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Editorial: Special issue on rare cancers

This special issue of *Current Problems in Cancer* focuses on recent advances in rare cancer and rare tumor research, as well as highlights the unique challenges to making progress for patients with these diseases. The articles cover a variety of topics across a broad range of rare tumors and cancers. From the need for accurate, early diagnosis to the newest therapeutic approaches, we hope these articles will be informative to clinicians, researchers, and advocates interested in learning more about rare tumors and cancers.

Rare cancers are defined by the United States National Cancer Institute (NCI) as those with an incidence of fewer than 15 per 100,000 people per year.[1] The widely accepted European definition of rare cancers[2] is those with an incidence of fewer than 6 per 100,000 people per year. Regardless of which definition is applied, rare cancers account for approximately one quarter of all cancers diagnosed each year in the United States and Europe[2, 3] and 5-year survival rates for rare cancers are significantly lower than those for common cancers in the United States and Europe.[4, 5] Despite the substantial burden of rare cancerous and noncancerous tumors in the United States and worldwide, development of treatments for these rare tumors and/or cancers (hereafter referred to as "rare tumors" to include both cancerous and noncancerous tumors) has historically proved to be an intractable challenge. For many rare tumors, the standard of care has not changed for decades; for others, there is no effective standard of care. Surgical resection, despite its limitations and potential morbidity (as an example, see the article on chordoma by Wedekind et al. in this issue), continues to be the primary approach to treatment of many rare tumors.

This slow, and in some cases nonexistent, progress in developing effective treatments for rare tumors is due to several factors and knowledge gaps along the entire research continuum. At one end of this continuum, limited availability of tumor tissue impacts ability to comprehensively characterize rare tumor biology (eg, genomics, transcriptomics, epigenomics, proteomics, etc.), or develop cell lines and animal models to test hypotheses and candidate therapeutics. At the other end, conducting clinical trials to test candidate therapies is very challenging, due to small overall numbers of affected patients who may be too geographically dispersed for any one clinical center to accrue enough patients to conduct a meaningful study. These issues exacerbate the difficulty in studying the natural history of rare tumors, which has limited our understanding of the biology and clinical course of many of these tumors. Although research on rare tumors has been challenging to conduct, past studies of certain rare tumors have helped illuminate fundamental mechanisms of tumorigenesis for both rare and common tumors.[6]

The definition of what qualifies as a rare tumor will likely continue to evolve as tumors become defined more frequently by their molecular aberrations rather than their organ of origin. Based on the traditional, organ-based classification of cancers, only 11 cancers would not be considered rare based on the US NCI's definition: prostate, breast, lung, colon, uterus, bladder, melanoma, rectum, ovary, non-Hodgkin lymphoma, and kidney.[3] However, a growing number of

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rare subtypes of these "common" cancers are being identified (for example, see the article on rare subtypes of kidney cancer by Webster et al. in this issue), and some of these subtypes share molecular alterations with cancers originating in different organs. One example of these rare subtypes is the subset of lung cancers that harbor an activating rearrangement of the anaplastic lymphoma kinase (ALK) gene ("ALK-positive" cancers). Lung cancer is considered a common cancer, with annual incidence in the United States of a little over 220,000 cases.[7] Only approximately five percent of all lung cancers are ALK-rearranged, accounting for approximately 11,000 cases per year in the US. ALK-activating mutations have also been identified in neuroblastoma, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor (see the article in this issue by Mahajan et al.) and other tumors[8, 9] although the details of the activating mechanism whether copy number gain, gene fusion, or activating mutation may have different biological effects. The classification of tumors by gene alteration, rather than by organ specificity, has implications for treatment that are starting to be recognized and realized.

Several advances have begun to accelerate progress in developing therapies for rare tumors. The relatively recent emphasis and evolving effort on precision medicine has resulted in changes in the way many clinical trials are conducted, as well as changes in the types of data and endpoints accepted by regulatory agencies. Randomized controlled trials, once considered the "gold standard" of clinical trials, have not been particularly feasible for testing therapies for rare tumors, due to the low incidence of these tumors in the overall population. Rather than relying on control arms in trials for therapies for rare tumors, opportunities to use external control data from previous trials or natural history studies are becoming a feasible approach (see article by Gross in this issue.) Patient-reported outcome (PRO) data are becoming an increasingly important component in trials on rare tumors. Tumor histology-agnostic clinical trials testing therapies targeted to a specific gene mutation are becoming the norm. For example, patients with tumors harboring neurotrophic receptor tyrosine kinase (*NTRK)*-fusions tend to respond to treatment with TRK inhibitors such as larotrectinib and entrectinib, regardless of the organ of origin of their tumors. These fusions have been identified in multiple rare and common cancer types.[10] The tissue agnostic FDA approval of the NTRK inhibitor larotrectenib for children and adults with NTRK gene fusions[11] serves as one example of novel regulatory approaches to rare tumors.

