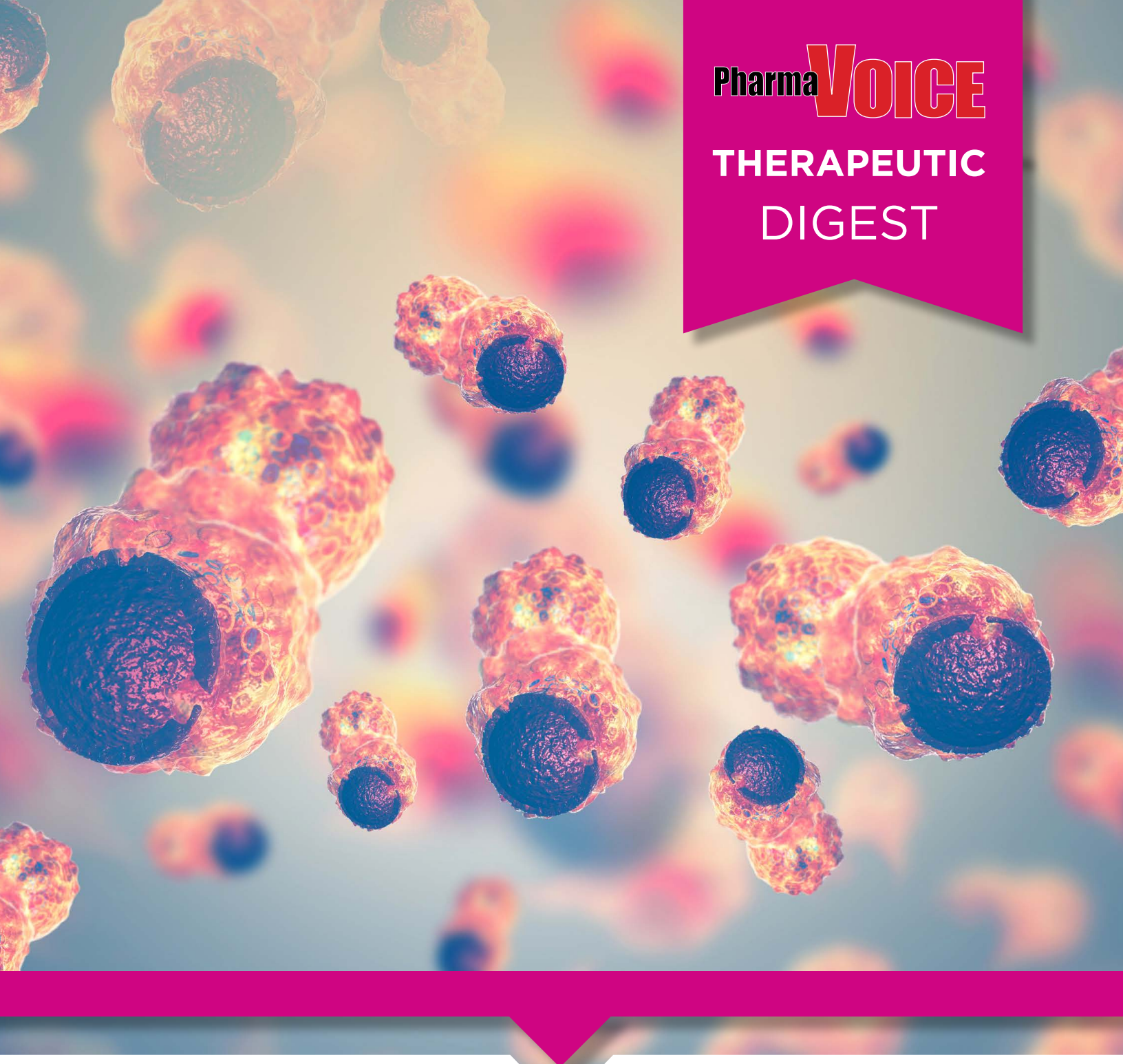

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EDUCATION HAS AN IMPACT

The Need for Digital CME for Physicians Treating Patients with CLL

Lauren Willis, PharmD, BCOP
Director, Clinical Strategy
Hematology/Oncology
Medscape Education
lwillis@medscape.net

Medscape Oncology

In the rapidly changing fields of medicine, such as hematology/oncology and specifically with respect to the management of patients with chronic lymphocytic leukemia (CLL), education is a key component of keeping clinicians current on changes to treatment paradigms. Continuing medical education (CME) is an effective option as it provides scientifically rigorous, independent, accurate, and clinically relevant information that hematologists/oncologists need to treat their patients.

The Changing Treatment Landscape

The assessment and treatment of patients with CLL has changed greatly in the past few years. In December 2018, a major shift took place in the treatment paradigm for CLL related to which patients received targeted therapies as opposed to chemoimmunotherapy. Since then, data have continued to emerge about novel regimens, and NCCN Guidelines® have changed several times to accommodate this data. In 2019, a study in *Clinical Lymphoma, Myeloma & Leukemia* found that education gaps existed for community hematologists/oncologists regarding the need to perform molecular testing on patients with CLL and the incorporation of new treatment regimens into practice.The study found that many hematologists/oncologists in community practice were not following testing guidelines and they were making incorrect treatment selections for patients based on out of date information.[1] Four new treatments and combinations have been approved for CLL since September of 2018, and even more are being evaluated and may be approved in 2020 and 2021. All of these rapid changes point to the need for effective, on-demand continuing education in order to keep clinicians current and practicing evidence-based medicine.

Leaders in the field of oncology agree. "As the landscape of CLL management continues to rapidly evolve, it is essential that physicians, advanced practice providers, pharmacists, nurses, and all members of the care team are able to help patients make the right therapeutic choice for them. There are an increasing number of options available, and as a result, it is becoming increasingly important to ensure that all members of the team are educated regarding these choices," said Dr. Jonathan B. Cohen, Assistant Professor at Emory University, Winship Cancer Institute in Atlanta, Georgia.

