VIOLA ADVISORY

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3Q19 Competitive Positioning in Hematologic Cancer: Lymphoma

TABLE 1: Key Biotech/Pharma Companies in Lymphoma – Key Valuation Metrics

Mkt. Cap (US$)		Mkt. Price 11/22/19	Fwd P/E	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
260.1B	RHHBY	38.07	13.9	23.6%	Buy	40.00	1%	6%
217.5B	MRK	85.45	15.1	13.0%	Buy	93.00	1%	14%
212.1B	PFE	38.33	14.0	-11.4%	Buy	41.00	21%	8%
204.7B	NVS	90.48	15.8	7.6%	Buy	98.00	5%	8%
137.1B	AMGN	230.74	14.5	20.2%	Buy	235.00	0%	2%
132.3B	BMY	56.45	9.0	7.7%	Buy	60.00	5%	14%
127.3B	ABBV	86.05	8.7	-3.6%	Buy	91.00	10%	7%
125.4B	AZN	47.97	22.7	26.9%	Buy	50.00	3%	4%
111.6B	LLY	116.20	17.7	1.1%	Buy	122.00	14%	7%
82.6B	GILD	65.26	9.4	2.9%	Buy	70.00	12%	7%

Source: Yahoo Finance, Ycharts.com, Viola Advisory LLC

Summary: **The arrival of new cancer drugs that introduce new treatment modalities from targeted therapies, to immunotherapy to cell and gene therapy is changing the current treatment paradigm across the hematologic cancer landscape, providing more treatment options to patients and practitioners. More importantly, the new drugs give optimism to patients in the advanced setting who previously had limited treatment options. New developments are also causing shifts in the hematologic cancer market as companies adapt to the evolving treatment paradigm. In this report, we examine how novel therapeutics in Non-Hodgkin lymphoma are bringing changes to treatment practices in the clinic as well as which market participants are gaining or losing share in the lymphoma market.**

5. Key Treatment Updates in Follicular lymphoma (FL)
6. Key Treatment Updates in Chronic lymphocytic leukemia (CLL)

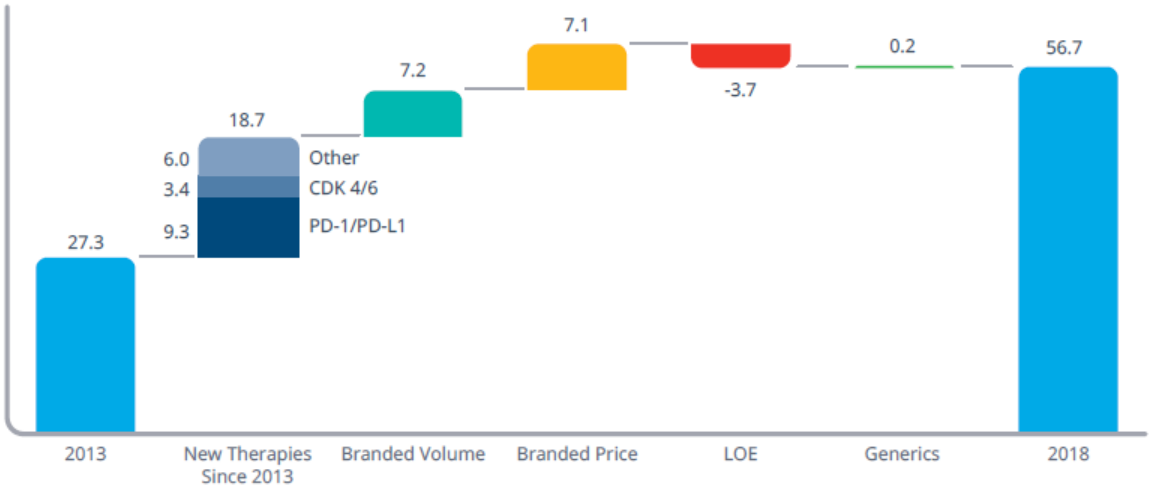
IV. Competitive Positioning in Hematologic Cancer – Lymphoma Market
   A. Lymphoma Market: Market Participants, Annual Sales and Y/Y Growth Rates
   B. Lymphoma Market: Share Gainers and Losers

I. Novel Cancer Therapeutics Drive Rapid Growth of Cancer Drug Spending

A. Rapid Growth of Cancer Drug Spending in the US: 2013 to 2018

Spending on cancer drugs in the U.S. has more than doubled since 2013, growing from $27.3 billion in 2013 to almost $57 billion in 2018 (see Figure 1). Around 64% of the growth came from the use of drugs launched within the past five years.

FIGURE 1: U.S. Spending on Cancer Drugs, 2013 – 2018 (US$B)



Note: LOE (loss of exclusivity) is defined as the growth for branded products after they lose exclusivity, usually after patent expiry.

