H. *Signal Transduct. Target. Ther.* **4**, 5 (2020).
5. Herbst, R. S. *et al. J. Clin. Oncol.* **38**, 18_suppl, LBA5–LBA5 (2020).
6. Harrison, P. T., Vyse, S. & Huang, P. H. *Semin. Cancer Biol.* **61**, 167–179 (2020).
7. Howlader, N. *et al. N. Engl. J. Med.* **383**, 640–649 (2020).
8. Seebacher, N. A., Stacy, A. E., Porter, G. M. & Merlot, A. M. *J. Exp. Clin. Cancer Res.* **38**, 156 (2019).
9. Middleton, G. *et al. Nature* **583**, 807–812 (2020).
10. Drilon, A. & Hellmann, M. D. *Nature* **583**, 688–689 (2020).
11. *Cancer Statistics in Japan.* Foundation for Promotion of Cancer Research (2019) https://ganjoho.jp/data/reg_stat/statistics/brochure/2019/cancer_statistics_2019.pdf
12. *Global Cancer Facts & Figures, 4th Edition* American Cancer Society (2018). https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-4th-edition.pdf
13. Skoulidis, F. & Heymach, J. V. *Nature Rev. Cancer* **19**, 495–509 (2019).