Effectiveness of Education on Clinical Behavior

It is not only critical that clinicians receive education, but it is vital that the education be effective. A 2020 peer-reviewed study published in collaboration with the FDA demonstrates the power of Medscape digital education to affect clinical behavior and positively impact public health. The study examined the efficacy of targeted short-form messaging and CME aimed at reducing overprescribing of fluoroquinolone antibiotics. The study examined nearly 24,000 high prescribers of fluoroquinolones and divided 11,774 into 3 treatment groups to evaluate and measure the effectiveness of communication and education methodology:

- Group 1 - Received short-form targeted messaging only (n = 8895)
- Group 2 - Received CME activity only (n = 1756)
- Group 3 - Received both short-form targeted messaging and CME (n = 1123)

The trial featured a case-matched control group (n = 11,774), and results were compared against that population. The study demonstrated the statistically significant impact of Medscape digital CME (with or without messaging) to reduce inappropriate clinical behavior.[2]

Medscape is the leading source of digital healthcare information for physicians worldwide[3] and is a trusted learning partner for the medical community, with a proven ability to deliver education that makes an impact. As new research becomes available and treatment landscapes change, Medscape Education is committed to providing effective digital CME to learners where, when, and how they want to learn.

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Written by Kristina Erfe Pines

Oncology

Progress and Challenges

Cancer is a disease that spans the breadth of the human experience. Observed in hominid fossils and human mummies, first described in ancient times by Egyptian and later by Greek physicians, it has manifested itself throughout human history. Affecting people of all ages, cancer cuts through society, causing suffering on a global scale. According to the World Health Organization, cancer is responsible for one in six deaths, which makes it the second-most common cause of death globally.

Through the ages, physicians who observed and described this disease were faced with its seeming intractability. The emergence of modern medicine changed that view through an initially slow accumulation of biological and therapeutic knowledge that accelerated with the advent of molecular cell biology and genetics in the latter part of the 20th century. This progress, together with more recent technological advances, have permitted an unprecedented understanding of the disease. Today, the word "cancer" refers to hundreds of distinct disease types that share similar fundamental properties. The importance of the tissue and cell type from which the disease originates is clear. It is known that the function of cancer cells at the molecular and metabolic level is crucial but is also highly context dependent. Cancer is also appreciated as a disease of change — a condition characterized by plasticity and heterogeneity, that evolves at genetic, phenotypic, and pathological levels, and progresses through different stages clinically. Beyond decoding of the genetic fingerprint and molecular makeup of a specific cancer type, research is underway to understand the importance of the systemic and local tumor environment in how the disease develops and manifests. The interplay with the immune system and immune tumor microenvironment has become especially apparent in recent years. Indeed, today, experts recognize that cancer heterogeneity, evolution, and local and systemic environment all have key roles not only in disease development but in the response or resistance to therapy and disease recurrence.

GENERAL OVERVIEW OF PROGRESS

Technological advances such as next-generation sequencing, integrated "-omics," imaging and single-cell methodologies have allowed profiling of different tumor types at a resolution and scale that were not possible previously. The ability to generate and share big data is fundamentally altering the way this disease is understood and treated — for example, by allowing the identification of biomarkers to select patients for clinical trials and evaluate therapy response. Data science has

become a core part of a field that is increasingly embracing computation, as in the form of artificial intelligence for extracting information from complex datasets. Nevertheless, the potential of such approaches to revolutionize data analysis for cancer screening, diagnosis, and therapy decisions comes with challenges.

Viewing cancer as a systemic disease characterized by evolution, heterogeneity and environmental inputs may seem commonplace now, but in reality, revealing one layer of complexity only underscores other complex features that need to be appreciated. The size, quality, and complexity of large datasets, such as those of The Cancer Genome Atlas, the International Cancer Genome Consortium, and the Human Cell Atlas (among others), mean that considerable work is needed to decode, interpret, and contextualize findings. Identifying tumor cell-intrinsic genomic and epigenomic attributes provides only a snapshot of tumor development and progression. A more complete picture may emerge with longitudinal information, as well as profiling of different cellular constituents of tumors, such as stromal and immune cells. Integrative "-omics" and single-cell approaches provide the ability to do so; however additional factors need to be considered. Among them are the peculiarities of tissue and tumor types, the size and characteristics of human-participant cohorts or the choice of preclinical animal model systems, the resolution and strength of the chosen methodology, and the quality of analytical tools. How data from individual patients versus larger cohorts are handled and analyzed — the information that can be obtained from each type of analysis and the extent to which tumor profiling studies may be more broadly generalizable, given the degree of inter-patient heterogeneity — are questions with which this field continues to grapple.

The developments noted above also have revolutionized the approach to treatment. The more granular understanding of cancer's molecular drivers and tumor-cell-intrinsic or extrinsic vulnerabilities, and the addition of next-generation sequencing testing to clinical practice, have given rise to targeted therapies and the concept of precision oncology — treatment tailored to individual patients, aiming to hit cancer-specific vulnerabilities, thereby hopefully reducing toxicities and improving quality of life for patients receiving treatment. High-throughput approaches, computational science, bioengineering, and nanomedicine are changing the landscape of drug and diagnostics development. The hard-won advances in tumor immunology have led to an explosion of cancer immunotherapies. These therapeutic breakthroughs in precision medicine and immuno-oncology have successfully introduced several therapeutic modalities into the clinic. However, as with historical cancer treatments, these new modalities still encounter the setbacks of therapy resistance and lack of response, as well as their own serious adverse events.

