**A Bayesian Clustering Approach to Develop a Novel Treatment-based Cancer Ontology**

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**Introduction and Background**

Two major issues in oncology are rational cancer reclassification and the efficient inference of the effectiveness of drugs against cancers other than their initial target, which we will refer to henceforth as the drug inference problem. Although the treatment of cancer has advanced significantly in the last 50 years, cancer remains the second most common cause of death in the United States and its prevalence is increasing [1]. Throughout the history of oncology, the discipline has been split into subfields based primarily on the anatomic location of cancer. The current partitioning of the field of oncology has led to the compartmentalization of knowledge. Even within the same subfield, there is a tendency to split further between untreated and relapsed patients, driven primarily by the exacting needs of clinical drug testing and approval.

Currently, many drugs are studied for one specific cancer and one specific context (e.g. untreated vs. relapsed or multiply relapsed), decreasing their potential impact considerably. As a result, discovering additional treatment contexts for a new drug can take a long time. For example, the drug imatinib was first found effective in chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs) in 2002 [2, 3]. Despite the fact that the drug was known to target c-KIT and that it has been known that certain melanomas harbor c-KIT mutations since 2005 [4], imatinib was not shown to be effective in the clinical setting for c-KIT mutated melanoma until 2011 [5]. This long process demonstrates the need for a global solution for oncology drug inference.

The development of large-scale biological databases has enabled researchers to explore patterns shared by cancer subtypes and target certain protein pathways crucial to the development of cancer for treatment via “targeted” inhibitors. The ontological methods developed in recent years in computational genomics provide new tools for such an analysis. In a bioinformatics context, ontology is defined as the study of hierarchical classifications generated from biological data that can be used to test biological hypotheses. For example, the Gene Ontology project has unified gene product databases and standardized data formats, enabling the automation of the inference of the functional importance of genes in large genomics studies [6]. Recent developments in bioinformatics sustained by genomic sequencing and ontological methods have attempted to provide computational solutions to the above two problems. These solutions have adopted an approach involving the construction of models for cancers based on specific biological mechanisms such as oncogenes, protein pathways, or gene functionality [7, 8, 9].

Such an approach based on biological mechanisms is powerful in directing future cancer research, but further investigations following its guidance sometimes cannot find supportive empirical outcomes. For example, after a highly significant single nucleotide polymorphism (SNP) was found in the v-Raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene in melanoma patients, the drug vemurafenib was developed to target the relevant protein and led to great improvements in the treatment of melanoma [10]. The *BRAF* SNP was later found to be present in a significant proportion of colorectal cancers, but the use of vemurafenib in colorectal contexts has largely failed [11, 12]. Since the current literature still cannot explain many common phenomena that have a high impact on treatment efficacy, including tumor-host interactions [13], drug efflux mechanisms [14], and other indirect mediators of drug resistance, approaches to drug inference that focus on a limited range of biological mechanisms are vulnerable to such challenges.

This study provides a unified solution to the problems of insufficient cross-specialty communication and of drug inference in cancer research by developing a novel cancer-context and drug ontology. Differently from previous approaches that attempt to pinpoint the biological causes of cancer, this approach is defined by a systematic, large-scale, quantitative analysis of the existing database of efficacious cancer treatment regimens. In contrast to previous cancer studies which build a biological model of cancer first and then infer drug efficacy accordingly, this study takes an inductive approach using data mining techniques to form a standardized cancer treatment database, then constructing the aggregate pattern of cancer subtypes. Furthermore, previous approaches consider a few key biological mechanisms that lead to cancer, whereas we black-box the currently unknown, complicated biological processes underlying cancer by using the effectiveness of existing treatment regimens as an indicator of their joint impact. An additional contribution of our approach is the global nature of the meta-analysis. Instead of comparing the mutations of only a few cancer subtypes at a time to infer drug efficacy on new targets, we compute the likelihood that any existing drug can be applied to any new target in the sorted clusters of cancers, allowing a more global drug inference study. Thus, our drug inference algorithm is capable of magnifying the effectiveness of existing cancer treatments.

