For the successful development of new immunotherapy and ADC drugs

Utilization of biomarkers

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Overview

Now, medicine is rapidly transitioning into an era of precision medicine, which is customized treatment for each patient. In particular, In the development of anticancer drugs, treatment strategies based on the molecular and cellular characteristics of tumors are becoming increasingly important. A biomarker is an indicator that can predict the characteristics of a disease or drug response, such as genetic mutations. There are various forms, such as gene/protein expression, circulating tumor DNA, etc. By utilizing these biomarkers, the patient's It is essential for new drug development and anticancer drug selection as it can predict treatment response in advance or monitor treatment progress. It is becoming a tool. In fact, a new drug development strategy that integrates biomarkers expands the treatment response group and improves progression-free survival (PFS). It is associated with improved survival and overall survival (OS), increasing the probability of success of development programs and shortening the development period. Conversely, development targeting a broad patient population without a biomarker carries a risk of failure. It is evaluated as a big deal. Accordingly, in order to develop domestic new drugs with global competitiveness, it is necessary to focus on biomarkers. I would like to introduce the necessity and trends, etc.

1. The necessity of biomarker development in the development of new immunotherapy and ADC drugs

1-1. The need for biomarkers in the development of immunotherapy

Immunotherapy drugs, including immune checkpoint inhibitors, have been used in cancer treatment for the past 10 years. Although it has brought about innovation, there is a large variation in response from patient to patient. For example, anti-PD-1/PD-L1 immune checkpoint inhibitors In some patients, it has shown long-term survival, but in many, it is ineffective. According to one analysis, As of 2018, 12.46% of all cancer patients in the United States showed a meaningful response to immune checkpoint inhibitor treatment.

It was only 1. In general, the objective response rate of immunotherapy monotherapy in solid tumors is around 15-30%.

In some cases (exceptions such as melanoma or MSI-H colon cancer, up to 40-60%), a significant number of patients

The efficacy is limited. To overcome the limitations of this low response rate, response can be predicted through biomarkers predicting treatment response,

such as expression of PD-L1 gene/protein, tumor mutational burden (TMB), and microsatellite instability (MSI).

A strategy to select expected patients is essential.2 For example, PD-L1 expression is associated with anti-PD-L1 in lung cancer, gastric cancer, etc.

1/PD-L1 is a universal indicator predicting the response to immunotherapy, and the drug is more effective in patients with high PD-L1 expression.

It has been proven to be effective. In addition, MSI-H/dMMR tumors are particularly sensitive to immune checkpoint inhibitors, and in 2017, the US

The FDA has approved Keytruda® for the treatment of patients with MSI-H or dMMR biomarkers, regardless of cancer type.

It has been approved for use. In this way, biomarkers serve as a basis for patient selection in the development and approval of immunotherapy.

The FDA recommends biomarkers and companion diagnostics because they can be used to increase treatment efficacy and avoid unnecessary treatments.

It is recommended. In the case of pharmaceutical companies, through biomarker research that reflects the characteristics of the patient's immune microenvironment,

It can identify the causes of treatment resistance and establish new combination therapy strategies.

1-2. The Need for Biomarkers in ADC Development

Antibody-drug conjugates (ADCs) are novel drugs that combine the target specificity of antibodies with the cytotoxicity of drugs, and are called “biological

It is a precision targeted treatment likened to a “missile.” In order to maximize the effect of ADC, it is necessary to target the target antigen.

Biomarkers are important. Traditionally, ADCs target proteins that are overexpressed on the surface of cancer cells (e.g. HER2, TROP2, etc.).

Since it is designed to target, finding patients with high expression levels of the antigen is key to treatment success. For example,

Enter Daiichi Sankyo's HER2-targeting ADC, Enhertu® (Trastuzumab deruxtecan), initially

It has been used only for overexpressing (HER2 3+ or amplified) breast cancer, but in clinical studies it has been used for HER2 low-expressing (HER2-low) breast cancer.

As it showed excellent efficacy in patients, the indications were expanded to patients with HER2 IHC 1+ or 2+.

