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Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer

Date: May 31, 2026

Metastatic pancreatic ductal adenocarcinoma (mPDAC) carries a dismal prognosis, with current second-line cytotoxic regimens yielding limited survival benefit. Oncogenic RAS mutations, present in the vast majority of these tumors, activate downstream proliferative and survival signaling. Daraxonrasib is a novel oral agent that suppresses RAS activity by binding to the active, GTP-bound conformation of both mutant and wild-type RAS isoforms.

This international, open-label phase 3 trial randomly assigned 500 patients with prior-treated mPDAC to either daraxonrasib (248 patients) or physician-selected standard chemotherapy (252 patients), with 91.8% of enrolled patients carrying RAS G12 alterations. The two primary efficacy measures were overall and progression-free survival specifically within the RAS G12-mutant subgroup, with secondary assessments encompassing the broader patient population (including G12, G13, Q61 mutations, and RAS wild-type), objective tumor response, and patient-reported outcomes.

In the RAS G12 population, daraxonrasib nearly doubled median overall survival compared with chemotherapy

(13.2 vs. 6.6 months), corresponding to a 60% relative reduction in the risk of death (hazard ratio, 0.40; $P < 0.001$). Progression-free survival was similarly improved (7.3 vs. 3.5 months; hazard ratio, 0.45; $P < 0.001$). Tumor shrinkage occurred in approximately one-third of daraxonrasib-treated patients, more than double the rate seen with chemotherapy (33.2% vs. 11.8%). Treatment-related grade 3 or higher toxicity were also less frequent with daraxonrasib (43.6%) than with chemotherapy (57.5%), and treatment cessation due to adverse effects was markedly lower (1.2% vs. 11.2%). The predominant daraxonrasib-related side effects were dermatologic and gastrointestinal in nature, typically low-grade and manageable with supportive care.

Daraxonrasib represents a significant therapeutic advance over conventional chemotherapy for previously treated mPDAC, affording substantial improvements in survival, disease control, and quality of life with a more favorable tolerability profile. These findings show that RAS(ON) inhibition is an effective precision-medicine strategy in this highly refractory malignancy.

Source: www.nejm.org

Finerenone in Persons with Chronic Kidney Disease without Diabetes

Date: June 4, 2026

As a nonsteroidal mineralocorticoid receptor antagonist, Finerenone has demonstrated renoprotective and cardiovascular benefits in patients with type 2 diabetes and chronic kidney disease (CKD). However, its efficacy and safety profile in patients with non-diabetic CKD had not been established prior to this investigation.

This phase 3, international, double-blind, randomized, placebo-controlled trial enrolled 1584 adults with type 1 diabetes, CKD (those with estimated glomerular filtration rate [eGFR] 25 to < 90 ml/min/1.73m²), and albuminuria (urinary albumin-to-creatinine ratio [UACR] 200 to < 3500). Participants were randomly assigned to receive finerenone (10 or 20 mg daily) or matching placebo, alongside standard renin–angiotensin system inhibitor therapy (angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB)). The primary endpoint was the total eGFR slope—the average annual change in kidney function from baseline through month 32—analysed using a two-slope linear spline mixed-effects model.

Over a median treatment period exceeding 3 years, the annual eGFR decline was slowed by 0.7 ml/min/1.73m²

with finerenone compared with placebo (-3.3 vs. -4.0 ml/min/1.73m² annually; 95% CI for difference, 0.3 to 1.1; $P < 0.001$). The composite kidney–cardiovascular outcome occurred less frequently with finerenone (13.9% vs. 16.9%; hazard ratio, 0.77; 95% CI, 0.60–0.99; $P = 0.04$). Hyperkalemia was more common with finerenone (17.0% vs. 13.3%), however serious hyperkalemia was rare ($< 1\%$) and led to treatment discontinuation in only 1.5% of finerenone recipients. Overall adverse event rates were comparable between groups.

In non-diabetic CKD patients already receiving RAS inhibitor therapy, finerenone slowed kidney function decline and reduced the risk of composite kidney–cardiovascular events compared with placebo, with a manageable safety profile. These findings provide additional evidence for finerenone's renoprotective benefits beyond the diabetic population, supporting its potential role as an additional therapeutic option in the broader CKD landscape.

Source: www.nejm.org

Adjuvant Pembrolizumab-Belzutifan Improves Disease-free Survival for Patients with Clear-Cell Renal-Cell Carcinoma

Date: July 2, 2026

Adjuvant pembrolizumab serves as a standard-of-care therapy after nephrectomy for clear-cell renal-cell carcinoma (ccRCC) patients at increased risk for recurrence. However, disease recurrence or death still occurs in approximately 40% of high-risk patients within five years. Belzutifan, a potent and selective hypoxia-inducible factor 2 α inhibitor, is clinically proven to slow tumour growth in specific kidney cancers with low-grade toxic effects.

