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Harnessing Market Disruption in the Era of CAR T: Brand Maximization Opportunities and Challenges in DLBCL

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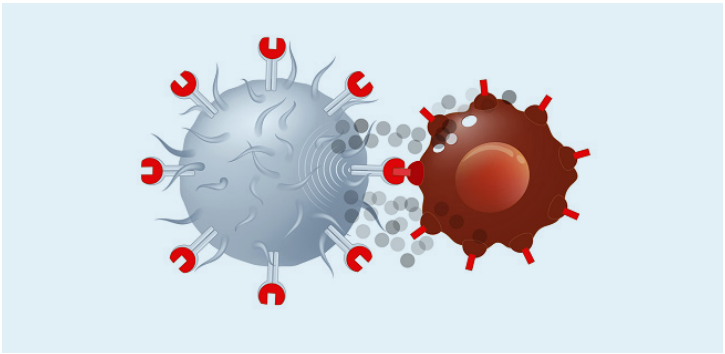
Molekule

Background

Anti-CD19 CAR-T has become a paradigm shifting treatment option for patients with relapsed or refractory (r/r) ALL and DLBCL with durable responses lasting multiple years. As trial data matures and real-world evidence builds, Yescarta continues to be supported in a wider patient population, simultaneously raising the regulatory benchmark required for accelerated approval in r/r DLBCL. This, in effect, has had several collateral consequences reshaping both the clinical and commercial DLBCL landscape offering NHL drug developers both challenges and opportunities.

Prior to Yescarta's and Kymriah's U.S. approvals, the regulatory benchmark to beat was based on evidence from the SCHOLAR-1 study, the largest reported analysis of outcomes evaluating salvage chemotherapy in r/r DLBCL, that resulted in an ORR of 26% (7% CR) and mOS of 6.3 months[1]. After 2 years, the overall survival was a mere 20%[1].



However, registrational trials evaluating CAR-T in r/r NHL patients more than doubled the short-term efficacy endpoint, ORR, and long-term outcomes, mOS. The pivotal Ph1/2 ZUMA-1 trial, which assessed now commercially available Yescarta, increased the best ORR to 72% (51% CR)[5] and after 12 months had a 59% OS rate[6]. An extended median follow-up of 27.1 months confirmed the long-lasting duration of remissions may be suggestive of a "cure" as 39% of all patients maintained an ongoing response[2]. Notably, in patients that achieved a CR, the mDOR and mOS was still not reached over two years post-infusion[2]. Similarly, the JULIET trial, which evaluated Kymriah in r/r DLBCL patients, increased the ORR to 52% (40% CR) and extended the mOS to 12 months[3]. We eagerly await updated ZUMA-1's 3-yr outcomes at ASH19 by Neelapu and colleagues (Abs. 203).

As CAR-T outcomes mature, a continuous impact is exerted on the overall competitive landscape. Specifically, submission timelines of non-CAR-T assets also aiming for approval in 3L+ r/r DLBCL based on single arm evidence, were consistently delayed throughout 2018 and 2019 (e.g. Selinexor, MOR208) – likely due to the "moving benchmark" required for regulatory approval following each successive data update with longer term follow up from ZUMA-1. As a result, the competitive threat of other novel assets faded as their prospects of accelerated approval through single arm trials deteriorated. As evidence of this, it is noteworthy that the FDA required MorphoSys to modify its single arm filing strategy to include a "synthetic control" arm and that the only r/r DLBCL approval since Yescarta and Kymriah's commercial debut was polatuzumab vedotin (anti-CD79b ADC) based on randomized Ph2 evidence.

Regulatory Challenges and Elusive Target Populations

In response, the FDA unofficially established an entirely new subpopulation based on CAR-T eligibility ("CAR-T ineligible") in an effort to help fulfill remaining unmet needs for patients. Three mid-stage DLBCL assets (5F9, MOR208, and Selinexor) under investigation in single-arm trials have delayed regulatory submissions on several occasions and adjusted their "target populations" to be focused on the ambiguous CAR-T ineligible population. The definition of "CAR-T ineligible" remains elusive and is primarily based on clinical judgement if a patient can survive CAR-T toxicities (e.g. CRS) and/or can survive the delays waiting for CAR-T. As we move forward, clinicians, biopharmaceutical developers, and regulators will all be responsible for formalizing what constitutes the "CAR-T ineligible" patient population.

