Small Cell Lung Cancer Scientific and Competitive Landscape

Dissertation submitted to

The IIHMR University, Jaipur

For the partial fulfilment for the award of the degree of

Master of Business Administration (MBA) in Hospital and Health Management

Submitted by

Dr Kopal Singhal

Under the supervision and guidance of

Mr. Ashish Bandhu

(Assistant Professor, IIHMR)

2022

Declaration by student

I hereby declare that this dissertation titled '**Small Cell Lung Cancer Scientific and Competitive Landscape'** is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Dr Kopal Singhal

Certificate

This is to certify that Dr Kopal Singhal in partial fulfilment of the requirement for the award of the degree of MBA (Hospital and Health Management from the IIHMR University, Jaipur has successfully completed her internship at the Indian Institute of Health Management Research, Jaipur from March 21st to June 18th,2022.

Place: Jaipur (WFH)
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TO WHOMSOEVER IT MAY CONCERN

This is to confirm that Kopal Singhal has successfully completed her dissertation in Intelligence & Insight team within Prescient Healthcare Group, from 21st March 2022 to 18th June 2022 under the guidance of Ria Kohli (Associate Engagement Manager).

During this tenure, she was found to be hardworking and sincere.

We wish Kopal all the best for her future endeavours. Please feel free to contact me should you need any further confirmation.

Kind regards,

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This is to certify that dissertation titled "**Colorectal Cancer: Scientific And Competitive Landscape**" is a record of the research work undertaken by (Name of Student) in partial fulfilment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA (Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

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Abstract

Background:

Small cell lung cancer (SCLC) is an aggressive neuroendocrine cancer that is strongly linked to cigarette smoking. Patients typically present with short-term symptoms and, in 60-65 per cent of the cases, metastatic disease. SCLC is a diverse disease with both extremely chemo-sensitive and chemo-resistant clones. As a result, a high proportion of patients respond to first-line chemotherapy but then succumb to the disease. Despite treatments, the prognosis for this disease remains poor, and novel therapies are required to improve survival.

Aim:

- The primary goal of this study is to gain a thorough understanding of the overview, current treatment algorithm, emerging treatment plans, and competitive timeline of small cell lung cancer
- The secondary goal is to comprehend the treatment landscape and competitive analysis, as well as to investigate the current SCLC treatment algorithm

Methodology:

- **DATA COLLECTION:** Secondary Data for the study was collected from clinicaltrials.gov for Small Cell Lung Cancer

- **No. of trials:** 254 trials of SCLC

- **STUDY RESEARCH CRITERIA:**

Inclusion criteria:

- Trials from Phase II, Phase III and completed were included.
- Only industry-sponsored trials were considered (US, EU, and Japan)
- Advance filter was applied, not yet recruiting, recruiting, enrolling by invitation, active not recruiting and completed and unknown status trials were selected
- Only industry sponsored trials were considered

Exclusion criteria:

- Preclinical, Phase I/II, Phase I, Phase IV were excluded
- Studies that were suspended, discontinued, terminated, or whose status was unknown were excluded educational institutes, research centres, hospitals, and privately funded studies were not included

- Assets included as **'Emerging Therapies'** fulfil the following criteria:
  - Therapies that are not previously approved as any line of therapy for the disease AND

- Therapies that have an active Phase 2 or Phase 3 trial that is registration-directed OR
- Therapies that have an FDA breakthrough or fast-track designation

- Assets included as **'Competitors'** fulfil the following criteria:
  - Therapies that are previously approved as any line of therapy for the disease
  - Only Competitors with ongoing registrational trials in the disease are included in the section "Competitor & Emerging Therapy Timelines"

- Assets under **'Other Pipeline Therapies'** fulfil the following criteria:
  - Therapies that are not previously approved in any indication (i.e., "new molecular entity" or "new therapeutic biological products") AND
  - Therapies at P2 or higher in development but are not known to be registration-seeking

DATA ANALYSIS:

An excel workbook was prepared in which two different sheets were made one for phase 2 and another phase 3. Relevant data was extracted on the basis of different criteria such as brand name, company name, phase, pipeline, special drug designation and results, etc. The relevant information was used to summarise heat map, current and emerging therapies and their timeline, potential upcoming therapy, emerging treatment algorithm and finally the current clinical benchmark.

Data analysis tools: MS Excel

Acknowledgement

The opportunity to complete a dissertation at Prescient Healthcare Group was both enriching and valuable. I am grateful to have met so many knowledgeable professionals who guided me through my research. I sincerely thank them for guiding me.

First and foremost, I'd like to thank the entire Intelligence and Insight team, PHG. Dr Aviral Maheshwari (Vice President), Nishika Bhan (Associate Director), Ria Kohli (Associate Engagement Manager), and Dr Karan Madhok (Senior Associate) who inspired, directed, and facilitated me in completing my research.
I am grateful to Mr Ashish Bandhu (Assistant Professor) for his constant guidance and support throughout the project. His valuable insights and suggestions were extremely beneficial to the successful completion of my project.

I am overwhelmed with humility and gratitude to recognize my significance to each and every one who has helped me in moving these thoughts beyond the level of straightforwardness and into something concrete. I'd like to express my heartfelt appreciation to my parents and friends for their continuous support.

Sincerely
Dr Kopal Singhal

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Abbreviations

BSC	Best supportive care
BTD	Breakthrough therapy
EU	Europe
CRT	Chemotherapy
IO	Immunotherapy
IV	Intravenous
FTD	Fast track designation
PCI	Prophylactic cranial irradiation
PS	Performance status
MRI	Magnetic Resonance Imaging
N	Node
R	Resection
RT	Radiotherapy
SCLC	Small cell lung cancer
TFI	Treatment Free interval
UK	United Kingdom
US	United States

Small Cell Lung Cancer Scientific and Competitive Landscape

CHAPTER 1
Introduction

- **Description:** Squamous cell lung cancer, also known as Squamous cell carcinoma, is a type of lung cancer. It develops in the centre of the lung, either the left or right bronchus. It is a distinct type of non-small cell lung cancer. Lung cancer is classified into two types. Small cell lung cancer (which accounts for 10% to 15% of all lung cancers and grows and spreads more quickly than NSCLC) and non-small cell lung cancer (which comprises 80 per cent to 85 per cent of all lung cancers which is further divided into Adenocarcinoma, large cell carcinoma and squamous cell carcinoma.)