A new biomarker that defines a group of patients who were previously classified as “HER2 negative” and thus were denied treatment opportunities

This is an example of reclassification. In this way, in ADC development, it is possible to accurately determine whether and at what level the target antigen is expressed.

Companion diagnosis is essential, and selecting patients based on biomarker criteria can increase the success rate of clinical trials.

On the other hand, ADC works by delivering drugs into cancer cells, but due to heterogeneity between tumors, it is not effective in some lesions.

The efficacy may be reduced due to low target expression. Therefore, treatment may be performed by quantifying antigen expression in multiple tumor sites.

Developing biomarkers to predict response or monitor changes in target expression or resistance mechanisms during treatment is also important.

remains a challenge. 3 To date, some ADCs have been approved without clear predictive biomarkers, but some

The development of biomarkers that can determine which patients will benefit most from ADC therapy remains an unmet need.

It is pointed out as a demand.

ÿ New drug cases where biomarker development is applied_Immunotherapy (Keytruda) and ADC (Enhertu)

1-3. Improving the success rate of new drug development and commercial value

Companion diagnostics (CDx) strategies using biomarkers are commercially beneficial for pharmaceutical companies.

In clinical trials, selecting a group of patients expected to respond to treatment with a biomarker increases the efficacy rate and reduces the number of patients.

It is easy to prove statistical significance with the number of patients, and clinical development time and cost can be reduced. In actual research

According to the results, the approval rate of anticancer new drugs is higher in cases that utilize biomarkers, and the development period is also longer.

It showed a tendency to shorten.4 This soon leads to reduced risk and increased investment efficiency, which increases the possibility of success.

Resources can be concentrated in the program. It can also be highlighted as precision medicine at the market stage after approval, so it is appropriate.

Gaining the trust of regulators and insurers and setting premium prices based on evidence that the drug is being administered to patients.

In addition, the companion diagnostic device itself forms a separate market, creating partnerships with diagnostic companies.

Additional revenue can be generated through technology licensing, etc. For example, the US FDA first approved the

Since the approval of the companion diagnostic HER2 IHC test (HercepTest), companion diagnostics linked to a number of treatments have been

It has been approved, and it has been reported that more than 56 companion diagnostic reagents have been approved cumulatively as of August 2023. This is

This means that it is becoming common for pharmaceutical companies to develop diagnostic tools alongside new drugs, and biomarker-based treatments

It shows that development has become mainstream. The global cancer biomarker market size is also expected to reach approximately KRW 30 trillion in 2023.

It is expected to expand at an annual growth rate of over 11% and exceed 60 trillion won by 2029, and is expected to be scientifically and commercially

Biomarker development has become an essential element in new drug innovation.

2-1. Expansion of Companion Diagnostics

Companion diagnostics are in vitro diagnostics that provide essential information for the safe and effective use of specific treatments.

Companion diagnostics has become a de facto standard strategy in the development of modern anticancer drugs, leading to the approval of many new drugs.

It is being approved along with a companion diagnostic test, for example, AstraZeneca's EGFR mutant targeting lung cancer

The treatment Tagrisso® was developed as a drug for patients with EGFR T790M mutation positivity, and was developed by Roche

In collaboration with Diagnostics, we developed the cobas® EGFR Mutation Test v2 tissue assay as a companion diagnostic, and at the same time

It was approved. This test accurately identifies patients who have developed the EGFR T790M mutation after previous treatment.

By administering the drug, a high response rate (~59%) was achieved in clinical trials and rapid approval was achieved.

As the Dx-Rx co-development model, in which new drugs and diagnostics are developed together, becomes established, pharmaceutical companies are

We have been investing in biomarker discovery and diagnostic kit development from the beginning.

The types of currently approved companion diagnostics are also diversifying. Initially, immunohistochemistry (IHC) or FISH-based

Single biomarker tests (HER2 protein expression, ALK rearrangement, etc.) were mainstream, but recently, next-generation sequencing

There is an increasing number of cases where multi-gene panels based on next-generation sequencing (NGS) are approved as companion diagnostics. For example,

In 2020, a broad cancer genomics panel called FoundationOne® CDx was approved for Keytruda's TMB-High (TMBÿ10)

Since it has been approved as a companion diagnosis for patient screening, comprehensive genetic indicators, rather than single genes, can also be used as a companion diagnosis.

