Drug Development in Oncology

an Overview

WITH DALTON

Peter Pekos

Company Vision

"Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

This technical report is intended to provide an overview to quality and regulatory professionals on oncology drug development. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

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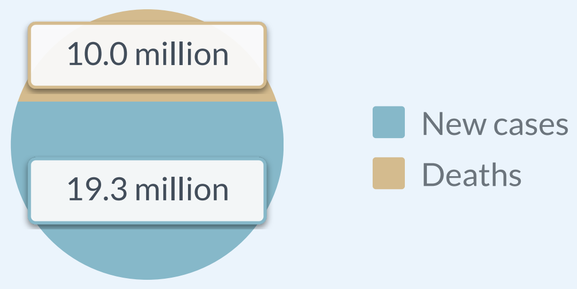
CANCER STATISTICS

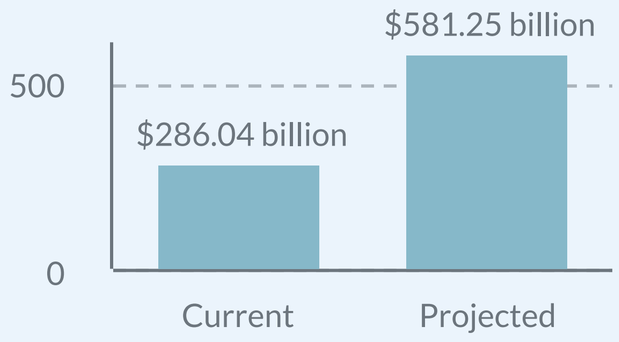
Cancer is the largest cause of mortality in the world, accounting for around 10 million deaths in 2020.

DID YOU KNOW?

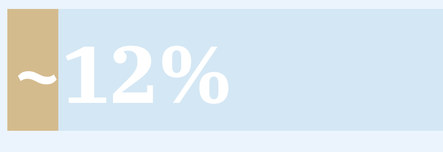
Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020.



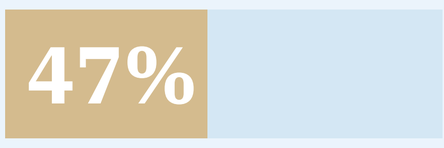
In 2021, the global oncology drug market size was valued at $286.04 billion USD and is projected to increase to over $581.25 billion USD by 2030.



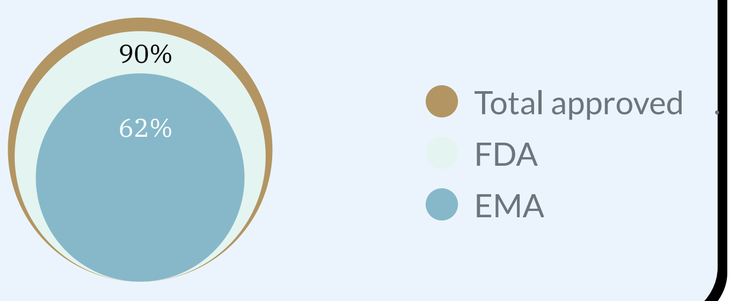
In 2020, breast and lung cancers were the most common cancers worldwide, accounting for 12.5% and 12.2% of all new cases diagnosed, respectively.



New cancer cases are predicted to increase by 47% globally from 2020 to 2040.



In 2021, 270 anticancer drugs were approved, of which 90% obtained FDA approval and 62% obtained EMA approval.



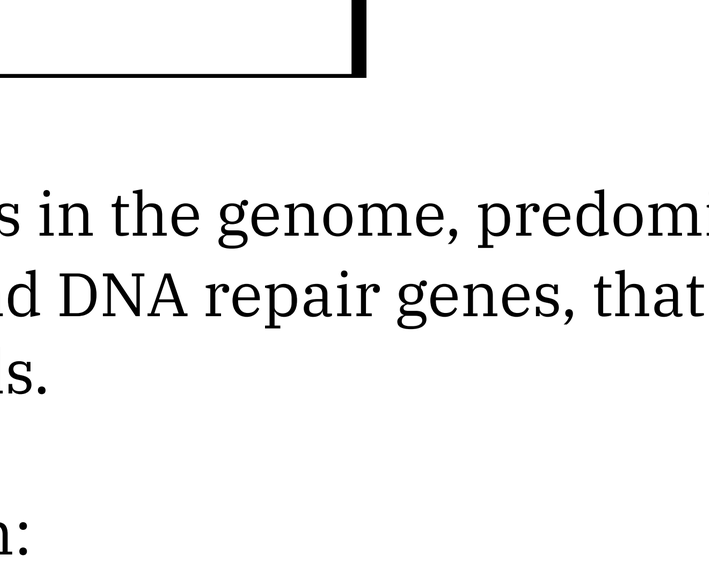
WHAT IS CANCER?