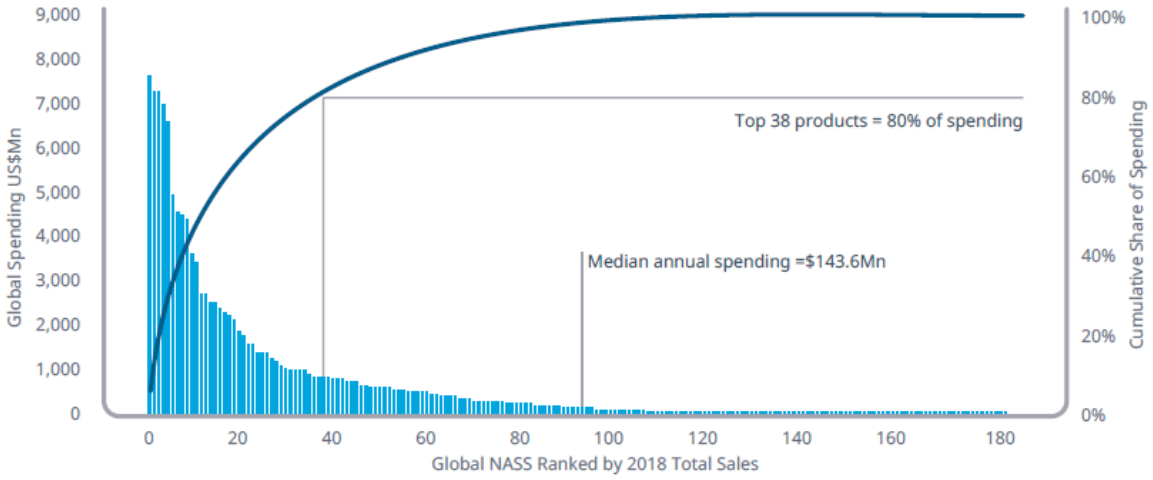
Source: IQVIA Institute, Dec. 2018

About 33% of the growth in oncology costs in the U.S. came from the uptake of innovative medicines launched since 2013. The largest spending growth of new therapies came from PD-1 and PD-L1 inhibitors, a new class of cancer drugs belonging to the immunotherapy group. All together, these therapies accounted for $9.3 billion while the CDK4/6 inhibitors for breast cancer contributed another $3.4 billion. The loss of patent exclusivity for some older brands contributed to $3.7 billion in lower brand costs.

B. Spending on Cancer medicines is highly concentrated

The top 38 cancer therapies accounted for around 80% of total spending in the cancer drug market (see Figure 2). Meanwhile, over half of cancer drugs have less than $143.6 million in annual sales. Those products with less than $143.6 million in sales accounted for only 2.2% of oncology spending, as they are often older and available as generics at lower costs.

FIGURE 2: Global Markets: Number of Oncologic Medicines Available and Average Spend per Product



Source: IQVIA Institute, Dec. 2018

Cancer medicines with the highest spending are used widely across countries. They are generally newer brands and often have multiple approved indications. Of the cancer medicines in use around the world, around 84% generated less than $1 billion per year for the companies that produce them and 70% made less than $500 million in 2018.

II. Solid Tumors vs. Hematologic Cancers

A. Incidence Rates: Solid Tumors vs. Hematologic Cancers

Solid tumors have much higher incidence rates compared to hematologic cancers. For example, within males, prostate and lung cancers accounted for 19% and 14% of new cancer cases respectively in 2018. Non-Hodgkin lymphoma and leukemia accounted for 5% and 4% of new cancer cases for males in 2018 (see Figure 3).

FIGURE 3: Estimated Number of New Cases in 2018 by Tumor Site, (by Gender)

Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	**856,370**	**100%**	**All sites**	**878,980**	**100%**

Note: Estimated new cases for Multiple Myeloma for both male and female is around 2% in 2018.

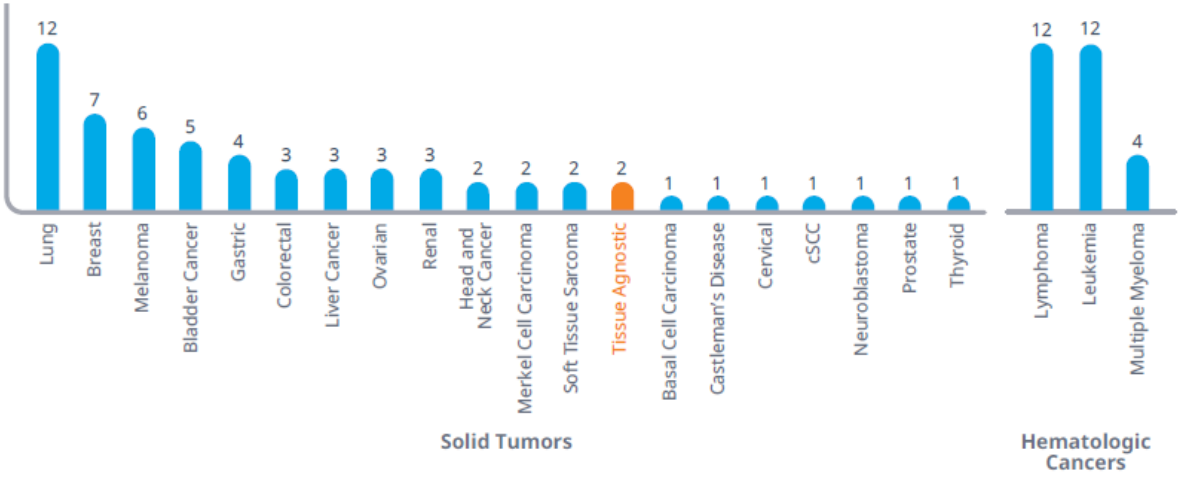
Source: Cancer Facts & Figures 2018, American Cancer Society

Within females, breast cancer and lung & bronchus cancer accounted for 30% and 13% of new cases respectively in 2018. Non-Hodgkin lymphoma and leukemia accounted for 4% and 3% of new cancer cases for females in 2018.

B. Large Number of Drug Approvals in Hematologic Cancers

Despite the lower incidence rate, roughly 31% of approved indications over the last 5 years were for hematologic cancers. Within this time period, 10 drugs receiving 12 indication approvals were for lymphoma (see Figure 4).

FIGURE 4: Number of New Active Substance Approvals in Oncology by Indication



Source: IQVIA Institute, April 2019

Lung cancer had the highest number of new indications approved for NASs in 2014-2018, with 12 new indications, followed by breast cancer with seven approvals. In addition, many approvals for drugs in cancers such as lung, breast and leukemia received subsequent approvals for mutation-specific types of these tumors, for example, a subsequent approval for ALK positive non-small cell lung cancer (NSCLC) after a primary approval for NSCLC. In 2018, larotrectinib became the second tissue agnostic oncology therapy to be approved following the subsequent approval of pembrolizumab for this indication in 2017.