Critically, this period of regulatory uncertainty provides an opportunity for both CAR-T and non-CAR-T competitors to protect their market position to the detriment of their competition. Working with regulators to define CAR-T eligibility will either build barriers to entry or tear them down, depending on whose data is controlling the narrative with regulators. Simultaneously, educating community oncologists to identify CAR-T eligible patients will become a critical pillar to commercial success and key lever to maximize market penetration. Otherwise, community oncologists will be left to decipher this vague term, potentially leaving CAR-T candidates unidentified and remiss of a cure.

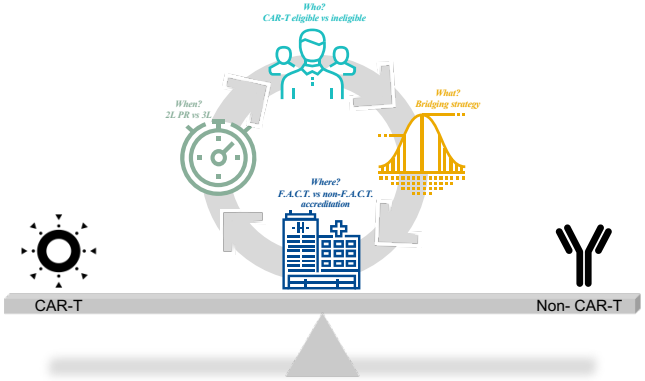


Figure 1. Schematic representing the dynamic factors influencing uptake of CAR-T versus non-CAR-T assets within the DLBCL landscape.

Patient identification, however, is just one challenge atop an evolving DLBCL landscape teetering between adoption of CAR-T vs. non-CAR-T assets. Patient access, referral patterns, and treatment capacity disadvantageously positions commercial CAR-T against DLBCL disease kinetics forging a race between time to CAR-T infusion vs. time to progression or death.

As a de facto "procedure", not a drug, CAR-T requires close coordination between multiple stakeholders to get a patient from the community oncology setting into a F.A.C.T.-accredited transplant center where CAR-T is currently available, often taking between 50-70 days from referral to infusion according to KOLs in the U.S. and Spain.

Upon relapse or no response to salvage chemo, a patient must be quickly referred for evaluation of CAR-T eligibility, gain approval for reimbursement, and receive bridging therapy followed by lymphodepletion while CAR-T cells can be manufactured for infusion. This can require up to 60+ days, a lengthy period for exceedingly refractory patients during which at least 25% of patients will not survive.[7]

CAR T Challenges and Opportunities (1/2)

These innate challenges of the CAR-T paradigm stemming from the lengthy manufacturing window (vein-to-vein >17-22 days) and even longer referral to treatment window (up to 60 days) creates opportunity for non-CAR-T competitors to position ahead of CAR-T as off-the-shelf alternatives. However, emerging real-world data (RWD) to be presented at ASH19 by Jain and colleagues (Abs. 245) shows diverging outcomes when including patients requiring bridging therapy.

These dynamics provide the value proposition for off-the-shelf approaches in DLBCL to compete directly with CAR-T (e.g. mAbs, ADCs, bispecifics, and allogeneic CAR-T). While most of the attention is focused on directly competing with CAR-T, there are at least two less crowded opportunities for non-CAR-T assets to integrate themselves within the CAR-T paradigm: first, as symbiotic assets ahead of CAR-T as bridging therapy or second, as follow-on maintenance therapy.

An optimal bridging therapy would slow a patient's disease progression or keep death at bay until reimbursement and CAR-T manufacturing is complete. To address this sizeable opportunity, a non-chemo-based asset should establish compelling trial evidence within the 60-day holding window to advantageously position themselves as the preferred bridging therapy ahead of CAR-T.

One dominant oncology biopharmaceutical company, Roche, recognized this patient dynamic early and has adapted an FDA-approved asset to fulfill this niche opportunity.

Roche's development plan for its anti-CD79b ADC Polivy (polatuzumab vedotin) exemplifies skillful navigation around potential label restrictions and represents the idealistic regulatory strategy in DLBCL.

Their randomized, controlled Ph2 results in r/r DLBCL patients who have received at least two prior therapies led to accelerated approval in June 2019 under FDA priority review 8-9 weeks ahead of anticipated approval despite two previous commercial CAR-T approvals.