It has been shown that some liquid biopsy-based tests (analysis of circulating DNA) are also approved as companion diagnostics.

Equivalent biomarker testing is also available for patients with insufficient tissue samples. Companion diagnostics are used to treat patients

Because it provides essential information for decision-making, regulatory authorities in each country strictly verify the accuracy and clinical utility of companion diagnostics.

Global pharmaceutical companies are responding to this by consulting with regulatory authorities from the early clinical stage.

We are establishing a strategy for biomarker validation and diagnostic reagent approval, and forming partnerships with specialized diagnostic companies.

Accelerating commercialization.

ÿ Examples of companion diagnostic products_FFPET*/Plasma tissue biopsy-based (Cobas® EGFR Mutation Test v2) and

NGS-based (FoundationOne® CDx) *FFPET: Formalin-Fixed Paraffin-Embedded Tumor Tissue

2-2. Latest Trends: Multi-Biomarkers and Tissue-Agnostic Anticancer Agents

In the past, biomarkers focused on individual genes or proteins were mainstream, but multiple biomarkers or complex The importance of indicators is emerging. It is difficult to explain the complex biological characteristics of cancer with a single indicator. A comprehensive score or signature concept is utilized. For example, to predict immune anticancer drug response. Interferon-gamma gene signature or immune cell infiltration integrating multiple gene expressions in the tumor microenvironment Immunoscore, etc. are being studied, and some have been used as criteria for patient selection in clinical trials. Also Development of complex biomarkers encompassing genome + immune system + microenvironment information through a multi-omics approach These efforts will lead to more precise identification of each patient's detailed characteristics and more accurate customized treatment. It is expected.

Meanwhile, looking at the FDA approval trend, it is clear that approval (tissue-agnostic approval) is increasing. Starting with the approval of the MSI-H indication (for all solid tumors) of the aforementioned Keytruda, pan-cancer treatments based on biomarkers such as NTRK gene fusion positivity, RET mutation, and TMB-H are being developed. This trend suggests that the clinical predictive power of biomarkers may be more important than the site of cancer occurrence. It is expected that the biomarker-centered paradigm will be further strengthened in future new drug development and approval. Pharmaceutical companies Now, clinical trials are being designed to target molecular subtypes rather than specific organ cancers, and to target one new drug. We are actively utilizing basket trials that test biomarker-positive patients with various types of cancer. At the same time, an epidemiological database is being built to accurately identify the patient pool corresponding to each biomarker. Analysis of real-world data (RWD) is also expanding. Nevertheless, in the clinical trial process, Using biomarkers related to drug action and drug resistance mechanisms obtained through analysis of the generated genomic information Companion diagnosis was most successful.

3. Global pharmaceutical company biomarker utilization case

3-1. Daiichi Sankyo

Daiichi Sankyo of Japan is a company that stands out in the global anticancer drug field with its ADC platform. We have a representative case of successful expansion of indications through biomarker strategy. Representative ADC new drug Enhertu® (Trastuzumab deruxtecan) is a HER2-targeting anticancer drug that is indicated for the treatment of patients with existing HER2 positivity (HER2 It was expected that the treatment would only be effective if the patient had IHC 3+ or gene amplification, but in clinical studies, HER2 It also showed excellent efficacy in patients with low-expression (HER2-low) breast cancer. Jointly developed with Daichi Sankyo AstraZeneca, based on the DESTINY-Breast04 clinical trial results that proved this, is targeting patients with HER2 IHC 1+ or 2+.

(previously classified as “HER2 negative”), which is an indication for the HER2 phenotype.

A new, more detailed biomarker classification has been introduced, and Enhertu is the world's first HER2-low patient

The market has expanded as a targeted therapy. This success is due to the relatively sensitive immunohistochemical test

(immunohistochemistry, IHC) Companion diagnosis detects even trace amounts of target expression and demonstrates clinical significance

This can be said to be the result of a biomarker strategy.