Cancer is caused by changes in the genome, predominantly in proto-oncogenes, tumor suppressor genes, and DNA repair genes, that lead to uncontrolled growth and spread of abnormal cells.

Genetic changes result from:

Errors during cell division

DNA damage from harmful substances in the environment (i.e., chemicals in tobacco, UV rays)



Genetic inheritance

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CANCER DIAGNOSIS

Cancer diagnostic tests include the following:

Lab tests

- Blood
- Urine
- Other body fluids

Imaging tests

- CT scan
- MRI
- Nuclear scan
- Bone scan
- PET scan
- Ultrasound
- X-rays

Biopsy

- With a needle
- With endoscopy exams such as colonoscopy or bronchoscopy
- With surgery

CANCER STAGING & GRADING

After cancer diagnostic tests are performed, further tests may be needed to identify the stage, grade, and/or risk group. This will aid in chosing the best treatment option. In the case of precision therapy, an FDA-approved companion diagnostic test may also be used to assess which FDA-approved therapy a patient may best benefit from based on the genetic abnormalities of their tumour.

1. Stage – refers to the size of the tumor and if it has spread. The most commonly used staging system is TNM.

   - The T refers to the size and extent of the main tumor.
   - The N refers to the number of nearby lymph nodes that have cancer.
   - The M refers to whether the cancer has metastasized.

2. Grade – refers to how normal or abnormal the cancer cells look. The more abnormal the cells look, the quicker they may grow and spread, deeming it a higher grade as it may require more aggressive and urgent treatment.

3. Risk Group

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TYPES OF ONCOLOGY THERAPIES

Chemotherapy

Administration (i.e., oral, IV, IP, IA, etc.) of cytotoxic and anti-cancer drugs to stop or slow the growth of cells that grow and divide quickly, including cancer cells.

Radiation therapy

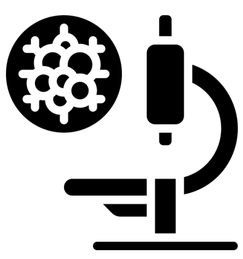
Uses high doses of radiation, either internally or externally, to kill or slow the growth of cancer cells, also affecting nearby healthy cells.

Hormone therapy

Blocks or interferes with the body’s ability to produce hormones in cancers that use hormones to grow, such as prostate and breast cancer.

Stem cell transplants

Helps recover the body's ability to produce stem cells after treatment with high doses of radiation therapy or chemotherapy; may also work against cancer directly.



Hyperthermia

Uses heat as high as 45 °C on the body tissue to help damage and kill cancer cells with little or no harm to normal tissue.

Photodynamic therapy

Uses a drug activated by light to kill cancer and other abnormal cells.

HIFU

High intensity focused ultrasound (HIFU) is an image-guided therapy aimed to kill cancer cells with high frequency sound waves.

Precision therapy

Customization of healthcare, with medical decisions, practices, and products being tailored to each individual cancer patient.

Learn more about individualized therapies with our upcoming whitepaper.

Immunotherapy

Tailored to the unique immune biology of each cancer patient to stimulate and orchestrate the body’s natural defenses as a treatment for their cancer while minimizing toxicities.

Examples include cancer treatment vaccines, immune system modulators, monoclonal antibodies, T-cell transfer therapy (i.e., TIL therapy and CAR T-cell therapy), and checkpoint inhibitors. Immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins, allowing T cells to kill cancer cells.

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DRUG DEVELOPMENT STAGES

Early Drug Discovery

- Accidental discovery
- Cell biology research
- Medicinal chemistry research
- Target identification & validation
- Lead optimization

Preclinical research

- In vivo, in vitro & ex vivo assays
- Dose range finding
- Proof of concept
- Bioavailability studies

Regulatory approval for clinical trials

Clinical research

Phase I	Phase II	Phase III
Length: several months ***Size:*** ~20-25 healthy subjects ***Designed to assess:*** pharmacokinetics, pharmacodynamics, safety, and maximum tolerated dose via dose escalation	***Length:*** several months – 2 years ***Size:*** ~100-400 patients with the target disease ***Designed to assess:*** safety & efficacy, optimal dosing and adverse effects	***Length:*** 1 – 4 years ***Size:*** ~1000 – 5000 patients with the target disease ***Designed to confirm:*** safety & efficacy data

Regulatory approval for market use (1 – 2 years)

Post-clinical research (Phase IV)

- Pharmacovigilance
- Adverse event reporting
- Real-world data collection*

**To learn more about real-world data and how it's used, check out our Whitepaper: Adopting Real World Evidence.*

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EXPEDITED APPROVAL PROCESS

The timeframe and drug development process typically takes up to 15 years. However, expedited review programs exist to facilitate the development process for certain medicines such as oncology drugs.