Polivy in combination with bendamustine and rituximab (BR) generated best ORRs of 70% with the majority of these patients (58%) achieving a CR[10]. This impressive efficacy was substantiated with long-lasting responses as 64% of responsive patients had a DOR that lasted at least 6 months. However, updated Polivy data at a median follow up of ~28 months showed that only 22% of patients remained in CR and only 31% remained progression-free[4].

We contend that Polivy's approval has also raised the bar for accelerated approval and has provided a first mover advantage for becoming one potential preferred bridging therapy, thereby entrenching current commercial DLBCL competitors. Real-world data (RWD) continues to emerge on commercial CAR-T that provide two essential insights i) CAR-T patients most often require bridging therapy and ii) patients that do require bridging may represent a harder to treat population than those who do not requiring bridging. At ASH19, Jain and colleagues (Abs. 245) will present RWD from ~260 commercial Yescarta patients (>2x size of ZUMA-1 population) that clearly demonstrate clinical outcomes are inferior in patients requiring bridging therapy. The authors concluded that patients receiving bridging therapy had poorer prognostic factors and after Yescarta infusion experienced worse overall survival compared with patients with no bridging. Importantly, the authors provided a clinical hypothesis that bridging therapy may identify a sub-group of lymphoma patients with a different biology, or have an effect on the host or the tumor microenvironment that may impact CAR-T efficacy. These conclusions carry provocative implications for CAR-T competitors in the DLBCL landscape suggesting that ZUMA-1 (excluded bridging) patients may have been far easier to treat than Kymriah's JULIET or liso-cel's TRANSCEND-NHL, both of which included patients requiring bridging therapy.

Polatuzumab, with or without BR, is currently identified by KOLs as one potential non-chemo based bridging strategy to keep chemo-refractory patients alive long enough to receive CAR-T. Numerous transplant centers in the EU are leveraging early access programs to utilize Polivy in this setting.

CAR T Challenges and Opportunities (2/2)

An efficacious, easily accessed therapy designated for use ahead of CAR-T begs the question, though, will CAR-T still be needed if patients achieve objective responses from bridging therapies? In our humble opinion, absolutely.

Long-term survival metrics, mOS and mPFS, validate this historical outlook. The mOS for Polivy plus BR is a modest 12.4 months[9], compared to 12 months for Kymriah-infused patients[12] and over 24 months for Yescarta-infused patients[2]. However, the mPFS for Polivy plus BR doubled (11.1 months[9]) that of CAR-T (less than 3 months for Kymriah11 and 6 months for Yescarta[2]). Despite this seemingly superior survival metric, the studied patient populations complicate inter-trial comparison. The median number of prior therapies, refractory patient population, and estimated survival impact trial endpoints.

Only 36% of patients had 3 or more prior therapies in Polivy plus BR, versus 50% and 69% for Kymriah and Yescarta, respectively. Meanwhile, the prevalence of patients' refractory to their last prior therapy was 75% from the Polivy + BR study[9] versus 50% for JULIET (Kymriah)[11]. Furthermore, the prevalence of primary refractory patients in ZUMA-1 (Yescarta) was 30% versus 50% for Polivy + BR[10]. Between the CAR-T studies, ZUMA-1 did not allow bridging therapy and therefore selected a healthier patient population that could survive approximately two months between lines of therapy.

Despite this seemingly superior survival metric, several disparities exists between each trial's study population baseline characteristics complicating cross-trial comparisons (e.g. median prior therapies, primary refractory status, IPI scores, and LDH) limiting conclusions based on long-term outcomes.

Conclusions

All things considered, the long-term sustained survival in an exceedingly chemo-refractory patient population demonstrates the necessity and value of CAR-T as a definitive therapy.

We do, however, expect Polivy to play a pivotal role in expanding the addressable CAR-T and ASCT eligible patient population based on Polivy's high best ORRs of 70% providing more patients sufficient time to make their way through the complex referral process to reach a F.A.C.T. accredited CAR-T center. Bridging with an agent that has high response rates lasting at least the necessary 60+ days that it takes to secure reimbursement, would ultimately expand the CAR-T population. Based on SCHOLAR-1, patients with a PR after salvage chemo represents approximately 12% of the 2L population. However, most of these patients are in community oncology centers (non-F.A.C.T.) accredited centers and to take full advantage of the expanding population either an improved referral process or expansion beyond F.A.C.T. centers should be a focal point for CAR-T developers.