Another key ADC pipeline from Daichi Sankyo is

Datopotamab deruxtecan (Dato-DXd) is a TROP2 protein inhibitor.

As a targeting ADC, triple-negative breast cancer and non-small cell lung cancer

Dato-DXd is in development for the global phase 3 clinical trial TROPION-

In the Lung01 study, the overall patient population did not meet expectations.

As the results came out, an AI-based quantitative pathology algorithm was used.

We performed a new TROP2 biomarker analysis using

The ratio of TROP2 expression in the cytoplasm compared to the tumor cell membrane was

Define the calculated index, normalized membrane ratio (NMR)-QCS,

ÿ Datopotamab deruxtecan

In the patient group with high levels of this index, the effect of Dato-DXd was significantly superior. Specifically, QCS-NMR

In patients with positive results, Dato-DXd reduced the risk of disease progression or death by 43% compared to standard anticancer drugs,

In the negative group, the effect was rather low. Daiichi Sankyo and AstraZeneca are using this AI pathology biomarker

Based on this, we are reestablishing appropriate patient selection and development strategies for Dato-DXd in the future. This is based on the latest technology.

This is an innovative case of utilizing biomarkers that have been grafted together, killing two birds with one stone: differentiation from competing drugs and increased clinical success rate.

Shows effort to catch.

In this way, Daiichi Sankyo is developing biomarkers in parallel with the goal of “administering the right ADC to the right patient.”

In addition, genetic biomarkers have been applied to the development of our own targeted anticancer drugs. For example,

Quizartinib, a targeted therapy for acute myeloid leukemia, was developed to be administered to patients with FLT3-ITD mutations.

It has been approved in Japan along with a test method to detect the mutation. Overall, Daichi Sankyo

In the development of new drugs including ADCs, precise patient segment definition and introduction of companion diagnostics will enhance development efficiency and product value.

We are pursuing a strategy to maximize our profits.

3-2. AstraZeneca

British-Swedish company AstraZeneca has been called a pioneer in precision medicine since it was early in developing biomarkers for new anticancer drugs.
It is a company that has introduced the strategy. In the early 2010s, Iressa®, a lung cancer treatment drug targeting EGFR mutations, was developed.
Starting with making mutation testing mandatory, we have now linked companion diagnostics to many of our anticancer drugs.
A representative example of AstraZeneca is Tagrisso (Tagrisso®, Osimertinib). Tagrisso is an EGFR
Developed as a third-generation EGFR tyrosine kinase inhibitor that shows remarkable efficacy against the T790M mutation, Roche's
The cobas® EGFR assay has been approved as a companion diagnostic to screen patients with T790M mutation positivity.
We conducted a clinical trial only targeting patients with the T790M mutation that is resistant to first-line treatment, and achieved high efficacy.
We were able to prove it and quickly achieve commercial success.

In the field of immunotherapy, AstraZeneca is developing Imfinzi® (Durvalumab), a PD-L1
The expression rate was used as an important biomarker. For example, in locally advanced non-small cell lung cancer (Stage III),
In the PACIFIC clinical trial, which administered durvalumab as maintenance therapy after chemoradiotherapy, the tumor PD-L1 expression was high.
The survival benefit was shown to be greater in patients with PD-L1 ÿ 1%. Accordingly, European approval is limited to patients with PD-L1 ÿ 1%.
As such, the PD-L1 biomarker was an important element in AstraZeneca's strategy for developing and approving immuno-oncology drugs.

Another example is the targeted anticancer drug Limparza® (Olaparib), developed by AstraZeneca and MSD.
Based on the fact that the jointly developed PARP inhibitor Lynparza is particularly effective in patients with BRCA1/2 gene mutations,
It was developed and created an approval case requiring gBRCA genetic testing as a companion diagnosis for breast cancer, ovarian cancer, etc.
This is a targeted treatment that targets the vulnerability of tumors (synthetic lethality), and is called germline BRCA mutation.
This is a successful case of selecting patients based on biomarkers.

