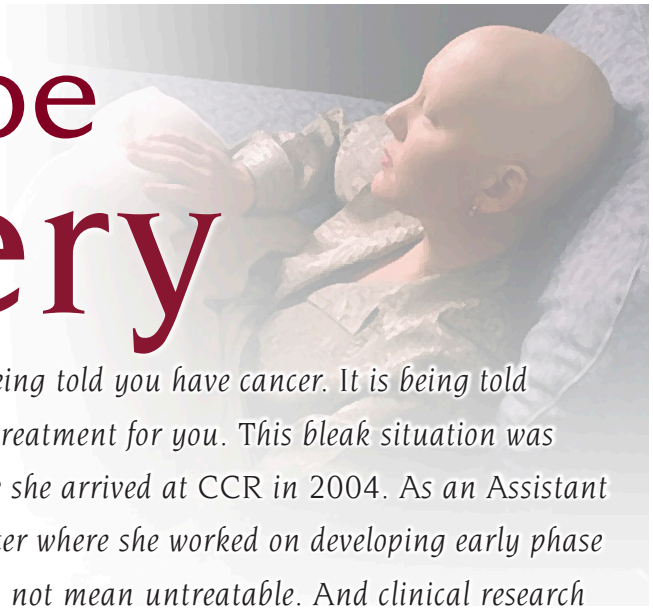
Bringing Hope Through Discovery

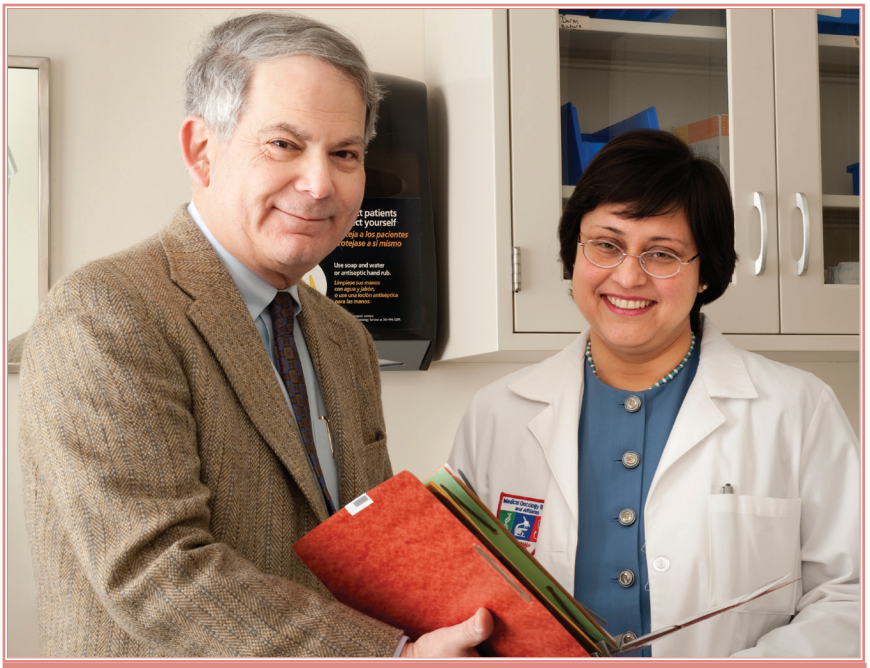


CCR clinicians know there is something worse than being told you have cancer. It is being told that your cancer is incurable, and there is no known treatment for you. This bleak situation was unacceptable to Shivaani Kummar, M.D., even before she arrived at CCR in 2004. As an Assistant Professor in medical oncology at the Yale Cancer Center where she worked on developing early phase drugs, her view was, and remains, that incurable does not mean untreatable. And clinical research provides her with the opportunity to increase treatment options for all cancer patients.

Since coming to CCR, Kummar has again focused her labor on early drug development as a Staff Clinician in CCR's Medical Oncology Branch. She is also Head of Early Clinical Trials Development, within NCI's Division of Cancer Treatment and Diagnosis (DCTD). Working closely together, the Kummar clinical team—clinical research coordinators, research nurses, nurse practitioners, and clinical fellows—is determined to see more discoveries translated into new therapy options for patients facing incurable cancers.

Setting out to establish new treatments, or better combinations of existing therapies, is a broad goal, so Kummar and colleagues take a comprehensive approach to drug discovery by offering more than a dozen new clinical trials at various stages of development. A few first-in-human phase 0 studies, which are early phase evaluations, investigate how the body responds to a drug and how the drug acts in the body. Several others look at drug safety and tolerance in phase 1 studies, and many more evaluate side effects and optimize a drug's effectiveness in pilot and phase 2 trials. All of the trials run by the Kummar team are kept small in size intentionally, so they can accumulate more in-depth data from a few representative patients which informs the further development of promising new agents.