To cluster cancers in a clinically meaningful way, the clustering algorithm needs to meet several criteria. We need a hypergraph to represent the relationships between cancer contexts and drugs, with edges corresponding to the set of cancer contexts treated by each drug. An effective algorithm needs to use edge weights, as certain treatments have more evidence of efficacy than others. The algorithm should determine the optimal number of clusters if the clustering is not hierarchical. Furthermore, the clusters should contribute to a probabilistic framework for drug inference, and each cluster should have an associated treatment profile. A soft clustering algorithm is optimal, as we should be able to capture uncertainty about whether a certain cancer should be assigned to one cluster or another. And finally, the algorithm should devalue unlikely treatment profiles in order to find the most plausible clustering.

Bayesian hypergraph clustering methods have addressed each of these concerns. Such algorithms can incorporate edge weights by linearly weighting each edge-wise calculation, ensuring that high-evidence treatments have more impact on the clustering. A Bayesian method naturally eliminates nodes from extraneous clusters, inferring the optimal number of clusters as a byproduct of maximizing the information score (negative log likelihood) of clustering [15]. These methods also provide probabilistic cluster assignments and edge generation between clusters and nodes. Additionally, some Bayesian algorithms calculate rational priors for the parameters, discounting unlikely treatment profiles [16]. By supporting such a cluster analysis, a Bayesian algorithm can provide a novel treatment-based ontology of cancers that addresses both the cancer reclassification problem and the drug inference problem simultaneously. We can then test the accuracy of the drug inference results against the existing literature and use this accuracy as a metric to confirm the quality of the reclassification.

**Methods**

The dataset used in this study is from the cancer regimen online knowledge management system of HemOnc.org (<http://www.hemonc.org>), a collaborative wiki maintained by oncologists. It contains over 260 antineoplastic drugs (FDA-approved and in clinical trials) and over 1100 regimens that are linked in a network, as of October 2013. Each regimen is linked to a supporting publication(s) by their unique PubMed ID, and is furthermore annotated with the strength of the clinical trial evidence (e.g. pilot studies with fewer than 20 patients, randomized-controlled trials, etc.) Some medications included in this dataset were excluded from this analysis as they are supportive. These included growth factors, bone modifying agents, and other supportive medications. Steroids were retained if and only if they were an integral part of a chemotherapy regimen. In HemOnc.org, cancers themselves are mainly classified by anatomic location, nature (for example, HER2-positive breast cancer), and treatment context in this dataset (adjuvant, refractory, etc.).

Most regimens in this dataset had already been classified into primary (untreated) and secondary (previously treated, a.k.a. relapsed/refractory) contexts, but a minority required further classification. For example, metastatic non-small cell lung cancer (NSCLC) regimens were not further sub-classified as first-line or second-line. We employed a heuristic word-matching method to distinguish primary treatments from second-line treatments using a naive classification algorithm run on the abstracts of PubMed papers associated with the treatments. For example, if “adjuvant” was found in the title of a paper, the associated treatment was considered a treatment for the untreated (primary) context. Slightly fewer than 50% of all PubMed papers referenced by the database that were not already classified in the metadata were successfully classified using this algorithm.

Edges are key in determining the optimal clustering of a network. The important edges in the network are first separated out by using the Alterovitz principal component analysis-based (PCA) algorithm [17]. This provides the function of preserving the most important treatments for each cancer, and thus increases the specificity of the treatment database. Details of cluster calculation are provided in the Appendix. Clinical interpretations were then assigned to these clusters by finding commonalities in the treatment strategies of the cancers. The principal treatment patterns found in these interpretations were then tested for statistical significance, using the Fisher’s exact test calculation of treatment information enrichment.

**Results**

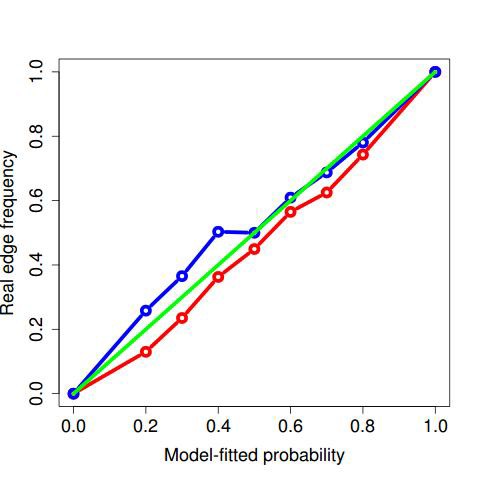
Although the noise level in the original graph was too high, the extraction of the most important features of GDDs resulted in a reduction from 936 edges to 589 edges. As each cancer has many minor treatments that interfere with optimal clustering, the extraction of important features by the topological abstraction algorithm directly enabled the Bayesian clustering. After abstraction, from the Bayesian algorithm, 19 clusters were found. The clusters ranged in size from 1 to 21; the 14 clusters with at least two cancers are shown in **Table 1**. With the confidences calculated for these cluster assignments and the θ-values calculated by the clustering algorithm for hyperedge incidence probabilities, extrapolated confidence in treatment efficacy was calculated using Equation (1). These clusters could generally be qualitatively characterized by a set of shared treatments without any consideration of the hyperparameters, confirming their clinical value. These treatments are briefly characterized in **Table 1**.

