Study on Disease Overview and Market Dynamics of Therapy Area Oncology

By

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Internship Training

At

ZS Associates India Private Limited

"Study on disease overview and market dynamics of therapy area oncology"

By

Ishita Srivastava

Under the guidance of

Associate Prof. Seema Mehta

MBA in Hospital and Health Management

2014 - 2016

Institute of Health Management Research

Jaipur

INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that Ishita Srivastava student of MBA Hospital and Health Management (PGDHM) from The IIHMR University, Jaipur has undergone internship training at ZS Associates, Gurgaon from February 8, 2016 to April 29, 2016.

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish her all success in all her future endeavors.

Dr. Ashok Kaushik
Dean, Academics and Student Affairs
The IIHMR University, Jaipur

Seema Mehta
Associate Professor
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SALES + MARKETING

May 10, 2016

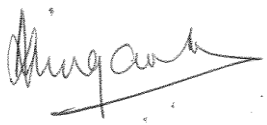
EXPERIENCE CERTIFICATE

This is to certify that Ms. Ishita Srivastava (13581) has served in our organization from February 08, 2016 to April 29, 2016. At the time of leaving she was working in the capacity of Knowledge Management Associate - Intern and based at New Delhi office.

This is to confirm that all information\Projects shared\worked in your Internship period is confidential and are not liable to be shared with anyone outside ZS network.

At last, wish you all success in future endeavors

For ZS Associates India Pvt Ltd



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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "Study of disease overview and market dynamics of therapy area oncology in the U.S." and submitted by Ishita Srivastava Enrollment No. 0150 under the supervision of Ass. Professor Seema Mehta for award of MBA in Hospital and Health Management of the University carried out during the period from February 8, 2016 to April 29, 2016 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

Signature

Acknowledgement

I would like to express the deepest appreciation to my Project Lead Ms. Bhavna Dora (Associate Consultant ZS Associates, Knowledge Management) for the vision and foresight which inspired me to conceive this project.

I am particularly indebted to my team member Surabhi Sharma who has shown the attitude and the substance of a genius and my PD manager Ms. Chhavi Anand who continually and persuasively conveyed a spirit of adventure in regard to research and scholarship, and an excitement in regard to teaching. Without their supervision and constant help this dissertation would not have been possible.

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I want to pay my gratitude towards the IHMR, Jaipur for providing me with the opportunity to work with such good organization.

To my parents for the unwavering love, faith and continued support and reassurance over the years.

By extension I'd like to offer my thanks to all the staff of the ZS Associates for their kind and polite behavior that made work more fun and comfortable to cope up with.

With warm regards,

Ishita Srivastava

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1. A Brief Overview of ZS Associates

ZS Associates is a sales and marketing outsourcing, staff augmentation, and technology firm headquartered in Evanston, Illinois that provides services for clients primarily in the pharmaceutical industry. ZS was founded in 1983 by AndrisZoltners and Prabha Sinha, who worked together as professors of marketing at the Kellogg School of Management at Northwestern University

The firm employs approximately 3,400 employees in 20 offices in North America, Asia and Europe. Most of the workforce is located in large outsourcing hubs in Puneand New Delhi, India. ZS works with 49 of the 50 largest drug-makers and 17 of the 20 largest medical device makers and also serves consumer products, financial services, industrial products, telecommunications, and transportation and logistics industries

ZS Associates is rooted in an academic partnership that began in the early 1970s. In **1973**, Andy Zoltners completed a PhD in integer programming algorithms at Carnegie Mellon University, devoting a chapter in his dissertation to sales territory alignment problems. Andy subsequently accepted a teaching position at the University of Massachusetts (UMass).

The following year, Andy crossed paths with PhD student PrabhaSinha, who was exploring the use of higher math in meal planning for the military. The two collaborated on the Multiple Choice Knapsack problem and co-wrote a paper on the topic. Eventually they realized that this line of thinking was highly applicable to the problems of sales force sizing and resource allocation.

Over the next several years, the pair worked with a number of companies, gaining practical experience applying modelling techniques to sales force problems.

In **1982**, Andy presented his and Prabha's mathematical models for sales force sizing and territory alignment to the Pharmaceutical Management Science Association (PMSA), using an early Apple computer to display sales territories on-site. Executives from many of the attending companies were stunned by the model's ability to quickly solve sales force sizing, sales resource allocation, and territory alignment issues and see solutions visually in real time, with one exclaiming, "I've been waiting my whole life for this!"

By **1983**, both Andy and Prabha were teaching at Northwestern's Kellogg School of Management. They lectured by day, and by night they worked on the many client projects that came their way. Already having consulted to eight companies, the two professors concluded that there was an opportunity to help many clients address critical sales force effectiveness issues, and so they incorporated ZS Associates, Inc.

1.1 ZS Associates Global Offices

ZS Associates is one firm with multiple offices positioned to provide the highest quality and most attentive service to our clients. Each office can effectively serve local or regional clients while also contributing to project teams working around the world, assembling the optimal mix of capabilities, experience, geography, language and culture

Americas	**Europe**	**Asia**
Boston	Barcelona	New Delhi
Chicago	Frankfurt	Pune
Evanston	London	Shanghai
Los Angeles	Milan	Tokyo
New York	Paris	
Philadelphia	Zurich	
Princeton		
San Diego		
San Francisco		
São Paulo		
Toronto		

2. Rationale of study:

Therapy Area Overview (TAO) provides the insight of a disease, its etiopathogenesis, treatment and market available for it in a concise manner. This information is used in internal decision making to help ZS identify its prospective clients. TAO also aids in forecasting for a disease by assessing the opportunity areas and competitive landscape for that disease. Itcould also be leveraged to provide business solutions to various pharmaceutical companies thereby helping them plan the launch of their drugs in the market.

Oncology has remained the interest area for various pharma companiesas cancer is the second leading cause of deaths in the U.S.In recent decades, tremendous progress has been made in the fight against cancer. Advances in molecular and genomic research have revealed underlying complexities and provided insights into cancer. Currently, more than 800 medicines and vaccines are in clinical testing for cancer.Despite these advancements, huge unmet need still exists in this therapy area making it an attractive market for the pharma companies.

Some of the common cancer includes Hepatocellular carcinoma which is the third leading cause of cancer deaths worldwide, with over 500,000 people affected; Bladder cancer which is the 9th leading cause of cancer worldwide and occurs mainly due to tobacco; Liver metastases which account for 95% of all hepatic malignancies in the U.S.

3. Research Question:

What is the disease overview and current market dynamics for primary & metastatic liver cancer, bladder cancer and acute lymphocytic leukemia in the U.S?

4. Study Objectives:

- To create Therapy Area Overview (TAO) of primary & metastatic liver cancer, bladder cancer and acute lymphocytic leukemia which includes their clinical overview, epidemiology and disease management
- To study the market dynamics of these cancers in the U.S

5. Literature Review

In an article published in 2003 in American journal, randomized trials for unresectable hepatocellular carcinoma were studied. The aim of this systematic review was to assess the evidence of the impact of medical treatments on survival. Randomized controlled trials (RCTs) that were published as full papers assessing survival for primary treatments of HCC were included and it was established that chemoembolization improves survival

In 2006, British journal of cancer published a systematic review which was undertaken to assess the published evidence for surgical resection of colorectal liver metastases efficacy and safety and to identify associated prognostic factors

In World journal of urology published in 2004, the association between smoking history, beverage consumption, diet and bladder cancer incidence was systematically reviewed and it was concluded that there is probably no association between total vegetable intake, vitamin A intake, vitamin C intake and bladder cancer and a possibly moderate inverse association with vitamin E intake

A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukemia was published in European journal of cancer care where the goal was to identify and summarize the published literature pertaining to the incidence, prevalence, mortality, etiology, clinical diagnosis, and management of acute lymphoblastic leukemia (ALL)

The New England Journal of Medicine in 2004 published a systematic review on the full disease coverage of acute lymphocytic leukemia. It reviewed various research papers on the etiopathogenesis, risk factors and management of the disease

In November 2000, JAMA journal of internal medicine published a report on risk factors for the rising rates of primary liver cancer in the United States**. In this,** the temporal changes in both age-specific and age-standardized hospitalization rates of primary liver cancer associated with hepatitis C, hepatitis B, and alcoholic cirrhosis **were examined and it was concluded that** Hepatitis C virus infection accounts for most of the increase in the number of cases of primary liver cancer among US veterans. The rates of primary liver cancer associated with alcoholic cirrhosis and hepatitis B virus infection have remained stable**.**

In BJU international journal published in November 2009, the effect of age and gender on bladder cancer was critically reviewed. Using MEDLINE, previous reports published between January 1966 and July 2009 were reviewed. While men were found to be three to four times more likely to develop bladder cancer than women, women present with more advanced disease and have worse survival rates It was also seen that the critical factor for the success of treatment for muscle-invasive bladder cancer in the elderly is patient selection. Elderly patients, when treated adequately, tolerate and respond well to cancer treatment.

Journal of clinical oncology in 2009 published a review on radiofrequency ablation of hepatic metastases from colorectal cancer. They conducted and analyzed a comprehensive systematic review of literature from Medline and the Cochrane Collaboration Library. It was established that hepatic resection can improve overall survival for patients with resectable colorectal hepatic metastasis.

Journal of clinical oncology published a report on relationship of acute lymphoblastic leukemia with chromosomal 5;14 translocation and hypereosinophilia. It was observed that majority of cases had 14q + chromosomal abnormalities and few had a similar translocation t(5,14), (q?,q32). Survival of the ALL patients with hypereosinophilia reported was similar to that of 52 age- and sex-matched historical-control patients without hypereosinophilia treated during the same time interval

In AASLD journal published in 2009, review on management of hepatocellular carcinoma was published. The report discussed about the various diagnostic techniques, surveillance and treatment modalities of the cancer. Chemoembolization, radioembolization and sorafenib were found to be widely used as treatment modalities.

6. Methodology

Study design: Systematic review and secondary desk research for primary & metastatic liver cancer, bladder cancer & acute lymphocytic leukaemia based on the following parameters: clinical overview, diagnosis, treatment, epidemiology and market dynamics

Data sources: Various research papers and articles on primary & metastatic liver cancer, bladder cancer and leukemia and publically available secondary research data source like Medscape, Epocrates, WebMD, SEER (Surveillance, Epidemiology and End Result), American Cancer Society, NCCN guidelines (National Comprehensive Cancer Network),obroncology; ZS specific data sources*

Data analysis

- Data for epidemiology is analyzed using MS Excel
- Data for market dynamics is analyzed using pivot tables and charts

Note: *(Names of data sources are confidential and cannot be shared as per the company policy)

7. Hepatocellular Carcinoma

7.1 Executive Summary:

- Hepatocellular carcinoma (HCC) is a primary malignancy of the liver that frequently occurs in the setting of chronic liver disease and cirrhosis
- In most cases, the cause of HCC is cirrhosis, autoimmune diseases of the liver, Hepatitis B or C virus infection, long term inflammation and hemochromatosis
- Common symptoms of HCC include abdominal pain or tenderness, especially in the upper-right part, easy bruising or bleeding, enlarged abdomen and yellow skin or eyes (jaundice)
- Asia and Africa have reported the highest incidence of HCC
- Over the past 20 years, the incidence of HCC has more than doubled
- Imaging is often sufficient to diagnose HCC in cirrhotic patients
- The mainstay of treatment is surgical resection and chemotherapy whereas biopsy is required for diagnosis in patients without cirrhosis
- Currently, there is only one product (sorafenib) approved for use in HCC
- The pipeline buzzing with activity, with the I/O molecules
- The value of the HCC market is set to grow by 172% and hit $1.4bn by 2019

7.2 Clinical Overview:

- Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis
- Tumors progress with local expansion, intrahepatic spread, and distant metastases

Etiology & Risk factors

Causes are not completely understood but risk factors include:

- Hepatitis B or Hepatitis C
- Cirrhosis
- Heavy drinking
- Obesity & Diabetes

- Iron storage diseases
- Foods with aflatoxin*

Sign & Symptoms

- Pain in the upper right part of belly
- A lump or feeling of heaviness in upper belly
- Bloating or swelling in belly
- Yellow skin and eyes
- Pale, chalky bowel movements and dark urine
- Loss of appetite, Weight loss, weakness

Multidisciplinary Team (MDT)

It includes:

- Gastroenterologists
- Medical, Radiation & Surgical Oncologists
- Interventional Radiologists
- Palliative care team

7.3 Classification

Based on the type of cells that becomes cancerous:

1. **Hepatocellular carcinoma (HCC)**: It is the most common type of liver cancer accounting for approximately 75 percent of all liver cancers
2. **Fibrolamellar HCC:** It is a rare type of liver cancer
3. **Cholangiocarcinoma** (bile duct cancer) : It account for 10-20 percent of all liver cancers
4. **Angiosarcoma**: It is also called hemangiocarcinoma and accounts for about 1 percent of all liver cancers
5. **Secondary liver cancer**: It is also known as a liver metastasis, develops when primary cancer from another part of the body spreads to the liver

7.4 Staging

Table 1.1

Hepatocellular Carcinoma: TNM Staging	
Stages	**Presentation**
Stage I (T1/N0/M0)	Solitary tumor ≤2 cm in the widest diameter without vascular invasion
Stage II (T2/N0/M0)	Solitary tumor ≤2 cm in the widest diameter with vascular invasion; or multiple tumors limited to one lobe, none of them >2 cm in the widest diameter, without vascular invasion; or solitary tumor >2 cm in the widest diameter, without vascular invasion
Stage III A (T3/N0/M0) Stage III B (T1-T3/N1/M0)	Solitary tumor >2 cm in the widest diameter with vascular invasion; or multiple tumors limited to one lobe, none of them >2 cm in the widest diameter, with vascular invasion; or multiple tumors limited to one lobe, some of them >2 cm in the widest diameter, with or without vascular invasion
Stage IV A (T4/any N/M0) Stage IV B (any T/any N/M1)	Multiple tumors in more than one lobe; or tumor(s) invading a large portal branch or one or more supra hepatic veins. Solitary tumor >2 cm in the widest diameter with vascular invasion

Fibrosis Score (F)	
Stage	**Score**
F0	Fibrosis score 0-4 (none to moderate fibrosis)
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)

Histologic grade (G)	
Stage	**Details**
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 1.2

Child-Pugh score

Parameters	1 point	2 point	3 point
Encephalopathy	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time Seconds over control INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2-3 4-10	>3 >10

Class A: 5-6 points- good operative risk

Class B: 7-9 points- moderate operative risk

Class C: 10-15 points- poor operative risk

Okuda staging system

Criteria:

- Disease involving >50% of hepatic parenchyma
- Ascites
- Albumin ≤3 mg/dL
- Bilirubin ≥3 mg/dL

Stages:

Stage A: 0 criteria

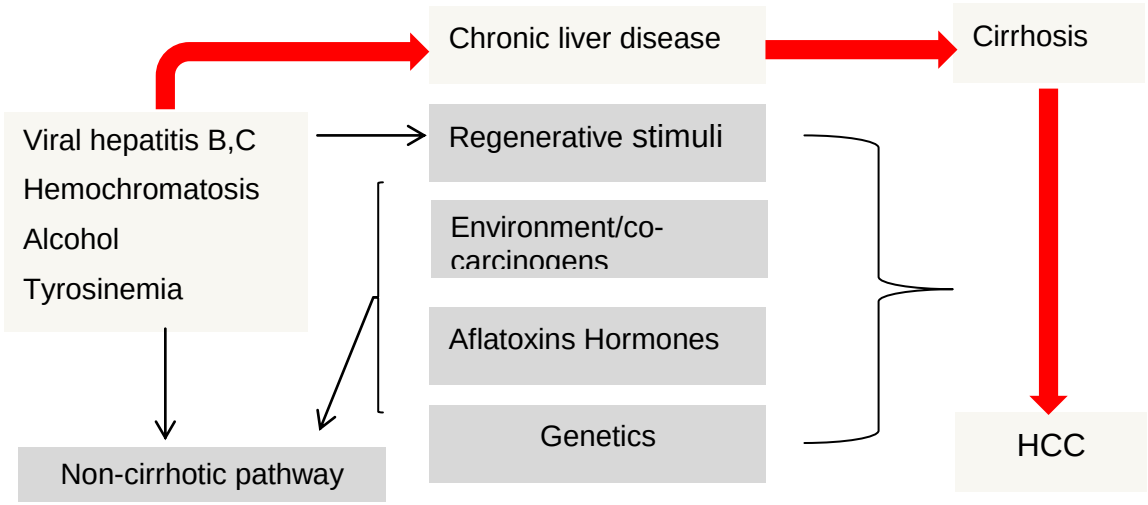
Stage B: 1-2 criteria

Stage C: 3-4 criteria

Table 1.3

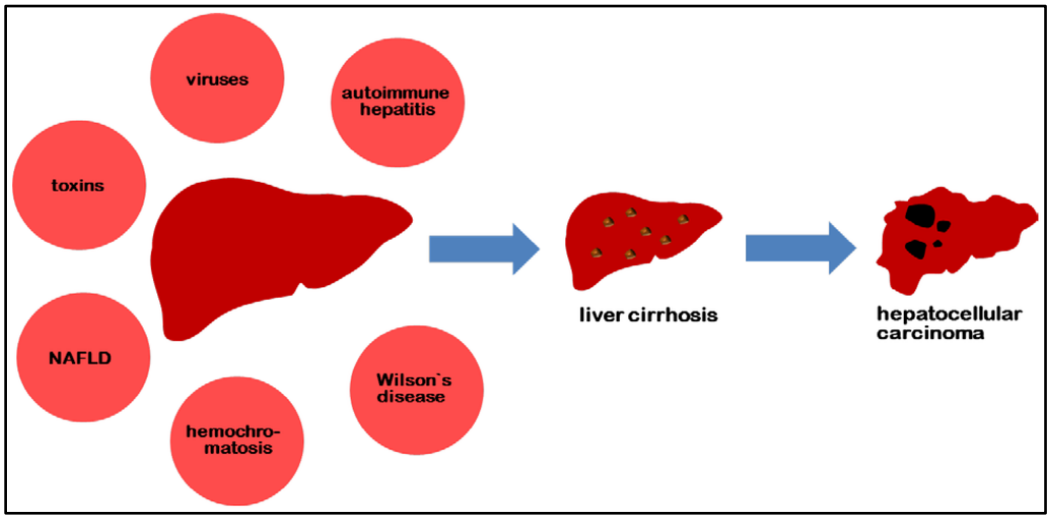
Barcelona clinic liver cancer (BCLC) staging classification	
Stages	**Description**
0 (very early stage)	Asymptomatic early tumors, resection
A (early stage)	Asymptomatic early tumors, resection, percutaneous ablation, transplantation
B (intermediate stage)	Asymptomatic multinodular tumors, intra-arterial therapies (chemoembolization and radioembolization)
C (advanced stage)	Symptomatic tumors and/or invasive tumors, sorafenib, phase II trial agents, or palliative treatments
D (end-stage disease)	Symptomatic treatment

7.5 Pathophysiology



Source: Medscape

Figure 1.1



7.6 Epidemiology

Table 1.4

Epidemiology (US): Ranks 13 in incidence	
Incidence	35,660 patients (2015)
Mortality	24,550 patients (2015)
Prevalence (as of 2012)	75,176patients
Median age at diagnosis(2008-2012)	63 years
Median age at death(2008-2012)	67 years
Overall 5 year relative survival(2005-2011)	17.2 %
Age adjusted incidence rates(2008-2012)	8.2 per 100,000 men and women per year
Age adjusted death rates	6.0 per 100,000 men and women per year

Chart 1.1

No. of cases stage-wise

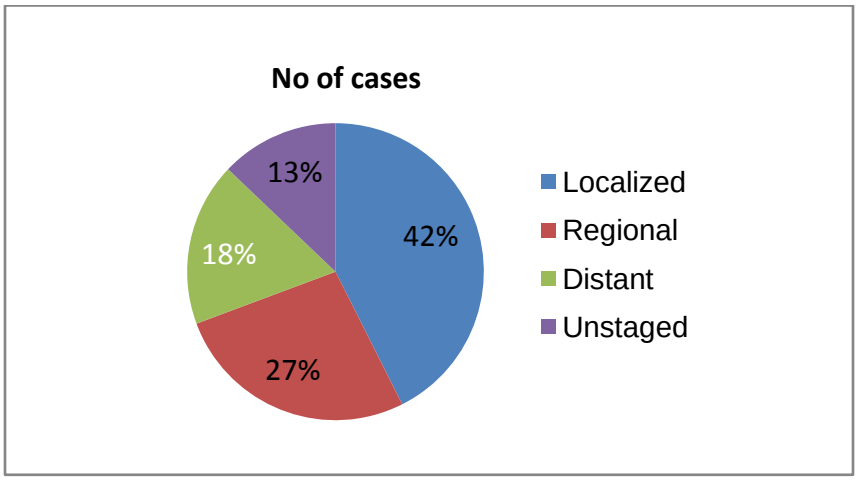
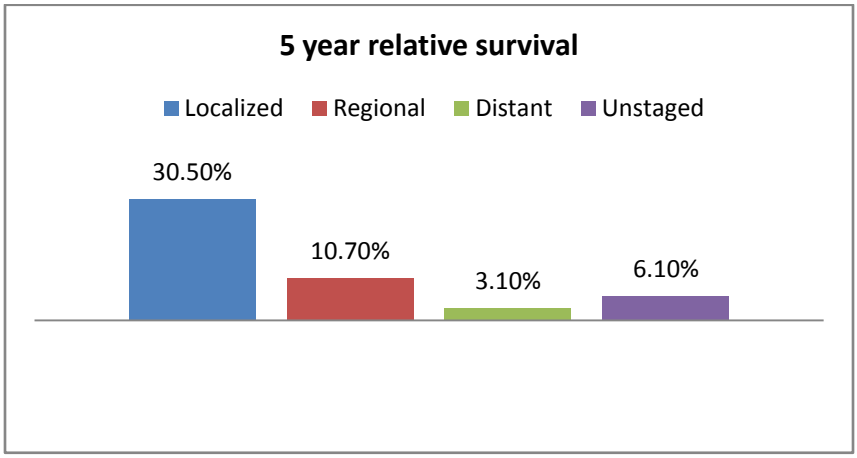


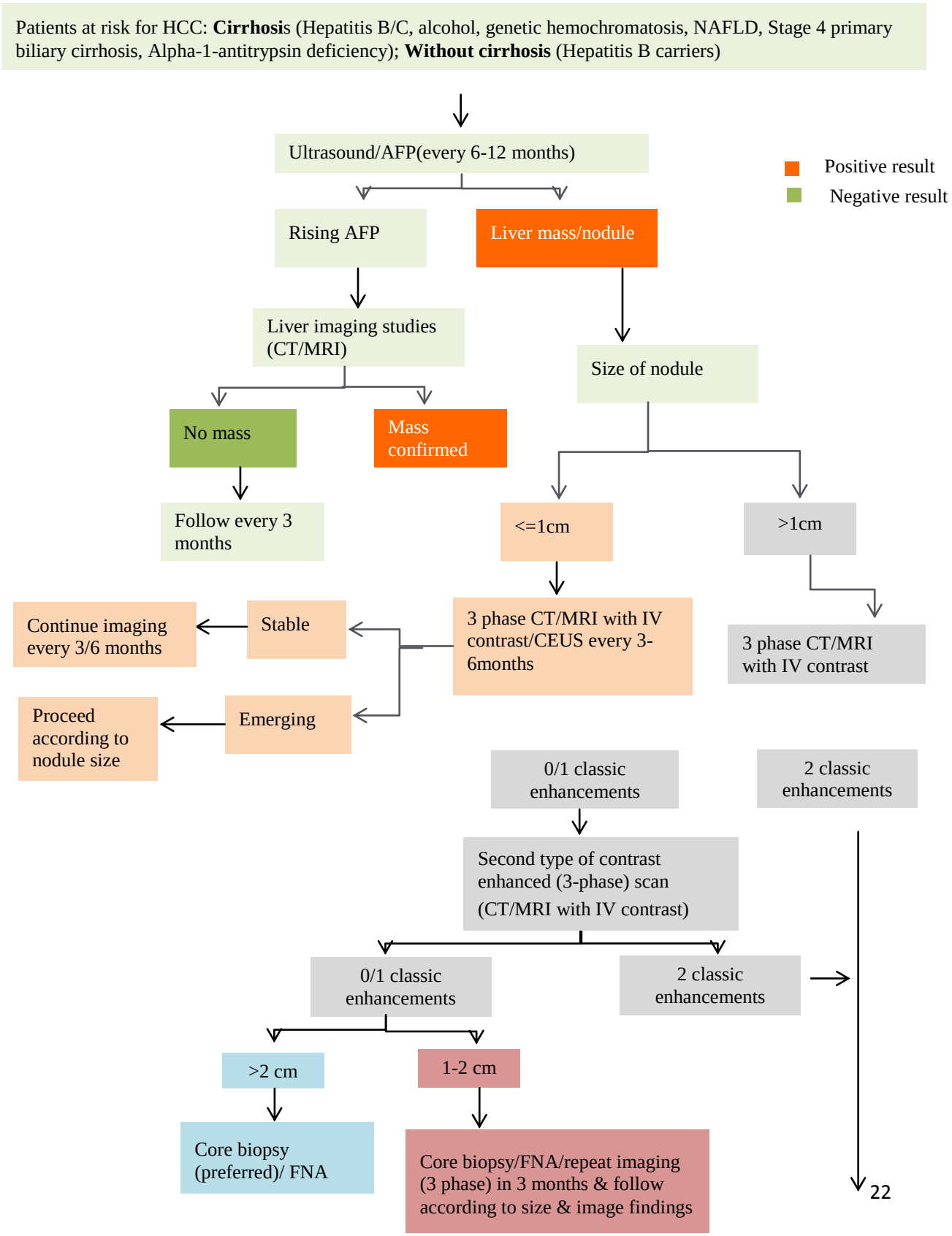
Chart 1.2

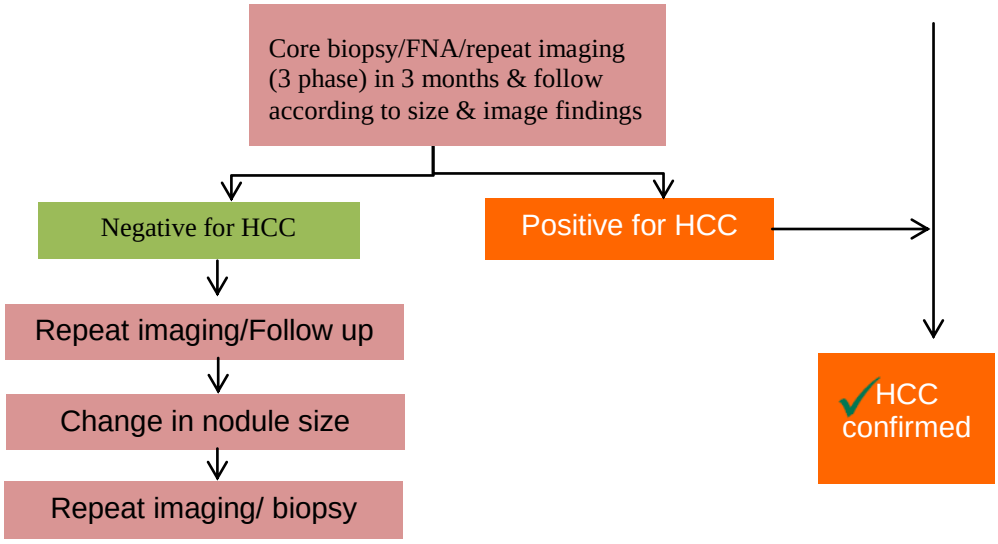


- High unmet need exists in metastatic patients where 5 year survival rate is the lowest & currently sorafenib is the only treatment option available

7.7 Diagnosis

Figure 1.2





Source: NCCN Guidelines Hepatocellular Carcinoma Version 1.2016

7.8 Treatment Approach

- Once HCC is confirmed, Multidisciplinary evaluation (assess liver reserve and comorbidity) and staging is done by:
  - History & physical examination
  - Hepatitis panel*
  - Bilirubin, transaminases, alkaline phosphatase, PT or INR, albumin, BUN, creatinine
  - CBC, platelets, AFP, Chest CT, Bone scan if clinically indicated

- Treatment is given according to the type of HCC
- First line of treatment is:
  - Resectable- surgical resection or transplant
  - Unresectable-
    - Systemic therapy with Sorafenib and other systemic therapy with or without radiotherapy
    - Locoregional therapy
    - Conformal or stereotactic radiotherapy
    - Best supportive care
    - Clinical trial
  - Metastatic disease-
    - Sorafenib

- Clinical trial
- Best supportive care

- Second line of treatment is clinical trial and best supportive care
- Surveillance includes:

  - Imaging (MRI/Multi phase CT) every 3–6 months for 2 years then every 6–12 months
  - AFP, every 3–6 months for 2 years, then every 6–12 months
  - Consultation with hepatologist for discussion of anti viral therapy for carriers of hepatitis