- **Onset/Risk Factors:** It usually begins in the cells that line the bronchi and other parts of the lungs, such as the bronchioles or alveoli.
  The following are risk factors:
    - Age: About two out of every three lung cancer cases are diagnosed in people over the age of 65
    - It is most prevalent among blacks, then whites, American Indians/Alaska natives, and Asian/Pacific Islanders
    - Other considerations: Tobacco use, secondhand smoke, prior radiation therapy to the lungs, air pollution, a personal or family history of lung cancer, and exposure to asbestos, radon, and other cancer-causing agents such as beryllium, arsenic, chromium compounds, mustard gas, chloromethyl ethers, and others are all factors

- **Symptoms and Diagnosis:** Early-stage lung cancer usually has no symptoms. It appears as the disease progresses. Coughing for more than 2 or 3 weeks, chest pain, wheezing, SOB, dizziness, coughing up blood, unexplained weight loss, loss of appetite, and bronchitis/pneumonia are all examples. Finger clubbing, difficulty swallowing, and swelling in the face or neck are some of the less common symptoms. Jaundice, bone pain, face swelling, arms or neck, headache, dizziness, weak limbs, and lumps in the neck and collarbone region are examples of advanced symptoms
    - Imaging tests such as X-rays or CT scans, as well as sputum cytology and tissue samples, can be used to diagnose lung cancer

- **Treatments:** Lung cancer can be treated in a variety of ways like Surgery, chemotherapy, angiogenesis inhibitors, radiation therapy, targeted drug therapy, and immunotherapy are all part of it

- **Prognosis:** The prognosis of patients affected is determined by the stage at which they are diagnosed.

When detected early, the five-year survival rate is 99 percent in the majority of cases. (1)

- **Unmet Needs:** It has a high level of clinical unmet need and is a disease area with a high rate of late-stage clinical trial failure, resulting in a lack of targeted treatment options. Despite the fact that most patients benefit from the newer agents, many patients still do not have a targeted therapy. There is still room for advancement and new treatments. (2) (3)

- **Epidemiology:** The average age of diagnosis is 65 or older.
  Estimated number of new cases in 2021: 235,760, accounting for 12.4% of all new cancer cases.
  Estimated deaths in 2021: 131,880 (representing 21.7 percent of all cancer deaths) (4) (5)

Current treatment algorithm

○ Limited stage SCLC

Adjuvant cisplatin-etoposide has demonstrated encouraging outcomes in the small number of SCLC cases and is presently utilized on a regular basis for therapy.

Key trends

- When considering surgical treatment for SCLC, extensive pathological mediastinal staging is required, and the goal of surgery should be a complete (R0) resection according to the International Association for the Study of Lung Cancer criteria.

- For patients with limited-stage (stage I-III) SCLC, the preferred ChT regimen is cisplatin plus etoposide. When cisplatin is not an option, carboplatin in combination with etoposide may be used, with equal or marginally inferior results observed in limited comparative studies.

○ Extensive stage

When immunotherapy fails to produce the desired results in patients with advanced SCLC, carboplatin-etoposide-atezolizumab is routinely employed.

Key trends

- PCI reduces the risk of symptomatic brain metastases and improves survival in patients in complete remission (5.4 per cent absolute improvement in 3-year OS)
- Cisplatin can be replaced with carboplatin in advanced-stage SCLC. However, when age (70 years old), PS, and toxicity profile are considered, cisplatin may be preferred for some patients.
- Based on two double-blind, phase III RCTs: IMpower133 and CASPIAN, new standards of care in first-line therapy for advanced-stage SCLC were established.

o Recurrent SCLC

Treatment choices are constrained in cases of platinum resistance and relapse.

- If there is <3 months Treatment Free Interval relapsed cases are treated with
  - Oral or i.v topotecan
  - Cyclofosfamide– doxorubicin – vincristine
  - Lurbinectedin
- If there are ≥3 months Treatment Free Interval relapsed cases are treated with
  - Rechallenge with platinum– etoposide Oral or i.v topotecan
  - Cyclofosfamide –doxorubicin– vincristine

Key trends

- The treatment-free interval (TFI) and response to first-line platinum-based induction therapy influence second-line treatment response rates.
- Topotecan is approved for use as second-line therapy in SCLC in the European Union. Prior to the development of topotecan, anthracycline-based regimens such as cyclophosphamide plus doxorubicin and vincristine were commonly used.
- Nivolumab and pembrolizumab were initially approved as monotherapies for the treatment of stage IV SCLC. However, after discussions with the FDA, the manufacturers of nivolumab and pembrolizumab both voluntarily withdrew the SCLC indication for their products in late 2020/early 2021, as both drugs failed to meet the OS endpoint. (15) (16) (17) (18)

Treatment Paradigms

- In the United States, 41 percent of patients are treated with atezolizumab/ carboplatin/ etoposide, 21 percent with carboplatin/ etoposide, and 11 percent with cisplatin/ etoposide. In the EU4+ UK, the criteria are nearly identical, with 33 percent of patients receiving atezolizumab/ carboplatin/ etoposide, 23 percent receiving carboplatin/ etoposide, and 15 percent receiving cisplatin/ etoposide as the first line treatment, whereas in Japan, the majority of patients receive carboplatin/ etoposide (41 percent), with only 25 percent receiving atezolizumab/ carboplatin/ etoposide and 14 percent with cisplatin/ etoposide as the first-line treatment.

- In the United States, the second-line treatment of choice varies between atezolizumab (25 per cent), lurbinectedin (17 per cent), and Durvalumab (12 per cent). Topotecan is the treatment of choice for 53% of patients in EU4 and the UK, atezolizumab for 10%, and cyclophosphamide/doxorubicin/vincristine for 7%. In Japan, amrubicin (43%) is the most used treatment, followed by atezolizumab (22%), and atezolizumab/carboplatin/etoposide (22%). (7 per cent).