An additional key consideration in the effort against cancer is the influence of the environment,

daily habits, and culture. We are gaining a better understanding of these facets of the disease, but such factors are often difficult to quantify and control in a real-world setting, or to model in the laboratory. The often late-stage presentation and therefore late diagnosis, of the disease continues to hamper therapy options, and metastasis remains a major cause of cancer deaths and a main focus of foundational cancer research. Socioeconomic factors lend an additional, devastating dimension: according to the World Health Organization, 70% of cancer deaths occur in low- or middle-income countries, but even in high-income societies, certain parts of the population bear a disproportionate burden of suffering. A large fraction of cancer cases and deaths may be preventable with greater epidemiological and mechanistic understanding of environmental and behavioral risk factors. The development and wider adoption of the Pap test and HPV vaccines against cervical cancer are singular successes that exemplify the importance of early detection and prevention in neutralizing the threat of cancer in a broad population. However, this remains a disease of disparities. Therefore, experts agree that it is essential that research continues to deepen our appreciation of the underlying causes of these inequalities and to work toward reversing them, always keeping the patient at the forefront of the cross-disciplinary scientific endeavor in this field. Developing more effective screening and diagnostic means and working toward providing accessible and affordable high-quality cancer care for the wider population will be essential for addressing cancer-health disparities.

THE TOP THREE MOST COMMON CANCERS IN AMERICA

Skin Cancer

Skin cancer is the most common malignant disease found particularly in Caucasians[1]. More than 1 million new cases are reported worldwide each year. The various types of skin cancer are named after the cells they originate from and their clinical behavior. The most common types are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), together referred to as nonmelanocytic skin cancers (NMSC), and malignant melanoma (MM)[2].

Nonmelanocytic Skin Cancers

NMSC is the most common malignancy found in humans. Each year 2 to 3 million new cases are reported worldwide, 1.3 million of those are found in the USA alone[3]. In Europe, Canada, the USA, and Australia the incidence is increasing by 3%-8% per year[4]. The incidence rate is thought to double in the next 30 years[5]. The most important etiological factors include UV light, ionizing radiation, and certain chemical carcinogens. A more detailed overview is shown in Table 1.

BCC represents 80%-85% of all NMSC, which makes it the most common skin cancer type. In the USA, 30% of all newly diagnosed cancers are BCC[6]. Worldwide, the incidence increases by 10% per year, mostly in older men, but also in young women[7].

The other type of NMSC is SCC, which represents 15%-20% of all NMSC, whose growth exhibits local destructiveness and surrounding tissue invasion, and also causes more death more frequently than BCC[8].

Malignant Melanoma

Skin melanocytes are cells that produce the skin pigment melanin, and MM affects them specifically. Its incidence is still on the rise in areas with light skinned populations that are overly exposed to sun radiation. Only Australia, with an incidence of 50–60/100,000, reports a slowly declining trend from 2005[9]. In Europe the incidence of this type of skin cancer is 10–20/100,000 inhabitants, while the USA stands at 20–30/100,000.

Even with MM representing a mere 4% of newly discovered cancers, it takes the sixth place as the most common female and seventh as the most common male cancer in Slovenia. In the rest of the world, the MM is more common in males than in females.

According to 2010 research, 13,200 new cases of MM are found annually, whereby the incidence in the Caucasian population is sixteen times greater than in Afro-Americans and 10 times greater than in Latin Americans[10]. The most prominent etiological factors are constitutional factors, UV light, and other factors, as shown in Table 1.

Important Risk Factors in Skin Cancer *Table 1*

Factor	Description	Incidence
BCC		
Ultraviolet light[11,12]	Increased incidence of BCC has been noticed in individuals with fair skin, weaker tanning ability, fair hair, blue eyes, older individuals, men, and those with frequent sun exposure	The incidence changes nearer to the Equator, where the ultraviolet B waves (UVB) are most frequent. Ultraviolet A waves (UVA) also have carcinogenic effects
Ionizing radiation[13,14]	Ionizing radiation causes BCC in humans and animals. The latency period in 20-30 years	Patients who have been exposed to 1 Gy (gray) of radiation had a greater risk of developing cancer. In individuals who have been exposed to 35 Gy of radiation, the risk was 40x greater compared with the general population
Chemical substances [15]	A large majority of chemical carcinogens cause SCC and not BCC. There are exceptions, such as arsenic in people and 3-methylcholanthrene and antramine in rats	BCC developed 30-40 years after chronic arsenic exposure, as a consequence of contaminated food, water, seafood, and so forth
SCC		
Extrinsic factors		
Ultraviolet light [16,17]	UV light is one of the most important factors. The most common sites of SCC are the head, neck, and the dorsal side of arms. People with type 1 skin according to Fitzpatrick are particularly at risk	SCC incidence increases nearer to the Equator; it doubles per 10° latitude towards the Equator
Ionizing radiation [18]	Gamma, Grenz, and X-rays are well known carcinogens	The incidence of cancer due to radiation increases linearly by 5.5% per 1 Sv
HPV [19]	HPV infection presents a risk for cervical SCC development, as well as certain genital and skin variants of SCC	Cervical, anal, and oropharyngeal cancers are almost always etiologically connected to a HPC infection; together with UVA, they are thought to be cocarcinogens for skin cancer
Chemical substances	Hydrocarbons, arsenic, and tobacco are well known carcinogens	Hydrocarbons were important etiological factors in certain professions (e.g. chimney sweeps); skin lesion development correlates to arsenic exposure
Intrinsic factors		
Genodermatoses [20,21]	Those with Xeroderma Pigmentosum (XP) are more susceptible to UVA radiation, which leads to skin and eye degeneration and the development of skin SCC, BCC, and MM	In individuals with XP, the incidence of cancer before the age of 20 is 2,000X greater than in the general population
Immunosuppression [22,23,24]	Chronic immunosuppression (e.g. long-term corticosteroid immunosuppression therapy or posttransplant therapy) increases skin cancer incidence	In Netherlands and Norway, the incidence in patients after heart or kidney transplant is 65 to 250 times greater; in the USA, 35% of individuals within 10 years of a heart transplant developed some form of skin cancer