The phase 3, double-blinded LITESPARK-022 trial randomly assigned 1841 adult participants with resected clear-cell renal-cell carcinoma in a 1:1 ratio to receive intravenous pembrolizumab 400 mg every 6 weeks for up to 9 doses plus either (1) oral 120 mg daily belzutifan (n=921) or (2) placebo (n=920) for up to 1 year. Eligible participants had intermediate-to-high risk, high risk, or M1 with no evidence of disease following surgery. The primary outcome was investigator-assessed disease-free survival (DFS), while key secondary outcomes included overall survival (OS) and safety.

At a median follow-up of 28.4 months, DFS was significantly prolonged with pembrolizumab-belzutifan

compared to pembrolizumab-placebo (hazard ratio for recurrence or death=0.72, 95% confidence interval [CI], 0.59-0.87, $P<0.001$), with 24-month DFS estimates of 80.7% versus 73.7%. Overall survival data remained immature (29% of target events) and showed no statistically significant difference between groups (hazard ratio for death=0.78, 95% confidence interval [CI], 0.51-1.19, $P=0.24$). Regarding toxicity, Grade 3 or higher adverse events occurred in 52.1% of the pembrolizumab-belzutifan group compared to 30.2% in the pembrolizumab-placebo group, primarily driven by a higher incidence of anemia (84.0% vs. 11.4%) and hypoxia (7.0% vs. 0.1%).

In conclusion, adding belzutifan to adjuvant pembrolizumab significantly improves disease-free survival in patients with resected clear-cell renal-cell carcinoma at increased risk for recurrence. Although the combination carries a higher incidence of Grade 3 or higher toxicities, its overall safety profile remains consistent with the known toxicities of each drug.

Source: www.nejm.org

Extended Dual Antiplatelet Therapy Reduces Composite Cardiovascular Deaths in Multivessel Coronary Artery Disease

Date: July 16, 2026

Multivessel coronary artery disease affects 40-60% of patients undergoing percutaneous coronary intervention (PCI), significantly elevating the risk of recurrent ischemic events and mortality from both treated and non-stented coronary segments. While 12 months of dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor is currently the golden standard following drug-eluting stent placement, extended treatment benefits remain uncertain due to concerns over elevated bleeding risks.

The open-label, randomized DAPT-MVD trial enrolled 8250 patients aged 18 to 75 across 97 Chinese institutions who had remained event-free for 12 months after drug-eluting stenting for multivessel disease. Participants were randomly assigned 1:1 to receive an additional 12 months of extended DAPT (n=4125) or aspirin monotherapy (n=4125) as placebo. The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke assessed in a time-to-event analysis. The primary safety end point was clinically relevant or major bleeding, classified with reference to Bleeding Academic Research Consortium (BARC) type 2 to 5.

Over a median follow-up of 34.3 months, extended DAPT significantly reduced primary efficacy events compared to aspirin monotherapy (5.8% vs. 6.8% 36-month cumulative incidence; Hazard Ratio=0.82, 95% confidence interval [CI], 0.69-0.98, $P=0.03$), primarily driven by a lower rate of nonfatal myocardial infarction (1.8% vs. 2.5%; Hazard Ratio=0.68, 95% confidence interval [CI], 0.50-0.93). Importantly, extended DAPT did not significantly increase clinically relevant or major bleeding (1.4% vs. 1.5%; Hazard Ratio=0.89, 95% confidence interval [CI], 0.61-1.30, $P=0.54$) or major BARC 3-5 bleeding (0.8% vs. 0.9%; Hazard Ratio=0.87, 95% confidence interval [CI], 0.53-1.43, $P=0.59$). Overall serious adverse events were similarly balanced between groups (27.7% vs. 28.0%, $P=0.77$).

In conclusion, extending DAPT with clopidogrel and aspirin for an additional 12 months in stable, event-free patients with multivessel coronary artery disease after drug-eluting stent implantation significantly reduces major adverse cardiovascular events. Furthermore, this ischemic benefit was achieved without increasing the risk of clinically relevant or major bleeding.