FDA

Fast-track designation – granted for drugs intended to treat serious conditions and fill an unmet medical need.

Breakthrough therapy designation – given to drugs intended to treat serious conditions which may demonstrate substantial improvement over existing treatments.

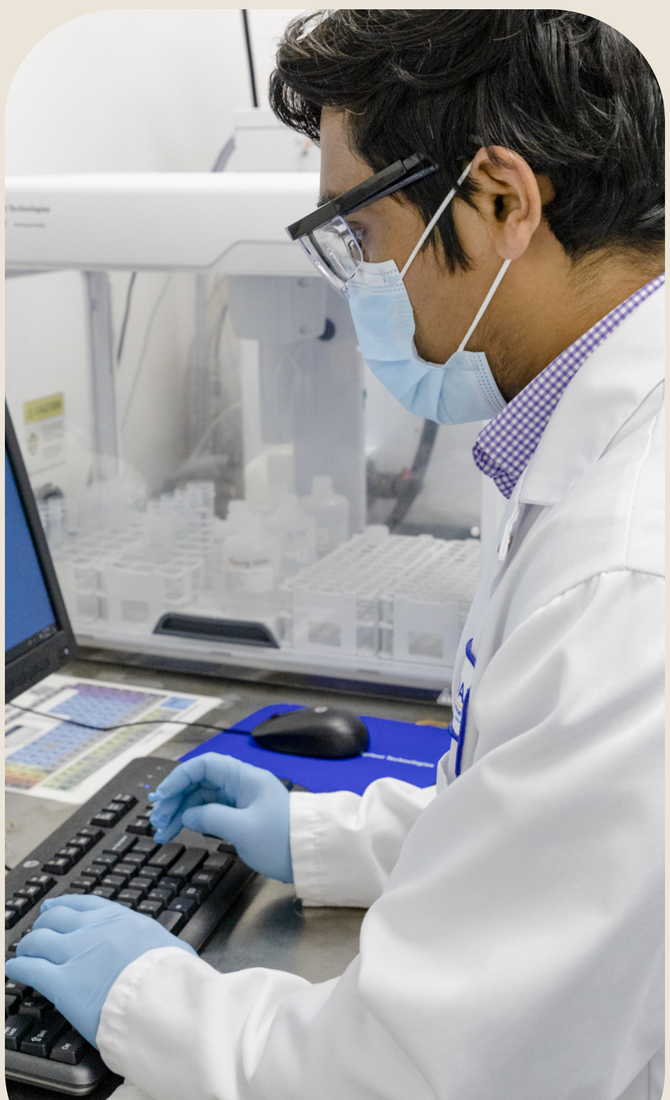
Accelerated approval pathway – provided for drugs intended to treat serious conditions that address an unmet medical need based on a surrogate endpoint.

Priority review designation – granted for drugs that treat a serious condition and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

HC

Conditional drug approval/ Notice of Compliance with conditions (NOC/c) – provided to drugs under the condition that the sponsor does further research to verify the drugs clinical benefit.

Priority review – for drugs intended to treat a serious, life-threatening, or severely disabling illness or condition for which the drug shows sufficient evidence of clinical effectiveness.



EMA

Conditional marketing authorization – for medicines that address an unmet medical need and target a seriously debilitating or life-threatening disease, a rare disease, or is intended for use during public health threat emergencies.

Priority medicines scheme (PRIME) – for medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without other alternatives.

Accelerated assessment – for medicines of 'major public health interest' in regard to therapeutic innovation, that deliver major therapeutic advantage for a condition with no satisfactory method of diagnosis, prevention, or treatment.

Exceptional circumstances – for cases where there is insufficient data to form a solid decision on benefit-risk due to rarity or ethical concerns.