CAR-T may also expand its eligible population within the DLBCL landscape by moving to earlier lines of therapy. As of May 2019, NCCN guidelines recommend Yescarta and Kymriah for 2L DLBCL patients achieving a PR following second-line salvage therapy.

Classically, patients in this situation would not be considered for ASCT, but we now anticipate these patients will be eligible for CAR-T regardless of their eligibility for transplant and we underscore the importance of recent NCCN guideline changes that speaks directly to this:

"The NCCN Guidelines recommend CAR T-cell therapy (axicabtagene ciloleucel and tisagenlecleucel) for patients achieving a PR following second-line therapy (regardless of their eligibility for ASCT) and for those with disease relapse after achieving CR to second-line therapy or progressive disease" [8]

A head-to-head comparison of CAR-T versus ASCT in the 2L setting is already underway through the ZUMA-7 trial[13]. An even earlier first line setting evaluation has initiated for high risk patients via the ZUMA-12[14]. As CAR-T progresses into earlier lines of therapy, the second alternative for non-CAR-T assets is to integrate themselves within the CAR-T paradigm as follow on maintenance therapy will become increasingly important.

While the adoption of CAR-T within the dynamic DLBCL landscape lies in the cross-roads of who (patient eligibility), what (bridging strategy), when (2L PRs vs. 3L), and where (F.A.C.T. vs non-F.A.C.T. centers), we can conclusively say that the unmet need in r/r DLBCL is rapidly evolving.

To achieve commercial success in DLBCL requires a deep understanding of both the clinical and commercial dynamics governing market adoption and how these interface across different sites of care. In order to successfully launch a CAR-T product one must skillfully overcome the aforementioned challenges with tailored commercial strategies that will establish a new model for healthcare delivery for cell therapy, establish new referral patterns, and maximize patient access.

Citations

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3. Schuster et al. "Primary analysis of Juliet: A global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large b-cell lymphoma." Blood Journal 130.suppl 1 (2017).

4. Roche ICML19 Industry Symposium

5. Yescarta FDA label Package insert

6. Neelapu et al. "Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma." 2017 The New England Journal of Medicine. DOI: 10.1056/NEJMoa1707447

7. Primary Research, CORAL investigator.

8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) B-Cell Lymphomas Version 3.2019

9. Sehn et al. "Polatuzumab Vedotin (Pola) plus Bendamustine (B) with Rituximab (R) or Obinutuzumab (G) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase 1b/2 Study." ASH 2018 Abstract 1683.

10. Sehn et al. "Randomized phase 2 trial of polatuzumab vedotin with bendamustine and rituximab in relapsed/refractory FL and DLBCL" ASCO 2018 presentation.

11. Borchmann et al. "An Updated Analysis of JULIET, a global pivotal phase 2 trial of tisagenlecleucel in adult patients with relapsed or refractory diffuse large b-cell lymphoma." EHA 2018 presentation.

12. Schuster et al. "Tisagenlecleucel in adult relapsed or refractory diffuse large b-cell lymphoma." The New England Journal of Medicine. Jan 2019.

13. NCT03391466

14. NCT03761056

Engagement:

TEAM BIOGRAPHIES

Dr. Paul Nunzio De Santis
-Director

Paul is a therapeutic expert in immuno-oncology, CAR-T, pharmacogenomics, immunology, and liver diseases (HCV, NASH). He has specialized in providing market research, competitive intelligence, and due diligence on commercial strategy to biotech companies, hedge funds, private equity, and VC firms since 2010.

Having a special interest in immuno-oncology and CAR-T since 2014, Paul has developed a reputation for identifying new sources of strategic importance facilitating competitive advantages for his clients. His therapeutic expertise has been validated and recognized by several Tier-1 consulting firms including the prestigious Gerson Lehrman Group (GLG) where he serves as a "Special Council Member" in immuno-oncology, CAR-T, and pharmacogenomics providing advice to both industry and financial services clients. His work at GLG has focused on commercial planning and intelligence projects for three of the top 20 BioPharma companies, and for funds managing $145M to $13B+ in assets under management.