Source: www.nejm.org

Ralinepag for the Treatment of Pulmonary Arterial Hypertension

Date: July 28, 2026

Pulmonary arterial hypertension (PAH) remains a life-threatening disorder caused by increase in pulmonary vascular resistance, frequently resulting in right-sided heart failure and early mortality. Although the therapeutic landscape has expanded over recent decades, its prognosis remains suboptimal. Ralinepag is a novel oral prostacyclin IP receptor agonist administered once daily, using its vasodilatory and antiproliferative properties to control prostacyclin signalling.

This international, double-blind, placebo-controlled phase 3 study randomly assigned 687 patients with PAH to receive either Ralinepag (n=350) or matching placebo (n=337) on the basis of standard-of-care therapy. Dosing started at 50 µg daily with weekly up-titration to each patient's maximum tolerated level. The study population was predominantly on dual background PAH therapy (80%) and had a mean baseline 6-minute walk distance of 438.9 m. The primary outcome was the time from randomisation to the first clinical worsening event, a composite of death from any cause, admission to hospital due to worsening PAH or right heart failure, initiation of parenteral or inhaled prostacyclin-pathway therapy, disease progression, or any unsatisfactory long-term clinical response.

During the median observation period, the primary composite endpoint was reached in 18% of the Ralinepag arm versus 36% of the placebo arm, corresponding to a 55% relative risk reduction (hazard ratio, 0.45; 95% CI, 0.33–0.62; $P<0.0001$). The treatment effect was most pronounced for components related to disease progression, prostacyclin-therapy intensification, and inadequate long-term response. Secondary analyses showed favourable shifts in NT-proBNP (24.3% relative reduction vs. placebo; $P=0.0013$) and 6-minute walk distance (20.4 m treatment effect; $P=0.003$). Tolerability concerns led to treatment cessation in 19% of Ralinepag recipients, which was substantially higher than the 3% observed with placebo, with most discontinuations occurring during the titration phase. Serious adverse event rates were comparable between groups (28% vs. 31%), and on-treatment mortality was similar (4% in each arm).

In a predominantly low-to-intermediate-risk PAH cohort receiving dual background therapy, Ralinepag presents a significant and clinically meaningful reduction in clinical worsening events, accompanied by improvements in haemodynamic biomarkers and functional capacity.

Source: www.nejm.org

Perioperative Apalutamide Plus Androgen-Deprivation Therapy Provides Better Pathological Response in High-Risk Localized Prostate Cancer

Date: August 6, 2026

Patients diagnosed with high-risk localized or locally advanced prostate cancer face a significant risk of disease recurrence, with up to 50% experiencing a relapse within five years of undergoing a radical prostatectomy. Apalutamide, an oral nonsteroidal androgen receptor inhibitor, blocks the androgen-receptor pathway that binds testosterone to cancer cells. The efficacy and safety of apalutamide in addition to androgen-deprivation therapy (ADT) in perioperative setting among patients with potentially invasive localized prostate cancer is currently unknown.

The double-blind, placebo-controlled study randomized 2109 patients in a 1:1 ratio to receive either (1) ADT plus oral apalutamide 240mg daily (n=1057) or (2) ADT plus placebo (n=1052). The treatment regimen consisted of six 28-day cycles of neoadjuvant therapy before surgery and six cycles of adjuvant therapy following radical prostatectomy with pelvic lymph-node dissection. The trial utilized two dual primary efficacy end points: a composite of pathological complete response (pCR) or minimal residual disease (MRD), and metastasis-free survival (MFS) as determined via conventional imaging or PSMA PET. Key secondary outcomes included event-free survival (EFS), time to the first subsequent treatment, and safety, which was assessed through the tracking of adverse events graded by standard criteria.

Over a median follow-up of 61.7 months, the apalutamide group demonstrated significantly superior efficacy outcomes, achieving a pCR or MRD rate of 8.9% compared to 1.0% in the placebo cohort ($P<0.001$). The 5-year MFS rate was also significantly higher with apalutamide at 78.2% versus 73.5% for placebo, representing a 20% reduction in the risk of distant metastasis or death (Hazard Ratio=0.80, $P=0.02$). Secondary end points including EFS and time to subsequent therapy similarly favored the apalutamide arm ($P<0.001$). Regarding safety, Grade 3 or 4 adverse events occurred in 39.6% of patients receiving apalutamide compared to 31.0% receiving placebo, a variance driven primarily by a higher incidence of skin rash in the apalutamide group.

To summarize, the addition of perioperative apalutamide to standard ADT significantly improves long-term oncologic outcomes and disease control for patients undergoing radical prostatectomy for high-risk prostate cancer. Although the treatment is associated with a higher incidence of adverse events, particularly rash, its robust clinical efficacy establishes it as a highly beneficial therapeutic strategy in this patient population.

Source: www.nejm.org