- For Third line 30% of the patients opt. for Nivolumab, 26% for atezolizumab/ carboplatin/ etoposide and 21% for lurbinectedin whereas in EU4 and UK 22% go for topotecan, 19% for vinorelbine and 18 % for cyclophosphamide/ doxorubicin/ vincristine compared to 35% amrubicin, 22% irinotecan and 11% carboplatin/ etoposide in Japan. (19) (20) (21) (22)

CHAPTER-2
Literature Review

Lung cancer is the second most common type of cancer diagnosed globally. SCLC affects approximately 14% of lung cancer patients in the United States.
An estimated 2,206,771 people worldwide were diagnosed with lung cancer by 2020. These figures include patients with both SCLC and non-small cell lung cancer. Although the black population is more likely than the white population to develop lung cancer, they are less likely to develop SCLC. People with SCLC have a 7 per cent 5-year survival rate.
Survival rates are affected by a variety of factors, including disease stage. The overall 5-year survival rate for people with localized SCLC, which means cancer has not spread outside of the lung, is 27%. The 5-year survival rate for regional SCLC, which means cancer has spread outside of the lung to nearby areas, is 16%. If cancer has spread to another part of the body, the 5-year survival rate is only 3%. Some people with advanced lung cancer, on the other hand, can live for many years after diagnosis.

Author, Year	Study Location	Sample size	Salient Features
Liguori et al., 2021	US	NA	This study examines the impact of immunotherapy on the survival of patients as well as the genomics of SCLC. It also includes details on upcoming novel therapies for the treatment of SLCL (6)
C Meijer, N H Mulder, GA Hospers, DR Uges and EG de Vries, 1990.	Europe	NA	Through this article, the authors studied the effect of GSH status of the cells when they are under continuous pressure of CDDP for the treatment of small cell lung carcinoma. (7)
J Clin Oncol, 2021.	NA	834 patients randomly selected	The authors wanted to establish that CheckMate-451, Nivolumab with ipilimumab maintenance therapy did not extend OS for ED-SCLC patients who did not progress on first-line chemotherapy. There were no more warning signs. (8)
T Sethi , R C Rintoul, S M Moore, A C MacKinnon, D Salter, C Choo, E R Chilvers, I Dransfield, S C Donnelly, R Strieter, C	NA	NA	A novel therapeutic strategy to enhance the response to chemotherapy in SCLC may be based on techniques that disrupt beta1 integrin-mediated survival signals. (9)

Haslett, 1999.			
P S Hodkinson 1, A C Mackinnon, T Sethi, 2007	NA	NA	A paradigm to explain the establishment of acquired drug resistance is provided by the ability of SCLC cells to survive treatment-induced cell cycle arrest and death with persistent DNA damage via ECM via beta1 integrin-mediated PI3-kinase activation. Therefore, new therapeutic approaches may focus on blocking integrin-mediated cell survival signals to increase response rates and cure rates for this deadly malignancy. (9)
G W Krystal 1, P Carlson, J Litz, 1997.	NA	NA	At its highest soluble concentration, the AG1296 chemical reduced the proliferation of 5 of 6 SCLC cell lines in complete media by an average of 50%. These findings imply that a novel class of drugs with potential for SCLC treatment may be tailored pharmacological inhibitors of Kit activity. (10)
Ting Zhou, Zhonghan Zhang, Fan Luo, Yuanyuan Zhao, Xue Hou, Tingting Liu, Kai Wang, Hongyun Zhao, Yan Huang, Li Zhang, 2020.	NA	Electronic databases, of 199 eligible articles, 14 were included.	To determine which first-line combo treatment among ES-SCLC patients is linked to the best tumour response. The combination of PD-L1 inhibitor and etoposide-platinum had the highest likelihood of ranking first for OS (0.87) and DCR, according to the surface under the cumulative ranking curve value (0.97). (11)
Yanyan Han, Dandan Liu, Lianhong Li, 2020.	NA	NA	In order to enhance cancer therapy, this review aims to summarise the function of PD-1 and PD-L1 in cancer. (12)
K Helin, K Holm, A Niebuhr, H Eiberg, N Tommerup, S Hougaard, H S Poulsen, M Spang-Thomsen, P	NA	NA	It is the the first study to describe the loss of p130 as the result of a genetic change, suggesting that not only pRB but also the other members of the family may contribute to tumorigenesis, and giving support to the finding that DNA tumour viruses specifically target every member of the retinoblastoma protein family. (13)

Norgaard, 1997.			
Eric E Gardner, Benjamin H Lok, Valentina E Schneeberger, Patrice Desmeules, Linde A Miles, Paige K Arnold, Andy Ni, Inna Khodos, Elisa de Stanchina, Thuyen Nguyen, Julien Sage, John E Campbell, Scott Ribich, Natasha Rekhtman, Afshin Dowlati, Pierre P Massion, Charles M Rudin, John T Poirier, 2017.	NA	NA	In both chemosensitive and chemoresistant small cell lung cancer models, adding an EZH2 inhibitor to standard cytotoxic therapy reduced the development of acquired resistance and improved chemotherapeutic efficacy. (14)

CHAPTER-3
Methodology

Key Research Question:

1. **What are the potential upcoming therapies for Small-cell Lung Cancer?**
2. **What is the competitive timeline for current and emerging therapies in Small Cell Lung Cancer?**

Aim:

- The primary goal of this study is to gain a thorough understanding of the overview, current treatment algorithm, emerging treatment plans, and competitive timeline of small cell lung cancer
- The secondary goal is to comprehend the treatment landscape and competitive analysis, as well as to investigate the current SCLC treatment algorithm

- **DATA COLLECTION:** Secondary Data for the study was collected from clinicaltrials.gov for Small Cell Lung Cancer

- **No. of trials:** 254 trials of SCLC

- **STUDY RESEARCH CRITERIA:**

Inclusion criteria:

- Trials from Phase II, Phase III and completed were included.
- Only industry-sponsored trials were considered (US, EU, and Japan)
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Exclusion criteria:

- Preclinical, Phase I/II, Phase I, Phase IV were excluded
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- Assets included as **'Emerging Therapies'** fulfil the following criteria:
  - Therapies that are not previously approved as any line of therapy for the disease AND
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DATA ANALYSIS:

An excel workbook was prepared in which two different sheets were made one for phase 2 and another phase 3. Relevant data was extracted on the basis of different criteria such as brand name, company name, phase, pipeline, special drug designation and results, etc. The relevant information was used to summarise heat map, current and emerging therapies and their timeline, potential upcoming therapy, emerging treatment algorithm and finally the current clinical benchmark.