AstraZeneca is also innovating in the ADC field through its recent collaboration with Daiichi Sankyo.
The expansion of the indication for Enhertu (HER2-low) mentioned in the Daiichi Sankyo case and the AI pathology biomarker (NMR-) of Dato-DXd
AstraZeneca's precision medicine know-how contributed greatly to the development of QCS. AstraZeneca developed its own
Digitizing tumor tissue slides with QCS platform and applying deep learning algorithm to quantify TROP2
By calculating the expression index, we have presented a new way to predict ADC effect. This is a traditional biomarker.
Moving beyond the dichotomous "yes/no" level, we use continuous scoring to identify patients who will benefit the most from treatment.
It's a cutting-edge approach.

In summary, AstraZeneca has a wide range of products, from small molecule targeted therapies to immuno-oncology drugs and ADCs.
We are implementing a biomarker-centric development strategy across our portfolio, which will enable us to clinically evaluate new drugs.
We have secured market competitiveness by maximizing value and providing optimized treatment to patients.
Based on its experience, AstraZeneca will continue to lead the way in complex biomarkers and AI utilization technologies.
It is expected that the introduction of this technology will lead to the era of precision medicine.

3-3. Ono Pharmaceutical

Ono Pharmaceutical Co., Ltd. of Japan is a company that has played a historical role in the field of immunotherapy and cancer treatment, and is collaborating with BMS to become a global
He is the main character who developed the first PD-1 inhibitor, Opdivo® (Nivolumab). Opdivo was launched in Japan in 2014.
It was first approved and then entered the global market, opening the era of anti-PD-1 immunotherapy. Ono Pharmaceutical
Based on this experience in developing immune-oncology drugs, we are also taking active steps toward utilizing biomarkers.

In the early stages of Opdivo development, the efficacy was explored across a wide range of cancers without a clear biomarker.
In follow-up clinical trials, it was found that PD-L1 expression level affected treatment outcome. Accordingly, some
In cancer, Opdivo was approved based on its efficacy in patients with high PD-L1 expression. For example,
For example, the combination of Opdivo and the CTLA-4 inhibitor Yervoy® (Ipilimumab) in the first-line treatment of non-small cell lung cancer
It was approved for patients with tumor PD-L1 ÿ 1%. The Korean Ministry of Food and Drug Safety also approved this combination therapy in 2020.
It has been approved for patients. This is based on the CheckMate-227 clinical study conducted by Ono Pharmaceutical (jointly with BMS).
In this study, the efficacy of combination therapy according to PD-L1 phenotype was analyzed.

Another notable effort is Ono/BMS's attempt at a tumor mutation burden (TMB) biomarker.
In an additional analysis of the CheckMate-227 study, the combination of Opdivo and Yervoy was shown to be effective in patients with lung cancer with TMB ÿ 10 mut/Mb.
Compared to chemotherapy, it showed a significantly improved progression-free survival rate (1-year PFS rate 43% vs 13%). 5 This is because TMB
It was an important discovery suggesting that it could act as a predictive biomarker for immunotherapy. Although it has not received regulatory approval,
Although not adopted as an official biomarker for high mutation burden, BMS and Ono hope that this data will be used to predict future high mutation burden.
We are continuing research to establish cancer treatment strategies and consider TMB in patient selection.

Ono Pharmaceutical is committed to developing next-generation immunomodulators and combination therapies even after Opdivo, and in this process,
We are exploring various biomarkers. For example, Ono has its own pipeline immune target substance, ONO-4578.
Pre- and post-treatment tumor microenvironment immune gene signatures in a clinical trial combining (EP4 receptor antagonist) with Opdivo
By analyzing the changes, we are studying biomarkers that increase the responsiveness of immunotherapy. We are also studying various
Broad R&D, including collaboration with partners to investigate correlations between immune-related biomarkers in patient-derived samples
I'm putting in effort.

