Commentary: Not only SMART clinically, but translationally!

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All thoracic surgeons by this time are aware of the phenomenal results in non-small cell lung cancer when immunotherapy is combined with chemotherapy.¹ These effects occur at the level of the tumor microenvironment, heterogeneously populated with T cells, dendritic cells, macrophages, as well as granulocytes. Checkpoint inhibition will “take the brakes off” of the inhibitory effect of immune cytotoxicity by modulating the PD-L1/PD-1 axis; however, studies have shown that you can get more “bang for your buck” when you add other therapies to the checkpoint inhibitors.

Early studies reveal that the chance for greater than 90% tumor kill, as well as long-term progression-free survivals and overall survivals,² increase remarkably with combination therapy. Most recently, a taste of these encouraging results has been reported by Nowak and colleagues³ for mesothelioma, with a doubling of response rates compared with single-agent CPI inhibitors. Underlying all of these attempts at combination therapy is the strategy to increase tumor immunogenicity either by the release of death-associated molecular patterns (ie, DAMPS or alarmins), promotion of anti-tumor CD8+ T cells, inhibition of myeloid-derived stem cell activity, or the increase of antigen expression.⁴

de Perrot and colleagues⁵ have led the way with the innovative use of preoperative radiation therapy followed by extrapleural pneumonectomy in mesothelioma with promising overall survival even in patients with lymph node involvement. Their present investigation of the effects of this therapy on the malignant pleural mesothelioma tumor microenvironment⁶ is a natural evolution of their in vivo work documenting a specific immune activation against the tumor associated with significant up-regulation of CD8+ T cells of preoperative nonablative hypofractionated radiation.⁷ Obviously, an eventual goal would be the combination of checkpoint inhibition or some other immunotherapy with the SMART protocol to enhance tumor responses, but the approach of de Perrot

and colleagues is to be congratulated, since theirs is the first study in human mesothelioma to study baseline effects of hypofractionated radiation without the influence of other neoadjuvants.

It is unfortunate that we do not have the original biopsy specimen to interrogate and compare with the SMART specimens harvested at the time of surgery, and this is planned for the next series of studies. Yet, there are valuable take-home points to be studied and validated in the future, including the variability of prognosis depending on the levels of CD8-Til, PD-L1, and PD-1, as well as variability of effects depending on the malignant pleural mesothelioma histology. Future studies must tell us what the phenotype and function of these CD8 Tils are and why they are “decreased” after radiation therapy, as well as whether other factors in the interferon gamma pathway, including IRF1 and IRF2, could explain the increase in PD-L1 and better survival in epithelioid tumors.^{8,9}

Finally, there are important T-cell receptor assays that could be performed on the tumors pre- and posttreatment, which can define the richness and clonality of T-cell receptor neoantigens, as described by Reuben and colleagues¹⁰ in the NEOSTAR study. These translational studies will be supplemented in the future by such techniques as single-cell RNAseq and digital spatial profiling of the microenvironment. When combined with mechanistic studies that detail the function of T-cell phenotypes, immunotherapists

Mechanisms for stimulation of CD8 T-cells by radiation (From *Acta Oncologica* 2019;58:9-20).

Central Message

Preoperative radiotherapy for mesothelioma alters the tumor microenvironment. Understanding immune-related radiation changes may improve survival by altering neoadjuvant tumor antigenicity.

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as well as surgeons will certainly be able to personalize and improve our therapies for pleural mesothelioma.

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