**Table 1:** Computed cancer context clusters with high relatedness. Shared treatment is the likely basis of relatedness; clusters without a shared treatment listed did not have obvious treatment-based commonalities. r/r: relapsed/refractory. Other acronyms are defined in the Glossary.

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Shared treatment | Members of cancer cluster | *p*-value |
| 1 | Nucleoside analogs | CML r/r, AML r/r, APL, PCNSL untreated, ALL un-  treated, T-NHL untreated | 5*.*95 *·* 10*−*6 |
| 2 | Platinums | Ovarian r/r, HL r/r, SCLC r/r, Sarcoma untreated, NSCLC  untreated | 8*.*21 *·* 10*−*2 |
| 3 | Platinums / taxanes | Breast r/r, Bladder untreated, Cervical untreated, H&N  untreated, Esophagus untreated, Breast HER2+ untreated | 1*.*63 *·* 10*−*3 |
| 4 | Immunotherapy | Melanoma untreated, Renal r/r | 3*.*93 *·* 10*−*5 |
| 5 | 5FU / Folinic acid | Pancreatic untreated, Esophagus r/r, Gastric untreated,  Colon r/r, Cervical r/r, Rectal untreated, HCC r/r | 1*.*22 *·* 10*−*4 |
| 6 | R-CHOP | HIV NHL untreated, MCL untreated, Aggressive NHL,  FL r/r, Thymoma untreated | 7*.*81 *·* 10*−*9 |
| 7 | *MTOR* inhibitors | Renal untreated, ALL r/r, MCL r/r | 1*.*60 *·* 10*−*2 |
| 8 | – | CML untreated, Brain, NET r/r | – |
| 9 | – | AML untreated, CLL | – |
| 10 | – | FL untreated, HL untreated | – |
| 11 | – | PCNSL r/r, T-NHL r/r | – |
| 12 | – | MDS untreated, Melanoma r/r | – |
| 13 | – | Anal untreated, Bone r/r, NET untreated, MPD untreated,  HCC untreated | – |
| 14 | – | Thymoma r/r, Amyloid, MZL r/r | – |

Six of the 14 clusters that had more than one cancer were found to have high statistical significance (p < 0.05), with the lowest having p < 10−8, as shown in **Table 1**. A clinical interpretation was found for one other cluster. Treatment strategies for other clusters were not evaluated due to the lack of data in the treatment database about those clusters. Ranking cancer-treatment pairs according to descending order of computed likelihoods, we found that input edges, edges that had already been placed in the database, represented the bulk of the high-likelihood edges, as shown in **Figure 1**.

The lower bound curve, at point 0.1k, denotes the real occurrence frequency of edges with computed confidence between 0.1(k − 1) and 0.1k, whereas the upper bound curve represents that of edges with confidence between 0.1k − 0.05 and 0.1k + 0.05. Taking the points (0.1, 0.1), (0.2, 0.2), . . . , (1.0, 1.0) as predicted values, we obtained R2 = 0.958 for the lower bound line and R2 = 0.960 for the upper bound line. The figure thus demonstrates that the Bayesian computed probabilities correspond quite clearly to the database’s edge incidence probabilities, showing that our clustering-derived incidence model closely approximates the original hypergraph.



**Figure 1**: Model-fitted probability vs. real edge frequency

For each possible edge, the probability of the edge occurring according to the Bayesian model was calculated. To measure the probabilistic approach’s performance on the drug inference problem, we took its ten highest-confidence newly inferred edges and reviewed the literature. These edges, their model-derived probabilities, and associated clinical trial references are shown in **Table 2**.