Actinic keratosis (AK) [25,26]	These lesions are the most common premalignant conditions; Bowen's disease and Erythroplasia of Queyrat are forms of SCC in situ that can sometimes develop into an invasive form	They represent one of the most common reasons for a dermatologist visit in the USA; in the USA, UK were present in 55% of fair skinned men and 37% of fair skinned women between the ages of 65 to 74
Other skin lesions	SCC often develops in scar tissue (e.g. healed burns), similarly, it also arises in areas of chronic inflammation, such as ulcers, sinus tracts, and inflammatory dermatoses	Approximately 1% of skin cancer develops in chronically irritated skin. In 95% it is SCC
Malignant melanoma		
Constitutional factors (race, pigmentation, and genetic predisposition) [27]	Skin type and sunlight are the main factors that influence MM incidence; the incidence of MM and other types of skin cancer is greater in patients with XP and albinism	On average, MM is 3–4 times more common in less pigmented races, compared with more pigmented ones; the number of melanocytic nevi that a person has on their skin is a good indicator of MM risk
Ultraviolet light [28,29]	The main environmental factor for MM and other skin cancer development is short wavelength UV light present in sunlight; the prominent effects of UV radiation are pyrimidine dimer formation, DNA base and nucleoprotein crosslinking, and polynucleotide chain disruption	Incidence increases nearer to the Equator, where the UVB dose in sunlight is highest; UVA also have carcinogenic effect
Other factors [30,31]	Multiple factors were proposed; occupation, diet, smoking, oral contraceptives, endometriosis, Parkinson's disease, TNF inhibitors, and so forth	Statistically significant links with the disease have not been found for most factors, with the exception of endometriosis and Parkinson's disease; correlation with MM has been found here

Current Therapeutic Approaches in Treating Skin Cancer

"Basic" Pharmacological Therapy

NMSC. There are many treatment options for the NMSC. The most appropriate is surgery through a radical excision. However, the treatment of choice for Bowen's disease is a local, topically applied 5-fluorouracil. Imiquimod and 5-fluorouracil can also be used for the treatment of superficial BCC (except for the nodular form). Morbidity and mortality have been significantly decreased by newer drugs that regulate some key cell receptors (i.e. 5-fluorouracil) and the immune response. Imiquimod (which does not affect the mortality) and interferons (i.e. IFN- α2b) are some of these. For systemic therapy, especially for MM, dacarbazine, temozolomide, or carboplatin/paclitaxel are also used[32]. Vismodegib is the first oral selective inhibitor of the Hedgehog signal pathway (HPI, Hedgehog Pathway Inhibitor). It binds selectively to the transmembrane smoothened protein

(encoded by the SMO gene), where it inhibits the hedgehog signaling pathway, which also inhibits tumor growth. Two clinical studies were performed, namely, ERIVANCE BCC and STEVIEW, where vismodegib was used in patients with advanced or metastatic BCC, some of which were also Gorlin syndrome patients[33].

MM. There have been no novel approaches in systemic metastatic MM treatment. Dimethyl triazeno imidazole carboxamide (DTIC, analogue temozolomide) is the only recommended monotherapy, though it was only effective in rare patients. In case of a lack of response to the DTIC therapy, a cisplatin (or its analogues) combined with other cytostatic drugs (carboplatin, nitrourea, tazanes, vindesine, and vinblastine) may be effective. Unfortunately, this comes at a cost of more unwanted side effects, while the prognosis remains unchanged[34].

Targeted Therapy

BRAF and MEK. The discovery that up to 66% of MM patients harbor activating mutations in serine/threonine-protein kinase (BRAF), which results in constitutively active kinase leading to unregulated growth and proliferation, has led to the development of different targeted therapies, as well as affecting the general diagnostic approach in patients with metastatic diseases. Hence, the testing for BRAF mutations should therefore be considered in all patients with metastatic disease, either by polymerase chain reaction (PCR) or immunohistochemistry (IHC)[35].

Highly selective BRAFV600 inhibitors such as vemurafenib and dabrafenib represented a breakthrough in the treatment of metastatic melanoma. Vemurafenib showed and improved response rate and median overall survival when compared with dacarbazine. Dabrafenib improved progress-free survival and median survival in stage IV MM patients, compared with those treated with dacarbazine[36].

The major issue in most patients is the development of resistance, whereas the mitogen-activated protein kinase (MAPK) pathway reactivation appears to play a major role[37]. Mitogen-activated protein kinase (MEK) is a serine/tyrosine/threonine kinase, which is an important part of the MAPK pathway.

Previous attempts at targeting MEK were limited by toxicity and limited antitumor ability. Newer MEL inhibitors (selumetinib, trametinib, cobimetinib, and binimetinib) have shown promise and have been developed along with BRAF inhibitors as a part of a combination therapeutic strategy[38].

As monotherapy, trametinib showed a survival advantage compared with conventional chemotherapy. Binimetinib has shown similar clinical efficacy in BRAF-mutant melanoma and activity in NRAS-mutant melanoma. Selumetinib has shown an improvement in progress-free survival when compared with chemotherapy. However, the overall response rates are lower than BRAF targeting therapies. Therefore, MEK inhibitors are used as part of a combination therapy of BRAF mutated diseases[39].

Immunotherapy

Interleukin 2. In the 1990s there was a breakthrough in the field of MM treatment. Following the therapies based on DNA-damaging agents, the newest treatment option for MM was immunotherapy in form of IL-2[40]. It is a protein, one of the first extensively described and characterized cytokines. The combination of these activated the proliferation of T, B, and NK cells, which are of vital importance for the homeostasis of the immune system. In 1998, the FDA approved the use of this as a therapeutic option.