7.9 Market Dynamics

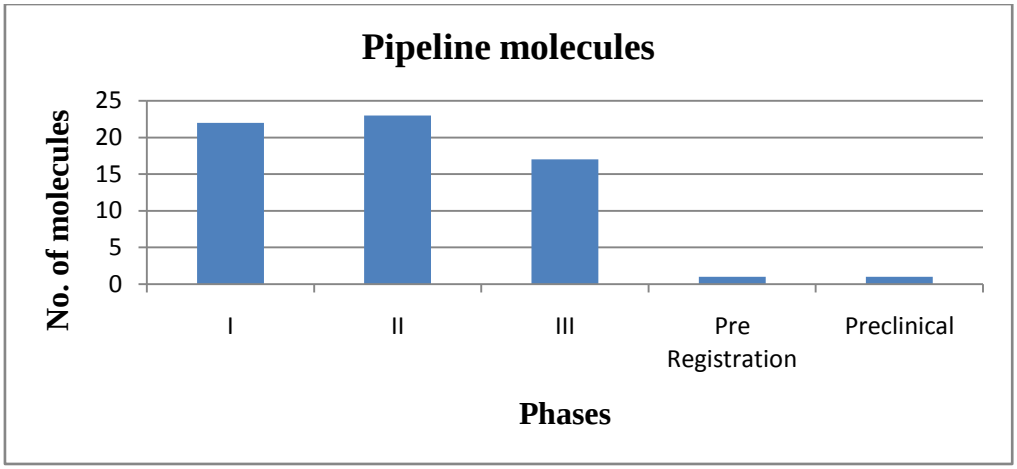
- Currently, there is only one product approved for use in HCC that is Nexavar (sorafenib) but its sales are going to decline steeply after its patent expiry in 2020

Table 1.5
Marketed Products

Drug Class	Company	Dosage	MoA	Side effects	Projected WW sales 2018	Patent expiry
Multi-kinase inhibitor	O: Onyx L: Bayer	400 mg (2 tablets) orally BD without food	Inhibitor of several tyrosine protein kinases : VEGFr, PDGF R &Raf family kinases	Cardiac ischemia, bleeding, hypertension, Gastrointestinal perforation, rashes	$1.463 billion	2020

- The value of the HCC market is set to grow by 172% and hit $1.4bn by 2019
- Currently, there are 17 molecules in Phase III, 23 molecules in Phase II and 22 molecules in Phase I for HCC

Chart 1.3



- Major companies having their drugs in pipeline are Bristol-Myers Squibb Co. with 4 molecules, Bayer Healthcare with 3 molecules; Pfizer, Eli Lilly, Astellas with 2 molecules

Chart 1.4

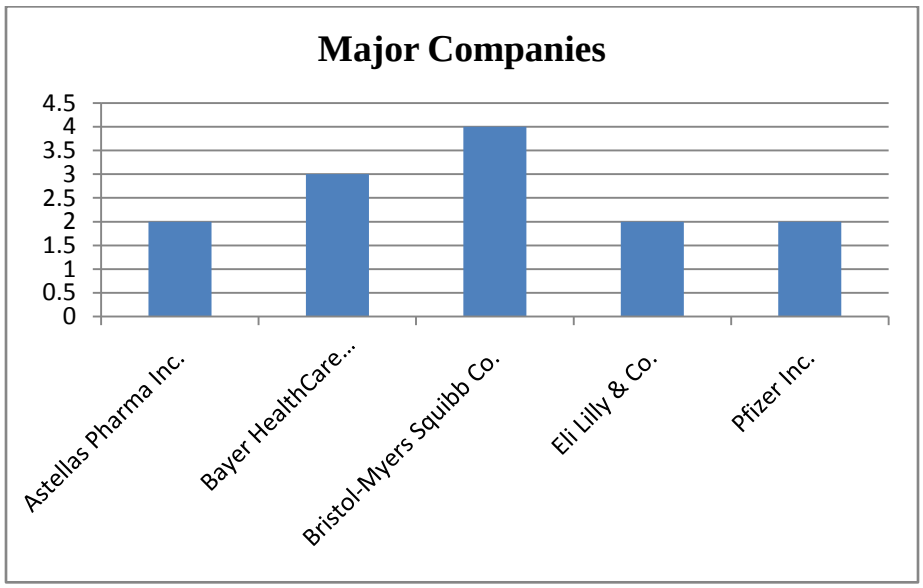
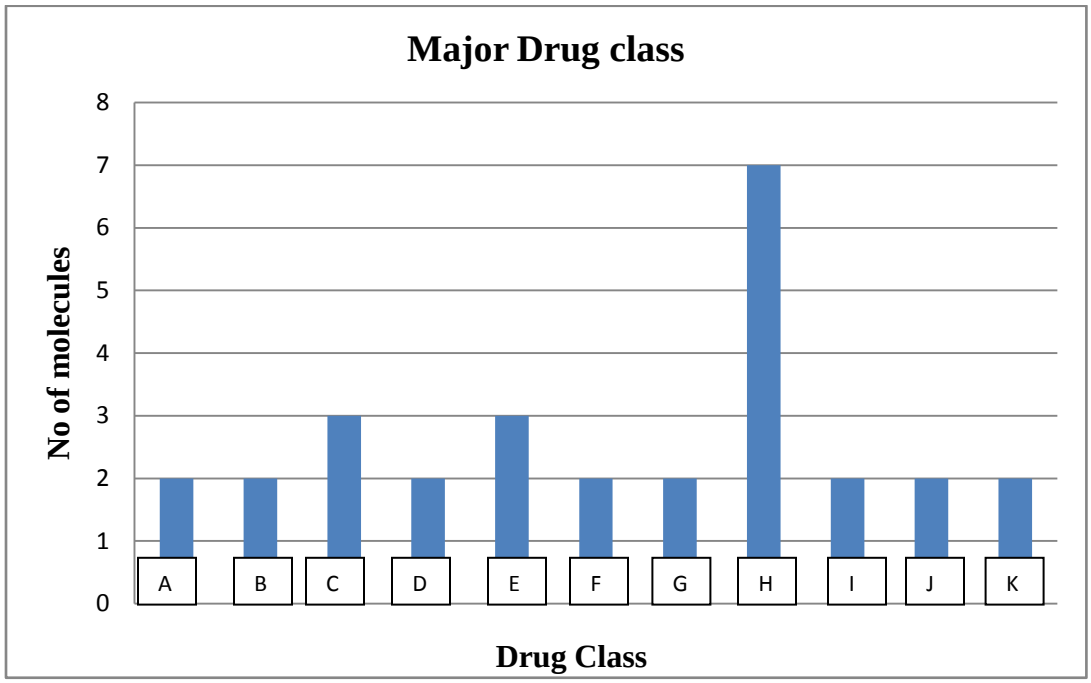


Chart 1.5



A: anti-IGF monoclonal antibody

B: chimeric monoclonal antibody (inhibits CD105 - humanized)

C: c-met kinase inhibitor

D: doxorubicin enhanced with lysolipid thermally sensitive liposomes (LTSL)E: HDAC inhibitor

F: Immunotherapy

G: Kinase inhibitor

H: Multiple tyrosine kinase inhibitor

I: Oncolytic virus

J: VEGFR-2 inhibitor

K: p53 activator

- Multiple tyrosine kinase is emerging as the major drug class with 7 molecules in pipeline followed by c-met kinase inhibitor and HDAC inhibitors

Table 1.6

Key Pipeline Agents (Phase III)			
Molecule Name	**Drug Class**	**Company**	**MOA**
Lenvatinib	VEGFr tyrosine kinase inhibitor	Eisai Co Ltd	Proto oncogene protein c ret inhibitors, VEGFr antagonists
Nivolumab	Anti-programmed death-1 (PD-1) MAb	Medarex, Ono Pharmaceutical	PDCD 1 protein inhibitors
Tivantinib	Mesenchymal epithelial transition (c-Met) kinase inhibitor	ArQule	Proto oncogene protein c met inhibitors
Ramucirumab	Anti-VEGF-2 MAb	Dyax	VEGFr antagonists
Cabozantinib	Mesenchymal epithelial transition (c-Met), RET & VEGFr-2 kinase inhibitor	Exelixis	Proto oncogene protein c met & c ret inhibitors, VEGFr 2 antagonists

8. Metastatic Liver Cancer

8.1 Executive Summary

- Secondary liver metastasis is more common is Caucasians, comprising of nearly 95% of all hepatic cancer
- In US, liver metastases account for 95% of all hepatic malignancies
- The primary sources of liver metastasis include:
  Colorectal, lung, breast, pancreas, stomach, melanoma, neuroendocrine
- After the lymph nodes, liver is the most common site of metastatic spread
- Although no symptoms are seen at early stage, later may include: jaundice, itchy skin, swelling & discomfort in the abdomen
- Most cases of liver metastases develop from colon or rectal cancers. This occurs in part because the blood supply from the intestines is connected directly to the liver through a large blood vessel called the portal vein
- Diagnosis majorly involves tumor marker tests & various imaging techniques
- There is no specific treatment for secondary liver metastases. Management of liver metastases is based on the primary source of tumor origin
  For example: Trastuzumab(Herceptin) used to treat breast cancer that has spread to the liver; Cetuximab (Erbitux) used in combination with chemotherapy to treat bowel cancer that has spread to the liver

8.2 Clinical Overview

- These are the tumors that have spread to the liver from other areas of the body
- Most common types of cancer that spread to the liver are:
  - Colorectal
  - Lung
  - Breast
  - Pancreatic
  - Stomach

- Melanoma
- Neuroendocrine

- After the lymph nodes, liver is the most common site of metastatic spread
- Majority of liver metastases present as multiple tumors. Only 10% of all cases present with a solitary metastatic lesion
- In more than three-quarters (3/4) of patients with liver metastases, there is involvement of both lobes of the liver

Etiology

- For cancers that occur in the gastrointestinal tract ,frequency of metastasis to liver is high due to the venous drainage of the gastrointestinal organs via the hepatic-portal system to the liver
- Other extra-abdominal tumors such as lung cancer, breast cancer and malignant melanoma, may also spread to the liver via haematogenous dissemination

Symptoms

- No symptoms at early stage, later may include:
- Loss of appetite. Nausea, fever
- Fatigue & weight loss
- Jaundice, itchy skin
- Discomfort or pain in the abdomen
- Swelling of the abdomen caused by a buildup of fluid
- Swelling of the ankles

8.3 Epidemiology

- In the U.S & Europe secondary liver cancer is more common than the primary liver cancer
- Primary liver cancer(HCC) varies in incidence from 30 per 100,000 population per year in high-risk regions, such as Asia and Africa, to less than 3 per 100,000 population per year in low-risk regions, such as northern Europe and North America
- Secondary liver cancers are much more common and represent the most common malignant tumor of the liver. The relative proportion of primary to secondary neoplasms is estimated to be 1:20
- Colorectal cancer (CRC) is the most common cancer metastasizing to the liver. It is expected that as many as 25% of patients with CRC will have liver metastases at presentation and 50% will have liver metastases developed metachronously

8.4 Diagnosis

- **Blood tests:**It includes complete blood count, hematocrit, platelet count, liver function tests, and alpha fetoprotein, which may be elevated in patients with liver cancer
- **Alphafetoporotein test:**When AFP is found in the blood of adults, they may have liver cancer (or another kind of cancer). AFP test can be misleading as some liver diseases that are not cancer can also raise AFP levels. So, AFP blood tests are not advised for everyone
- **CT Scan:**It identifies the tumor(s) and pinpoints their size and location in the liver, as well as their relation to the vascular / biliary structures. It can also identify metastases in organs and tissues around the liver
- **Ultrasound:**It is used to check for an enlarged liver or changes in its shape or texture. It is also used to guide a biopsy needle or laparoscopeto a specific area of the liver. Colonoscopy is used to check for colorectal cancer
- **MRI:** It is used to find small metastatic tumors in the liver. It is usually used when doctors are not certain about the results of other imaging tests such as CT scan or ultrasound

- **PET Scan:** It is used to check for metastases in organs and tissues around the liver. It is often used when there is a history of colorectal or stomach cancer
- **Tumor marker tests:** It is done if patient had cancer before. These tests measure the amount of a specific protein in the body. For example, carcinoembryonic antigen (CEA) is a tumor marker measured in the blood. It is usually checked during follow-up after treatment for colorectal cancer. An increase in CEA levels over time could mean the cancer has come back and it may have spread to the liver
- **Angiography:** Angiography is an x-ray method used to look at blood vessels. This can help surgeons decide whether the cancer can be removed and, if so, how best to plan the operation
- **Liver biopsy:** Depending on the size of the tumor or mass, physician may recommend that the biopsy be taken in one of several ways:
    - By using a minimally invasive surgical technique known as laparoscopy
    - By fine needle or thick needle aspiration(a core biopsy), using a computed tomography(CT or CAT) scan or ultrasound to guide the needle placement
    - Through an endoscope(a thin, lighted, flexible tube) inserted in the mouth, passed through the stomach, and into the first part of the intestine. A tool can be passed from the endoscope through the intestinal wall to remove a sample of tissue

8.5 Treatment

Chemotherapy

Used to help stop or slow the growth of cancer and relieve symptoms

- Systemic chemotherapy: Drugs circulate throughout the body to destroy cancer cells
- Hepatic arterial infusion (HAI: Used to treat liver metastases when cancer has only spread to the liver and the tumors can't be removed by surgery. Floxuridine (FUDR) is the most common chemotherapy drug used in HAI
- Chemoembolization or transarterial chemoembolization (TACE): Used to stop or slow the growth of liver metastases when the cancer has only spread to the liver
- Targeted therapy: Uses drugs that find and attach to specific substances (such as proteins) on the surface of or inside cancer cells. These substances help send signals that

tell cells to grow or divide Ex: **bevacizumab** (Avastin) or cetuximab (Erbitux) is used for colorectal cancer; erlotinib (Tarceva) is used for pancreatic cancer

Surgery

- Used to treat liver metastasis when only one area or a few areas of cancer are found. The surgery, called liver resection, removes the part of the liver that contains cancer. It is most often used for colorectal cancer that has spread to the liver

Ablation Therapy

- Mainly used to treat small liver tumors when surgery can't be done because it's not safe or possible
- **Radiofrequency ablation (RFA):** Uses electrical currents to create heat that destroys cancer cells
- **Cryotherapy:** Uses extreme cold to freeze and destroy abnormal and cancerous cells or tissue
- **Percutaneous ethanol injection:** Uses a needle to inject ethyl alcohol directly into a liver tumor which kills cancer cells and shrinks the tumor

Radiation therapy

- Used in rare cases
- **Radioembolization:** Also called selective internal radiation therapy. It delivers radiation directly to liver tumors
- **Stereotactic body radiation therapy:** May be used when there are 1–3 small liver metastases. It avoids treating healthy liver tissue around the tumor with radiation

Hormonal therapy

- It adds, blocks or removes certain hormones to slow or stop the growth of cancer cells that need hormones to grow
- Drugs, surgery or radiation therapy can be used as hormonal therapy