Paul has provided due diligence and provided strategic advisory services on commercialization strategy for pioneering CAR-T companies, where his work has focused on developing innovative solutions to overcome the numerous clinical and commercial obstacles. Seeking to identify and quantify key barriers to market adoption, he has developed a deep expertise in understanding patient access, treatment capacity, and toxicity management.

Additionally, he has developed a broad network of leading CAR-T key opinion leaders that served as a qualitative source of primary research. He continues to maintain this network today for both immuno-oncology and CAR-T related projects.

Paul is a pharmacist by training and earned his doctorate of Pharmacy (PharmD) from the University of New Mexico in 2010. He received his undergraduate education from the University of Denver before returning to the University of New Mexico to complete his doctorate in Pharmacy. His clinical training is supplemented with 5 years of cancer research experience spanning from in-vitro discovery to clinical trials. He also completed research fellowships with Pfizer Global Research and Development and Ionis Pharmaceuticals.

Dr. De Santis has covered PAH since 2014 covering Gilead Sciences, where he conducted market research and commercial analytics on Letairis (Endothelin Receptor Antagonist). In addition, he completed a clinical rotation in a cardiology specialty clinic that managed PAH patients and heart failure patients.

THERAPY AREA & SUBJECT MATTER EXPERTISE

- Immuno-Oncology *(large and small molecules)*
- CAR-T/adoptive cellular therapies
- Pharmacogenomics
- Physician Education
- Training in oncology
- Liver Diseases
- Molecular Diagnostic
- Immunology
- Reimbursement
- Commercial Analytics
- Addressable Market Analysis
- Advanced Forecasting
- Discounted Cash Flow Valuation
- M&A valuation and analysis

ACADEMIC

PharmD
University of New Mexico

M.A.
Molecular Biology,
University of Denver

LANGUAGES SPOKEN

English

Spanish

Dr. Samantha Kurtz
-Consultant

Sam is a scientifically trained oncology professional with seven years of experience in breast cancer research, alongside significant regulatory and bio-investment training. Academically, her experience in oncology spans disease biology, translational science, and therapeutic strategies that harness medical device and engineering solutions. Her doctoral thesis focused on the application of transpapillary drug delivery as a local, non-invasive alternative for breast cancer prevention.

Through an FDA internship and participation in the New Orleans BioFund, Sam also gained US regulatory and venture investment perspectives. Within the FDA's Division of Post-Market Surveillance, she advanced a device reporting program that longitudinally tracked and analyzed medical device reports. At the New Orleans BioFund, she performed due diligence on local biotechs with a variety of concentrations and investment models. She subsequently participated in entrepreneurial business competitions, gaining four podium finishes for pitching oncology investment opportunities.

Sam completed her BS in Biology, through an Arkansas Governor's Distinguished Scholarship, and MS in Biomedical Engineering at the University of Arkansas. She completed a Ph.D. in Bioinnovation, a multi-disciplinary traineeship established by the National Science Foundation (NSF), through Tulane University.

THERAPY AREA & SUBJECT MATTER EXPERTISE

- Competitive Intelligence
- Business development search & evaluation
- Drug delivery devices
- Market access & Reimbursement
- Go-to-market strategy
- Oncology
- Customer Insights
- Forecasting
- Hematology
- Strategic and CI workshops
- Immunology
- Rare diseases / Gene therapies

ACADEMIC

Ph.D.
Bioinnovation, Tulane University

M.S.
Biomedical Engineering, University of Arkansas

B.S.
Biology, University of Arkansas

LANGUAGES SPOKEN

English

Siddharth Subramaniam
-Senior Consultant

Sid started his career as a molecular biologist in the Translational Medicine Lab at ACTREC (India's foremost cancer research hospital) where the team was trying to identify novel mechanisms for metastasis and ways to prevent it. However, he soon realized that a narrow focus - on a single target/ pathway is not enough and decided to move into consulting to get a more holistic/ bird's eye view of things.

His background in Oncology due to his M.Sc. in Cancer immunology and strong understanding of the mechanics behind the various molecular pathways due to his research experience provided the base required to integrate with the commercial side. His education and experience in CI and market research have molded Sid into a well-rounded therapy area expert with a strong understanding of the developments and current trends in oncology.