Interferon. Interferons have been, in the past 30 years among the plethora of drugs, tested for the treatment of MM, both in randomized and nonrandomized studies. Of all the adjuvant options, the IFN- α therapy has proved the most efficient and has since been adopted as part of the standard treatment. It has a broad spectrum of positive effects on the immune system and can aid the removal of the melanoma cells, which might have remained after the operation. It also exhibits an antitumor activity in metastatic diseases[41].

Cytotoxic T-Lymphocyte-Associated Protein 4. Breakthroughs in immunotherapy have also enabled the use of T-cell activation regulation by blocking cytotoxic lymphocyte associated antigen-4 (CTLA-4) in MM therapy. Ipilimumab is a human IgG1 monoclonal antibody that demonstrated an improvement in overall survival through this mechanism even in patients with advanced MM[42].

Programmed Death 1. Clinical benefit has also been seen in programmed death 1 (PD-1) blocking antibodies. Pembrolizumab and nivolumab are antibodies, used in the treatment of distant melanoma metastases. Nivolumab has successfully increased overall survival and one-and two-year survival rates when compared with dacarbazine and ipilimumab. It appears to be very well-tolerated, with mild and manageable unwanted side effects such as rash, diarrhea, and pruritus[43].

Pembrolizumab is a humanized anti-PD-1 IgG4 antibody that has also demonstrated a clinical benefit in patients with advanced MM. It also appears to be well-tolerated with a few unwanted side effects. PD-1 pathway inhibiting drugs also show promise in hematological malignancies[44]. Clinically, both CTLA-4 and PD-1 directed monotherapies have proven benefit in advanced MM.

Adoptive Cell Immunotherapy (ACT). ACT refers to the process of administering autologous or allogenic tumor-reactive T or NK cells to patients with the intent of achieving tumor regression. This process occurs through the isolation of lymphocytes with high affinity for tumor antigens, which can be selected ex vivo, stimulated, expanded, and infused back into the patient and represents an area of great promise in the treatment of metastatic MM. It has been shown that numerous antigen-specific T cells can be isolated from excised tumors in MM. The limitations of this approach are the potential logistical and technical hurdles from patient selection, tumor resection, and expansion of adequate numbers of viable tumor infiltrating lymphocyte (TIL) cultures. To address some of these, novel strategies, such as genetically modified T cells, are being developed.

Lung Cancer

After decades of failed clinical trials and persistently dismal lung cancer survival outcomes, the 2010s ushered new developments into the beleaguered field of lung cancer research. Treatment progress gained momentum and finally reached a tipping point in the mid-2012s, with the number of advances over the last five years outweighing all the advances in the five decades.

Surgery

Surgical oncologists worldwide increasingly turned to video-assisted thoracic surgery (VATS) in the 2010s to manage early-stage lung cancer, with many centers now favoring this minimally invasive approach over open thoracotomy to reduce surgical morbidity. Multiple observational studies and meta-analyses pointed to fewer postoperative complications and better short- and long-term survival with VATs lobectomy compared with open lobectomy. However, data from a large randomized trial supporting the advantage of this approach were heretofore lacking — that is, until the British VIOLET study, the largest randomized trial ever to compare clinical outcomes following VATS versus open surgery in patients with early-stage disease.

At the end of 2019, the VIOLET investigators reported that patients who underwent VATS lobectomy experienced significantly fewer in-hospital complications compared with those who

underwent open lobectomy, as well as a shorter length of stay. Importantly, these benefits were attained without compromising early oncologic outcomes (i.e., R0 resection rates or lymph node upstaging) or increasing serious adverse events in the early postoperative period. Results for patient-reported pain, quality of life, and disease recurrence at one year are still awaited.

Some centers have explored other techniques to further decrease the invasiveness of surgery, including segmentectomy, single-port VATS, and robotic-assisted thoracic surgery, with promising signals of success.

Radiotherapy

For patients with early-stage NSCLC that is unsuitable for surgery, stereotactic ablative radiotherapy (SABR) offers an alternative. Both the American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology established guidelines to standardize SABR delivery to patients with peripherally located, early-stage, node-negative NSCLC who are not candidates for surgery or who refuse to undergo surgery, cementing this modality as a standard of care over conventional external beam radiotherapy. Given its success in treating inoperable lung cancer, ongoing research is now focused on whether SABR can be used in lieu of surgery in early-stage disease. Two large randomized trials, the Joint Lung Cancer Trialist's Coalition STABLE-MATES trial (NCT02468024) and the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR) trial (NCT02984761), were launched during the last five years to compare SABR versus surgery in patients with operable stage I NSCLC.

Molecular Testing

Following the discovery of oncogenic drivers in lung cancer in the early 2000s and initial forays into developing tyrosine kinase inhibitors (TKIs) to target those mutations, the field has embraced molecular testing as a tool to guide and individualize treatment selection for patients. The first endorsement of molecular testing came in 2013 when the College of American Pathologists, the IASLC, and the Association of Molecular Pathologists jointly released guidelines recommending EGFR and ALK analysis of either the primary tumor or a metastatic lesion for all patients with advanced-stage adenocarcinoma, regardless of clinical risk factors. The associations since expanded the guidelines in 2018 to include ROS1, BRAF, MET, RET, HER2, and KRAS, underscoring the wide breadth of targets and corresponding therapies now available for lung cancer treatment[45].

A study conducted by the Lung Cancer Mutation Consortium in the United States elegantly illustrated the importance of screening for driver mutations as a standard component of the diagnostic workup for NSCLC[46]. Of 733 patients with adenocarcinoma who underwent genotyping

for 10 oncogenic drivers, 64% harbored a targetable driver mutation. Notably, patients with an oncogenic driver who received targeted therapy survived a median of 3.5 years, whereas patients with a driver mutation who did not receive targeted therapy survived a median of 2.4 years. Median OS for patients without a driver mutation was 2.1 years. A nationwide study conducted by the French Cooperative Thoracic Intergroup that included more than 17,600 patients with advanced NSCLC subsequently reported similar findings, bolstering the clinical benefit and prognostic utility of molecular profiling[47].