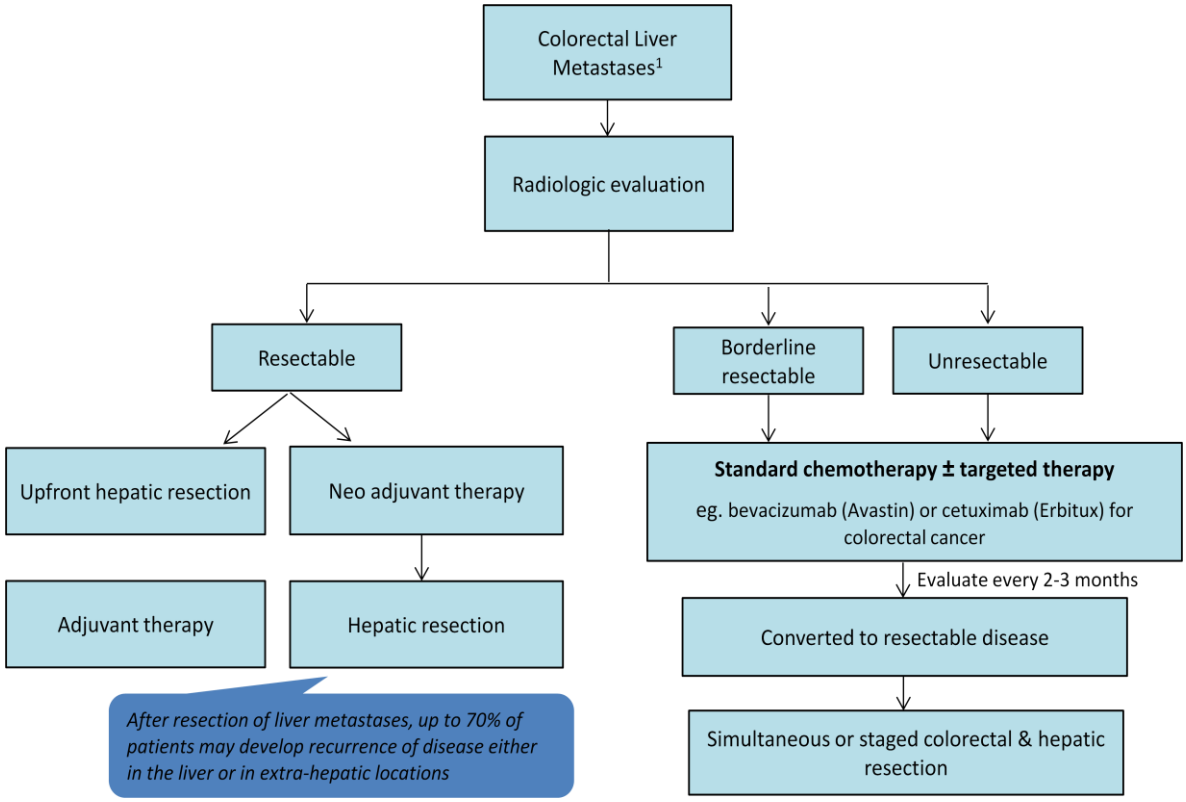
Used specially for breast cancer

Pain medicine

- In metastatic liver cancer, pain can happen when the capsule around the liver is stretched
- Most common pain medicines used for liver metastases are:
- Opioids such as morphine (MS Contin, Statex, MOS) and codeine
- Corticosteroids such as dexamethasone (Decadron, Dexasone)

  Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil, Nuprin)

Figure 1.3: Treatment for metastasis from colorectal region



Source: GI Oncology Journal

8.6 Market Dynamics

Table 1.7

Type of therapy	Product	Company	MOA	Indication	Phase
Drug delivery system	Melphalan drug delivery system - Delcath Systems	Originator: Yale University School of Medicine	Alkylating agents; DNA synthesis inhibitors; Immuno suppressants	Liver metastases	Marketed
Targeted	Stivarga (regorafenib)	Bayer	VEGFR* 3 antagonists, Proto oncogene protein inhibitors	HCC(Second-line therapy or greater) Liver metastases	Phase III
Chemo	Doxorubicin liposomal	Originator: Celsion corp. Licensee: Yakult Honsha	RNA synthesis inhibitors, Type II DNA topoisomerase inhibitors	HCC(First-line therapy, Inoperable/ Unresectable) Liver metastases	Phase II
Targeted	TKM PLK1	Alnylam	Polo-like kinase 1 inhibitors; RNA interference	Adrenocortical carcinoma, HCC, Liver metastases	Phase I
Targeted	Cyramza (Ramucirumab)	Eli Lilly	VEGFR* 2 antagonists	HCC,Liver metastases,Colorectal cancer	Phase I

- Chemotherapy and targeted therapy are often used in addition to, or as an alternative to, other treatments for liver metastases

9. Bladder Cancer

9.1 Executive Summary

- Bladder cancer begins in the bladder, most often in the cells that line the inside of the bladder
- It is typically a disease of the old age and hematuria is considered as its first sign
- Important diagnostic technique for bladder cancer is cystoscopy and biopsy (transurethral resection of bladder tumor)
- The expected incidence of bladder cancer is 76,960 patients (about 58,950 in men and 18,010 in women
- The rates of new bladder cancers and of cancer deaths have been dropping slightly in women in recent years whereas in men, incidence rates have been decreasing and death rates have been stable
- The US market is expected to continue to generate the majority of sales, with its revenue increasing from $139.4m in 2012 to $181.1m by 2017, at a CAGR of 5.4%
- Chemotherapy remains the mainstay of primary treatment with BCG therapy being the most commonly used adjuvant therapy
- Valstar had been the dominant player in the market since long whereas atezolizumab is expected to emerge as the market leader in the near future

9.2 Clinical Overview

- Bladder cancer is the 9th leading cause of cancer worldwide
- It is a common urologic cancer generally originating in the urothelium, which is a 3- to 7-cell mucosal layer within the muscular bladder

Risk Factors

- Bladder inflammation: People with birth defects that affect the bladder, chronic bladder (urinary) infections, persistent cystitis, or bladder stones, are more susceptible
- Smoking and other chemical exposure: Smokers are at twice the risk of developing bladder cancer. People exposed to arylamines -- painters, leatherworkers, machinists, metalworkers, and rubber and textile workers -- are at increased risk for bladder cancer
- Consumption of nitrates in smoked and cured meats
- Chemotherapy: eg- Cyclophosphamide and Ifosfamide
- Use of the herb *Aristolochia fangchi:* Generally used for weight loss
- Genetic and familial disorders: eg- Lynch syndrome

Symptoms

- Blood in the urine(Hematuria): First sign of bladder cancer
- Changes in bladder habits
  - Frequent urination
  - Pain or burning during urination
  - Feeling to go right away, even when the bladder is not full
  - weak urine stream
- Advancer bladder cancer has following symptoms:
  - Being unable to urinate
  - Lower back pain on one side
  - Loss of appetite and weight loss
  - Feeling tired or weak
  - Swelling in the feet

- Bone pain

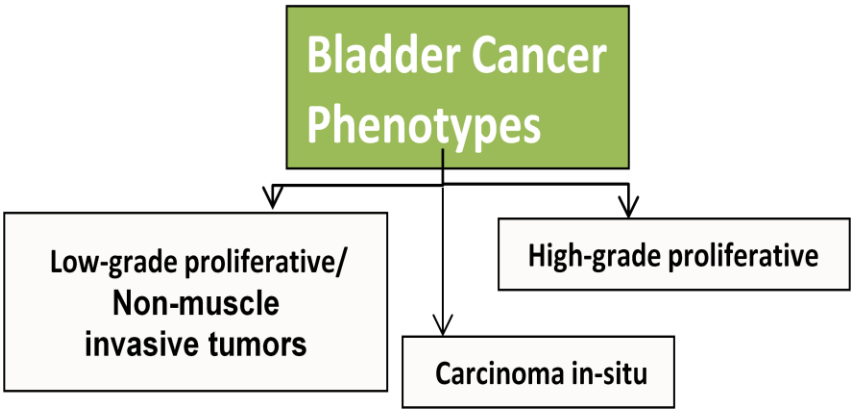
Complications

- Emotional impact: depression
- Urinary diversion: an alternative way of passing urine out of the body is created during the operation which can be done through:
  - Urostomy
  - Continent urinary diversion
  - Bladder reconstruction
- Sexual problems:
  - Erectile dysfunction
  - Narrowing of the vagina
- Recurrence

9.3 Classification

Classification based on histology

- **Transitional (urothelial) cell carcinoma**
  Constitutes 90% in North America, South America, Europe, and Asia
- **Squamous cell carcinoma(SCC)**
  Around 5% in the United States
- **Adenocarcinoma**
  ~ 2% of bladder cancers
- **Nonurothelial primary bladder tumors**
  - Extremely rare
  - May include small cell carcinoma(0.3-0.7% of all bladder cancers), carcinosarcoma, primary lymphoma, and sarcoma



9.4 Staging

Table 1.8

Primary Tumor (T)	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: “flat tumor”
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

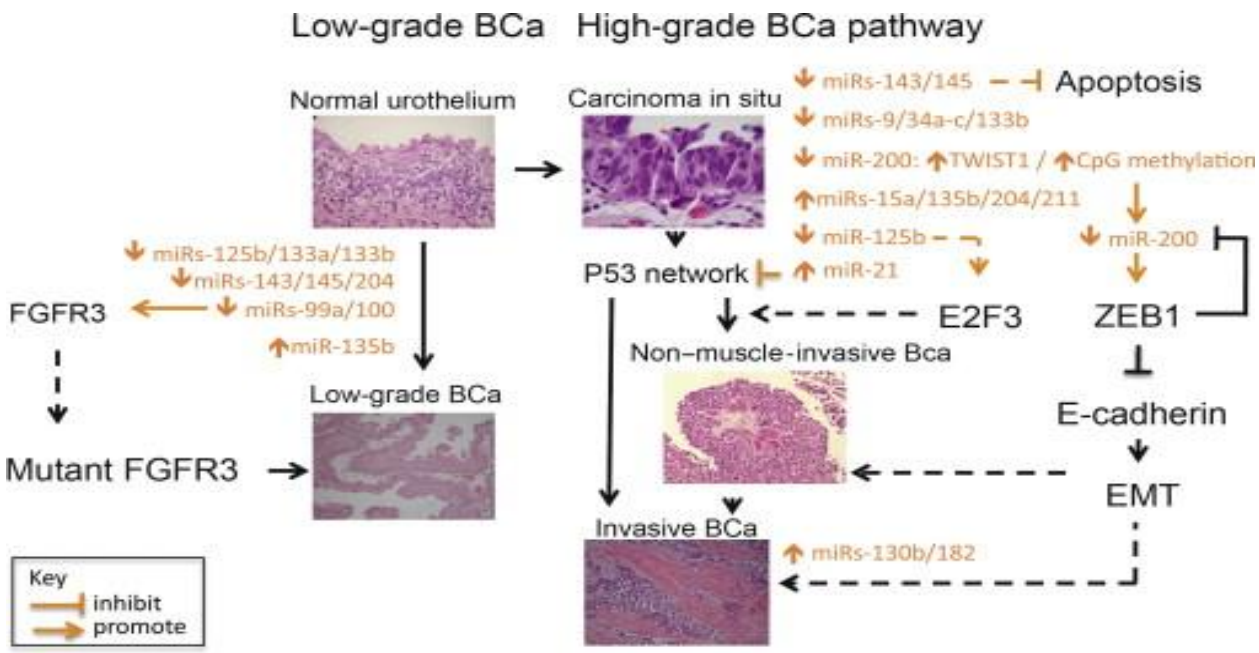
Regional lymph nodes (N)	Description
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant metastasis (M)	Description
MO	No distant metastasis
M1	Distant metastasis

Stage 0a: Ta, N0, M0; **Stage 0is:** Tis, N0, M0; **Stage I:** T1, N0, M0; **Stage II:** T2a/T2b, N0, M0; **Stage III:** T3a/T3b/T4a, N0, M0; **Stage IV:** T4b, N0, M0 or Any T, any N, Mo/M1

9.5 Pathophysiology

Figure 1.4



Source: .europeanurology.com

Low- and high-grade bladder cancer have different molecular pathways

- Low-grade tumors have downregulation of many miRNAs whereas in high-grade BCa, upregulation is most common
- Few altered miRNAs are shared between low- and high-grade cancers (only miR-153b), in contrast to high-grade noninvasive and invasive high-grade BCa types (which shared many miRNA alterations)
- Two of the most downregulated are miRs-99a/100, and these are shown to target FGFR3, causing upregulation prior to its mutation
- High-grade tumors are characterized by upregulation of miR-21, which probably reflected a p53-targeting role

9.6 Epidemiology

Table 1.9

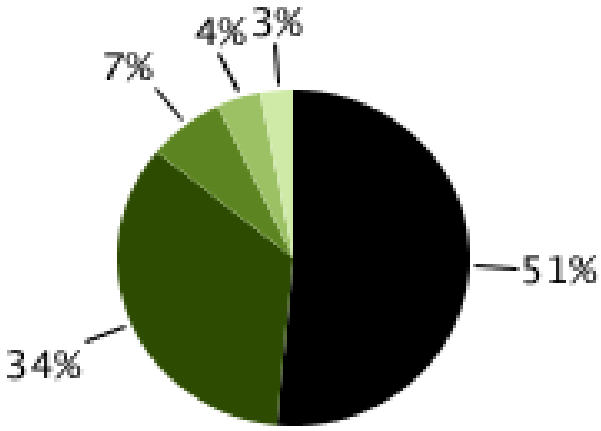
Epidemiology (US): Bladder cancer represents 4.5% of all new cancer cases in the U.S	
Incidence (E) (2016)	76,960 (about 58,950 in men and 18,010 in women)
Mortality (E) (2016)	16,390 (about 11,820 in men and 4,570 in women)
Prevalence (as of 2010)	577,403 patients
Median age at diagnosis (2008-2012)	73 years
Median age at death (2008-2012)[2]	79 years
Overall 5 year relative survival (2005-2011)	77.4 %

Variation among cohorts

- **Age**: The likelihood of being diagnosed with bladder cancer increases with age. More than 70% of people with bladder cancer are older than 65 years old.
- **Gender:** Men are three to four times more likely to develop bladder cancer than women, but women are more likely to die from bladder cancer than men. Before smoking rates for women increased, men were five to six times more likely to develop bladder cancer than women.
- **Race:** Caucasians are more than twice as likely to be diagnosed with bladder cancer as black people, but black people are twice as likely to die from the disease