In summary, Ono Pharmaceutical Co., Ltd. is a first mover in the field of immunotherapy and anticancer drugs, and is developing key biomarkers such as PD-L1 and TMB.
We have been at the forefront of utilizing biomarker-based patient group selection strategies in the development of new drugs.
Through this, we are contributing to maximizing the therapeutic effect of immunotherapy and accelerating the overcoming of incurable cancer.
there is.

3-4. MSD (Merck & Co.)

MSD (Merck, USA) is leading the global anticancer drug market with its immunotherapy drug Keytruda® (Pembrolizumab).
It is a leading pharmaceutical company and one of the most innovative companies in the utilization of biomarkers.
Keytruda has shown efficacy in a number of cancers, but the response rate varies depending on the level of PD-L1 expression.
Biomarkers have been introduced into patient selection strategies early on, for example, in primary metastatic non-small cell lung cancer.
In treatment, Keytruda monotherapy is approved only for patients with PD-L1 TPS ÿ 50% and has become the standard treatment.
In the patient group with low PD-L1 expression, a differentiation strategy was taken to develop a combination therapy with chemotherapy. In this way, PD-L1
Keytruda's indication-specific development strategy with IHC detection kits (e.g. Dako 22C3 pharmDx) is based on biomarker
It is evaluated as a best practice in commercialization.

One of MSD's greatest achievements in the biomarker field is the expansion of biomarker-based indications. In 2017
Keytruda received the first-ever tumor-agnostic approval from the FDA, which allows Keytruda to be administered to patients with MSI-H
(microsatellite instability high) or dMMR (mismatch repair defective) tumors.
This decision is based on the idea that if there is a specific genetic biomarker, treatment can be done with the same drug regardless of the site of occurrence.
It is a case that has great significance as it opens a new regulatory paradigm. In 2020, TMB-
Keytruda's indications have also been expanded for high (high mutation burden) solid tumors. FDA FoundationOne
Accelerated approval to screen patients with TMB ÿ 10 using CDx NGS assay to use Keytruda monotherapy
By doing so, it presents another biomarker-based treatment option. This successive success is a testament to MSD's active
It was possible through a biomarker clinical development strategy and persuasion based on accumulated data. Keytruda has been used to treat MSI-
It is widely used in patients with various biomarkers such as H, dMMR, TMB-H, and PD-L1, and each
Biomarkers are becoming a key criterion for drug selection.

MSD is also working on exploring novel biomarkers as it pursues combination therapy strategies. For example,
In the development of Keytruda and Lenvima® (Lenvatinib) combination therapy, the tumor microenvironment immune profile and blood
We are analyzing complex biomarkers such as cytokines to study which patient groups have the greatest synergy effect.
And when resistance occurs, secondary biomarkers (e.g., loss of PD-L1 expression due to JAK1/2 mutations) are identified.
Efforts are being made to develop strategies for overcoming this.

Meanwhile, MSD is seeking to expand its portfolio by investing in the ADC field in addition to immuno-oncology drugs.
In 2020, we acquired ADC development company VelosBio and secured ROR1 target ADC (VLS-101).
It is being developed as an ADC that can be used in combination with immunotherapy. In this way, MSD is developing biomarkers for new drugs with various mechanisms.
We have achieved success by incorporating strategies and will continue to lead the precision medicine market in the future.
I'm looking forward to it.

3-5. Bristol-Myers Squibb (BMS)