(*Photo: R. Baer*)



James Doroshow, M.D., and Shivaani Kummar, M.D.

Phase 0 trials were conceptualized by James H. Doroshow, M.D., Director of DCTD and NCI Deputy Director for Clinical and Translational Research, as part of a national collaboration to improve the way clinical trials are conducted in cancer. The first step in shortening the drug development timeline was the addition of a new small-scale "proof-of-concept" trial called a phase 0 trial, prior to the formal phase 1 trials where they examine dose escalations of a drug. An ideal phase 0 trial comes armed

(*Photo: R. Baer*)

The Kummar Team: Front row: Yvonne Horneffer and Shivaani Kummar, M.D.; Second row: Lamin Juwara, Khanh Do, M.D., Abhilasha Nair, M.D., Giovanna Speranza, M.D., Deborah Allen, James Doroshow, M.D., Michelle Eugeni, Jennifer Zlott, and Ramya Parthasarathy, Not pictured: Janelle Bingham, Lauren Powell, and Woondong Jeong, M.D.

with a reliable assay that can monitor the changes that happen in the tumor with drug administration. It validates that a suspected target has been hit in human patients—as predicted from earlier non-human cancer models.

Kummar and her clinical team moved phase 0 trials from proposed concept to reality when they ran the first successful trial at NCI in 2006. They tested ABT888, also known as veliparib. This new drug inhibits an enzyme called poly (ADP-ribose) polymerase that is essential for repairing damage to DNA. The team used a rigorous assay to measure poly (ADP-ribose) in tumor tissue. Armed with the assay, they showed that ABT88 inhibited its target enzyme in tumor cells and in white blood cells. With data and a reliable assay from the phase 0 trial as a guide, veliparib has progressed on to more than 50 phase 1 and phase 2 trials nationwide that are now testing the new agent in various combinations with chemotherapy drugs. Cancers being treated in these trials include many types of solid tumors as well as lymphoid cancers, at all stages of disease.

In addition to running phase 0 trials, Kummar and her clinical team have made significant progress in several phase 1 and phase 2 studies. She reported to the American Society of Clinical Oncology in June 2011 the promising results from a phase 2 trial that evaluated cediranib for a rare cancer (makes up less than 1 percent of soft tissue sarcomas) called alveolar soft part sarcoma (ASPS). ASPS gets the "alveolar" part of its name from the arrangement of cells seen by the pathologist. Alveoli are small air sacks deep within the lung where oxygen is absorbed into the body, and this cancer, when examined under the microscope, appears similar to lung air sacks. ASPS results from a rare translocation between the ASPL locus on chromosome 17 and the TFE3 locus on the X chromosome (der(17) t(X;17)(p11q25)). This cancer strikes the young and frequently spreads, establishing small metastatic colonies throughout the body, especially in the lungs and even the brain of young patients. Until cediranib came along, there was no systemic drug known to be efficacious for metastatic ASPS.

Because pathologists consistently

Kummar Clinical Team

Research Nurses:

Deborah Allen, R.N., O.C.N.

Ramya Parthasarathy, B.S.N., R.N., O.C.N.

Jennifer Zlott, B.S.N., R.N., O.C.N.

Michelle Eugeni, B.S.N., R.N., O.C.N.

Nurse Practitioners:

Yvonne Horneffer, C.R.N.P.

Lamin Juwara, C.R.N.P.

Clinical Research Coordinators:

Janelle Bingham, R.N.

Lauren Powell

Clinical Fellows:

Khanh Do, M.D.

Abhilasha Nair, M.D.

Woondong Jeong, M.D.

report ASPS as highly vascularized, this rare cancer appeared to be a good candidate for an anti-angiogenic strategy. So the Kummar team tested cediranib, a potent oral inhibitor of all three vascular endothelial growth factor receptor (VEGFR-1,-2,-3) tyrosine kinases that are needed for tumor vascularization.

The Kummar clinical trial included 36 ASPS patients, and cediranib showed substantial single-agent activity against their cancers, with a greater than 40 percent response rate (partial responses) and a disease control rate (DCR) of 78 percent. They also analyzed the gene expression profile of tumors over the course of treatment and showed that cediranib had an effect on genes in the angiogenesis pathway, and it also affected genes in the inflammatory response pathways.

Cediranib has yielded several long-lasting responses, but, in anticipation of the possibility that drug resistance or disease recurrence might eventually develop, Kummar and her colleagues are identifying and testing alternative anti-angiogenesis drugs. The Kummar team, along with several other major cancer centers, is now testing sunitinib, another anti-angiogenesis inhibitor. Toward that goal, they are conducting a multicenter, randomized phase 2 study with Dana-Farber Cancer Institute in Boston, Mass., and with The University of Texas M.D. Anderson Cancer Center in Houston to compare cediranib with sunitinib in ASPS patients. Patients will receive either cediranib or sunitinib alone, and then they will switch to the other drug if their disease progresses.