Sid specializes in providing quick turnaround projects requiring science driven insights. He is exceptionally capable when it comes to handling requests from the new program/ development teams looking to focus or prioritize indications and combinations. As a team lead at Value Edge (now WNS Global Services), Sid was responsible for handling and maintaining working relationships and providing quality service to blue-chip pharma companies.

THERAPY AREA & SUBJECT MATTER EXPERTISE

- Prioritization *(Assets & Indications)*
- Asset Differentiation
- Solid and Hematological Tumors
- Clinical & Preclinical data analysis
- Infectious disease & antibiotics
- Immunotherapy in oncology
- Competitive Intelligence

ACADEMIC

M.Sc.
Cancer Immunology & Biotechnology,
University of Nottingham, UK

B.Tech Biotechnology
Vellore Institute of Technology, India

LANGUAGES SPOKEN

- English
- Tamil
- Hindi
- Marathi

Dr. Michael Marlatt

-Director & Head of New York Office

Michael is a uniquely experienced competitive intelligence (CI) and therapeutic area expert, having led significant engagements with both pharmaceutical and biotechnology clients. A seasoned project manager, Michael has a breadth of experience with competitive landscaping, product differentiation, launch preparedness, lifecycle management, and organizational development. His major therapeutic expertise is in CNS, oncology, rare, and infectious diseases. He brings first-hand experience delivering clinical and commercial insights for pipeline and marketed products to a breadth of clients, ranging from Top-20 pharma companies to privately held biotech firms.

Michael is a research scientist by training, who began his career with Merck Research Labs in Neuroscience Drug Discovery. Following his PhD, Michael joined Deallus Consulting, a global CI and strategy firm based in London, where he developed further as project manager and functional CI expert. At Deallus, he held major responsibility for delivering global CI and strategy projects across therapeutic areas and diagnostics. From Deallus, Michael was recruited to Occam Global, a retained executive search and strategy firm based in New York, specializing in organizational development for venture capital backed healthcare and technology companies.

Michael completed his BS and MS at Case Western Reserve University in Biochemistry and Pathology respectively. He completed his PhD through a Marie Curie Fellowship at the University of Amsterdam (The Netherlands) and National Institutes of Health (USA).

THERAPY AREA & SUBJECT MATTER EXPERTISE

- Competitive Simulation Workshops
- Sales Force Effectiveness
- Rare Diseases
- Immunology and Inflammation
- Life Cycle Management
- Diagnostics
- (Pre- and Peri-LOE strategy)
- Regulatory Strategy
- Oncology
- Virology
- CNS

ACADEMIC

Ph.D.
University of Amsterdam
The Netherlands

M.Sc.
Case Western Reserve University

B.S.
Case Western Reserve University

LANGUAGES SPOKEN

English

Dr. Mark Powzaniuk

-Director & Head of Oncology

Dr. Mark Powzaniuk joined Molekule Consulting in 2019 after spending 19 years within the pharmaceutical industry. As a seasoned pharmaceutical professional, Mark brings a unique background of science and business acumen. His experiences include Basic Research, Project Management, Business Integration, and Finance. Most recently, Mark was head of Global Competitive Intelligence, Oncology at Merck.

Mark started his career as a Post-Doctoral Research Fellow in the Bone Biology Department at Merck. After completing his fellowship, he joined Merck Project Management with increasing roles of responsibility and gaining both clinical and commercial experience. While obtaining his M.B.A., Mark transitioned from Project Management to Business Integration and Finance. In this role, he was the finance lead for Safety Assessment and involved in the planning and execution of integration strategies after the Schering-Plough Merck merger. After a successful finance career, Mark was made head of Global Competitive Intelligence, Oncology at Merck. In this role, he built a world-class competitive intelligence organization focused on end-to-end strategic support of Merck Oncology.

Mark completed his B.S. in Biology at Cabrini College. He obtained his Ph.D. from Thomas Jefferson University in Genetics and Molecular Biology and an Executive M.B.A. from Villanova University. In addition, Mark has his PMP Certification and Six Sigma Green Belt.

THERAPY AREA & SUBJECT MATTER EXPERTISE

- Oncology
- Competitive Simulations and Workshops
- Competitive Intelligence Strategy and Processes
- Immuno-Oncology
- Vaccine
- Project Management
- Life Cycle Management
- Business Development and Licensing
- Neuroscience

ACADEMIC

Ph.D.
Thomas Jefferson University

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- English
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