Chart 1.6

Distribution of patients based on the stages



Percent of Cases by Stage

- **In Situ (51%)**

Only in Originating Layer of Cells

- **Localized (34%)**

Confined to Primary Site

- **Regional (7%)**

Spread to Regional Lymph Nodes

- **Distant (4%)**

Cancer Has Metastasized

- **Unknown (3%)**

Unstaged

Chart 1.7

5 year relative survival

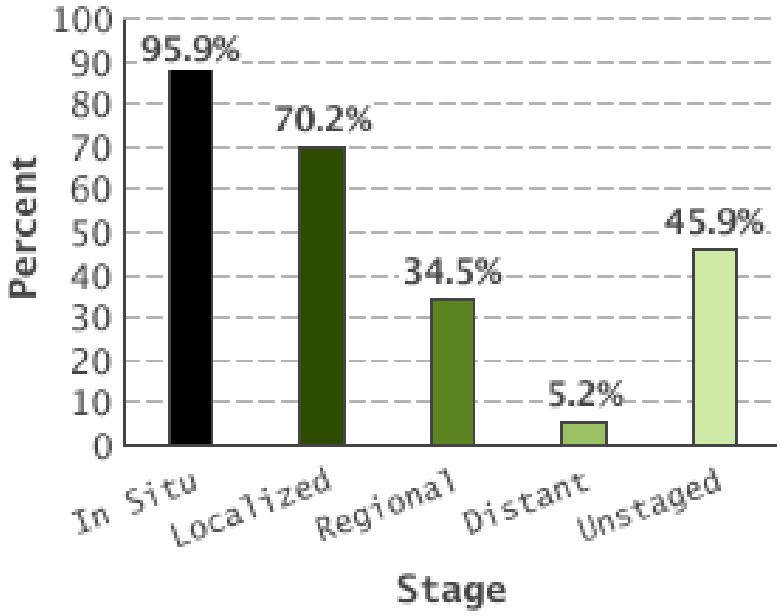
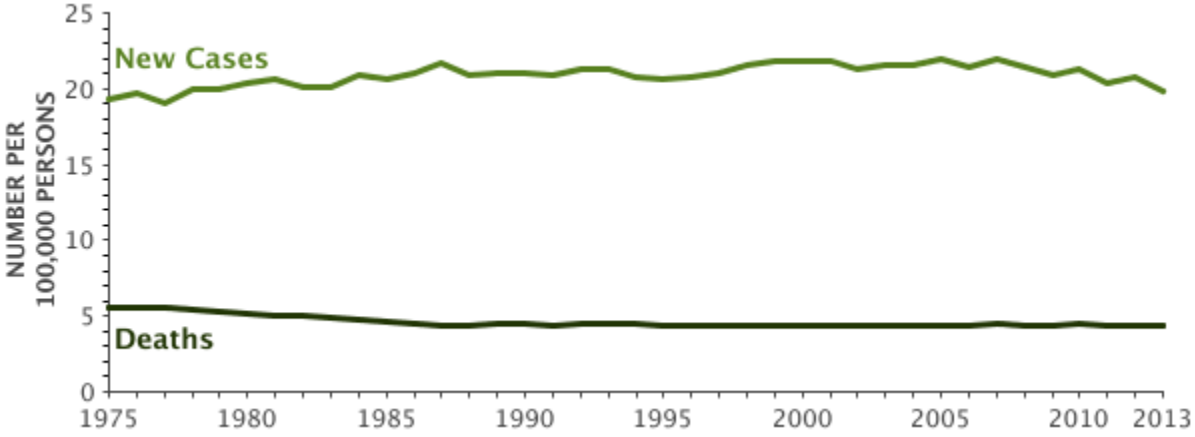


Chart 1.8

New Cases, Deaths and 5-Year Relative Survival



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	71.5%	73.8%	76.0%	79.7%	81.1%	80.3%	80.0%	77.5%

- Opportunity area lies in distant metastatic patients where 5 year relative survival is least and 4% of the population suffers from it

9.7 Diagnosis

- **Urinalysis**

  To check for blood and other substances in a sample of urine

- **Urine cytology**
  - To look for the presence of any cancer or pre-cancer cells
  - Not a perfect test
- **Urine culture**
  - Done to see if an infection (rather than cancer) is the cause for urinary symptoms
  - Urinary tract infections and bladder cancers can have similar symptoms
- **Urine tumor market tests**
  - Looks for specific substances released by bladder cancer cells
  - Include the tests for NMP22 (Bladder Chek) and BTA (BTA stat), the Immunocyt test, and the UroVysion test
- **Cystoscopy**
  - Used when the bladder cancer is suspected
  - Fluorescence cystoscopy (also known as blue light cystoscopy) help the doctor see abnormal areas that might have been missed by the white light normally used
- **Transurethral resection of bladder tumor (TURBT)**
  - A procedure used to biopsy an abnormal area
  - Looks for depth & grade of bladder cancer (high/low grade)
- **Intravenous pyelogram (IVP)**
  - Also called an *intravenous urogram* (IVU), it is an x-ray of the urinary system taken after injecting a special dye into a vein
- **Retrograde pyelogram**

- Used to look for tumors in the urinary tract in people who can't have an IVP

- **Other Imaging techniques**
  - **CT scan:** Provide detailed information about the size, shape, and position of any tumors in the urinary tract, including the bladder
  - **MRI**: Particularly useful in showing if the cancer has spread outside of the bladder into nearby tissues or lymph nodes. A special MRI of the kidneys, ureters, and bladder, known as an *MRI urogram*, can be used instead of an IVP to look at the upper part of the urinary system
  - **Ultrasound**: Can be useful in determining the size of a bladder cancer and whether it has spread beyond the bladder to nearby organs or tissues
  - **Chest X-ray**: Done to see if the bladder cancer has spread to the lungs
  - **Bone scan:** Help look for cancer that has spread to bones

9.8 Treatment

Figure 1.5

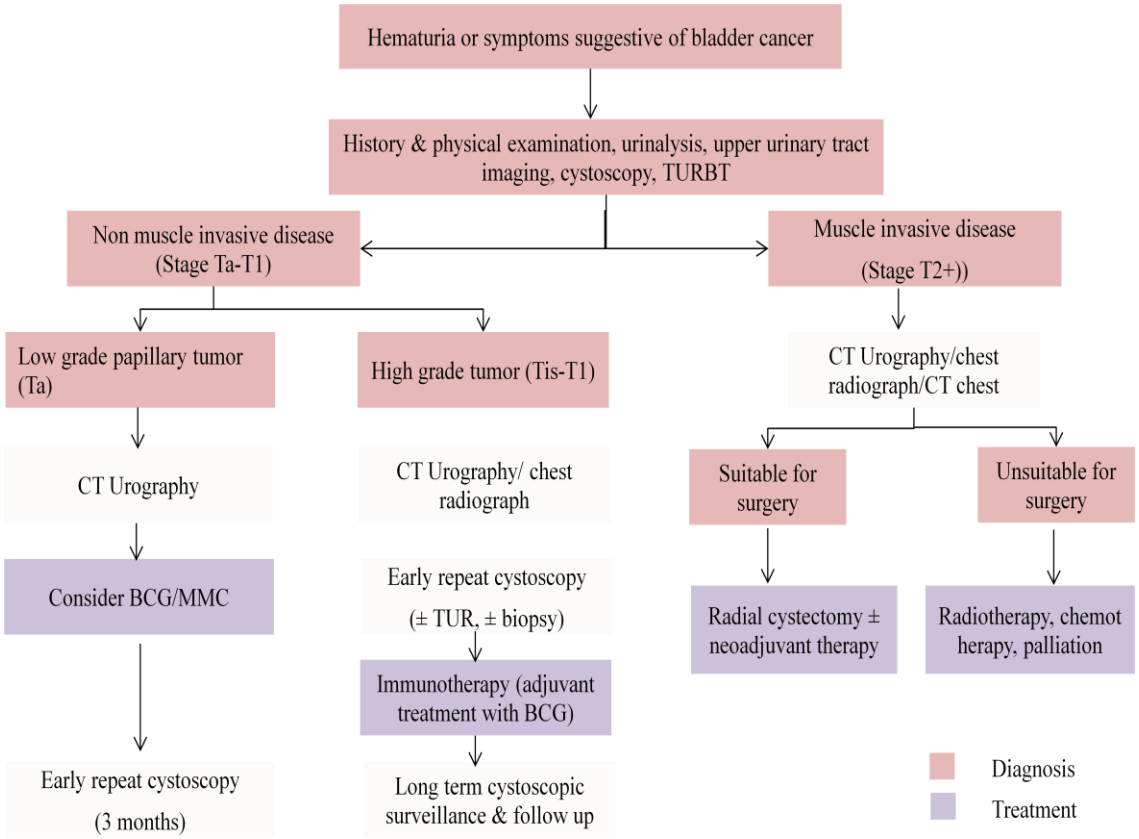
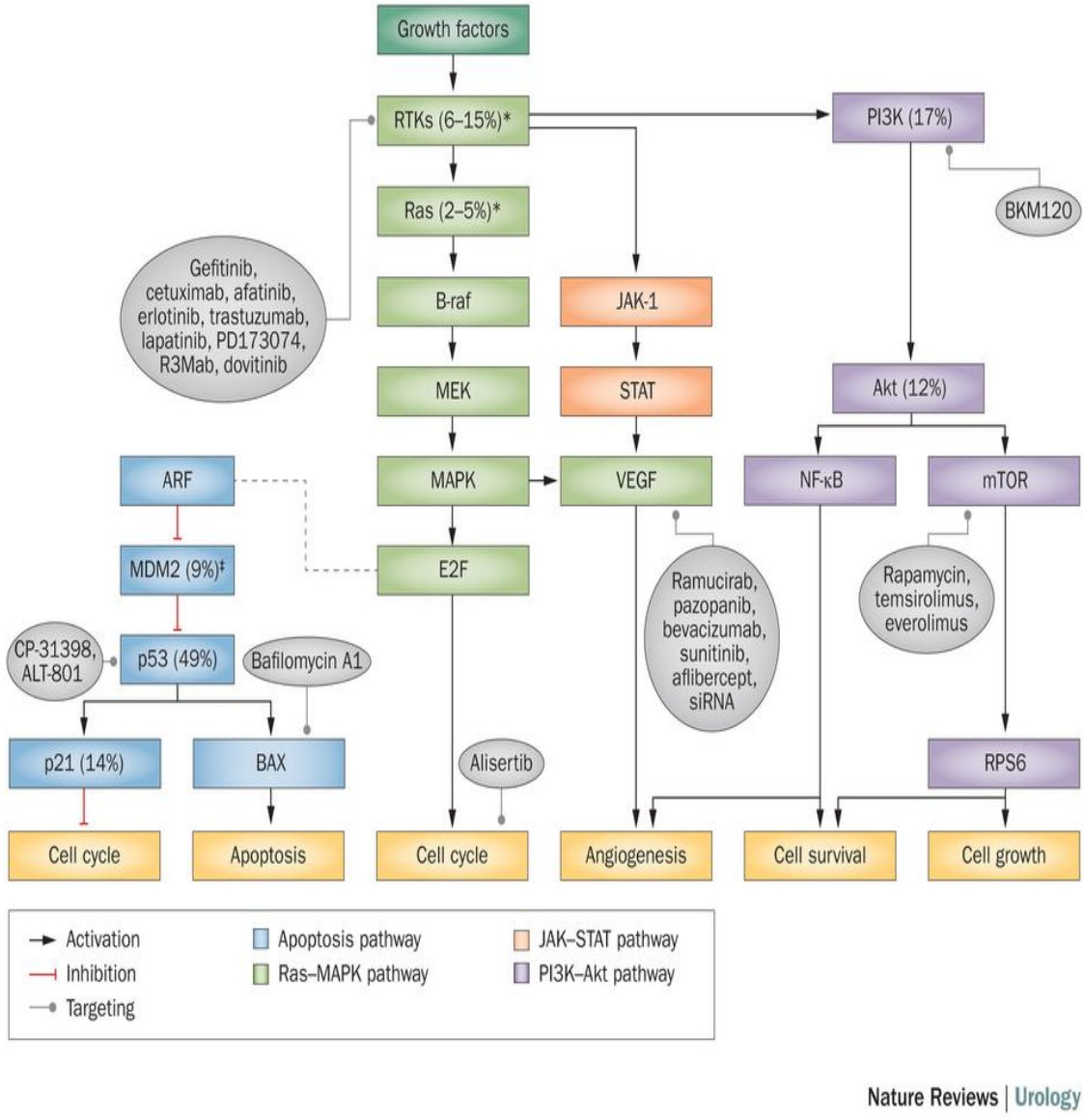


Figure 1.6



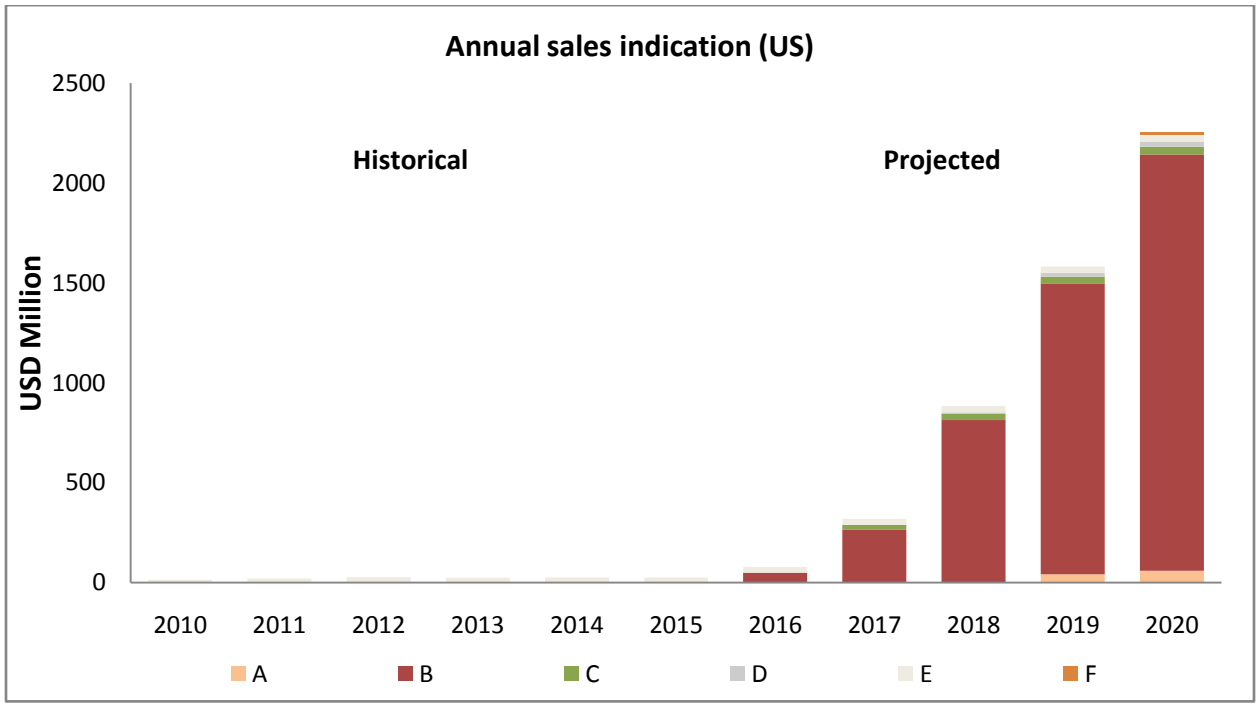
Source: naturejournal.com

BCG is used majorly as the treatment modality for bladder cancer

- Targeted therapies are expected to enter soon in the treatment area of bladder cancer

9.9 Market Dynamics

Chart 1.9



*Sales figures have been sanitized as the data is confidential and cannot be shared as per the company's policy