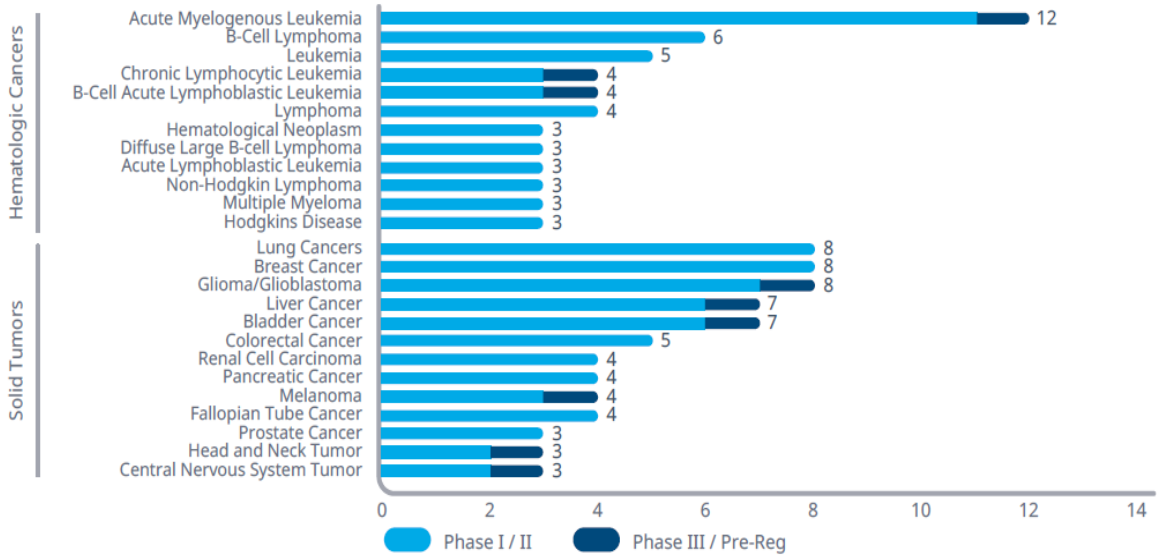
C. The Search for Molecular Targets and Mechanisms of Action

Precision medicine and targeted therapies involve looking for specific molecular targets and pathways. In total, the immuno-oncology (I/O) pipeline in 2018 included 43 cancer types, including solid tumor, metastasis and general cancer. The subset of the top 25 cancer types includes 52 separate mechanisms of action (see Figure 5 below).

Within the top 25 tumor types, almost half are hematologic cancers with acute myelogenous leukemia accounting for products with 12 separate next-generation mechanisms such as INDO inhibitors, OX-40 receptor agonists and CD33 modulators. I/O mechanisms are demonstrating benefits across both solid tumors and hematologic cancers which was generally not the case in earlier generations of oncologic treatments.

The PD-1/PD-L1 drug class accounted for 14 different tumor types across hematologic and solid cancers. This drug class remains the mainstay of the immune checkpoint inhibitors. B-lymphocyte antigen CD19 inhibitors account for 12 different types of tumors with CD19 being the antigen construct in currently available CAR-T therapies.

FIGURE 5: Top 25 Cancers and the Number of Mechanisms Targeting Each, Phase I Through Pre-Registration



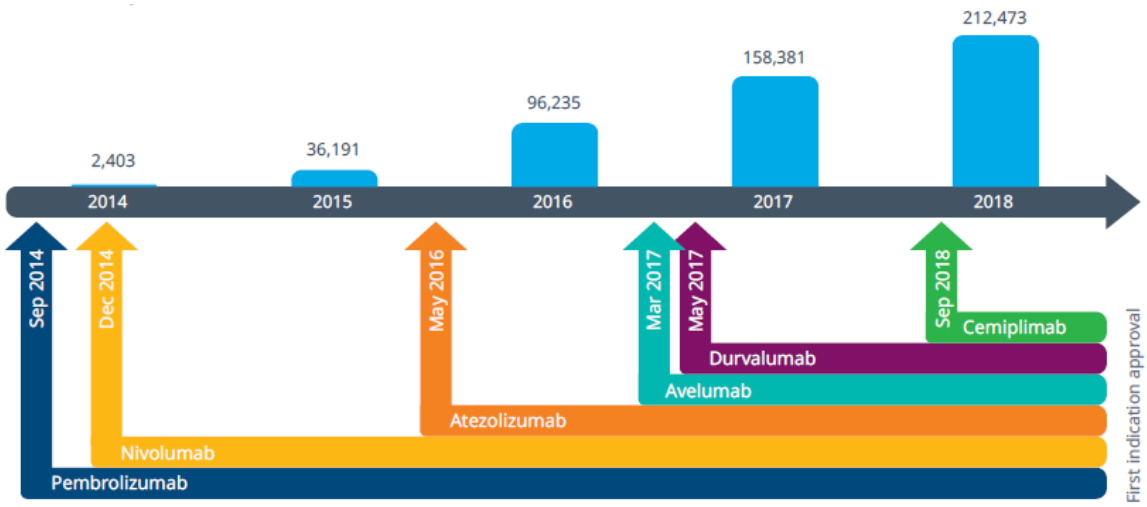
Source: Clarivate Analytics Cortellis, Feb. 2019 and IQVIA Institute, March 2019

D. Rapid Growth of Patients receiving Checkpoint Inhibitors

The introduction of PD-1 and PD-L1 checkpoint inhibitors over the past five years has dramatically improved outcomes for patients with a wide range of solid tumors. These drugs work by using the patient's own immune system that is otherwise inhibited or impaired in its ability to identify and target cancer cells.

The number of treated patients using one of these agents has more than doubled in the past two years, largely focused on the two earliest approved agents which have the widest range of approved uses and together account for more than 90% of the treated patients (see Figure 6).

FIGURE 6: Unique Patients treated with PD-1 and PD-L1, United States, 2014 - 2018



Source: IQVIA Real World Evidence, Medical Claims, Dec. 2018

More than 200,000 patients were treated during 2018, up from 2,403 in 2014 when pembrolizumab became the first approved drug of this type to launch in September 2014. There have been dozens of indications approved for these medicines since that time, but together they represent some of the most advanced types of treatments available to patients with cancer.

III. Overview of Hematologic Cancer

A. Hematologic Cancer: Market Concentration, Size and Growth Rate

The hematologic cancer market is segmented into 3 market sub-types – leukemia, lymphoma and multiple myeloma. The largest market in terms of the number of market participants is the lymphoma market with 17 companies. In terms of revenue, the lymphoma market had total sales of $13.1 billion with a 13% y/y growth rate as of 2018 (see Table 2).