In their quest for bringing hope through treatment options, the Kummar clinical team is also looking at creative combinations of existing drugs that can disrupt several cancer signaling pathways at once.

One example of a new combination being studied in colon cancer builds upon knowledge that cetuximab targets the epidermal growth factor receptor, which is expressed in the majority of these solid tumors. Recognizing that one possible mechanism of drug resistance to cetuximab is through the Ras-Raf pathway, which controls cell growth, division, and differentiation,

Representative Phase 1 and Phase 2 Trials of the Kummar Clinical Team

New Agent/Combo	Desired Effect
Pazopanib and Tivantinib	Disrupts blood vessel formation and the MET pathway
MK-2206 and AZD6244	Disrupts both AKT and MEK pathways (Merck and AstraZeneca drugs)
Cyclophosphamide and Veliparib	Damages tumor DNA and PARP inhibitor prevents its repair
EZN-2208 and Bevacizumab	Disrupts cancer's DNA replication with longer acting version of the active form of camptothecin 11 that inhibits topoisomerase 1 and blocks new blood vessel formation (Enzon drug)
Belinostat	Turns silenced genes back on to limit cancer's growth. Being evaluated in patients with liver abnormalities
Z-Endoxifen	Disrupts estrogen-receptor-driven growth in patients with hormone positive cancers
Vorinostat	Turns silenced genes back on to limit cancer's growth; being tested as a treatment for adenoid cystic cancer, a rare disease
Phase 0 trial of IPdR Absorption, Metabolism, and Safety	Tests whether IPdR is absorbed in humans to eventually develop it as an oral radiosensitizer
EZN-2968	Blocks the hypoxia inducible factor 1 alpha (HIF) production (Enzon drug)
Indenoisoquinolines LMP400 and LMP776	Blocks topoisomerase 1 needed to cut DNA during cancer cell's replication (non-camptothecin inhibitors)

and another common cancer ally is the vascular endothelial growth factor receptor (VEGFR2) pathway, the team is combining cetuximab therapy with sorafenib. Because sorafenib disrupts both Raf kinase and VEGFR2 tyrosine kinase activity, this strategy could enhance the clinical potency of cetuximab in metastatic colon cancer, especially in patients with KRAS mutation positive colorectal cancer.

The chart on the previous page provides some additional examples of new strategies being tested. These treatments range from drugs that inhibit the action of histone deacetylases and change the shape of chromatin to agents that directly disrupt cancer's replication activities.

An advantage of discovering effective combination treatments in addition to new agents is that, once they are identified, they may prolong or even eliminate the drug resistance that often develops during seemingly successful therapies. Another is that lower doses of each drug may be used when they act in unison. This should reduce the collateral damage to normal cells and tissues.

Kummar speaks for her entire team in summing up their focus this way, "Cancer is innovative and resourceful in its attempt to proliferate and metastasize. However, we will continue to work with researchers in various cancer-related disciplines to bring forth novel agents for the treatment of cancer. We will not rest until there is a treatment option for every incurable cancer."

To learn more about Dr. Kummar's research and clinical trials, please visit her Web site at http://bethesdatrials.cancer.gov/investigator-profiles/default.aspx?investigatorid=127.

Patients or doctors interested in finding out what clinical trials are under way at the NIH Clinical Center need only visit bethesdatrials.cancer.gov.

Disease Control Rate (DCR): A Surrogate Marker

In clinical trials, a surrogate marker for the effect of a certain treatment looks like it correlates with a real clinical event—like cure or death—but the link is not guaranteed. That is why the NIH defines them as "a biomarker intended to substitute for a clinical endpoint."

Surrogate markers are used when the primary endpoint is undesired (for example, death), or when the number of events is too small to be statistically significant. During new drug development, the U.S. Food and Drug Administration (FDA) will often accept evidence from clinical trials that show a direct clinical benefit to surrogate markers.

Disease control rate (DCR) is one such surrogate marker. For most clinical trial treatments, patients will exhibit stable disease (SD) or progressive disease (PD) more often than a complete response (CR) or partial response (PR). DCR is a hopeful surrogate marker that opposes PD. It includes CRs, PRs, and SDs.

CCR's Treatment Trials by Phase

The majority of CCR's early-phase studies, from pre-Phase 1 (preIND) through Phases 1 and 2, are proof-of-principle trials that answer some of the basic questions about optimizing a new drug's dose, safety, and mode of delivery.