BMS of the United States is another pioneer in the field of immuno-oncology and a global company with a rich oncology pipeline.
As a pharmaceutical company, we are actively promoting the use of biomarkers. BMS is developing PD-1 inhibitor Opdivo® and
As the developer of the CTLA-4 inhibitor Yervoy®, we pioneered a combination therapy strategy utilizing these two immunotherapy agents.
Interestingly, BMS, unlike MSD, did not strictly apply the PD-L1 biomarker during the initial development of Opdivo.
A broad strategy was taken, which also created some confusion in the first-line treatment market, for example, in first-line non-small cell lung cancer.
The CheckMate-026 study failed to demonstrate efficacy in patients with low PD-L1 expression, and subsequently
A change in strategy was inevitable. To make up for this, BMS is developing a new biomarker for tumor
Mutational burden (TMB) was presented. In the CheckMate-227 clinical trial, in the patient group with high TMB (ÿ10 mut/Mb),
It was confirmed that the combination of Opdivo and Yervoy showed a significant improvement in progression-free survival compared to chemotherapy, and
Based on this, we applied for FDA approval using TMB as a biomarker. Although the FDA ultimately approved the TMB standard,
Although not approved, this study suggests that TMB is useful in predicting immunotherapy response and is similar to PD-L1.
It has been proven that it provides independent information. BMS has since expanded the combination therapy to all patients with PD-L1 status for 2 weeks.
With the success of obtaining approval as a first-line treatment (CheckMate-9LA) in combination with abbreviated chemotherapy, it is also effective in the PD-L1 negative group.
It was shown that a combined effect can be achieved.

BMS is continuously developing new immune-modulating targets and exploring biomarker strategies accordingly.
In 2022, BMS will launch a combination therapy of relatlimab, the world's first LAG-3 immune checkpoint inhibitor, in combination with Opdivo
It was approved by the FDA as Opdualag® (Relatlimab). At that time, there was an analysis that the presence of dual expression of LAG-3 and
PD-L1 in the tumor microenvironment affected clinical outcomes, but the approval conditions did not include explicit biomarkers.
The requirements were not included. However, BMS will also look into appropriate biomarkers for these next-generation immune targets in the future.
It is highly likely that this will be used as a basis for patient selection.

Additionally, BMS acquired various targeted therapy and cell therapy assets through the acquisition of Celgene in 2019.
We have secured it, and we are applying the biomarker strategy here as well. For example, the target antibody developed by Celgene
Bemarituzumab was tested in a clinical trial targeting only patients with FGFR2b protein overexpression in gastric cancer.
The pipeline was transferred to BMS after showing efficacy. Since FGFR2b is overexpressed in only about 30% of patients, this
Phase 2 FIGHT clinical trial results in which the drug was administered only to patients who were FGFR2b positive by detecting the biomarker by IHC
The study showed a trend toward improved survival. FGFR2b companion diagnostics are also being used in the ongoing phase 3 trial.
If successful, it is expected to create another case of antibody therapy + biomarker rather than ADC or cell therapy.

In summary, BMS is utilizing multiple biomarkers (PD-L1, TMB, etc.) in its immunotherapy drugs, as well as through mergers and acquisitions.
We are also increasing development competitiveness by applying accurate biomarker targeting to various new drug candidates that we have secured.

This will provide optimal treatment for a wide range of cancer types and improve treatment outcomes for patients with incurable cancer.
We are aiming for.

3-6. Amgen

Amgen in the United States is a biotech pharmaceutical company with strengths in developing innovative new drugs based on molecular biology.
It is active in both targeted therapy and immunotherapy. Amgen is also developing new drugs through a biomarker strategy.
There are many cases where value has been increased. A representative example is the world's first KRAS mutation targeting treatment.
Lumakras® (Sotorasib) is a KRAS G12C mutation that has long been considered a “refractory target.”
However, Amgen succeeded in blocking it with a small molecule compound and received FDA approval for Lumacras in 2021.
At this time, the FDA approved Qiagen's therascreen KRAS G12C PCR test as a companion diagnostic test along with Amgen's LumaCras,
only if the patient's tumor has a KRAS G12C mutation as determined by pathology.
Traditionally, about 13% of lung cancer patients have the KRAS G12C mutation.
By accurately identifying these, Lumacras showed superior efficacy (objective response rate ~37%) only in this patient group.
It has established itself as a visible precision treatment. Amgen has collaborated with diagnostic companies since the development stage of Lumacrase, and has been conducting tissue tests.
In terms of diagnostic infrastructure, we have also secured a companion diagnostic that detects KRAS G12C using liquid biopsy.
We took preemptive action.