Systemic Therapy

In 2010, only approximately 20% of patients with lung cancer were expected to live five years beyond their initial diagnosis, largely owing to the late onset of disease. Moreover, only two targeted therapies, gefitinib and erlotinib, were available to target just one driver mutation, EGFR. As of 2020, nearly 20 new agents — targeted therapies, checkpoint inhibitors, and anti-angiogenic agents — have transformed the treatment landscape, and OS rates are beginning to creep upward as a result. In 2016, the five-year OS rate had reached 23.5%, and it is expected to continue to its climb as an increasing number of patients hit the five-year mark since the initial introduction of novel therapies.

Lung Cancer U.S. Drug Approvals 2010-2020 *Table 2*

Year	Drug Name	Notes
2011	Crizotinib	Label expansion approved for ALK-rearranged advanced NSCLC
2013	Erlotinib	Approved for EGFR-mutated advanced NSCLC
	Afatinib	Approved for EGFR-mutated advanced NSCLC
2014	Ramucirumab	Approved in combination with docetaxel for metastatic NSCLC progressing on/after platinum-based chemotherapy
	Certinib	Granted accelerated approval for ALK-positive metastatic NSCLC
	Gefitinib	Granted Orphan Drug Designation for EGFR mutation-positive advanced NSCLC
2015	Necitumumab	Approved in combination with gemcitabine/cisplatin for metastatic squamous NSCLC
	Gefitinib	Approved for EFGR-mutated advanced NSCLC
	Osimertinib	Granted accelerated approval for EGFR T790M+ advanced NSCLC progressing on/after EGFR TKI
	Alectinib	Approved for ALK-rearranged advanced NSCLC progressing on or intolerant to crizotinib
	Nivolumab	Approved for metastatic NSCLC progressing on/after platinum-containing chemotherapy
	Pembrolizumab	Approved for metastatic PD-L1-expressing NSCLC progressing on/after platinum-containing chemotherapy

2016	Crizotinib	Approved for ROS1-positive metastatic NSCLC
	Afatinib	Approved supplemental NDA for metastatic squamous NSCLC progressing after platinum-based chemotherapy
	Atezolizumab	Approved for metastatic NSCLC progressing on/after platinum-containing chemotherapy/TK1 if EGFR/ALK+
	Pembrolizumab	Approved first line for metastatic PD-L1-expressing NSCLC with no EFGR or ALK genomic tumor aberrations
	Pembrolizumab	Approved for metastatic PD-L1-expressing NSCLC progressing on/after platinum-containing chemotherapy
2017	Alectinib	Approved as first-line treatment of ALK-positive advanced NSCLC
	Brigatinib	Granted accelerated approval for ALK-rearranged NSCLC progressing on or intolerant to crizotinib
	Certinib	Approved for ALK-positive metastatic NSCLC
	Dabrafenib/ trametinib	Approved for BRAF V600E mutation-positive metastatic NSCLC
	Pembrolizumab	Approved as first line combination with pemetrexed/carboplatin for metastatic non-squamous NSCLC
	Osimertinib	Granted full approval for EGFR T790M+ advanced NSCLC progressing on/after EGFR TKI
2018	Osumertinib	Approved for metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations
	Dacomitinib	Approved for metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations
	Lorlatinib	Approved for ALK-positive metastatic NSCLC progressing on crizotinib + ≥1 other ALK inhibitor or progressing on 1L alectinib or ceritinib
	Larotrectinib	Granted accelerated approval for advanced solid tumors with an NTRK gene fusion and no known acquired resistance mutations for which no satisfactory treatment alternatives exist
	Dirvalumab	Approved for unresectable stage III NSCLC that has not progressed following concurrent platinum-based chemotherapy + RT
	Nivolumab	Approved for metastatic SCLC that progressed after platinum-based chemotherapy + ≥1 other line of therapy
	Pembrolizumab	Approved as first-line treatment in combination with (nab-) paclitaxel/carboplatin for metastatic squamous NSCLC
	Atezolizumab	Approved in combination with paclitaxel/ carboplatin + bevacizumab for metastatic non-squamous NSCLC with no EGFR or ALK mutations
	Afatinib	Supplemental NDA approved for first-line metastatic EGFR-mutated NSCLC
2019	Entretinib	Approved for ROS1-positive metastatic NSCLC and granted accelerated approval for advanced solid tumors with an NTRK gene fusion and no known acquired resistance mutations for which no satisfactory treatment alternatives exist
	Pembrolizumab	Approved as monotherapy for stage III, PD-L1 expressing NSCLC unsuitable for surgery or definitive CRT and with no EGFR or ALK mutations
	Atezolizumab	Approved as first line in combination with carboplatin/etoposide for extensive-stage SCLC
	Atezolizumab	Approved as first line in combination with nab-paclitaxel/ carboplatin for metastatic non-squamous NSCLC with no EGFR or ALK mutations

Abbreviations: 1L-first line, CRT-chemoradiation, NDA-New Drug Application, RT-radiation therapy, TPS-tumor proportion score
Source: FDA

Targeted Therapy

The field of lung cancer research intensified the pace of targeted therapy development in the 2010s, rolling out agents directed against new oncogenic drivers and iteratively introducing more potent agents with higher barriers to genetic resistance.

Five first-line EGFR-targeted agents reflecting three generations of development have come to market since the identification of EGFR sensitizing mutations more than 15 years ago. The newest of these, osimertinib, has emerged as the frontrunner in the first-line setting in NSCLC in many regions of the world based on both efficacy and safety, displacing erlotinib, afatinib, gefitinib, and dacomitinib as a preferred standard of care. This is largely based on the results of the Phase III FLAURA trial, which documented significant improvements in median progression-free survival and median overall survival with osimertinib compared with erlotinib or gefitinib, in tandem with a milder toxicity profile, less frequent central nervous system progression, and improved post-progression outcomes[48,49].