TABLE 2: Hematologic Cancer: Market Size, No. of Companies and Y/Y Growth (by Sub-Type)

Sub-Type	No. of Companies	Mkt. Size (US$M) 2017	Mkt. Size (US$M) 2018	Y/Y Growth (%) 2017	Y/Y Growth (%) 2018
Leukemia	10	4,491	4,369	-1%	16%
Lymphoma	17	11,572	13,131	12%	13%
Multiple Myeloma	7	12,529	15,536	26%	24%

Source: Viola Advisory Oncology Database

The multiple myeloma market has the highest market concentration with only 7 market participants and sales of $15.5 billion in 2018. Of the three market sub-types, multiple myeloma also had the highest growth rate with 24% y/y growth in 2018.

The leukemia market is the least concentrated market with 10 market participants and total sales of $4.3 billion in 2018 (roughly one-third the size of the lymphoma market.) Sales in the leukemia market declined by 1% y/y in 2017 but rebounded in 2018 with the market growing at a pace of 16% y/y.

B. Hematologic Cancer: Prevalence and 5-Year Survival Rates (by Sub-Type)

The majority of leukemias, lymphomas and other blood cancers diagnosed are of B-cell origin. B-cells (or B lymphocytes) are a type of white blood cell (WBC) that is made in the bone marrow and found in the blood and lymph tissue. White blood cells are part of the immune system that help the body fight infection and other diseases. However, B-cells seem to be more prone to mutation (i.e., becoming cancerous) than other white blood cells as they go through the process of maturing and becoming a fully functional B-cell.

For example, an immature WBC that has just begun to specialize to become a myeloid cell might give rise to acute myeloid leukemia (AML). Whereas, if a fully mature B-cell living in a lymph node goes wrong, it's likely to cause a non-Hodgkin lymphoma (NHL). There are many different types of blood cancer. Table 3 summarizes the most important types of hematological cancer, their estimated annual new cases in 2018 and their 5-year survival rates.

TABLE 3: Hematologic Cancer: New Cases and 5-Yr. Survival rates (by Sub-Type, both genders, US, 2018)

Indication	Estimated New Cases	% of Total	5-Yr. Survival
Lymphoma	83,180	100%	--
- Hodgkin Lymphoma (HL)	8,500	10%	88%
- Non-Hodgkin Lymphoma (NHL)	74,680	90%	73%
Multiple Myeloma (MM)	30,770	100%	51%
Leukemia	60,300	100%	--
- Acute lymphocytic leukemia (ALL)	5,960	10%	15%
- Chronic lymphocytic leukemia (CLL)	20,940	35%	70% - 75%
- Acute myeloid leukemia (AML)	19,520	32%	5%
- Chronic myeloid leukemia (CML)	8,430	14%	90%
- Other leukemia	5,450	9%	--

Source: Cancer Facts & Figures 2018, American Cancer Society

The most prevalent type of blood cancer is lymphoma with an estimated 83,180 new cases in 2018. This is followed by leukemia with 60,300 new cases and multiple myeloma with 30,770 new cases in 2018. In terms of 5-year survival rate, the prognosis for Hodgkin Lymphoma is at 88%. Improvements in treatment mean that about 85% of people now survive for at least 5 years after diagnosis. For other diseases, such as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML) and certain aggressive forms of NHL, the outlook for patients is bleaker.

The most common form of lymphoma is non-Hodgkin Lymphoma which makes up about 90% of the disease. There are over 60 different types of non-Hodgkin Lymphoma. These cancers develop in the lymph nodes or other lymph tissues; the cancer can therefore occur almost anywhere in the body. Table 4 shows the various sub-types of NHL by percent of total and their 5-year survival rates.

TABLE 4: Non-Hodgkin Lymphoma Sub-types (by % Total and 5-year survival rate)

Non-Hodgkin Lymphoma sub-type:	% Total	5-Yr. Survival
- Diffuse large B-cell lymphoma (DLBCL)	30%	60%
- Follicular lymphoma (FL)	20%	87%
- Mantle cell lymphoma (MCL)	5% - 7%	40%
- Small lymphocytic lymphoma (SLL)	5%	n/a
- Nodal marginal zone B-cell lymphoma	1%	78%
- Lymphoplasmacytic lymphoma	1%	n/a

Source: Cancer.net (accessed 11/17/19) and Vickers, E., "A Beginner's Guide to Targeted Cancer Treatments", Wiley Blackwell, 2018.

The most prevalent form of NHL is diffuse large B-cell lymphoma (DLBCL) comprising about 30% of total NHL cases. The second most common form of NHL is follicular lymphoma (FL) which makes up around 20% of total NHL cases. This is followed by mantle cell lymphoma (MCL) with around 7% of total NHL. DLBCL is an aggressive disease with a 5-year survival rate of around 60%. Aggressive cancers are fast growing and would cause death quickly if left untreated. The most common age to be diagnosed with DLBCL is around 60.

In contrast, follicular lymphoma (FL) is an indolent disease with a 5-year survival rate of around 87%. Indolent cancers (also described as low-grade or chronic) tend to develop very slowly. A person may have a chronic leukemia or indolent lymphoma for months or years without having many symptoms. And it may be many months or years before their disease gets worse and needs aggressive treatment. Mantle cell lymphoma (MCL) is the third most common NHL sub-type. MCL can have features of both indolent and aggressive lymphomas. It mostly affects men over 50 years and has a 5-year survival rate of around 40%.

C. Evolving Treatment Paradigm of Non-Hodgkin Lymphoma (NHL)

Table 5 shows how the paradigm for treating NHL has evolved over the last 20 years.