As a control group, the bottom ten inferred edges, picked from above 1% confidence, were also considered in the literature review (not shown). As shown in the last column of **Table 2**, we found that while eight of the ten high-confidence edges had mentions in Phase II/III literature and the other two were being studied in non-clinical contexts, only two of the ten low-confidence edges had mentions in Phase II/III literature. Indeed, one of the low-confidence pairs was found to have a negative instead of positive relationship between treatment and cancer. A significant difference (p = 0.023) therefore exists between the high-confidence and low-confidence edges inferred by the clustering algorithm, and this demonstrates that our algorithm is capable of differentiating between promising treatments and treatments that are likely to fail.

**Table 2**: Inferred treatment recommendations and confidence levels

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Cancer subtype | Probability | Reference |
| Fluorouracil | HCC r/r | 0.88 | [18] |
| Dexamethasone | Bladder untreated | 0.83 | [19] |
| Carboplatin | Sarcoma untreated | 0.79 | [20] |
| Cisplatin | Sarcoma untreated | 0.79 | [21] |
| Gemcitabine | Sarcoma untreated | 0.79 | [22] |
| Folinic acid | HCC r/r | 0.74 | [23] |
| Temozolomide | CML untreated | 0.72 |  |
| Methotrexate | APL r/r | 0.70 | [24] |
| Cytarabine | T-NHL untreated | 0.70 | [25] |
| Cytarabine | CML r/r | 0.70 | [26] |

**Discussion and Conclusion**

The results demonstrate the strength of the treatment-based Bayesian clustering algorithm and provide a simultaneous solution to the cancer reclassification problem and the drug inference problem. While previous works represent the biologically-motivated approach to oncology, such as splitting breast cancer into different molecular subtypes [27], this study represents a new direction of global network meta-analysis on existing treatment regimen data. Our meta-analysis takes a holistic, inductive approach, using clinical efficacy data as its main variable, which reflects the entirety of all biological mechanisms behind cancer and the accumulated wisdom of a large and complex international clinical trial apparatus. Our treatment-based ontology sheds light on several rational cancer reclassifications. For example, in the traditional anatomy-based model, renal cancer and melanoma are deemed to be unrelated. According to our treatment-based ontology, however, they belong to the same cluster because they are similarly treated diseases, commonly found to coexist [28], and commonly treated by the same specialists. Such a reclassification could reorganize oncological knowledge, as the traditional divisions among anatomical locations will be replaced by the patterns of shared treatment efficacies.

Although our approach does not open the black box of the biology behind cancer, it does consider these mechanisms indirectly, through treatment efficacy. Instead of considering etiology directly, we first reclassify cancers based on treatment efficacy, and then suggest further investigations into similarities in the underlying biology. For example, in the case of renal and melanoma cancers (cluster 5), our new reclassification suggests that specialists working on the two cancers may jointly investigate new approaches to immunotherapy. Similarly, thymoma, which is treated primarily by anthracycline-based regimens, unexpectedly occurred in the B-cell non-Hodgkin’s lymphoma clusters. Thus, similarities in the underlying etiologies of cancers in this cluster may be jointly investigated by their respective specialists. All of these examples had high statistical significance for treatment information enrichment, as shown by **Table 1**.

Previous efforts at drug inference have focused on SNPs and oncogenes, among other biological mechanisms. As the development of drugs such as vemurafenib has shown, the challenge to this approach is that it considers only a small number of the biological mechanisms that jointly determine drug efficacy and is therefore often ineffective as a solution to the drug inference problem. As a result, the potential impact of new chemotherapy drugs is limited to one cancer until oncologists slowly begin to experimentally apply them to other cancers.

Though drug inference has often been performed on a local scale, comparing the genetic and molecular profiles of two cancers at a time, we take a global approach to the problem of drug inference, unifying it with a cancer reclassification model. Our focus on treatment efficacy rather than its main causal factors enabled this study to map global similarities between cancer subtypes by first finding clusters, then computing probabilities for the efficacy of repurposed drugs in a unified model. The effectiveness of the Bayesian algorithm at the drug inference problem is demonstrated by its differentiation between likely and unlikely treatment recommendations. As the last column of **Table 2** demonstrates, likely treatment candidates had a high correlation with appearances of Phase II/III clinical trials in the literature. Unlikely treatment candidates, in contrast, had a much lower frequency of mentions in the literature. Thus, the drug inference extrapolations were clinically relevant. This suggests that a global model for cancer reclassification may be able to simultaneously address the drug inference problem.