An array of treatment options likewise now exist for patients with ALK rearrangements. These include the first-generation ALK TKI crizotinib; the second-generation agents ceritinib, alectinib, and brigatinib; and the third-generation agent lorlatinib. In the Phase II study supporting lorlatinib approval for second- or later-line treatment of ALK-positive disease, objective response rates in patients previously treated with at least one ALK TKI reached 47%[50]. Notably, among 81 patients with measurable brain lesions at baseline, lorlatinib yielded an objective intracranial response in 63%, with a median duration of response of 14.5 months.

Inhibitors of ROS1-rearranged NSCLC entered the scene in 2016 with the approval of crizotinib for ROS1-positive tumors. This has since been followed by the approval of entrectinib for ROS1-positive metastatic NSCLC based on an integrated analysis of three ongoing phase I and II trials (ALKA-372-001, STARTRK-1, and STARTRK-2). The analysis showed that entrectinib yielded an objective response in 77% of patients with ROS1 fusion–positive NSCLC and maintained that response for a median of 24.6 months[51].

Other targeted therapies approved for metastatic NSCLC in just the last few years include dabrafenib/trametinib for patients with BRAF V600E mutation–positive disease, along with larotrectinib and entrectinib for patients with disease harboring the NTRK gene fusion who lack viable treatment options.

Immunotherapy

The introduction of immune checkpoint inhibitors in 2015 represents a major milestone in lung cancer treatment. At that time, nivolumab, pembrolizumab, and atezolizumab monotherapy each demonstrated the ability to prolong survival by approximately two to three months when pitted against the prior standard, docetaxel, in previously treated squamous and non-squamous NSCLC in randomized trials[52,53,54]. After becoming established for second- or later-line treatment, efforts quickly escalated to move immunotherapy into the first-line setting, along with routine testing for tumor PD-L1 expression, where the effects of checkpoint inhibitor therapy appeared to be more pronounced. Pembrolizumab was the first to break this new ground by demonstrating superior median PFS and OS compared with platinum-based chemotherapy in patients with high PD-L1 expression. Since that time, frontline use of a checkpoint inhibitor, either alone for tumors with high PD-L1 expression or in combination with chemotherapy regardless of PD-L1 tumor expression, has now become a standard of care for patients with advanced NSCLC lacking a driver mutation, followed thereafter by continuation of immunotherapy for at least two years in an effort to maintain response.

The checkpoint inhibitor breakthroughs do not stop there. Durvalumab first established a new standard of care in unresectable stage III NSCLC based on evidence that use of the immunotherapy as consolidation following the completion of chemoradiotherapy significantly prolonged both OS and PFS as compared with placebo[55]. In 2018, checkpoint inhibitors made headway in extensive-stage SCLC, with atezolizumab being the first to significantly prolong median OS when combined with carboplatin/etoposide, as compared with carboplatin/etoposide alone.

Anti-angiogenic therapy

In 2014, ramucirumab became the second anti-angiogenic agent to enter the NSCLC treatment landscape after bevacizumab, which was originally approved for NSCLC in 2006. Authorization of the VEGFR-2 inhibitor was based on the phase III REVEL trial conducted in more than 1,200 patients with squamous and non-squamous NSCLC whose disease progressed during or after a first-line platinum-based regimen. Patients who received docetaxel plus ramucirumab realized superior outcomes compared with patients who received docetaxel plus placebo, both for median OS and median PFS.

Prostate Cancer

The management of prostate cancer has changed significantly in recent years, particularly the use of imaging, with the introduction of prostate magnetic resonance imaging as routine in the diagnostic pathway, and the increasing use of prostate-specific membrane antigen positron emission tomography for early stratification in the salvage setting for failure of primary treatment in localized disease. In addition, upfront combinations of androgen deprivation therapy with other systemic treatments have yielded significant gains in overall survival for patients with metastatic disease. There has also been an increasing recognition of the association between germline DNA repair defects and progressive disease, and interest in the potential to identify patients for therapies that target these defects. There have been significant changes in how prostate cancer is diagnosed and managed in the past five years, with the introduction of new clinical pathways that were unprecedented just a decade previously.

Detection

Although randomized controlled trial data suggest that prostate-specific antigen (PSA) testing results in a small reduction in prostate cancer mortality, its widespread use in case-finding is controversial because of the low specificity of the test, the morbidity of prostate biopsy, and the risks of overdiagnosis and overtreatment of clinically insignificant cancers[56]. Advances in prostate magnetic resonance imaging (MRI) go some way to addressing the issues of overdiagnosis through improved risk stratification. These advances include the incorporation of multiple MRI techniques ('sequences'), such as diffusion-weighted and contrast-enhanced images, as well as the development of the Prostate Imaging Reporting and Data System (PIRADS), which is a five-point standardized reporting system for MRI-detected abnormalities, where 1 = clinically significant cancer highly unlikely to be present, and 5 = clinically significant cancer highly likely to be present[57]. Higher PIRADS scores are often associated with tumors of higher volume and grade, and meta-analysis of MRI performance indicates a pooled sensitivity of 0.89 and specificity of 0.73 for prostate cancer[58]. In contrast, the sensitivity of traditional imaging modalities (e.g. computed tomography [CT] and ultrasonography) in this setting is low.

One advantage of visualizing areas of abnormality prior to biopsy is that these areas can be specifically targeted, reducing the sampling error inherent in systematic biopsies. This can be done by taking extra cores under transrectal ultrasound guidance from the abnormal area identified on the MRI ('cognitive fusion'), using co-registration software that can overlay regions of interest from the MRI onto the ultrasound image, or via an 'in-bore' biopsy, where the biopsy is taken with real-time

MRI. The latter has the advantage of being able to directly image the needle sampling the area of interest, providing confidence that the appropriate area has been biopsied. Adding targeted cores to a systematic biopsy increases the detection of clinically significant cancer, although the findings are not universal[59,60,61]. However, the utility is much greater for patients with a prior negative biopsy for whom a clinical suspicion remains[62].