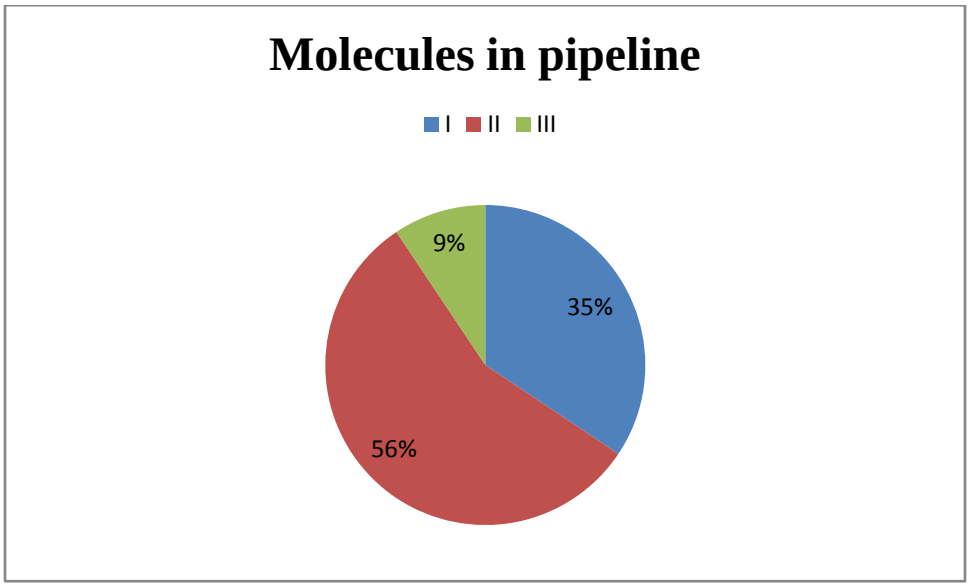
- Market for bladder cancer is expected to rise significantly 2016 onwards with the introduction of new drugs
- Atezolizumab is expected to emerge as the market leader in near future

Table 2.0

Key Marketed Products

Drug	Drug Class	Company	Dosage	MOA	Side effects	Patent expiry
hexyl aminolevulinate	Antineoplastic agents, tumor detection	PhotoCure, BioSyent, Ipsen	Reconstitute powder with 50 mL of diluent under aseptic conditions	Photosensitisers	Bladder spasm, dysuria, hematuria, bladder pain, procedural pain, urinary retention and headache	-
Valstar (valrubicin	Anthracycline	Anthra Pharma, Almirall S.A.,GE Healthcare	800mg administered intravesically once a week for six weeks	DNA repair enzyme inhibitors, Reactive oxygen-species stimulants, Type II DNA topoisomerase inhibitors	Local bladder symptoms, dysuria, urinary urgency, bladder spasm, hematuria, bladder pain	Sep '05
Immunocyst (BCG bladder vaccine)	Cancer vaccine	Sanofi Pasteur, Alliance Pharma plc, Sanofi K.K.	One vial of BCG suspended in 50 ml preservative-free saline	Immunostimulants	Bladder irritability, "Flu-like" symptoms, disseminated sepsis	-

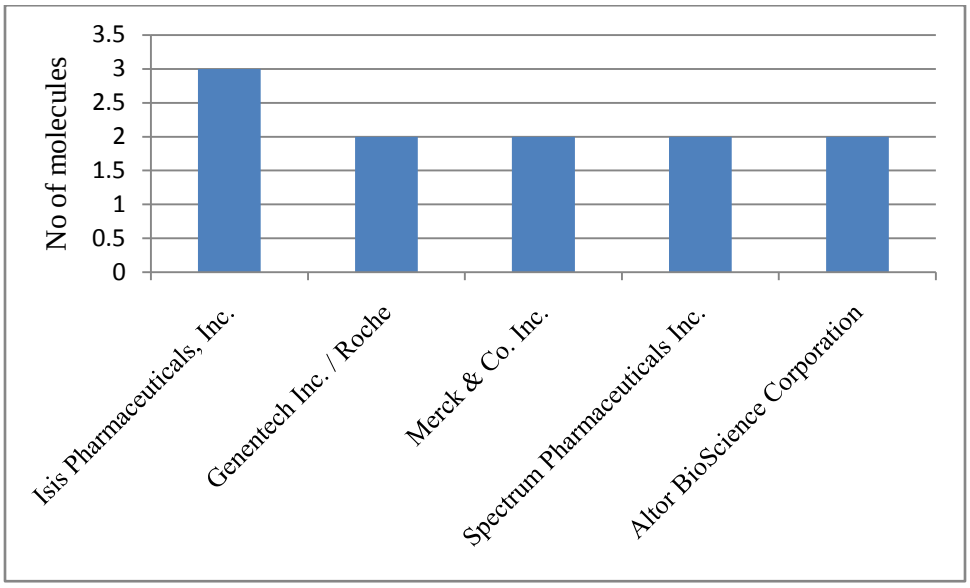
Chart 2.0



- Currently, 56% molecules are in Phase II and 35% in Phase I which shows the market for bladder cancer is expected to grow widely in the near future

Chart 2.1

Major Companies with molecules in pipeline



- Major company with 3 molecules in pipeline is Isis Pharma followed by Genentech, Merck & Co, Spectrum pharma and Altor Bioscience with 2 molecules in pipeline
- Major drug classes with 4 molecules in pipeline are Hsp27 inhibitors and monoclonal antibodies

10. Acute Lymphocytic Leukemia

10.1 Executive Summary

- Acute lymphocytic leukemia (ALL), also called *acute lymphoblastic leukemia*, is a cancer that starts from the early version of white blood cells called *lymphocytes* in the bone marrow
- Leukemia cells usually invade the blood fairly quickly. They can then spread to other parts of the body, including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles
- ALL is rare in adults, but it is the most common childhood leukemia as well as the most common childhood cancer
- Risk factors for ALL in children include exposure to chemotherapy or radiation therapy and genetic disorders, Down's syndrome in particular. In adults, older age (above 70 years) is associated with increased risk for ALL
- The clinical presentation of ALL is non-specific; symptoms include fatigue or lethargy, fever, night sweats, weight loss, dizziness, infections, easy bruising or bleeding, and dyspnea
- The diagnosis of ALL is generally based on the presence of ≥20% of bone marrow lymphoblasts upon the examination of bone marrow aspirate or biopsy
- TKIs are widely used as treatment options for Ph+ ALL cases
- US generates over half of all the sales within the ALL market, at a CAGR of 0.4% over 2013–2022
- Tyrosine kinase inhibitors constitutes the major market share of ALL including major drugs like Sprycel & Gleevec whereas many new drugs like Inotuzumab, CTL019 are expected to launch in the near future

10.2 Clinical Overview

- Acute lymphoblastic leukemia (ALL) is a malignant (clonal) disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- It may be distinguished from other malignant lymphoid disorders by the immunophenotype of the cells, which is similar to B- or T-precursor cells
- ALL is rare in adults, but it is the most common childhood leukemia as well as the most common childhood cancer
- Clinical signs of ALL are nonspecific, and include fatigue, fevers, night sweats, dizziness, and susceptibility to infection, bleeding, or bruising
- Risk factors for ALL include exposure to chemotherapy or radiation therapy and genetic disorders

Symptoms

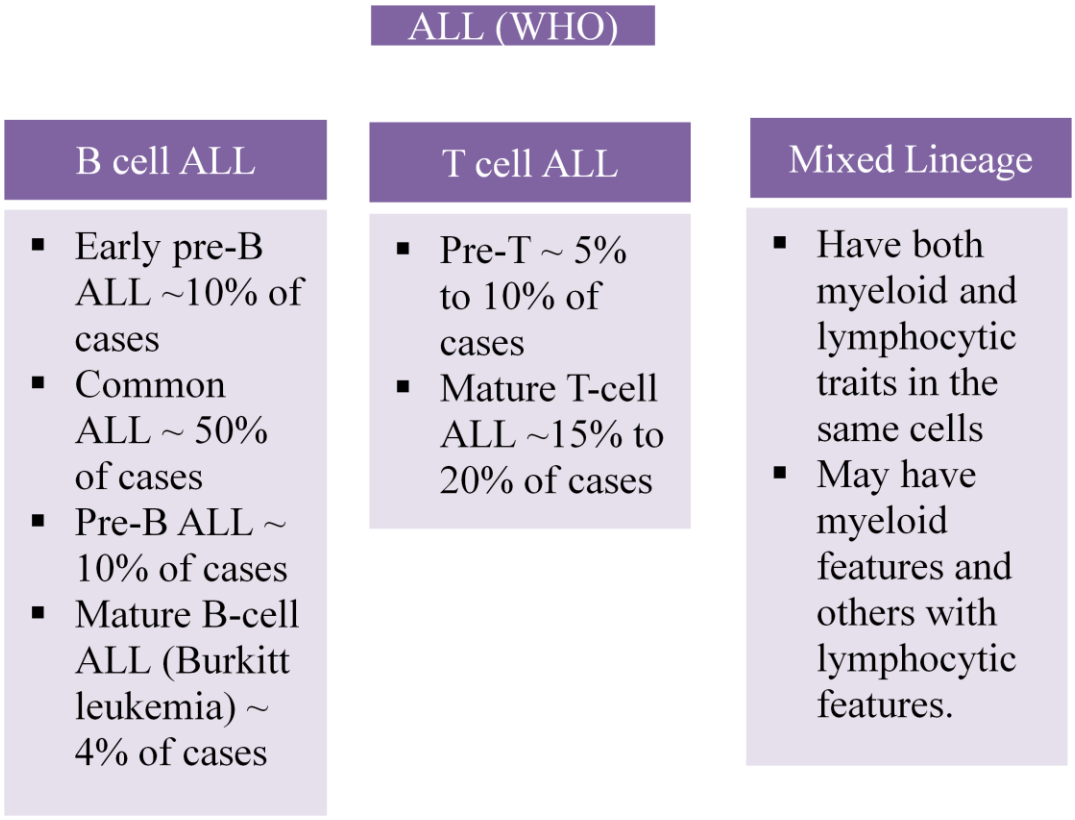
- Bleeding from the gums
- Bone pain
- Fever
- Frequent infections or severe nosebleeds
- Lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin
- Pale skin
- Shortness of breath
- Weakness, fatigue or a general decrease in energy
- In children, joint or extremity pain may be the only presenting symptom

Risk Factors

- **Previous cancer treatment:** Children and adults who've had certain types of chemotherapy and radiation therapy for other kinds of cancer

- **Exposure to radiation**. People exposed to very high levels of radiation, such as survivors of a nuclear reactor accident
- **Genetic disorders.** Certain genetic disorders, such as Down syndrome, are associated with an increased risk of ALL
- **Having a brother or sister with ALL.** People who have a sibling, including a twin, with ALL have an increased risk of ALL

10.3 Classification



10.4 Pathophysiology

- Malignant cells of ALL are lymphoid precursor cells (i.e., lymphoblasts) that are arrested in an early stage of development
- This arrest is caused by an abnormal expression of genes, often as a result of chromosomal translocations
- The most common translocation in ALL in adults is known as the Philadelphia chromosome, which is a switch of DNA between chromosomes 9 and 22. This is seen in around 25% of all cases of ALL in adults
- Other, less common translocations are those between chromosomes 4 and 11, or 8 and 14
- The lymphoblasts replace the normal marrow elements, resulting in a marked decrease in the production of normal blood cells
- Consequently, anemia, thrombocytopenia, and neutropenia occur to varying degrees
- The lymphoblasts also proliferate in organs other than the marrow, particularly the liver, spleen, and lymph nodes

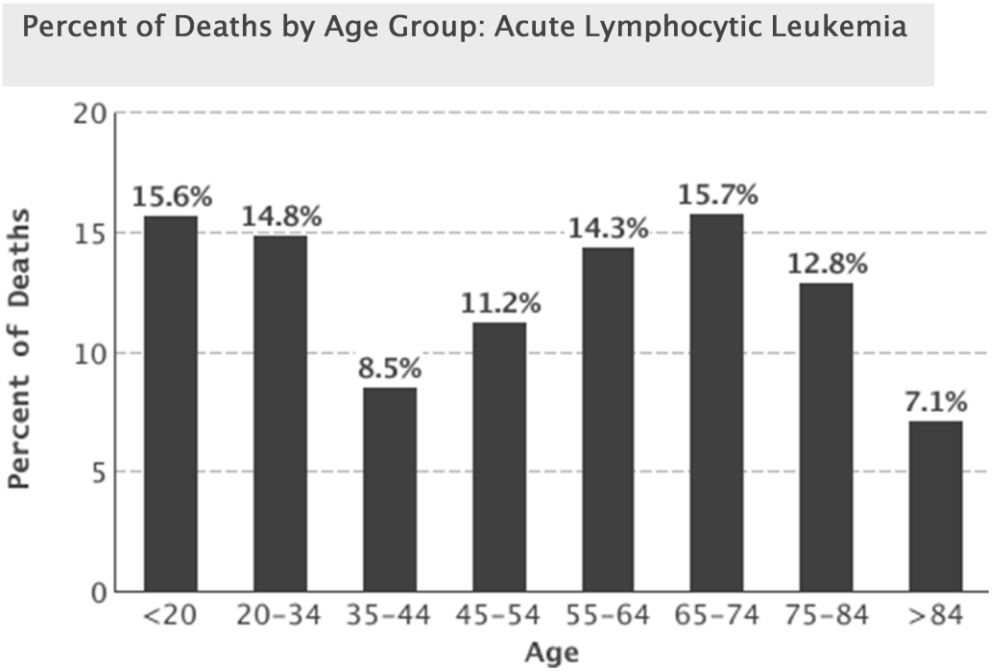
10.5 Epidemiology

Table 2.1

Epidemiology (US): ALL is most frequently diagnosed among people aged <20	
Incidence (E)	About 6,590 (3,590 in males and 3,000 in females) (2016)
Mortality(E)	About 1,430 (800 in males and 630 in females) (2016)
Prevalence (as of 2012)	75,176patients
Median age at diagnosis(2008-2012)	14 years

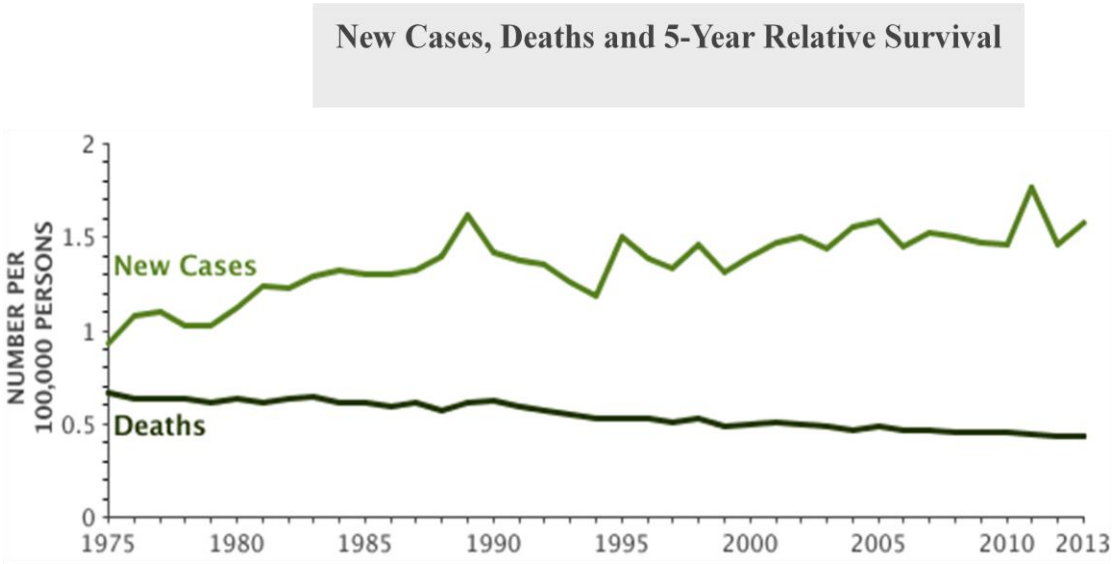
Median age at death (2008-2012)	54 years
Overall 5year relative survival(2005-2011)	67.5%