Data analysis tools: MS Excel

CHAPTER-4
Results

The shorter doubling time of small cell lung cancer, which results in death, makes it one of the most aggressive cancers. This report will emphasize in-depth knowledge of the small cell lung cancer overview, existing treatment algorithm, emerging therapy strategies, and competitive timeframe. The competitive analysis of SCLC therapy possibilities and a thorough grasp of the emerging prospective treatment options as well as information on the potential molecule's sponsored company are two major goals of the report. The available treatment algorithm will also be highlighted.
In the current competitive landscape, companies such as Astra Zeneca, Merck, Beigene, Jazz Pharmaceuticals, and others are working on developing new drugs for the treatment of SCLC.

Competitive Heat Map and Timeline

- Therapies that have previously been approved as any line of treatment for the disease, with only Competitors conducting ongoing registrational trials in the disease. These are either marketable, registered, or awaiting FDA Breakthrough / Fast Track designation therapies.

(**Breakthrough designation/ BTD**: Breakthrough Therapy Designation (BTD) was introduced by the US FDA Safety and Innovation Act of 2012 to help shorten the development and review time of promising new drugs intended to treat serious or life-threatening diseases with unmet medical needs and **Fast track designation/ FTD**: The Fast-Track Designation process aids in the development and expediting of new drugs that treat a serious medical condition and meet an unmet medical need. By accelerating these processes, new drugs can reach patients in need faster than they would otherwise through traditional routes.)

- The current modalities of treatment for SCLC are as follows:

- **Tecentriq:**
  - It is a PD-1 inhibitor molecule from Genentech. It has been clinically approved in the first line based on the Impower133 trial. It is marketed in the United States, Europe, and Japan and is used in conjunction with carboplatin and etoposide.
- **Imfinzi:**
  - It is an oral PD-1 inhibitor from Astra Zeneca. It has been clinically approved in the first line based on CASPIAN trial. It is marketed in the United States, Europe, and Japan and is used in combination with tremelimumab, platinum-based chemotherapy.

- 2 new phase III trials Adriatic (in combination with tremelimumab) and Luminance (in combination with platinum chemo and etoposide) are currently ongoing

➢ **Cosela:**

- Genentech's cyclin-dependent kinase inhibitor is taken orally. It has been marketed in the United States, Europe, and Japan as a first-line based on NCT02499770 (in combination with Etoposide and Carboplatin) and NCT03041311 (in combination with Carboplatin, etoposide and atezolizumab) and second-line agent based on NCT02514447as a single agent

➢ **Zepzelca:**

- Jazz Pharmaceuticals manufactures intravenous alkylating agent Zepzelca. It has been marketed in the United States as a single agent in the second line based on NCT02454972.
- Two trials in phase III are currently underway, one in the first line **IMforte** (in combination with Atezolizumab) and **LAGOON** (as a Single agent or in combination Irinotecan) as the second line.

➢ **Keytruda:**

- Merck manufactures intravenous PD-1 inhibitor Keytruda.
- There are currently three ongoing trials that are **KEYLYNK-013** (in combination with Olaparib), **REACTION**
  (In combination with Chemo) and **KEYNOTE-604**
  (In combination with Etoposide)

➢ **OPDIVO:**

- BMS's OPDIVO is an intravenous PD-1 inhibitor.
- Currently, 2 ongoing trials are undergoing in Phase III **CheckMate331** (as a single agent) and **CheckMate 451**
  (In combination with Ipilimumab)

➢ **Defobarasertib:**

- It is an aurora kinase B inhibitor administered intravenously
- A Phase II trial **TAZMAN** in combination with durvalumab is ongoing currently

➢ **Ociperlimab:**

- Beigene's TIGIT protein inhibitor is administered intravenously.
- Currently, it's in **Phase II** in combination with Tislelizumab and Chemo.

Competitive Heat Map for Current & Emerging Therapies in SCLC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/2)

Agent	ROA and MOA	1st Line		2nd Line	3rd Line and beyond
1. Tecentriq (Atezolizumab) Genentech	IV PD-1 inhibitor	MARKETED IN US, EU, JP IMpower133 (+ Carboplatin + Etoposide, ▲ +)			
2. Imfinzi (Durvalumab) AZ	Oral PD-1 inhibitor	MARKETED IN US, EU, JP CASPIAN (±tremelimumab + platinum-based chemotherapy, ▲ +)			
		ADRIATIC (+ Tremelimumab, ▲)	LUMINANCE (+ platinum chemo + etoposide)		
3. Cosela (Trilaciclib) Genentech	Oral Cyclin dependent kinase inhibitor	MARKETED IN US, EU, JP		MARKETED IN US, EU, JP NCT02514447 (SA, ▲ +)	
		NCT02499770 (+ Etoposide + Carboplatin, ▲ +)	NCT03041311 (+ Carboplatin + etoposide + atezolizumab, ▲ +)		
4. Zepzelca (Lurbinectidin) Jazz Pharmaceuticals	IV Alkylating agents	IMforte (+ Atezolizumab, ▲)		MARKETED IN US NCT02454972 (SA, ▲ +)	
				LAGOON (SA/ + Irinotecan, ▲)	

Table 4.1.a)

Competitive Heat Map for Current & Emerging Therapies in SCLC

Marketed, registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/2)

Agent	ROA and MOA	1st Line			2nd Line	3rd line and Beyond
5. Keytruda (Pembrolizumab) Merck	IV PD-1 inhibitor	KEYLYNK-013 (+ Olaparib, ▲)	REACTION (+ Chemo, ▲, +)	KEYNOTE-604 (+ Etoposide, ▲ +)		
6. Opdivo (Nivolumab) BMS	IV PD-1 inhibitor				CheckMate331 (SA, ▲, ⊘)	
					CheckMate 451 (+ Ipilimumab, ▲, ⊘)	
7. Barasertib AZ	IV Aurora kinase B inhibitors	TAZMAN (+ Durvalumab)				
8. Ociperlimab BeiGene	IV TIGIT protein inhibitors	Phase II (+ Tislelizumab + Chemo, ▲)				

Table 4.1.b)

Competitive timeline

- The purpose of the analysis is to guide the clients on the events that may impact their ability to compete in their market over time
- These events can include new product launches as well as the release of new trial data or approvals for currently approved products
- Therapies that have previously been approved as any line of therapy for the disease are included in this.
- PCD, Registration-seeking status, or FDA Breakthrough / Fast Track designation therapies are used to calculate timelines.