Ongoing studies such as the NCI-MATCH trial[12] are capitalizing on our rapidly increasing knowledge about activating and fusion mutations and epigenetic modifications in various types of tumors to precisely target treatments to patients based on the specific alterations present in their tumors. Enrollment of patients with rare tumors on these trials may yield information that will lead to future rare tumor-specific phase II trials. Articles in this issue by Plant-Fox et al., O'Sullivan Coyne et al., and O'Neill et al. provide rationale for applying rare tumor treatment approaches based on both histopathologic and molecular classifications.

To address some of the challenges inherent in developing therapies for rare tumors, we launched the MyPART (My Pediatric and Adult Rare Tumor) network, a Cancer Moonshot^{SM} – funded effort to increase engagement of patients, family members and advocacy in rare tumor research[13]. We are conducting a natural history study of rare solid tumors to comprehensively and longitudinally evaluate children and adults with rare solid tumors through collection of clinical, tumor, and PRO data. One of MyPART's goals is to increase communication and collaboration between all stakeholders involved in rare tumor research to accelerate the development of effective therapies for these tumors. Working together with all stakeholders (see article on the importance of advocacy by Reinke in this issue) and sharing information and resources will be critical to assuring continued progress. This progress promises to benefit patients as well as future research on both rare and common tumors. While progress cannot come quickly enough for the patients and families facing the diagnosis of a rare tumor, recent examples of success demonstrate that the future is starting to look brighter and more effective therapies will hopefully soon be within our grasp.

References

1. US NIH National Cancer Institute: Dictionary of Cancer Terms: “rare cancer; 2021 *https://www.cancer.gov/publications/dictionaries/cancer-terms/def/rare-cancer* accessed June 23, 2021.
2. Keat N, Law K, McConnell A, Seymour M, Welch J, Trimble T, et al. International Rare Cancers Initiative (IRCI). *Ecancermedicalscience*. 2013;7 ed20. doi:10.3332/ecancer.2013.ed20.
3. Greenlee RT, Goodman MT, Lynch CF, Platz CE, Havener LA, Howe HL. The occurrence of rare cancers in U.S. adults, 1995-2004. *Public Health Rep*. 2010;125:28–43. doi:10.1177/003335491012500106.
4. DeSantis CE, Kramer JL, Jemal A. The burden of rare cancers in the United States. *CA Cancer J Clin*. 2017;67:261–272. doi:10.3322/caac.21400.
5. Gatta G, Capocaccia R, Botta L, Mallone S, De Angelis R, Ardanaz E, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol*. 2017;18:1022–1039 doi:10.1016/S1470-2045(17)30445-X.
6. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68:820–823 doi.
7. US NIH National Cancer Institute Surveillance. *Epidemiology, and End Results Program: Cancer Stat Facts: Lung and Bronchus Cancer*. National Cancer Institute; 2021 *https://seer.cancer.gov/statfacts/html/lungb.html* accessed June 24, 2021..
8. Hallberg B, Palmer RH. Mechanistic insight into ALK receptor tyrosine kinase in human cancer biology. *Nat Rev Cancer*. 2013;13:685–700. doi:10.1038/nrc3580.
9. Yau NK, Fong AY, Leung HF, Verhoeft KR, Lim QY, Lam WY, et al. A pan-cancer review of ALK mutations: implications for carcinogenesis and therapy. *Curr Cancer Drug Targets*. 2015;15:327–336. doi:10.2174/1568009615666150225123712.
10. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15:731–747. doi:10.1038/s41571-018-0113-0.
11. . *US Food and Drug Administration: FDA approves larotrectinib for Solid Tumors With NTRK Gene Fusions*. U.S. Food and Drug Administration; 2018 *https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions* accessed June 24, 2021.
12. US National Cancer Institute. *NCI-MATCH Trial (Molecular Analysis for Therapy Choice)*. National Cancer Institute; 2021 *https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match* accessed June 24, 2021.
13. US NIH National Cancer Institute Center for Cancer research. *MyPART - My Pediatric and Adult Rare Tumor Network*. National Cancer Institute; 2021 *https://www.cancer.gov/pediatric-adult-rare-tumor/* accessed June 24, 2021.

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