Chart 2.2



- The graph shows that maximum deaths occur in the age groups <20 and 65-74 years; making them the high priority groups
- Although rates for new acute lymphocytic leukemia cases have been rising on average 0.6% each year over the last 10 years; death rates have declined to a great extent

Chart 2.3



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	31.0%	49.0%	56.0%	55.8%	61.7%	62.6%	67.5%	71.7%

- With the improvement in treatment modalities, 5-year relative survival has increased drastically from 31% in 1975 to approx. 72% in 2008

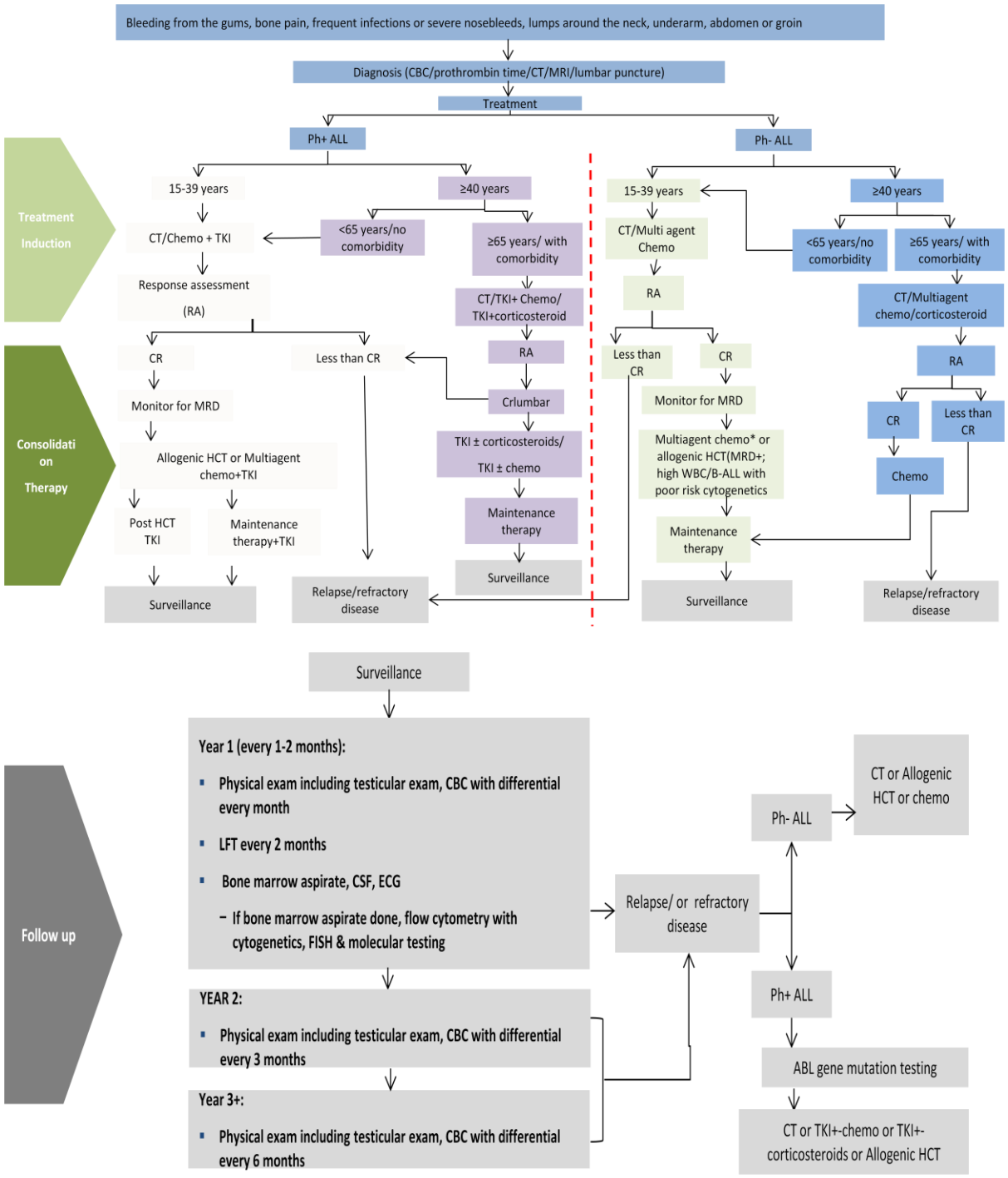
10.6 Diagnosis

Blood Test:

- Includes complete blood count with differential blood count, coagulation studies, peripheral blood smear, chemistry profile including lactic dehydrogenase, uric acid, liver function studies, and BUN/creatinine
- May reveal too many white blood cells, not enough red blood cells and not enough platelets
- May also show the presence of blast cells
- **Bone marrow aspiration & biopsy:**
- Bone marrow is checked for cancerous cells and – if found – the type of acute leukemia is determined
- Definitive for confirming leukemia
- **Imaging tests**
- Includes chest x-ray, computed tomography, multiple-gated acquisition scanning, ECG
- Help determine whether cancer has spread to the brain and spinal cord or other parts of the body
- **Spinal fluid test**
- Done to see whether cancer cells have spread to the spinal fluid
- **Other tests**
- Includes flow cytometry, cytogenetics, polymerase chain reaction, gene expression profiling
- Often done to plan the treatment

10.7 Treatment

Figure 1.7



Source: NCCN Guidelines ALL Version 1.2016

10.8 Prognostic factors

- Age: Younger patients tend to have a better prognosis than older patients
- Initial white blood cell count: People with a lower WBC count (less than 30,000 for B-cell ALL and less than 100,000 for T-cell ALL) at the time of diagnosis tend to have a better prognosis
- ALL subtype: Generally T-cell ALL has a better prognosis, while mature B-cell ALL (Burkitt leukemia) has a poorer prognosis
- Chromosome abnormalities: Presence of a translocation between chromosomes 4 and 11 in the leukemia cells predicts a poorer outlook, so does extra chromosome 8 or a missing chromosome 7
- Response to chemotherapy: Patients who go into a complete remission (no visible leukemia in the bone marrow – see below) within 4 to 5 weeks of starting treatment tend to have a better prognosis

10.9 Market dynamics

- US generates over half of all the sales within the ALL market, at a CAGR of 0.4% over 2013–2022
- Currently, Tyrosine kinase inhibitors are the major key players dominating the whole market

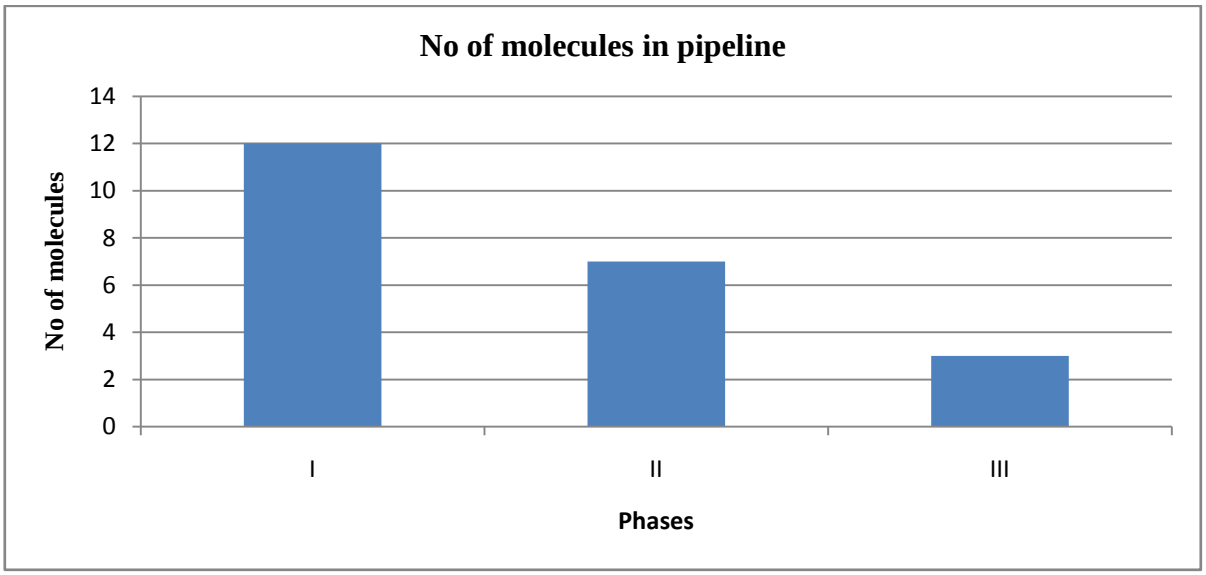
Table 2.2

Key Marketed Products

Drug Class[2]	Drug[1,2]	Company[1]	Dosage[3]	MOA[1]	Side effects[3]
Tyrosine kinase inhibitor	Sprycel (dasatinib)	Bristol-Myers Squibb	140 mg once daily	Bcr-abl TKI, EphA2 receptor antagonists, PDGFr beta antagonists, proto oncogene protein c-kit, Src-family kinase inhibitors	Myelosuppression, fluid retention, and diarrhea
	Gleevec (imatinib)	Novartis	Adults Ph+ 600 mg/day, Pediatrics Ph+ 340 mg/m²/day	Bcr-abl TKI, PDGF inhibitors, PDGFr antagonists, proto oncogene, protein c-kit inhibitors, signal transduction pathway inhibitors	Edema, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain
DNA synthesis inhibitor	Clolar (clofarabine)	O: Southern Research Institute	Pediatric dose: 52 mg/m² iv infusion over 2 hours daily for 5 days	Apoptosis stimulants, DNA synthesis inhibitors	Neutropenia, pruritus, pyrexia, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation.
Antineoplastic agents	Cyclo phosphamide	Roxane Lab	1 mg per kg per day to 5 mg/kg/day	Alkylating agents, Immunomodulator	Neutropenia, fever, alopecia
Asparaginase	Oncaspar (pegaspargase)	O: Enzon Pharmaceuticals	2,500 IU/m2 im or iv	Aspartate-ammonia ligase inhibitors	Anaphylaxis, CNS thrombosis, coagulopathy, elevated trans aminases, hyper bilirubinemia, hyperglycemia, and pancreatitis
	Erwinaze (crisantaspase)	O: Health Protection Agency	25,000 IU/m2 im or iv 3 times a week	Amidohydrolase stimulants, Aspartate-ammonia ligase inhibitors	Hypersensitivity, hyperglycemia, transaminases abnormal, pancreatitis, local reactions, thrombosis,

					hyperbilirubinemia
Antimetabolites	Nelarabine*	GlaxoSmithKline	Adults: 1,500 mg/m² iv over 2 hours, Pediatric: 650 mg/m² iv over 1 hour daily for 5 days	DNA inhibitors	**BBW:** Neurologic reactions; anemia, thrombocytopenia, neutropenia

Chart 2.4



- Market of ALL is buzzing with new drugs with 12 molecules in Phase I and 3 molecules ready for the launch
- Around 22 companies are competing for the ALL market which include major companies like Novartis, Pfizer, Sanofi, Merck & co.
- TKIs have been the dominant players since many years but in the near future anti –CD 19 monoclonal antibodies are expected to rule over the market
- 6 new molecules are in pipeline under this drug class

11. Business Implications

General implications: TAO: Onboarding process; repository; assess opportunity area; plan new drug launch

Specific implications: Clinical overview & Disease management – onboarding process

Epidemiology – target population, assess unmet needs, trends in epidemiological patterns

Market dynamics – recent developments, competitive landscape, plan the launch using information regarding patent expiry & first launch

12. Disclaimer:

The finding of market dynamics does not represent the whole market as only publically available data has been used for the study.

13. Ethical considerations:

The following study being based on secondary/desk research will derive data from publically available data sources so there are no associated ethical considerations for the study.