Competitive Timeline for Current & Emerging Therapies in SCLC

Registration-seeking, or FDA Breakthrough / Fast Track designation therapies (1/2)

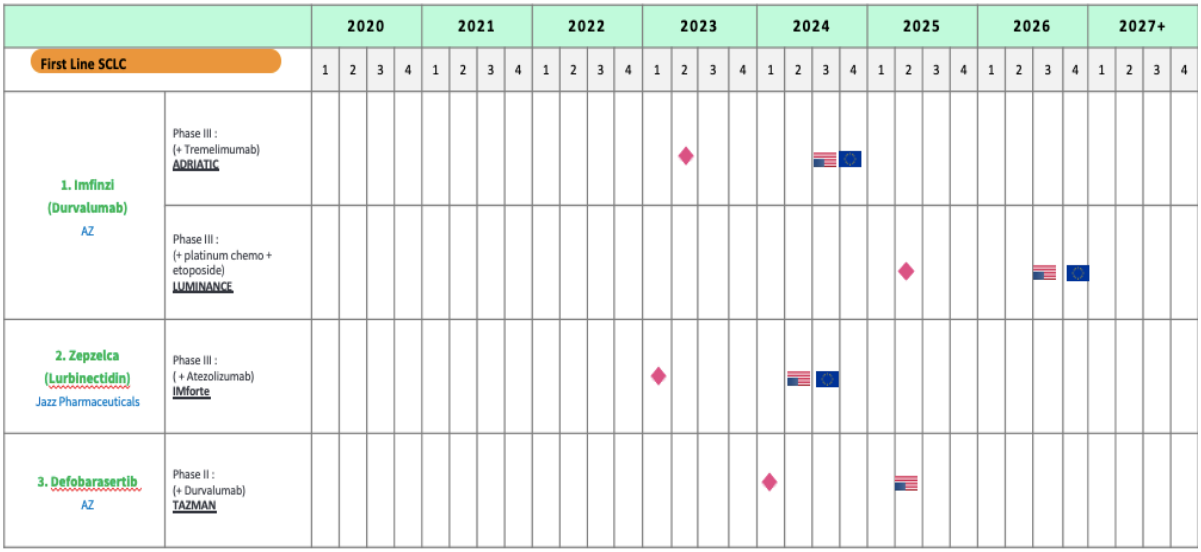

Table 4.2

Competitive Timeline for Current & Emerging Therapies in SCLC

Registration-seeking, or FDA Breakthrough / Fast Track designation therapies (2/2)

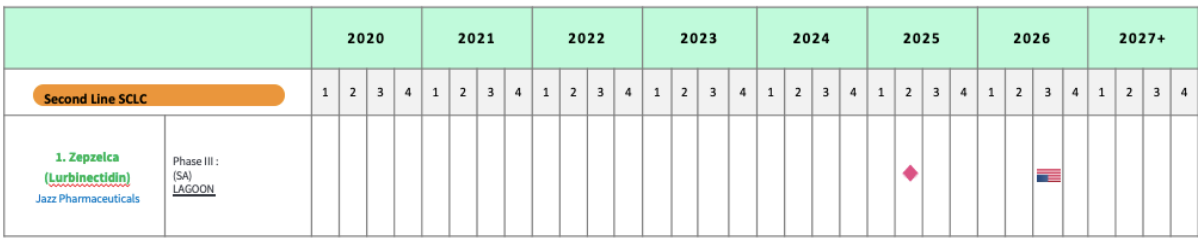

Table 4.3

Potential Upcoming therapies

- Potential therapies are emerging therapies that include trials that have no special designations such as FTD or BTD, have no results, and are present in the company pipeline as a company asset like Pembrolizumab/Vibostolimab, RRx-001, Tarlatamab and BMS-986012.

Other Potential Upcoming Therapies

Product	Interventional Arms	Company	Disease Area	LoT	Developmental Phase	MoA	Trial ID
Pembrolizumab/Vibostolimab	**Experimental:** Pembrolizumab/Vibostolimab; **Active Comparator:** Atezolizumab	Merck Sharp & Dohme Corp.	Extensive-Stage Small Cell Lung Cancer	1L	Phase 3	PD-1 inhibitor	KEYVIBE-008 NCT05224141
RRx-001	**Experimental:** RRx-001 + eLOOP Device; **Active Comparator:** Cisplatin/carboplatin plus etoposide;	EpicentRx, Inc.	Small Cell Lung Cancer	3L/ 3L+	Phase 3	anti-CD47-SIRPα	(REPLATINUM) NCT03699956
Tarlatamab	**Experimental:** Part 1: Tarlatamab Low Dose; **Experimental:** Part 1: Tarlatamab High Dose; **Experimental:** Part 2: Dose Expansion	Amgen	Relapsed/Refractory Small Cell Lung Cancer	2L/ 2L+	Phase 2	DLL3-targeting HLE BiTE® immune therapy	(DeLLphi-301) NCT05060016
BMS-986012	**Experimental:** Arm A: Carboplatin + Etoposide + Nivolumab + BMS-986012; **Experimental:** Arm B: Carboplatin + Etoposide + Nivolumab	Bristol-Myers Squibb	Extensive-stage Small Cell Lung Cancer	1L	Phase 2	Fucosyl GM1 ganglioside inhibitors	NCT04702880

Table 4.4

Emerging Treatment Algorithm Overview for SCLC

- Assets included as **'Emerging Therapies'** fulfill the following criteria:
  - Therapies that are not previously approved as any line of therapy for the disease **AND**
  - Therapies that have an active Phase 2 or Phase 3 trial that is registration-directed **OR**
  - Therapies that have an FDA breakthrough or fast-track designation

➢ When SCLC is diagnosed it can present as either in limited-stage or in extensive-stage. In limited-stage disease the tumour is confined to the lung whereas in extensive-stage disease tumour cells are spread to other parts of the body.

Note:

➢ Performance Score: The PS describes the current state of symptoms and functions in terms of ambulatory status and the need for care. PS 0 indicates normal activity, PS 1 indicates some symptoms but is still near fully ambulatory, PS 2 indicates less than 50%, PS 3 indicates more than 50% of daytime in bed, and PS 4 indicates completely bedridden.

➢ Prophylactic cranial irradiation: Radiation therapy to the head to reduce the risk that cancer will spread to the brain.