**For details on the incentives of each program, and for the expedited review programs from other regulatory bodies such as SwissMedic, please visit our [Global Expedited Review Programs & Incentives Whitepaper.]*

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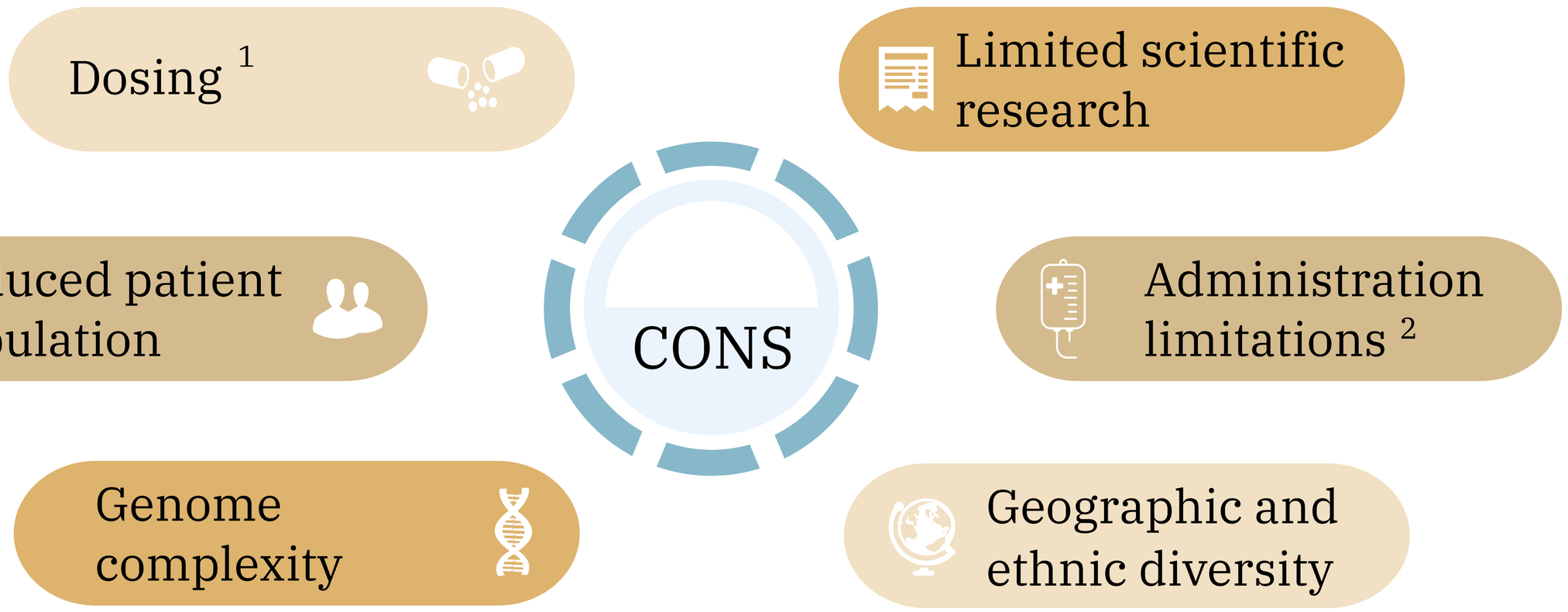
CHALLENGES IN ONCOLOGY DRUG DEVELOPMENT



[1] Currently studies tend to look at only the maximum tolerated dose of a drug. However, dosing decisions are becoming increasingly important in oncology, requiring different doses to be evaluated.

[2] Oral administration barriers include low solubility/dissolution rate, low drug stability, enzymatic degradation, and low solubility/dissolution rate. Another example is intravenous administration limitations such as short half-life, fast metabolism and rapid elimination, nonspecific distribution to healthy tissues, and limited therapeutic efficacy of monotherapy.

REGULATORY ONCOLOGY NEWS IN 2022

In February, Carvykti becomes the second CAR T-cell therapy approved for multiple myeloma in the US. With the recent approval of ciltacabtagene autoleucel, people with advanced multiple myeloma now have another choice for CAR T-cell treatment (Carvykti). Read more here.

In February, clinical studies demonstrated that the target medicine trametinib can treat a rare form of ovarian cancer known as low-grade serous ovarian cancer. Read more here.

In April, clinical studies revealed that combining ivosidenib (Tibsovo) with the chemotherapy drug azacitidine may be a new treatment option for some people with acute myeloid leukemia (AML) who have a mutation in the IDH1 gene. Read more here.

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In June, the FDA published the final guidance on expanding eligibility in clinical trials to include patients with incurable cancers, regardless of whether they've received alternative treatments, under the condition that no scientific rationale to exclude these patients exist: Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings. Read more here.

In June, the FDA authorized the combination of the targeted drugs dabrafenib (Tafinlar) and trametinib (Mekinist) for almost any form of an advanced solid tumor with a specific BRAF gene mutation. Read more here.

According to a JAMA Network Open research in June, the FDA approves novel cancer treatments faster than EMA. However, more drugs under accelerated approval in the US were withdrawn compared to Europe. This demonstrates that quicker review timeframes do not necessarily translate into better outcomes. Read more here.