Recurrent disease

Biochemical recurrence (BCR) occurs in 27%–53% of patients after primary curative therapy and is defined differently depending on the modality of primary treatment: following radiotherapy, PSA needs to be >2 ng/mL higher than the PSA nadir level; after prostatectomy, any detectable PSA represents the presence of disease[63]. A proportion of men with BCR will progress to metastases and death; others will have local recurrence and may be curable with salvage treatment (i.e. salvage radiation for patients who underwent prostatectomy, or salvage prostatectomy following primary radiotherapy).

The key to determining who will benefit from local versus systemic therapy depends on the ability to determine the site of relapse. Given that recurrent disease can be detected biochemically often well before it is identifiable radiologically by CT or bone scan, treatment decisions regarding who should proceed with salvage are often imprecise, with many patients exposed unnecessarily to the morbidity of treatment without any therapeutic benefit. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has had a significant impact on decision making in this space.

PSMA is an enzyme expressed on the cell surface of prostate epithelium and other tissues, and sites expressing the protein can be imaged by detecting binding of radio-labelled PSMA ligand by PET. PSMA-PET has greater sensitivity for low-volume metastatic prostate cancer than traditional staging (combined CT and bone scan), with metastatic deposits being detectable even at PSA levels <1 ng/mL[64]. Patients with a scan that is negative for metastatic disease (with or without evidence of uptake locally) may have a better response to local salvage treatment, whereas those positive for metastatic disease may be better served with systemic therapies. There is also interest in the use of PSMA-PET (CT or MRI) as a primary staging modality for patients with intermediate- and high-risk disease prior to definitive local therapy (replacing the standard staging CT and bone scan), with early evidence suggesting greater sensitivity[65]. It is currently not funded for this indication, although this may change if prospective comparative studies are positive. Another area of ongoing interest is the concept of oligometastatic disease, which is well established in other tumors and posits that some patients with a limited number of metastases (<3 or <5, depending on the author) may represent

a "curable" metastatic state. Early detection with molecular imaging may allow these sites to be specifically targeted with local treatment, thus avoiding or delaying the need for systemic therapy. Results from stereotactic ablative body radiotherapy (an image-guided hypo-fractionated radiation technique that can be used to give very high doses of radiation to a target volume with usually minimal toxicity)[67] or salvage surgery in this setting show some promise, but long-term outcomes and the ideal patient characteristics have yet to be determined.

Metastatic disease

Established metastatic prostate cancer is incurable; for 80 years, castration/androgen deprivation therapy (ADT) was the standard treatment, followed by palliation once patients inevitably no longer responded (castration-resistant prostate cancer [CRPC]. This changed in 2004 when the taxane chemotherapeutic agent docetaxel was reported to prolong survival for patients with metastatic CRPC[68]. This has been followed by the approval of a slew of new systemic agents over the past 15 years, all of which are administered in combination with ADT and have been shown to improve survival, further increasing the therapeutic options available to patients[69].

Prostate Cancer Systemic Treatment Options *Table 3*

Timing of Treatment	Agent
Metastatic hormone-sensitive prostate cancer	Docetaxel
	Abiraterone
	Enzalutamide
	Apalutamide
Non-metastatic castration-resistant prostate cancer	Enzalutamide
	Apalutamide
	Darolutamide
Metastatic castration-resistant prostate cancer	Docataxel
	Cabazitaxel
	Abiraterone
	Enzalutamide

Source: FDA

First-line therapy

The biggest paradigm shift has been the finding that upfront administration of combination therapy at the time of diagnosis of metastatic disease (metastatic hormone-sensitive prostate cancer) confers a far greater overall survival benefit (approximately 10–18 months) than chemotherapy or androgen signaling–targeted inhibitors started at the onset of castration resistance (approximately two–four months)[70]. This was first shown with six cycles of chemotherapy (docetaxel)[71], but has since also been shown with newer androgen signaling–targeted inhibitors such as abiraterone[72], enzalutamide[73], and apalutamide[74]. here is some evidence that combination treatment of ADT with docetaxel has greater effect in patients with high-volume disease (visceral metastases or >4 bone lesions with >1 beyond the vertebral bodies and pelvis)[75]. However, this is not universal and appears less pronounced with androgen signaling–targeted inhibitors[76]. The choice of agent is usually determined by patient factors.

First-Line Therapy Agents *Table 4*

Agent	Mechanism of Action	Adverse Effects
Chemotherapy		
Docetaxel	Taxane Chemotherapy	Myelosuppression, neuropathy, fatigue, nausea/ vomiting/ diarrhea, peripheral edema
Cabazitaxel		
Androgen signaling-targeted inhibitor		
Abiraterone	CYP17A1 inhibitor (prevents androgen synthesis)	Hypertension, fluid retention, cardiac disorders, liver function test abnormalities
Enzalutamide	Androgen receptor inhibitor	Fatigue, seizures, back pain, arthralgia, peripheral edema, headache, hypertension
Apalutamide		Hypertension, rash, gastrointestinal upset, fatigue, hypothyroidism, fracture, falls, QT prolongation

Source: FDA

CONCLUSION

It has been thousands of years since the ancient Greek physician Hippocrates strove to understand this disease and named it "cancer" from the Greek word karkinos, meaning "crab," possibly as an allusion to the blood vessels emanating from tumors. We are now in the enviable position of having a much more refined understanding of the disease and we know that cancer has no panacea. Instead, it requires synthesis of knowledge, collaboration between fields and a deeper appreciation of the challenges facing patients, clinicians, and scientists from different disciplines. Fortunately, this is an era of thriving biomedical research that has seen the field of cancer research expand into a vibrant, multidisciplinary community that seeks new and innovative ways to engage collectively and tackle this disease.

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