Limited stage SCLC

There are 3 stages:

- Stage I
- Stage II
- Stage III

  - If the tumour is small enough in stage I or II, surgical treatment or resection is recommended. In the event that the tumour returns after surgery, adjuvant cisplatin-etoposide (4 cycles) is administered.
  - In stage III, a tumour that has grown in size is treated with chemoradiation therapy to shrink the size of the tumour before surgical treatment is considered.
  - If the performance score is 0-1 and age is ≤70 Prophylactic cranial irradiation is done along with treatment with the following medications.
    - Durvalumab + Tremelimumab/ Durvalumab (ADRIATIC)
    - Pembrolizumab + Olaparib (KEYLYNK-013)
    - Atezolizumab (ACHILES)

- If the Performance score is 2 and the age ≤70 Prophylactic cranial irradiation is done

- If Age is >70 or frail Shared decision-making for Prophylactic cranial irradiation is done

Key Takeaways

- The success of introducing immune checkpoint inhibition with durvalumab as consolidation therapy after CRT for NSCLC has fostered an interest in this approach in limited-stage
- The combination of pembrolizumab and Olaparib is also being studied in newly diagnosed patients in this setting
- The Norwegian University of Science and Technology is currently running a clinical trial to study whether atezolizumab prolongs survival in LD SCLC patients who have undergone chemo-radiotherapy, while the National Cancer Institute is studying the effects of adding atezolizumab to the usual CRT therapy for the treatment of limited-stage SCLC

Emerging Treatment Algorithm Overview for SCLC (1/3)

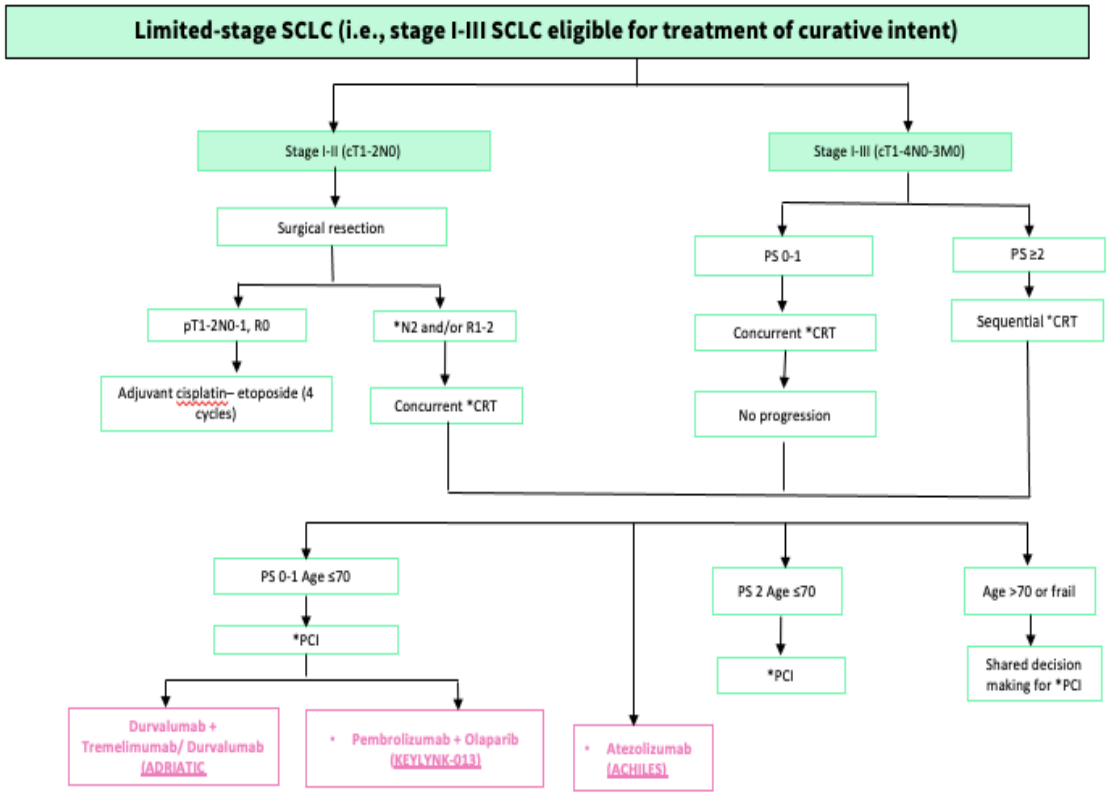

Figure 4.1

Extensive-stage SCLC

- In extensive stage SCLC performance score is measured. Depending upon the score the treatment modalities are set.

- If PS is 0 to 1 and there are no contraindication for immunotherapy current treatment is
- Carboplatin–etoposide– atezolizumab (4 cycles) and maintenance atezolizumab Platinum–etoposide– durvalumab (4 cycles) and maintenance durvalumab
-
- If PS is 0 to 1 and there are no contraindication for immunotherapy options for future treatment may be considered.
    - Atezolizumab + Lurbinectidin (Imforte)
    - Atezolizumab+ tiragolumab (SKYSCRAPER-02)
    - BMS 986012 + Carboplatin + Etoposide + Nivolumab NCT04702880
    - Durvalumab + AZD2811(TAZMAN)
    - Ipilimumab + Nivolumab (CheckMate 451)

- If PS is between 0 to 1 and there are contraindications for immunotherapy

    - Carboplatin–etoposide 4-6 cycles Carboplatin–oral topotecan Cisplatin–irinotecan

- In response to the treatment if the PS is 0 to 2 Consolidation thoracic radiotherapy is an option

- If the patient is aged and PS score is between 0-2 prophylactic cranial irradiation or magnetic resonance imaging surveillance is done

- If PS is ≥2 due to SCLC then treatment will be Carboplatin–etoposide 4-6 cycles Carboplatin–gemcitabine 4-6 cycles

- If the PS response is 0-2 below options for future treatment may be considered.
    - Atezolizumab +Carboplatin + etoposide (MAURIS)
    - Durvalumab + cisplatin or carboplatin + etoposide (LUMINANCE)
    - Durvalumab + platinum etoposide(CANTABRICO)

- If the Ps score is ≥2 due to comorbidities best supportive care is the choice of treatment