14. Conclusion

Parameters	HCC	Metastatic liver cancer	Bladder cancer	ALL
Clinical overview	Primary malignancy of the liver that frequently	These are the tumors that have spread to the liver from other areas of	Begins in the bladder, most often in the cells that line the inside of	A cancer that starts from the early version of white blood cells called *lymphocytes* in

	occurs in the setting of chronic liver disease and cirrhosis	the body Most common types of cancer that spread to the liver are: Colorectal, Lung, Breast, Pancreatic, Stomach, Melanoma, Neuroendocrine	the bladder. It is typically a disease of the old age and hematuria is considered as its first sign	the bone marrow
Epidemiology	HCC represents 2.2% of all new cancer cases in the U.S; Over the past 20 years, the incidence of HCC has more than doubled	More common is Caucasians, comprising of nearly 95% of all hepatic cancer	Rates of new bladder cancers and cancer deaths have been dropping slightly in women in recent years whereas in men, incidence rates have been decreasing and death rates have been stable	Rare in adults, but it is the most common childhood leukemia as well as the most common childhood cancer
Diagnosis	Primarily done by the use of various imaging techniques	Majorly involves tumor marker tests & various imaging techniques	Important diagnostic technique for bladder cancer is cystoscopy and biopsy (transurethral resection of bladder tumor)	Based on the presence of ≥20% of bone marrow lymphoblasts upon the examination of bone marrow aspirate or biopsy
Treatment	The mainstay of treatment is surgical resection and chemotherapy	Management is based on the primary source of tumor origin. Chemotherapy	Chemotherapy remains the mainstay of primary treatment with	Tyrosine kinase inhibitors are widely used as treatment options for Ph+ ALL cases

	whereas biopsy is required for diagnosis in patients without cirrhosis	and targeted therapy are often used in addition to, or as an alternative to, other treatments	BCG therapy being the most commonly used adjuvant therapy	
Market dynamics	Currently, only one product (sorafenib) approved for use in HCC whereas the pipeline buzzing with activity, with I/O molecules	Cyramza, Stivarga, Doxorubicin liposomal are the few approved drugs	Valstar had been the dominant player in the market whereas atezolizumab is expected to emerge as the market leader in near future	TKIs constitutes the major market share of ALL including major drugs like Sprycel & Gleevec whereas many new drugs like Inotuzumab, CTL019 are expected to launch in the near future

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Appendix

Pipeline molecules for HCC

Company	Brand / Generic / Investigational	Class	Phase
Celsion Corporation	**ThermoDox®**	doxorubicin enhanced with lysolipid thermally sensitive liposomes (LTSL)	Preclinical
Northwest Biotherapeutics Inc.	**DCVax®**	Immunotherapy	Prereg
Apricus Biosciences, Inc.	**PrevOnco™ (+ doxorubicin)**	anti-ulcer (lansoprazole)	III
ArQule Inc.	tivantinib ; *ARQ 197*	c-Met kinase inhibitor	III
Bayer HealthCare Pharmaceuticals Inc.	**Nexavar®** ; sorafenib	multi-targeted protein kinase inhibitor	III
Bristol-Myers Squibb Co.	Brivanib	VEGFR-2 inhibitor	III
Bristol-Myers Squibb Co.	**Cometriq™** ; cabozantinib ;*XL 184*	multiple tyrosine kinase inhibitor (MET and RET)	III
Bristol-Myers Squibb Co.	Brivanib	VEGFR-2 inhibitor	III
Celsion Corporation	**ThermoDox®**	doxorubicin enhanced with lysolipid thermally sensitive liposomes (LTSL)	III
Daiichi Sankyo, Inc.	tivantinib ; *ARQ 197*	c-Met kinase inhibitor	III
Eisai Inc.	lenvatinib ; *E7080*	multiple tyrosine kinase inhibitor	III
Eli Lilly & Co.	**Cyramza™** ; ramucirumab ; *IM C-1121B*	anti-VEGFR-2 monoclonal antibody	III
Exelixis Inc.	**Cometriq™** ; cabozantinib ;*XL 184*	multiple tyrosine kinase inhibitor (MET and RET)	III
Light Sciences Oncology	**Aptocine™**	light activated drug treatment	III
Onxeo	**Livatag®** ; *BA-003*	nanoparticle doxorubicin	III
Onyx Pharmaceuticals Inc.	**Stivarga®** ; regorafenib	kinase inhibitor	III
Onyx Pharmaceuticals Inc.	**Nexavar®** ; sorafenib	multiple tyrosine kinase inhibitor	III
Polaris Pharmaceuticals, Inc.	*ADI-PEG 20*	pegylated arginine deiminase	III
Transgene SA	Pexa-Vec ; *JX594/TG6006*	oncolytic virus	III
4SC AG	resminostat ; *4SC-201*	HDAC inhibitor	II
4SC AG	resminostat (+ sorafenib) ; *4SC-201*	HDAC inhibitor	II
Abbott Laboratories	*ABT-869*	multiple tyrosine kinase inhibitor	II
Acceleron Pharma, Inc.	dalantercept ; *ACE-041*	ALK inhibitor	II
Amgen Inc.	*AMG 386*	Fc-peptide fusion protein targeting angiopoietins (peptibody)	II

Aslan Pharmaceuticals	varlitinib ; *ASLAN001*	pan-HER inhibitor	II
Astellas Pharma Inc.	*OSI-906*	dual IGF-1R and IR tyrosine kinase inhibitor	II
Bayer HealthCare Pharmaceuticals Inc.	refametinib ; *BAY 86-9766*	MEK inhibitor	II
Can-FiteBioPharma Ltd.	*CF-102*	adenosine receptor agonist	II
CASI Pharmaceuticals Inc.	*ENMD-2076*	aurora A/angiogenic kinase inhibitor	II
Delcath Systems, Inc.	**The Delcath system™**	drug delivery platform	II
Eli Lilly & Co.	galunisertib ; *LY2157299*	kinase inhibitor	II
EMD Serono, Inc. / Merck KGaA	tepotinib	c-Met kinase inhibitor	II
Genentech Inc. / Roche	*ABT-869*	multiple tyrosine kinase inhibitor	II
GenSpera, Inc.	mipsagargin ; *G-202*	PSA activated prodrug	II
Novartis AG	patupilone ; *EPO906*	epothilone	II
Novogen Inc.	triphendiol	multiple signal transduction regulator	II
Peregrine Pharmaceuticals Inc.	bavituximab (+ sorafenib)	anti-phospholipid monoclonal antibody	II
Pfizer Inc.	**Inlyta®** ; axitinib ; *AG013736*	multiple tyrosine kinase inhibitor (VEGFR-1, 2, 3, PDGFR, cKIT)	II
Pfizer Inc.	*PF-03446962*	ALK1 inhibitor	II
SillaJen, Inc.	*JX-594*	oncolytic poxvirus	II
Tekmira Pharmaceuticals Corporation	*TKM-PLK1*	polo-like kinase 1 (PLK1) inhibitor	II
Vicus Therapeutics, Inc.	*VT-122*	prostaglandin E2 inhibitor	II
Astellas Pharma Inc.	**Xtandi®** ; enzalutamide	oral androgen receptor antagonist	I
AstraZeneca plc	*MEDI-573 (+ sorafenib)*	anti-IGF monoclonal antibody	I
Bayer HealthCare Pharmaceuticals Inc.	ipafricept	Wnt protein inhibitor	I
Blueprint Medicines, Inc.	*BLU-554*	inhibitor	I
Bristol-Myers Squibb Co.	nivolumab	PD-1 inhibitor	I
Celgene Corporation	*CC-122*	pleiotropic pathway modulator	I
Cellular Biomedicine Group	*Unnamed*	tumor stem cell specific dendritic cell (TC-DC) therapy	I
Cleveland BioLabs, Inc	quinacrine ; *CBL0102*	p53 activator	I
Dicerna Pharmaceuticals, Inc.	*DCR-MYC*	RNAi therapeutic	I

GlaxoSmithKline plc	mapatumumab ; *HGS-ETR1*	anti-TRAIL receptors 1 and 2 monoclonal antibody	I
Immunicum AB	Intovax	immunotherapy	I
MedImmune, LLC	*MEDI-573 (+ sorafenib)*	anti-IGF monoclonal antibody	I
Mirna Therapeutics, Inc.	*MRX34*	microRNA	I
MultiVir, Inc.	*AD-p53*	Adenoviral	I
Omnis Pharma Inc.	*VSV*	oncolytic virus	I
OncolysBioPharma Inc.	*OBP-301*	HDAC inhibitor	I
Provectus Pharmaceuticals, Inc.	*PV-10*	rose bengal disodium	I
Samumed, LLC.	*SMO4755*	Wnt inhibitor	I
Tekmira Pharmaceuticals Corporation	*TKM-PLK1*	polo-like kinase 1 inibitor	I
Threshold Pharmaceuticals Inc.	*TH-302 (+ sorefanib)*	hypoxia-activated prodrug (HAP)	I
Tracon Pharmaceuticals, Inc.	*TRC105*	chimeric monoclonal antibody (inhibits CD105 - humanized)	I
Tracon Pharmaceuticals, Inc.	*TRC105 (+ sorafenib)*	chimeric monoclonal antibody (inhibits CD105 - humanized)	I

Pipeline molecules for Bladder cancer

Company	Brand / Generic / Investigational	Class	Area of Study	Phase	Partnership
Spectrum Pharmaceuticals Inc.	**EOquinp®** ; apaziquone	alkylating agent	Non-invasive Bladder cancer	III	Allergan, Inc.
Sanofi	larotaxel ; *XRP9881*	taxane (semi-synthetic)	Bladder cancer	III	
BioCancell Ltd.	*BC-819*	DNA Plasmid	Bladder cancer	III	
Telormedix SA	*TMX-101*	toll-like receptor 7 (TLR7)	Bladder cancer	II	
Spectrum Pharmaceuticals Inc.	**Folotyn®** ; pralatrexate	antifolate	2nd line metastatic transitional cell Bladder cancer	II	
Sorrento Therapeutics, Inc.	Cynviloq	monoclonal antibody	Bladder cancer	II	
OncoGenex Pharmaceuticals, Inc.	apatorsen ; *OGX-427*	Hsp27 inhibitor	Bladder cancer	II	
Mirati Therapeutics Inc.	Mocetinostat	HDAC inhibitor	Bladder cancer	II	
Merck & Co. Inc.	**Keytruda®** ; pembrolizumab	monoclonal antibody	Bladder cancer	II	
Merck & Co. Inc.	**Keytruda®** ; pembrolizumab	monoclonal antibody	Bladder cancer	II	
Heat Biologics, Inc.	vesigenurtucel-L ; *HS-410*	cytotoxic t-cell specific adjuvant	Bladder cancer	II	
GlaxoSmithKline plc	*MAGE-A3*	antigen-specific cancer immunotherapeutic	1st line metastatic Bladder cancer	II	
Genentech Inc. / Roche	**Tarceva®** ; erlotinib	HER1/EGFR inhibitor	Bladder cancer	II	Astellas
Eli Lilly & Co.	cyramza	anti-VEGFR-2 monoclonal antibody	Bladder cancer	II	
Celgene Corporation	**Abraxane®** ; nab¨-paclitaxel	microtubule inhibitor	Bladder cancer	II	
BioClin Therapeutics, Inc.	*B-701*	FGFR3 monoclonal antibody	Bladder cancer	II	
Bavarian Nordic A/S	*CV-301*	immunotherapy	Bladder cancer	II	
Altor BioScienc	*ALT-801*	p53-TCR/IL-2 fusion protein	Bladder cancer	II	

e Corporation Aeterna Zentaris Inc.	zoptarelin doxorubicin ; *AEZS-108*	cytotoxic peptide conjugate	Bladder cancer	II	
Cold Genesys, Inc.	*CG0070*	oncolytic virus	Bladder cancer	II	
Telesta Therapeutics Inc.	*MCNA*	mycobacterium cell wall-DNA complex	Bladder cancer	II	
Seattle Genetics Inc.	*ASG-15ME*	antibody drug conjugate (ADC)	Bladder cancer	I	Astellas
Rexahn Pharmaceuticals, Inc.	*RX-3117*	DNA synthesis inhibitor	Bladder cancer	I	
Isis Pharmaceuticals, Inc.	*Apatorsen (+ gemcitabine and cisplatin)*	Hsp27 inhibitor	Bladder cancer	I	OncoGenex
Isis Pharmaceuticals, Inc.	*Apatorsen (+ carboplatin)*	Hsp27 inhibitor	Bladder cancer	I	OncoGenex
Isis Pharmaceuticals, Inc.	*Apatorsen*	Hsp27 inhibitor	Bladder cancer	I	OncoGenex
Genentech Inc. / Roche	*RG7446*	monoclonal antibody	Bladder cancer	I	
Eisai Inc.	**Halaven®** ; eribulin mesylate ;*E7389*	halichondrin B analog (synthetic)	Bladder cancer	I	
Bristol-Myers Squibb Co.	**Opdivo®** ; nivolumab	PD-1 inhibitor	Bladder cancer	I	
Altor BioScience Corporation	*ALT-803*	IL-15 Superagonist Complex	Bladder	I	
Agensys, Inc.	*ASG-15ME*	antibody drug conjugate	Bladder cancer	I	Seattle Genetics
ADC Therapeutics SA	*ADCT-502*	anti-CD19 monoclonal antibody (surface antigen specific for B cells)	Bladder cancer	I	

Pipeline molecules for ALL

Company	Brand / Generic / Investigational	Class	Area of Study	Phase
Amgen Inc.	blinatumomab ; *MT103*	anti-CD19 monoclonal antibody (surface antigen specific for B cells)	2nd line metastatic Acute Lymphocytic Leukemia (ALL)	III
Celator Pharmaceuticals, Inc.	*CPX-351*	combiplex technology platform: cytarabine-daunorubicin	Acute Lymphocytic Leukemia (ALL)	III
Pfizer Inc.	inotuzumab ozogamicin ; *PF-5208773*	antibody drug conjugate (anti-CD22 monoclonal antibody linked to CalichDMH - humanized)	Acute Lymphocytic Leukemia (ALL)	III
ARIAD Pharmaceuticals Inc.	**Iclusig™** ; ponatinib ; *AP24534*	pan-BCR-ABL inhibitor	Newly diagnosed Ph+ Acute Lymphocytic Leukemia (ALL)	II
ERYtech Pharma, Inc.	**Graspa®**	encapsalated L-asparaginase	Acute Lymphocytic Leukemia (ALL)	II
ImmunoGen Inc.	*SAR3419*	anti-CD19 monoclonal antibody (maytansin-loaded)	B-cell Acute Lymphocytic Leukemia (B-ALL)	II
Immunomedics Inc.	epratuzumab	anti-CD22 monoclonal antibody	Acute Lymphocytic Leukemia (ALL)	II
MorphoSys AG	*MOR208 (XmAb¨5574)*	anti-CD19 monoclonal antibody (humanized)	Acute Lymphocytic Leukemia (ALL)	II
Sanofi	*SAR3419*	anti-CD19 monoclonal antibody (maytansin-loaded)	B-cell Acute Lymphocytic Leukemia (B-ALL)	II
Xencor, Inc.	*XmAb¨5574*	anti-CD19 monoclonal antibody (humanized)	Acute Lymphocytic Leukemia (ALL)	II
ADC Therapeutics SA	*ADCT-402*	anti-CD19 monoclonal antibody (surface antigen specific for B cells)	Acute Lymphocytic Leukemia (ALL)	I
Bio-Path Holdings, Inc.	*BP-100-1.01*	lipsomal growth factor receptor bound protein-2	Acute Lymphocytic Leukemia (ALL)	I
BioCryst Pharmaceuticals Inc.	forodesine HCL	PNP inhibitor	Acute Lymphocytic Leukemia (ALL)	I
Deciphera Pharmaceuticals LLC	rebastinib ; *DCC-2036*	BCR-ABL kinase inhibitor	Acute Lymphocytic Leukemia (ALL)	I
Enzon Pharmaceuticals Inc.	*EZN-3042*	RNA antagonist (survivin antagonist)	2nd line metastatic Acute Lymphocytic Leukemia (ALL)	I
Juno Therapeutics, Inc.	*JCAR015*	CD19 inhibitor	Acute Lymphocytic Leukemia (ALL)	I
Kite Pharma, Inc.	*KTE-C19*	chimeric antigen receptor	Acute Lymphoblastic Leukemia	I
Merck & Co. Inc.	*SCH 900776*	cell cycle inhibitor	Acute Lymphocytic Leukemia (ALL)	I
Novartis AG	**Tasigna®** ; nilotinib	multiple tyrosine kinase inhibitor	Acute Lymphocytic Leukemia (ALL)	I
Onconova Therapeutics Inc.	*ON?013105*	cyclin D1 inhibitor	Acute Lymphocytic Leukemia (ALL)	I

OncoVista Innovative Therapies Inc.	cordycepin ; *OVI-123*	nucleoside analog	Acute Lymphocytic Leukemia (ALL)	I
Seattle Genetics Inc.	*SGN-CD19A*	antibody drug conjugate (anti-CD19)	Acute Lymphocytic Leukemia (ALL)	I