

Dear friends of clinical journal club - load the file down at <https://www.mdc-berlin.de/cjc>. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 54-year-old woman with infiltrating ductal carcinoma of the right breast that had been treated with lumpectomy, locoregional radiation, and chemotherapy presented to the emergency department with a 4-week history of cough, fever, and dyspnea. On physical examination, an occasional cough was noted. Lung auscultation was normal. Computerized tomography (CT) of the chest is shown. What is the most likely diagnosis? You are offered: Drug-induced pneumonitis, Idiopathic pulmonary fibrosis, Lymphangitis carcinomatosa, and Radiation pneumonitis. Guilt by association is the clue. Neoadjuvant nivolumab (checkpoint inhibition) plus chemotherapy significantly improved pathological complete response and event-free survival in patients with resectable non–small-cell lung cancer (NSCLC) in a phase 3 trial. Data are needed on overall survival. N Engl J Med now presents long-term overall survival from this study. Long-term outcomes were clearly improved by nivolumab. Substance P and the neurokinins A and B all belong to the neurokinin family of neuropeptides, binding to several receptors. Elinzanetant inhibits the neurokinin-3 receptor and relieves menopausal “hot-flush” symptoms. Women receiving endocrine therapy for hormone receptor (HR)–positive breast cancer or its prevention among those at high risk for breast cancer commonly have vasomotor symptoms. Data are lacking on the effects of elinzanetant, a neurokinin-targeted therapy shown to be effective in treating vasomotor symptoms, in this population. Investigators performed a phase 3 trial involving women 18 to 70 years of age with moderate-to-severe vasomotor symptoms associated with endocrine therapy for HR-positive breast cancer or its prevention. Elinzanetant significantly reduced the frequency of these vasomotor symptoms. Myeloid cell-line production is regulated by granulocyte–macrophage colony-stimulating factor (GM-CSF), a multipurpose cytokine. Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by progressive surfactant accumulation and hypoxemia caused by autoantibodies against GM-CSF, which alveolar macrophages require to clear surfactant. Massive surfactant accumulation sharply reduces alveolar gas exchange. Molgramostim is a formulation of inhaled

recombinant human GM-CSF, but its efficacy and safety in patients with aPAP have not been studied sufficiently. In a phase 3, double-blind, placebo-controlled trial, investigators randomly assigned patients with aPAP to receive molgramostim at a dose of 300 µg or placebo once daily for 48 weeks. The primary end point was the change from baseline to week 24 in the diffusing capacity of the lungs for carbon monoxide (DLCO), which was adjusted for hemoglobin concentration and expressed as a percentage of the predicted value. Secondary end points adjusted for multiplicity were the change from baseline in DLCO at 48 weeks and the change from baseline in the St. George's Respiratory Questionnaire total (SGRQ-T) and activity (SGRQ-A) scores (scores range from 0 to 100, with lower scores indicating better quality of life) and in exercise capacity at 24 and 48 weeks. Molgramostim effectively improved DLCO in these patients. Cemiplimab is a PD-1-directed antibody, similar to nivolumab. Patients who have cutaneous squamous-cell carcinoma with high-risk features are at risk for recurrence after definitive local therapy. The benefit of systemic adjuvant therapy options has not been well established in clinical trials. In a phase 3, randomized trial, investigators enrolled patients with local or regional cutaneous squamous-cell carcinoma, after surgical resection and postoperative radiotherapy, at high risk for recurrence owing to nodal features (extracapsular extension with largest node  $\geq 20$  mm in diameter or at least three involved nodes) or non-nodal features (in-transit metastases, T4 lesion [with bone invasion], perineural invasion, or locally recurrent tumor with  $\geq 1$  additional risk feature). Adjuvant cemiplimab or placebo (usual care) were compared in these high-risk patients. The checkpoint-inhibitor therapy was successful in improving disease-free survival. The N Engl J Med review is on the role of artificial intelligence in post-graduate medical education. We learn about large-language models, deskilling, never-skilling, and mis-skilling. The weekly N Engl J Med case concerns a 32-year-old woman with fatigue, myalgias and a Wenckebach electrocardiogram phenomenon. A selfie solves the mystery. The Lancet first presents an entire meta-analysis on the value of spironolactone treatment in dialysis patients and underscores the fact that there was none. DGAT2 is an enzyme that plays a key role in the final step of triacylglycerol (TAG) synthesis by catalyzing the addition of a third fatty acid to diacylglycerol, forming storage fat. DGAT2 is an integral membrane protein primarily located in the endoplasmic reticulum (ER), but it can also associate

with lipid droplets (LDs) to facilitate localized TAG synthesis and LD expansion. Its function is essential for TAG storage in lipid droplets and for cellular processes like fat accumulation and hepatic triglyceride production. Lancet presents a randomized trial showing that antisense oligonucleotide DGAT-2-inhibitor therapy is effective in treating metabolic-associated steatosis hepatitis. Lancet then presents a randomized-controlled trial of community mental-health strategies in ameliorating or preventing mental illness. SADI-S is a single anastomosis, duodenal-ileal bypass, with sleeve gastrectomy treatment for massive obesity. Roux-Y gastric bypass is another commonly performed operation for massive obesity. Which operation is better? A randomized trial shows that SADI-S is (somewhat) superior to Roux-Y gastric bypass. Next, a Lancet commission reports on surgical health policy 2025-35 for tomorrow's surgical needs worldwide. A further commentary closes with suggestions regarding bioethics for the planet. *MUC19* is the gene encoding a mucous glycoprotein, not only responsible for nasal discharge but also for immune protection from pathogens. In Science Magazine, we learn through paleogenomics that *MUC19* was passed from Denisovans to Neanderthals, and eventually to Homo sapiens even to Native American. In Washington Post we are informed on how ChatGPT and large language models affect the way we speak and presumably think (or don't). So, protection is where you find it! Join me on Wednesday, August 27 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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