Key Takeaways

- Lurbinectedin's combination with atezolizumab is being looked at carefully in the extensive-stage SCLC maintenance setting
- Atezolizumab is also under investigation in combination with carboplatin and etoposide to test its safety and efficacy in patients with untreated extensive-stage SCLC
- AstraZeneca is studying the combination of durvalumab and etoposide along with platinum-based chemotherapy in extensive-stage SCLC, with the LUMINANCE trial being conducted in North America, Europe, and Turkey

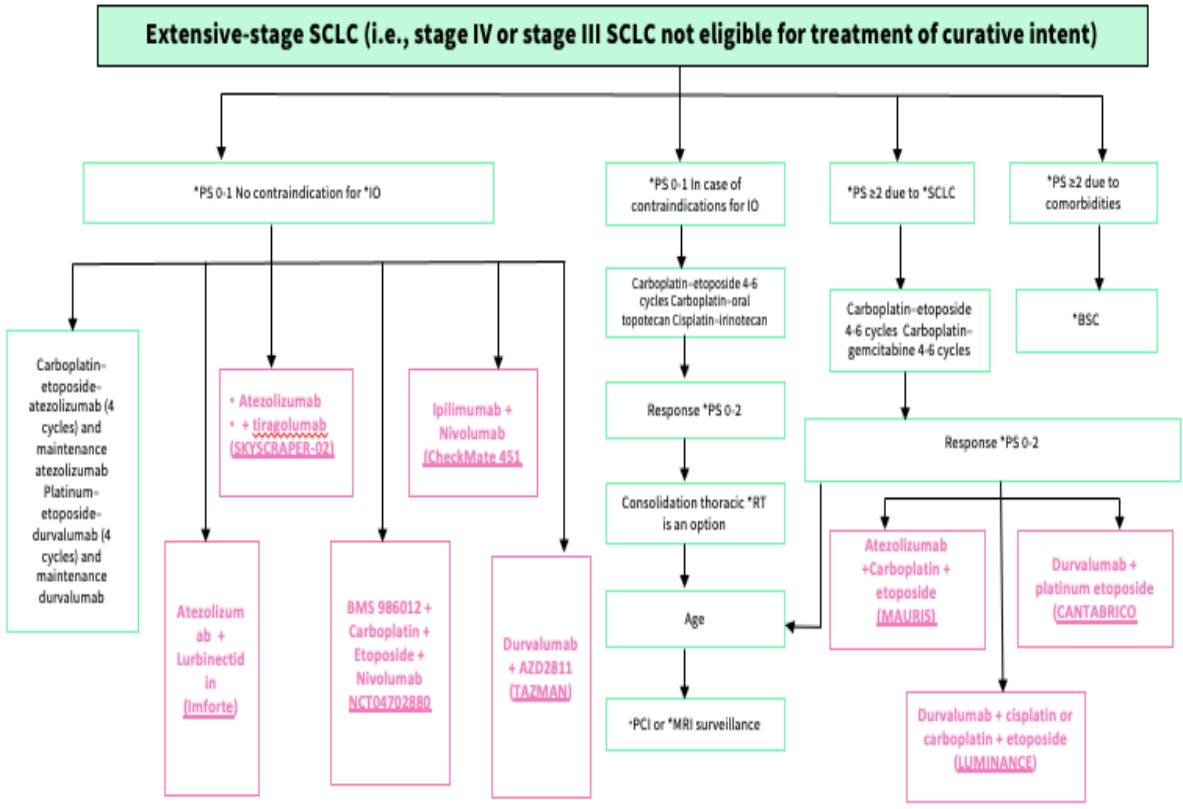

Figure 4.2

Recurrent SCLC

- Recurrent SCLC compromise of second-line treatment or beyond
- Treatment choices are constrained in cases of platinum resistance and relapse.
- In case of Refractory and/or PS >2
    - BSC Lurbinectedin is the current treatment
    - Durvalumab with Tremelimumab (NCT02937818) option for future treatment may be considered.
- In case of PS 0-2 treatment option are
    - Oral or *i.v topotecan
    - Cyclofosfamide– doxorubicin – vincristine
    - Lurbinectedin

    - 2 more Emerging treatment may be considered
        1. RRx-001 + Cisplatin /carboplatin + etoposide (REPLATINUM)
        2. Tarlatamab monotherapy (DeLLphi-301)
- In case of Platinum-sensitive relapse (≥3 months *TFI) treatment options are:
    - Rechallenge with platinum– etoposide Oral or i.v topotecan
    - Cyclofosfamide –doxorubicin– vincristine
    - Oral or i.v topotecan
    - Cyclofosfamide– doxorubicin – vincristine
    - Lurbinectedin

Key takeaways

- EpicentRx, has a CyNRGY platform, which is led by their first-in-class investigational treatment sourced from a portfolio of aerospace-derived small molecules and is being studied in a 3L+ setting for patients with SCLC
- Tarlatamab, a DLL3-targeting HLE BiTE® immune therapy, is being studied in a phase II trial in patients with relapsed/refractory SCLC after two or more prior lines of treatment
- AstraZeneca, is studying the combination of durvalumab and tremelimumab, in platinum refractory extensive stage SCLC