The inductive statistical method of treatment efficacy analysis adopted by this study suggests a new way of discovering cancer knowledge by analyzing the rapidly accruing digital data on cancer treatments. At one level, it offers an alternative to models built on key genetic profiles and biological mechanisms. At another level, however, it also complements these biological models by providing a new way to organize cancer specialties and infer drug efficacy according to the treatment-based clusters identified by our statistical algorithm.

In our work towards solving the cancer reclassification and drug inference problems, we have identified several important questions and limitations that must be addressed to perfect the power of our clustering algorithms and to extend the impact of our findings. One of the potential improvements to our approach is the inclusion of comparative treatment effectiveness data in the analysis. There are two possible approaches to adjusting the Bayesian algorithm to accommodate these data. One is to adjust the Bayesian model. New hyperpriors can be designed for the distribution of treatment effectiveness, and the EM quantitative method described can be extended by these hyperpriors. However, another approach is simply to use the existing model with edge weight modifications. We consider the first approach to be more quantitatively sound.

Another way to make more information available to the clustering algorithm would be to provide more information on absolute efficacy, in the form of negative edges. If a certain drug was found in a study to be completely ineffective against a particular cancer, a separate ineffective hyperedge should be created to include this information in clustering considerations. Although hemonc.org does not focus on complete inclusion of negative clinical trial information, as it is meant to be a treatment guideline database, a more comprehensive database would yield better clusters. Furthermore, the possibility remains that the unit of our clustering, the cancer treatment context, is not the best disease unit to use. For example, gastrointestinal stromal tumors are included in the sarcoma contexts, but are treated differently from most sarcomas. Dividing cancers into contexts in some other way may provide more information or better clusters.

In general, the inclusion of direct biological mechanisms in our inductive approach could provide a powerful syncretic method that would solve all three problems that have been mentioned in this paper: cancer reclassification, cancer diagnosis, and drug inference; whereas our algorithm only addresses two of these problems. In addition to addressing these problems in clinical oncology, cancer treatment network analysis can also yield better ways to organize other processes relating to cancer care, such as drug production. Cancer drug shortages are a major problem in cancer treatment [29]. We can track sudden bursts in publications in particular clusters using a network analysis algorithm running on a cancer treatment network. Thus, it may be possible to predict drug shortages in the future, ensuring that production can be increased before the demand spike.

Analytical models of cancers based on biological etiologies have characterized cancer meta-analysis and drug inference thus far. The inductive, global, treatment-based approach outlined in this paper directly analyzes treatment efficacy data to provide a unified solution to both cancer reclassification and drug inference. Our combination of topological abstraction and Bayesian techniques was effective at elucidating the structure of the cancer treatment network provided by the regimen database, discovering hidden commonalities between cancers with high statistical significance.

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**Appendix**

Let the shortest distance matrix of graph *GDDs*, the bipartite graph consisting of edges between chemotherapeutic drugs and cancers they treat, be *D*. We perform PCA on the set of row vectors of *D*, and project all vectors into the vector space defined by the principal components. We then discard all but the 20 principal components that contribute

the highest variance, and then project all vectors back into the original vector space. We form a modified matrix *Dt* with these vectors as row vectors. We then redraw *G* to form *Gt*, in which an edge between *i* and *j* exists if and only if *Dij ≤* 1*.*5.

*t*

A Bayesian clustering algorithm due to Vazquez [15] was then applied to the modified hypergraph. From *Gt*, we defined a hypergraph *H* , with hyperedges corresponding to the disease adjacency sets of the drugs in the database. Then define *a* to be the adjacency matrix of *H* ; that is, *aij* = 1 if and only if vertex *i* belongs to edge *j*.

Let *B* denote the Beta function. We define:

*B*(*p*; *α, β*) = 1

*B*(*α, β*)

A similar limit applies for *γ* in this case.

*pα−*1(1 *p*)*β−*1; *D*(*π*; *γ*) = 1

*−*

*B*(*γ*)

*K*

*γk −*1

*π*

*k*

*k*=1

(1)

We apply a Variational Bayes expectation-maximization (EM) algorithm. We minimize an upper bound *F* on the negative log likelihood of the data by performing a convergent algorithm that converges at the most likely cluster assignment probability matrix and adjacency probability matrix. Variational approximations for probabilities and pa- rameters are first computed, followed by cluster probabilities, at every step of the convergent algorithm.