TABLE 5: Twenty Years of Drug Innovation in Non-Hodgkin Lymphoma

1999	2002	2005	2006	2011	2013
Anti-CD25:	**Anti-CD20:**	**Chemotherapies:**	**R-CHOP** approved for DLBCL	**Anti-CD30:**	**BTK inhibitors:**
Denileukin diftitox (Ontak) in CTCL	Ibritumomab Tiuxetan (Zevalin) in FL; obinutuzumab (Gazyva) in CLL in 2013	Nelarabine (Arranon) in TCL; bendamustine hydrochloride (Treanda) in CLL in 2008; pralatrexate (Folotyn) in TCL 2009	**HDAC inhibitors:** Vorinostat (Zolinza) in TCL; romidepsin (Istodax) in CTCL in 2009; belinostat (Beleodaq) in PTCL in 2014 **Proteasome inhibitor:** Bortezomib (Velcade) in PTCL	Brentuximab vedotin (Adcetris)	Ibrutinib (Imbruvica) in MCL, CLL; acalabrutinib (Calquence) in MCL in 2017 **IMiD:** Lenalidomide (Revlimid) in MCL

2014	2016	2017	2018	2019
PI3K inhibitors:	**BCL-2 inhibitor**	**CAR T-cell therapy:**	**Anti-PD-L1:**	**Anti-CD79:**
Idelalisib (Zydelib) in CLL; copanlisib (Aliqopa) in FL in 2017; duvalisib (Copiktra) in CLL/SLL in 2018	Venetoclax (Venclexta) in CLL/SLL	Axicabtagene ciloleucel (Yescarta) in B-cell lymphomas; tisagenlecleucel (Kymriah) in B-cell lymphomas in 2018	Pembrolizumab (Keytruda) in PMBCL **CCR4-directed:** Mogamulizumab-kpkc (Poteligeo) in MF/SS **Biosimilars:** Rituximab-abbs (Truxima) in FL, CD20-positive B-cell lymphomas; rituximab-pvver (Ruxience) in CLL in 2019	Polatuzumab vedotin-piiq (Polivy) in DLBCL

Note: CTCL – cutaneous T-cell lymphoma; TCL – T-cell lymphoma; PTCL – peripheral T-cell lymphoma; PMBCL – primary mediastinal large B-cell lymphoma; MF – mycosis fungoids; SS – Sezary syndrome; R-CHOP – rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IMiD – immunomodulatory drug and HDAC – Histone deacetylase.

Source: Friedberg, J.W. "Rituximab sets the pace in changing lymphoma landscape, OncologyLive, vol.20, No. 20, 10/18/19

Although the pace of advancement was slow from 1999 to 2011, it did seem to pick up over the last six years from 2013 onwards. This was due in large part to the completion of the Human Genome Project in 2003 which identified the estimated 30,000 genes in the human DNA and the sequences of their chemical bases. This enabled scientists to identify the mutated genes in cancer tumors and to develop precision medicine and highly specific targeted therapies to stem the growth of these malignant tumors.

1. R-CHOP has become the Standard of Care in NHL

When discussing therapeutic advances in lymphoma treatment, rituximab (Rituxan) frequently plays a central role. The FDA first approved rituximab in 1997 for relapsed/refractory (r/r) low-grade or follicular CD20-positive B-cell non-Hodgkin lymphoma based on results of a single-arm clinical trial that showed modest efficacy (48% overall response rate). Since its approval, rituximab has had a transformative effect on the management of B-cell lymphoma.

Results of randomized trials have since shown overall survival benefits for rituximab combined with chemotherapy in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, as well as the drug's value in treatments following stem cell transplantation. Currently, rituximab is the standard treatment of care for B-cell lymphomas.

DLBCL is the most common form of B-cell lymphoma. Although DLBCL is a hematological cancer, the cancerous B-cells do not typically circulate in the blood. Initially, they remain in the lymphatic system where tumors can become large. Once diagnosed, most patients undergo six cycles of combination immunochemotherapy known as R-CHOP. This is a cocktail of 5 drugs: four chemotherapy agents (collectively known as CHOP) and rituximab, an antibody that binds to a unique B-cell surface marker (CD20) to trigger cell death.

CHOP, by itself, has been used since the early 1990's to successfully treat about 55% of patients. The addition of rituximab in the early 2000's increased remission rates to higher than 74%. For many patients, R-CHOP is a cure that permanently removes the cancer. But for others, it either fails to lead to remission or it leads to an initial remission but is later followed by a relapse. For patients in either of those situations, the odds of survival drop considerably.

Second-line treatment is a more aggressive salvage chemotherapy, which requires removing stem cells from the patient's bone marrow and then returning them after chemotherapy so that they can form new blood cells. However, only 1 in 4 patients show a response to this treatment. At present, if a DLBCL is diagnosed at an advanced stage, the 5-year survival rate after diagnosis is 50%. For people with earlier-stage tumors, the 5-year survival rate is 65% to 70%.

2. Key Treatment Updates in Hodgkin Lymphoma (HL)

Frontline setting for advanced-stage HL: A great deal of progress has been made in this setting. A new trial was published in 2018 on the use of brentuximab vedotin (Adcetris) in combination with AVD [doxorubicin, vinblastine, and dacarbazine] compared with the traditional therapy of ABVD [doxorubicin, bleomycin, vinblastine and dacarbazine] in advanced-stage HL. The trial showed that progression-free survival (PFS) with brentuximab vedotin and AVD was superior to ABVD. But overall survival (OS) at 3 or 4 years of follow-up did not show a significant difference.

Relapsed setting of HL: In the relapsed setting, there was a large study that was published in December 2018 that looked at the use of brentuximab vedotin as consolidation therapy for patients who failed or relapsed on

standard therapy and underwent bone marrow transplant. Traditionally, the patient probably still has a 50% chance of relapse after autologous stem cell transplant (ASCT). Therefore, one of the areas under clinical investigation is to determine how long-term survival and PFS can be improved in patients with HL after bone marrow transplant.

Third-line Setting of HL: In the third-line setting, there is an immunotherapy with a PD-1 blockade. Two agents were approved by the FDA. The first was nivolumab (Opdivo) and the other was pembrolizumab (Keytruda). Both agents showed significant activity in patients who relapsed after ASCT or who were on second-line therapy. Both agents have similar efficacy and toxicity profiles. The complete response (CR) rate as monotherapy for both agents ranged from 20% to 25%; the overall response rate (ORR) was around 70% with about a 50% partial response rate.

A third study also showed that by combining brentuximab vedotin with nivolumab, the CR rate as well as duration of response and PFS were further improved. Moreover, the toxicity profile of the combination was manageable. Currently, there is also a clinical trial ongoing for an anti-CD30 CAR T-cell product. There are several trials available to patients with HL who are interested in the use of CAR T-cell therapy.