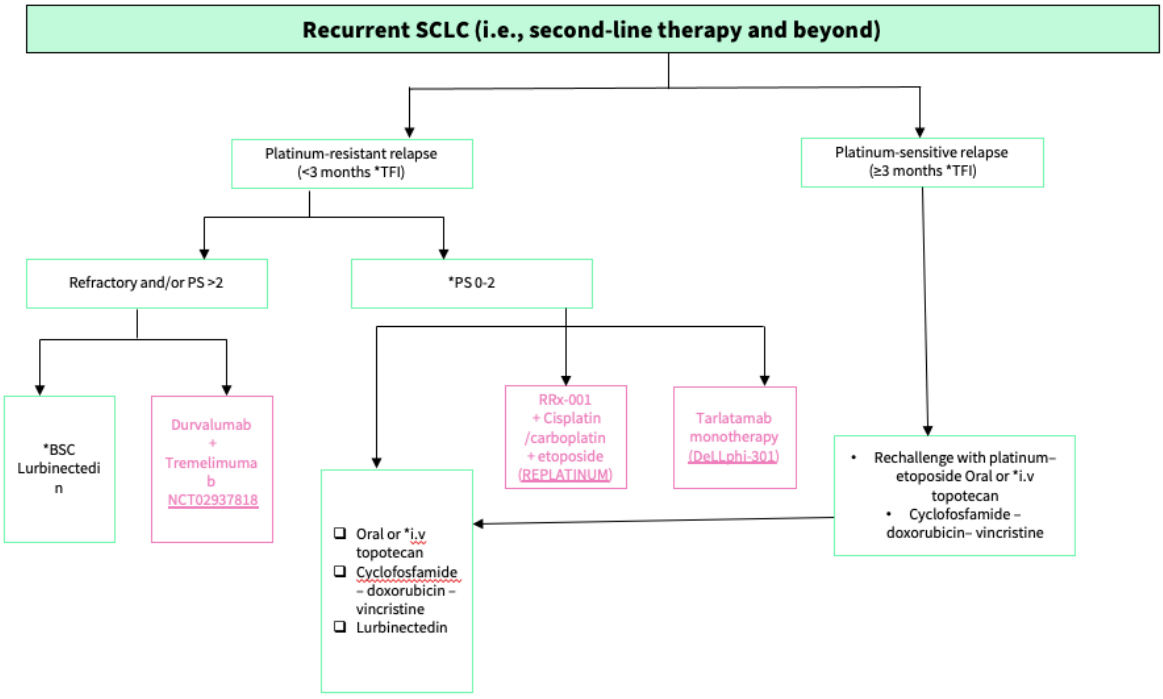

Figure 4.3

Benchmark

Trials for approved molecules in combination with newer molecules in the first and second line for emerging therapies for SCLC treatment are included.

- First line Benchmark trials include **TECENTRIQ**, **IMFINZI®** and **COSELA**
- Second line Benchmark trials include **Zepzelca** and **COSELA**

Current Clinical Benchmarks

Marketed Products – Small Cell Lung Cancer

First Line SCLC	Trial Description	Efficacy		Safety
TECENTRIQ (Atezolizumab) PD-1 inhibitor Patients With Untreated Extensive-Stage Small Cell Lung Cancer	**IMpower133** (N= 403)	**Tecentriq (n = 201)** Median OS= 12.3 months Median PFS=5.2 months Median DOR= 4.2 months	**Comparator arm (n=202)** Median OS= 10.3months Median PFS=4.3 months Median DOR= 3.9 months	Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, respiratory failure, neutropenia, and death
IMFINZI® (durvalumab) PD-1 inhibitor Patients With Extensive Disease Small-Cell Lung Cancer	**CASPIAN** (N= 978)	**Imfinzi (n=268)** Median PFS = 5.1 months Median OS= 10·4 months ORR = 68%	**Placebo (n=269)** Median PFS= 5.4 months Median OS = 10·5 months ORR = 58%	Any-cause serious adverse events were reported in the durvalumab plus tremelimumab plus platinum-etoposide group, 85 (32%) in the durvalumab plus platinum-etoposide group, and 97 (36%) in the platinum-etoposide group
COSELA (Trilaciclib) Cyclin-dependent kinase 4 and 6 inhibitors Untreated Extensive Stage Small Cell Lung	**NCT03041311** (N=107)	**Cosela (n=54)** No of patients with neutropenia: 1 No of patients with RBC transfusion after 5 weeks: 7	**Placebo** (n=53) No of patients with neutropenia: 26 No of patients with RBC transfusion after 5 weeks: 11	Nineteen percent of patients receiving COSELA had Grade 3 or 4 decreased hemoglobin compared with 28% of patients receiving placebo
	NCT02499770 (N=77)	**Cosela** (n=39) Number of patients with severe neutropenia=2	**Placebo** (n=38) Number of patients with severe neutropenia=16	Ten percent of patients receiving COSELA had Grade 3 or 4 decreased hemoglobin compared with 18% of patients receiving placebo

Second Line SCLC	Trial Description	Efficacy			Safety
Zepzelca (Lurbinectidin) Alkylating agents Patients With Selected Advanced Solid Tumors	**NCT02454972** (N=345)	**Zepzelca (n=105)** ORR: 35% mDOR: 5.3 months	**Zepzelca CTFI < 90 days (n=45)** ORR: 22% mDOR: 4.7 months	**Zepzelca CTFI > 90 days (n=60)** ORR: 45% mDOR: 6.2 months	Permanent discontinuation due to an adverse reaction occurred in 1.9% of patients with SCLC. Most adverse reactions were Grade 1 or 2
COSELA (Trilaciclib) Cyclin-dependent kinase 4 and 6 inhibitors **Untreated Extensive Stage Small Cell Lung**	**NCT02514447** (N=61)	**Cosela (n=32)** DSN (days): mean (SD)= 2 (3.9) Number (%) of patients with severe neutropenia= 13 (40.6%)	**Placebo (n=29)** DSN (days): mean (SD)= 7 (6.2) Number (%) of patients with severe neutropenia= 22 (75.9%)		Thirty-eight percent of patients receiving COSELA had Grade 3 or 4 decreased hemoglobin compared with 59% of patients receiving placebo

Table 4.5

CHAPTER-5
Disscusion

- The preliminary understanding of the undertaken research suggested that the treatment of small cell lung cancer (SCLC) is characterized by a significant level of clinical unmet need and is a disease area that has suffered from a high rate of late-stage clinical trial failure, resulting in a lack of targeted treatment option which is, to some extent, based on the limited underlying understanding of SCLC biology.
- The open-source data available aided in the identification of the epidemiology of the disease to understand the extent and probability of wide-spreading, risk factors, available treatments, and unmet needs. Hence, it directed the research toward the two major goals - the identification of potential upcoming therapies and the competitive timeline.

Chapter- 6
Conclusion

- The potential upcoming therapies treatment paradigm was promising and included a multitude of molecules that are currently under later development phases.
- It was evident that the current R&D efforts are not limited to a single stage of disease and were rather distributed in early as well as later stages
- The most optimistic treatment and combinations were durvalumab + tremelimumab, pembrolizumab + olaparib, and atezolizumab in stage I-III SCLC. In the extensive-stage SCLC, atezolizumab, durvalumab, and ipilumab combinations with the standard of care chemotherapy were evident. Lastly, in the recurrent SCLC, durvalumab + tremelimumab, RRs-001 + SoC, and tarlatamb monotherapy were the major ones.

Chapter-7
Recommedations

- The research can support potential players in the market to identify the most suitable time for planning their launch in order to have minimum competitors and maximum market share

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Annexure

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