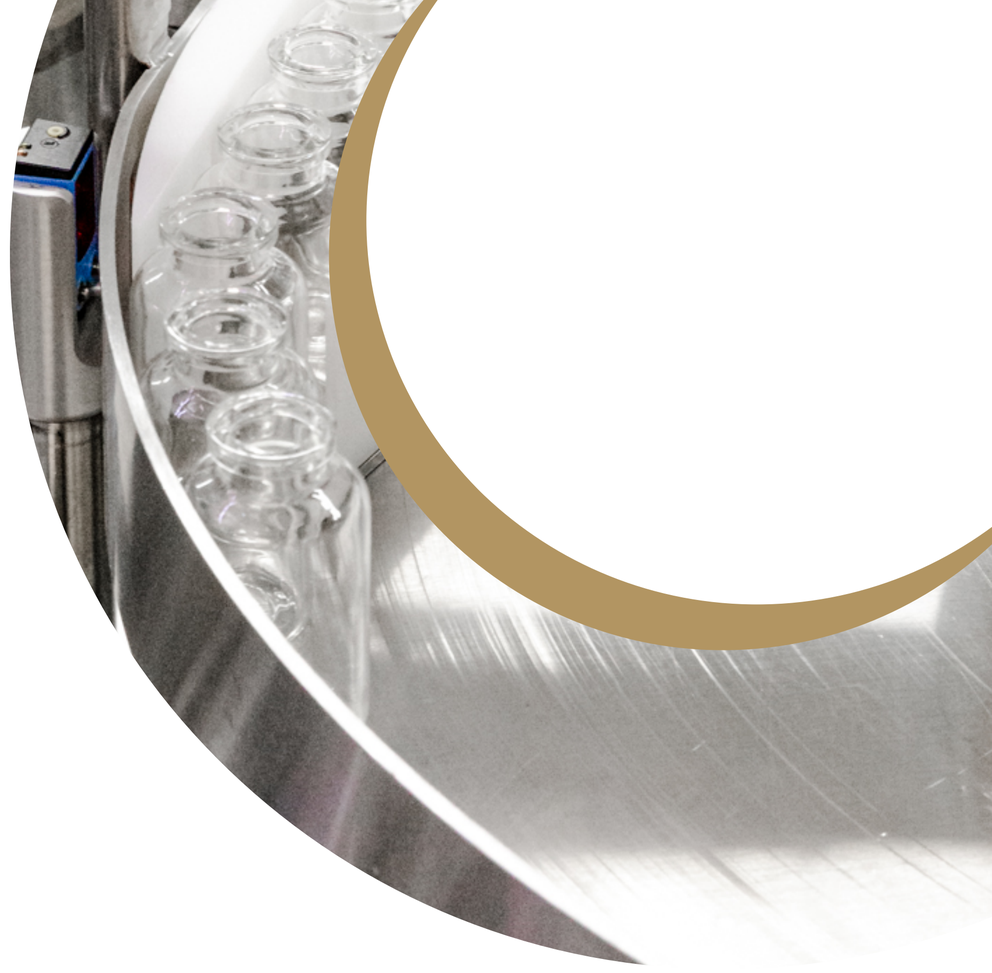
In July, EMA recommended a conditional marketing authorisation for Tecvayli (teclistamab) in the EU for the treatment of relapsed and refractory multiple myeloma. Meanwhile, in October the FDA Approved Teclistamab-cqyv for Relapsed or Refractory Multiple Myeloma. Read more here.

In July, findings from a clinical trial revealed that combining chemotherapy with the immunotherapy drug pembrolizumab (Keytruda) can increase the life expectancy of certain patients with advanced triple-negative breast cancer. Read more here.

In July, the FDA issued a draft guidance (*Real-Time Oncology Review (RTOR) Guidance for Industry)* to assist in the identification of new cancer treatments that may qualify for expedited review by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). Read more here.

In October, the FDA released the final guidance on the development of acute amyloid leukemia (AML) drugs: *Acute Myeloid Leukemia (AML): Developing Drugs and Biological Products for Treatment*. Read more here.

Dalton's
Services



We bring over 35 years of experience developing products for our clients that are compliant, transferable, and scalable.

At Dalton we can help with drug innovation through our cGMP APIs. Our skilled scientists can support your drug discovery process through API synthesis for all stages of pre-clinical and clinical trials as well as small scale commercial manufacturing. We provide integrated process development, API manufacturing and finished dose manufacturing at a single location with the expertise required for developing a process that is robust, transferable, and scalable to meet your requirements.

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For more information on services we provide, visit our website.

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