Let *K* be an initial upper bound for the appropriate number of clusters. Let *θkj* be the probability that a vertex in cluster *k* will belong to hyperedge *j*. Let *p* be a matrix of probabilities of cluster assignments. Let *π* denote the hidden frequency vector describing cluster sizes. This frequency vector is relevant because it allows us to define a

prior *D*(*π*; *γ*) that punishes uneven clusterings. Let *γ* denote a vector, indexed by group indices *k*, where *γk* refers to the sum of the probabilities of each node falling in cluster *k*. In all of our equations, *R*(*θ*)*, R*(*π*) denote likelihood estimates for *θ, π*, respectively. Also, define

*(A*(*φ*)*)* =

*dφP* (*φ|D*)*A*(*φ*)*,*

for any function *A* on the parameters *φ*.

The following algorithm is then iterated until *F* varies by less than a certain threshold *E* (we chose 10*−*6):

*mik* = *(*ln *πk )* + ) *aij (*ln *θkj )* + (1 *− aij* )*(*ln(1 *− θkj* )*)*

*j*

*αkj* = *E* + ) *pik aij*

*ij*

*R*(*π*) = *D*(*π*; *γ*)

*emik*

*pik* =  

*emis*

*s*

*R*(*θ*) = *B*(*θkj* ; *αkj , βkj* )

*kj*

*(*ln(*θkj* )*)* = *ψ*(*αkj* ) *− ψ*(*E* + *γk* )

*(*ln(1 *− θkj* )*)* = *ψ*(*E − γk − αkj* ) *− ψ*(*E* + *γk* )

*(*ln(*πk* )*)* = *ψ*(*γk* ) *− ψ* ) *γk* 

*k*

*γk* = *E* + ) *pik*

*i*

*F* = ) *pik* ln *pik −* ) ln *B*(*αkj , βkj* ) *−* ln *B*(*γ*)

*ik kj*

(2)

Similar equations are defined for *β*.

After the algorithm finishes, the elements of *p* are the desired probabilities. Summing over all potential cluster assignments, we can then estimate the likelihood that a certain drug works on a certain disease.

To determine the quality of the clusters derived from the Bayesian algorithm, Fisher’s exact test was applied in an enrichment analysis of treatment information. Clinical interpretations were assigned to each cluster, consisting of treatments shared among the diseases in the cluster. The frequency of the occurrence of these shared drug hyperedges in that cluster was then compared to the frequency in *GDDs*, from which *p*-values were derived.

As the Bayesian algorithm calculates *φt*

*kj*

= log *θkj*

and *pik*

, we can determine the exact model-derived likelihood

*P* (*i ∈ Gj |φ*) = ) *eθkj p*

*ik*

*,* (3)

*k*

where *Gj* represents the neighborhood of treatment *j*. Clusters resulting from the Bayesian hypergraph clustering algorithm were filtered by confidence, and only cluster assignments with confidences higher than 0.95 were retained.

The PCA-based topological abstraction algorithm was run using 20 principal components. After topological ab- straction was complete, the Bayesian hypergraph clustering algorithm was applied to the resulting graph, excluding edges between pairs of drugs and pairs of diseases. Likelihoods were calculated using Equation (1).

**Glossary**

5-FU: 5-fluorouracil

ALL: Acute lymphocytic leukemia

AML: Acute myelogenous leukemia

APL Acute promyelocytic leukemia

CLL: Chronic lymphocytic leukemia

CML: Chronic myelogenous leukemia

FL: Follicular lymphoma

HCC: Hepatocellular carcinoma

HIV NHL: Human immunodeficiency virus-related non-Hodgkin lymphoma

HL: Hodgkin lymphoma

H&N: Head and neck carcinoma

MCL: Mantle cell lymphoma

MDS: Myelodysplastic syndrome

MPD: Myeloproliferative disorders

MTOR: Mammalian target of rapamycin

MZL: Marginal zone lymphoma

NET: Neuroendocrine tumor

NHL: Non-Hodgkin lymphoma

NSCLC: Non-small cell lung cancer

PCNSL: Primary central nervous system lymphoma

R-CHOP: Rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone

SCLC: Small-cell lung cancer

T-NHL: T-cell Non-Hodgkin lymphoma