3. Key Treatment Updates in diffuse large B-cell lymphoma (DLBCL)

Over the last 20 years, several Phase 3 trials have been completed to improve the outcomes of patients with DLBCL. Several agents were tested but none of them were able to beat R-CHOP. One trial evaluated R-CHOP in combination with ibrutinib (Imbruvica) in activated B-cell (ABC) DLBCL in a large trial. The study did not show any PFS or OS benefit when ibrutinib was added to R-CHOP, even in ABC DLBCL.

In February 2019, Celgene announced the Phase 3 trial of lenalidomide combined with R-CHOP. Unfortunately, it did not meet the primary endpoint and did not show a PFS or OS benefit. Final data have not yet been published. Trial results presented by Celgene were disappointing since the two agents showed promising results in Phase 2 trials. There is a need therefore to look for more agents.

Another trial compared dose-adjusted EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab] with R-CHOP. Unfortunately, the trial showed no difference in OS benefit. There was also no significant difference in PFS for all groups.

Besides these 3 trials, other trials published about 1 or 2 years ago added other agents such as bortezomib (Velcade) to R-CHOP. However, the Phase 3 trial did not show a difference in the long-term OS. It did show a PFS benefit, but there were also toxicities.

Recent FDA approval of polatuzumab vedotin (Polivy) in r/r DLBCL

A new drug called polatuzumab vedotin (Polivy) was approved by the FDA on June 10, 2019 for use in patients with r/r DLBCL based on data from small, randomized Phase 2 trials that compared polatuzumab vedotin plus bendamustine and rituximab (BR) compared with BR alone. Each arm had 40 patients and compared with BR alone, polatuzumab vedotin plus BR seemed to be superior in terms of ORR and CR. In addition, PFS and OS were more than doubled compared with BR. The agent therefore received accelerated approval from the FDA for use in patients with relapsed/refractory DLBCL.

Polatuzumab vedotin seems very promising for DLBCL. Currently, DLBCL has an upfront therapy with R-CHOP and clinicians can also offer a CAR T-cell therapy. However, even with CAR T-cell therapy, there is only a 40% CR rate. Most patients, or half of them do not respond to or relapse after CAR T-cell therapy. For these

patients, there are very little options available. Furthermore, polatuzumab vedotin is relatively easy to administer but it comes with toxicities such as neuropathy; however, in general, it is very well tolerated when used in combination with BR.

There are also Phase 3 trials just completed that explored the use of polatuzumab vedotin in the frontline setting. Expect preliminary reports within a couple of years that could provide clinicians with insight as to whether this agent can improve outcomes for DLBCL patients in the frontline setting.

Latest Developments on CAR T-cell Therapy in DLBCL

There was also an update on CAR T-cell therapy for DLBCL in the relapsed setting. Updated data from the ZUMA trials with axicabtagene ciloleucel (axi-cel; Yescarta) were released earlier this year. At 24 months of long-term follow-up, the CR rate continues to look promising. The CR rate is 40% with an ORR of over 50%. Moreover, the OS is also improved. Yescarta was approved by the FDA for use in patients with DLBCL about 1.5 years ago. It is expected that clinicians will be looking to use more CAR T-cell products for their transplant-ineligible patients.

Data from the JULIET trial which evaluated tisagenlecleucel (Kymriah) were also published. Updated data showed a similar response rate at 12-months follow-up producing a 40% CR rate and a duration of response that was durable for patients who had a complete response.

The third trial, TRANSCEND-NHL-001 trial is evaluating lisocabtagene maraleucel (JCAR017; liso-cel). The abstract for this trial was presented a few years ago but there has not been a new update on this trial since then. An accrual for a Phase 2 trial was just completed and more data is expected to arrive for this agent.

4. Key Treatment Updates in Mantle cell lymphoma (MCL)

In r/r MCL, several data on new agents have been published. The first is ibrutinib which was approved in 2013. The other agent is a second-generation BTK inhibitor called acalabrutinib (Calquence) and it was approved by the FDA in 2017 based on Phase 2 data.

In both trials, the agents showed significant activity. No head-to-head comparison has been made with ibrutinib and acalabrutinib but it seems that acalabrutinib may have a better response rate based on these non-comparative Phase 2 trials.

In terms of overall response and toxicity, both agents seem to be active. Both came with toxicities including increased risk of bleeding and atrial fibrillation. Acalabrutinib was not reported to show a significant increase in atrial fibrillation. However, there was a slight increase of cardiac risk with ibrutinib.

Another promising agent in MCL treatment is venetoclax (Venclexta), which showed encouraging data; however, it has not yet been approved and further data are needed.

In addition to the single agents, the combination of lenalidomide plus rituximab is also being studied. One is being done in the frontline setting for patients who are now transplant candidates. At 4 to 5 years of follow-up in the small studies, responses appear to be very durable.

5. Key Treatment Updates in Follicular lymphoma (FL)

Treatment progress in follicular lymphoma has been disappointing since not much progress has been made in this space. However, several agents are under clinical investigation such as CAR T-cell therapy and Phase 2 trial data read-outs are expected.

One data read-out that is expected is on a CD22-targeted antibody-drug conjugate (ADC) that could be active for follicular lymphoma. The agent was already evaluated in a Phase 1 trial and is currently in Phase 2. It appears to be a promising drug.

In addition to the anti-CD22 ADC agent, polatuzumab vedotin has also shown to be very active in FL. A larger trial with this agent is ongoing. Beyond this, there are also PI3K inhibitors that are currently undergoing clinical trials.

6. Key Treatment Updates in Chronic lymphocytic leukemia (CLL)

The most exciting change in CLL is the substitution of chemotherapy in the upfront setting by targeted therapies such as ibrutinib (Imbruvica), acalabrutinib (Calquence), and venetoclax (Venclexta). However, younger patients with a mutated IgHV gene may still be considered for chemotherapy, but essentially practitioners think everyone else should be treated with one of these novel targeted agents.