Amgen is also using biomarkers to develop antibody drugs. Five Prime, acquired by Amgen in 2021
Therapeutics' main pipeline, bemarituzumab, is an antibody treatment for patients with FGFR2b overexpression in gastric cancer, and is
the same substance as the FGFR2b target drug from BMS mentioned above. Amgen is conducting phase 2 clinical trials of FIGHT.
Based on the results, this drug was acquired and is currently in a global phase 3 trial using FGFR2b IHC testing as a companion diagnostic.
In progress. In this way, Amgen is developing a suitable biomarker, either through M&A or through its own development.
We are pursuing a strategy of strengthening our pipeline by securing therapeutics.

In the immunotherapy field, Amgen has developed a bispecific antibody technology called BiTE (Bispecific T-cell Engager).
It has established its own position. The first BiTE drug, BylincytoTM (Blinatumomab), is a B cell
It is an innovative immunotherapy that links T cells to the CD19 antigen of tumor cells in acute leukemia. Here,
The biomarker is the target antigen CD19, and since all B cell leukemias express CD19, a separate patient
Although screening tests were not necessary, there were cases in which cancer cells mutated to CD19 negative during treatment and relapsed.
CD19 assay was used as a monitoring biomarker. Amgen subsequently applied BiTE technology to various solid tumors.
are expanding, for example, AMG 160 is in development as a BiTE targeting the PSMA antigen in prostate cancer.
In this case, it is expected that the effect will be greater in patients with higher PSMA expression, so PSMA was used when recruiting patients in clinical trials.
We are also conducting biomarker evaluations such as PET scans.

In summary, Amgen is developing molecular targeted therapies (KRAS, FGFR2b, etc.) and innovative immunotherapies (BiTE, etc.).
We are establishing optimized biomarkers for each program and making them the core of our clinical and commercialization strategies.
Through this, we aim to provide the best treatment benefits to the right patients, and the company's research and development
Investments are also focused on genomics and biomarker science.

4. Conclusion and Implications

The importance of biomarkers in the development of new immunotherapy and ADC drugs is clearly evident through scientific research and industry trends.
It is being confirmed that biomarkers increase the probability of clinical success of new drugs, shorten the development period, and ultimately
It is the key to maximizing healthcare efficiency and patient benefits by providing treatment to the right patients. Global
As seen in the case of pharmaceutical companies, companies that have adopted a precision medicine strategy based on biomarkers are developing immuno-oncology drugs and
There have been successive innovations in the ADC field. On the other hand, without biomarkers, there is heterogeneity in patient responses.
It has also been empirically demonstrated that it is difficult to overcome and fully realize the potential of new drugs.

In the future, the development of new anticancer drugs will go beyond single targets or single biomarkers to include multiple biomarkers and combination treatments.
As we move into the era of biomarker development, pharmaceutical companies and investors will need to have integrated biomarker development capabilities.
It will be the core of competitiveness. Specifically, it will utilize the latest technologies (AI-based pathology, NGS, liquid biopsy, etc.) to
We need to develop sensitive and reliable companion diagnostics and strategically incorporate biomarkers into clinical trial design.
In addition, the regulatory environment requires data proving the clinical utility of biomarkers, so from the beginning
Robust biomarker validation studies should be conducted in parallel.

From an investor's perspective, companies that have secured biomarker platform technology or companion diagnostic partnerships are likely to be the future leaders in anticancer drugs.
It is highly likely that it will gain an advantage in the market. The global trend is already toward the joint growth of the therapeutics-diagnostics industry.
It has become an era where how well biomarkers are utilized determines the commercial success of new drugs.
Especially for innovative but complex drugs such as immunotherapy and ADC, accurate patient targeting is essential.
Investing in R&D for this is also a rational choice from a risk management perspective.

In conclusion, biomarker development is a critical factor in determining the scientific and commercial success or failure of the development of new immuno-oncology and ADC drugs.
In the precision medicine paradigm that respects the biological diversity of patients, pharmaceutical companies are using biomarkers
It can broaden the horizon of treatment and increase the probability of success, and investors should pay attention to companies with such strategies.
In the future, more advanced biomarker technologies and new drugs utilizing them will be introduced, enabling more cancer patients to benefit from them.
We hope to provide you with the benefits of personalized treatment.

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