As recently as two years ago, clinical practitioners thought there was equivalency between ibrutinib and standard chemotherapy such as fludarabine, cyclophosphamide, and rituximab (FCR), and bendamustine and rituximab (Rituxan; BR). But since the 2018 ASH Annual Meeting, clinicians now prefer ibrutinib to any chemotherapy for most patients, except for younger patients carrying the mutated IgHV gene.

The most recent update in the CLL space is the approval of obinutuzumab (Gazyva) combined with venetoclax for the upfront management of CLL. It is believed to be more advanced because unlike ibrutinib, obinutuzumab and venetoclax is a 1-year short-course duration of therapy, whereas treatment with ibrutinib is essentially indefinite.

Still, there is not much long-term data with the venetoclax/obinutuzumab combination as there is with ibrutinib. That might give patients some pause because not everyone is willing to take something that is less established in the field. However, the venetoclax/obinutuzumab combination would be a good option for patients who are looking to be on therapy for one year or less.

There is also ongoing research on new regimens that would give less chemotherapy and add more targeted therapies to boost the CR rate, which would in turn lower the minimal residual disease (MRD) to a negative rate and achieve better results than the current 6 cycles of standard FCR.

Another change in the relapsed/refractory setting is the arrival of a new class of agents such as PI3K inhibitors. So far, a third PI3K inhibitor has been approved by the FDA and is providing more options for patients.

Targeted Therapies being investigated in CLL

A targeted therapy that is currently being studied is BTK inhibitors. Studies have shown that blocking the molecules in the B-cell receptor signaling pathway has induced responses. BTK is one example of a molecule in that pathway that if blocked, will cause cancer cells to undergo apoptosis and die, thus producing therapeutic activity.

Another molecule under investigation is BCL-2 which is overexpressed in CLL cells. Inhibition and targeting of BCL-2 is very effective as seen with the responses of venetoclax (Venclexta)–based therapy. Perhaps resistance to venetoclax relates to the expression of MCL1, which is another member of the BCL-2 family. Investigators are working on strategies to target MCL1, either directly or indirectly, and evaluating those agents in clinical trials.

Another targeted molecule is PI3K, which is also an active member of that signaling pathway. When PI3K is inhibited, it has been shown to produce response and remission in therapeutic activity.

One other molecule in the B-cell receptor signaling pathway that is also being studied is Syk – a protein that has been targeted for small molecule inhibition. Despite seeing less activity on monotherapy with Syk inhibitors, investigators are nonetheless continuing to work on strategies with small molecule inhibitors on other members of the signaling pathway.

CAR T-cell Therapy being explored in CLL

CD19-directed CAR T-cell therapy is currently approved for patients with relapsed acute lymphoblastic leukemia (ALL) up to age 25 and in adults with diffuse large B-cell lymphoma that is refractory to treatment. Data have shown durable responses in those two patient categories. In CLL, CAR T-cell therapy is still investigational. TRANSCEND CLL 004 trial is a Phase 1/2 clinical trial that is ongoing with liso-cel – a CD19-directed CAR T-cell therapy that is being evaluated in patients with CLL.

In smaller single-center Phase 1 trials, reports of activity with CD19-directed CAR T-cell therapy in CLL have reported lower CR rates than seen in other diseases such as ALL. Despite showing durability, CR rates have been in the 20% to 30% range, which is relatively low compared to ALL, where the CR rate is in the 80% to 90% range.

The TRANSCEND CLL 004 study has early results which will be updated at the 2019 ASH Annual Meeting. The CR rate appears to be about 50%, which is encouraging. There is still more work that needs to be done with CD19-directed CAR T-cell therapy in CLL.

IV. Competitive Positioning in Hematologic Cancer – Lymphoma Market

A. Lymphoma Market: Market Participants, Annual Sales and Y/Y Growth Rates

We now examine the market participants in the lymphoma space. Table 6 shows who the companies are that are currently taking share and the companies that are giving up share. The data points were collected from company financial statements (SEC filings) and were consolidated into our proprietary database for further analysis. The data will be updated annually at the end of the 4Q reporting period and will comprise of annual sales figures of all FDA approved oncology drugs for that year.

TABLE 6: Lymphoma Market – Size, Growth Rate and Market Players (by US$ Million Sales, 2017 - 2018)

				Sales (US$ Million)					
Generic	**Sub-Type**	**Brand**	**Manufacturer**	**FY 2017**	**Y/Y chg.**	**% of Total**	**FY 2018**	**Y/Y chg.**	**% of Total**
ibrutinib	MCL, WM, CLL	Imbruvica	AbbVie	2,573	41%	22%	3,590	40%	27%
venetoclax	CLL	Venclexta/ Venclyxto	AbbVie+Roche (U.S.)/ AbbVie (ROW)	122	*	1%	344	*	3%
acalabrutinib	CLL, MCL	Calquence	AstraZeneca	3	--	0.0%	62	*	0.5%
copanlisib	FL	Aliqopa	Bayer	--	--	--	--	--	--
nivolumab	HL	Opdivo*	Bristol-Myers Squibb	792	31%	7%	943	19%	7%
romidepsin	PTCL, CTCL	Istodax	Celgene	76	-5%	1%	63	-17%	0.5%
chidamide	PTCL	Epidaza (China FDA approval in 2015)	Chipscreen Biosciences	--	--	--	--	--	--
idelalisib	CLL, FL, SLL	Zydelig*	Gilead Sciences	80	-13%	1%	70	-12%	1%
axicabtagene ciloleucel	DLBCL	Yescarta	Gilead Sciences	7	--	0.1%	264	*	2%
mogamulizumab	MF, SS	Poteligeo	Kyowa Hakko Kirin	--	--	--	19	--	0.1%
pembrolizumab	HL	Keytruda*	Merck & Co.	190	126%	2%	430	126%	3%
tisagenlecleucel		Kymriah	Novartis	6	--	0.1%	76	*	1%
ofatumumab	CLL	Arzerra	Genmab/Novartis	--	--	--	--	--	--
obinutuzumab	CLL, FL	Gazyva	Roche	279	41%	2%	392	40%	3%
rituximab	NHL	Rituxan (U.S.)/ MabThera (ROW)	Roche	5,862	0%	50%	5,218	-10%	40%
pixantrone	NHL	Pixuvri (acquired from CTI Biopharma on 10/3/19)	Servier Pharma	1	--	0.0%	--	--	--
brentuximab vedotin	HL, ALCL	Adcetris	Seattle Genetics/ Takeda Pharmaceutical	308	16%	3%	477	55%	4%
belinostat	PTCL	Beleodaq	Spectrum Pharmaceuticals	12	-1%	0.1%	12	-1%	0.1%
bortezomib	MCL	Velcade	Takeda Pharmaceutical	1,260	-9%	11%	1,170	-7%	9%
duvelisib	CLL, SLL, FL	Copiktra (FDA approved on 9/24/18)	Verastem Oncology	--	--	--	--	--	--
			Total	11,572	12%	100%	13,131	13%	100%

Note: *Viola Advisory sales breakdown by cancer sub-type

Source: Viola Advisory Oncology Database

B. Lymphoma Market: Share Gainers and Losers

Market Share Gainers

1. **Imbruvica (ibrutinib, AbbVie)** – Perhaps the biggest winner in the lymphoma market is AbbVie's Imbruvica (ibrutinib). Imbruvica brought in roughly $3.6 billion in sales and posted an impressive 40% y/y growth rate for 2018. Moreover, Imbruvica was able to grow its market share from 22% in 2017 to 27% in

2018, a gain of 5 percentage points. Sources of market share growth for Imbruvica are in the front-line setting for CLL where it could potentially be the next standard of care treatment – potentially replacing the current FCR and BR chemotherapies. Finally, Imbruvica belongs to a group of targeted therapy drugs called BTK inhibitors that were able to show impressive survival benefits (ORR: 82.7, PFS: 79%) in Phase 3 trials versus chemotherapy treatment.

2. **Opdivo (nivolumab, Bristol-Myers) and Keytruda (pembrolizumab, Merck)** – these two drugs are both PD-1 checkpoint inhibitors that showed significant activity in HL patients who progressed after second-line therapy or relapsed after ASCT. Although both Opdivo and Keytruda are used mostly in solid tumors, their efficacy and toxicity profiles in HL (ORR: 70%, CR: 20%-25%) are positive enough to warrant further testing in other hematologic cancer indications. Opdivo and Keytruda each hold a 7% and 3% share respectively, in the lymphoma market in 2018.

3. **Adcetris (brentuximab vedotin, Seattle Genetics/Takeda Pharmaceutical)** – Adcetris is an antibody drug conjugate that is utilized in patients with advanced-stage HL. Adcetris given to patients after autologous stem cell transplant (ASCT) showed an impressive survival benefit (3-yr. PFS: 61% vs. 43% placebo). This is important as this patient group has a high risk of relapse. Moreover, when combined with Opdivo, the CR rate, the duration of response and PFS were further improved. Moreover, the toxicity profile of the combination was manageable. Annuals sales of Adcetris grew by 55% y/y to $477 million in 2018 and market share grew from 3% in 2017 to 4% in 2018.

4. **Calquence (acalabrutinib, AstraZeneca)** – Calquence was FDA approved in 2017 is a second-generation BTK inhibitor. Calquence made its mark in the front-line setting of CLL where it is considered to be a potential replacement to the standard of care. Phase 2 clinical trial results showed acalabrutinib in combination with obinutuzumab (Gazyva, Roche) produced impressive response rates (ORR: 95%, CRR: 16%). Moreover, in Phase 2 clinical trial in mantle cell lymphoma (MCL), acalabrutinib as a single agent showed impressive response and survival rates (ORR: 81%, CRR: 40%, 12-month PFS: 67%). Sales of Calquence for 2018 was only $62 million but given the recent FDA approval in CLL and SLL on 11/21/19, expect sales to ramp-up in 2020.

5. **Yescarta (axicabtagene ciloleucel, Gilead Sciences)** – Yescarta was the first CAR T-cell therapy approved (10/18/17) by the FDA for certain types of NHL. Updated data from the ZUMA trials showed the CR at 40% and ORR at over 50% after 24 months of long-term follow-up. Furthermore, OS continues to show improvement. Yescarta brought in $264 million in sales in 2018 and market share grew from 0% to 2% between 2017 and 2018.

Market Share Losers

1. **Rituxan (rituximab, Roche)** – this foundational therapy which has served as the backbone for R-CHOP since 2006 and is currently the mainstay for many clinical trial comparator studies, has seen a steady erosion in market share. Sales fell by 10% y/y to $5.2 billion in 2018; in addition, market share dropped from 50% in 2017 to 40% in 2018 – a steep 10% loss. Rituxan will likely continue to see secular headwinds in the near-term with the market entry of biosimilars recently approved in 2018 – Truxima (approved for FL and CD-20 positive B-cell lymphomas) and Ruxience (approved for CLL). Furthermore, the increasing preference for targeted therapies in CLL front-line setting instead of traditional chemotherapy will likely lead to further market erosion.

2. **Velcade (bortezomib, Takeda Pharmaceutical)** – Velcade is used as the standard of care in multiple myeloma (MM) in a combination of bortezomib (Velcade), lenalidomide (Revlimid) and dexamethasone – known as RVd. However, like CLL, the traditional regimens in first-line setting are currently evolving as other more powerful regimens become available. Patients and doctors can now choose whether

carfilzomib (Kyprolis) plus lenalidomide and dexamethasone would be a more suitable choice for a combination therapy. In addition, newer studies are showing that adding monoclonal antibodies to this regimen such as daratumumab (Darzalex) may improve patient outcomes and yield more durable responses. Furthermore, Velcade is also facing the threat of generics entering the market. Velcade had been expected to lose exclusivity last November 2017, but in July 2018, a US appeals court reinstated the drug's key patent till 2022. It is still not clear when equivalent copycats will hit as a dozen companies are challenging the patent. Velcade has seen a steady drop in sales from $1.26 billion (-9% y/y) in 2017 to $1.17 billion (-7% y/y) in 2018. The company's market share also fell from 11% in 2017 to 9% in 2018.

Disclosure Information

Analyst Certification

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