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What Pharmacists Need to Know About Targeted Therapies

SYLLABUS

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This independent CE activity is supported by an educational grant from **Genentech, Inc** and **OSI Oncology.**

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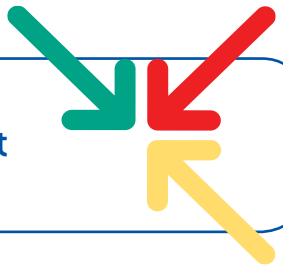

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Sincerely,

Robert S. Stern
President
Projects In Knowledge, Inc.

Dear Colleague:

Cancer therapy has come a long way since the time when the only available treatments were relatively ineffective and caused major systemic side effects. Since the 1980s and 1990s, with the advent of new molecular biology tools, cancer has been studied at both the genetic and molecular level. This is providing a better understanding of the pathways controlling the normal cell cycle, including cell suicide mechanisms and a variety of growth factors. Proteins in these pathways have been identified as potential targets for therapeutic intervention. Additional research is under way with the intent of developing improved targeted therapeutic interventions, with optimized therapeutic ratios, based on a more in-depth understanding of the molecular basis of cancer.

Starting with Dr. Judah Folkman's seminal work in defining the role of angiogenesis in the growth and spread of tumors, research has generated a variety of targeted therapies. Not only do these therapies reduce tumor burden and often improve survival, they generally do so with fewer side effects and less overall systemic toxicity. However, these targeted therapies do have unique toxicities that need to be closely monitored. The recent addition of several targeted therapies to the cancer treatment armamentarium has definitely expanded therapeutic options for our patients.

Applying these innovations to improve the care of our patients with cancer requires not only an understanding of the therapies, but also a knowledge of how these agents can be incorporated into treatment strategies that provide optimal patient care. The CE-accredited, on-demand webcast *What Pharmacists Need to Know About Targeted Therapies* is designed to help you develop a better understanding of these innovative therapies and how they can be integrated into cancer therapy. This engaging program covers the following key topics: molecular basis of cancer, mechanism of action of targeted therapies in tumor growth, efficacy and safety of targeted therapies used in the treatment of solid tumor types, and a discussion of the present and future roles of targeted therapies.

What Pharmacists Need to Know About Targeted Therapies offers you—on demand 24/7 from the convenience of your computer screen—a timely and enriching educational opportunity. I invite you to go to your computer and take advantage of this useful program. Thank you.

Sincerely,

Hai T. Tran, PharmD

Chair

Drugs or Investigational Agents Mentioned in This Presentation

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Gemtuzumab ozogamicin	Mylotarg®
Ibritumomab tiuxetan	Zevalin®
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Thrombospodin	—
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Trastuzumab	Herceptin®
VEGF-TRAP	—
ZD2171	—
ZD6474	—

Program Information

Target Audience

This CE activity is directed to oncology pharmacists involved in the care of cancer patients.

Activity Goal

The goal of *What Pharmacists Need to Know About Targeted Therapies* is to provide the latest data on the use of targeted therapies in the treatment of solid tumors.

Learning Objectives

- Differentiate among major cellular signaling pathways involved in cancer development to identify potential targets for therapeutic interventions.
- Assess how targeted therapies may work in the treatment of various solid tumors utilizing knowledge of the mechanism of action of these agents on cancer growth.
- Analyze the efficacy and safety of targeted therapies in the treatment of solid tumors based on recent clinical trial results.
- Evaluate treatment strategies for patients with solid tumors by integrating an understanding of the mechanisms, efficacy, and safety of current and emerging targeted therapies.

CE Information: Pharmacists

Projects In Knowledge is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity has been planned and implemented in accordance with the ACPE Criteria for Quality and Interpretive Guidelines. The ACPE Universal Program Number assigned to the program, for 1 contact hour (0.1 CEU), is 052-000-06-021-H01.

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Cathy Eng, MD, has disclosed that she will reference unlabeled/unapproved use of bevacizumab in clinical trials for breast cancer.

Jon D. Herrington, PharmD, BCPS, BCOP, is on the speakers bureau of Amgen Inc; his wife is an employee of Pfizer Inc. Dr. Herrington has disclosed that he will not reference any unlabeled/unapproved uses of drugs or devices.

Tarek Mekhail, MD, MSc, FRCSI, FRCSEd, has received grant/research support from Celgene Corporation, Genentech, Inc, Merck & Co, Inc, and Vion Pharmaceuticals, Inc; is on the speakers bureau of Genentech, Inc, Eli Lilly and Company, and Sanofi-Aventis; and owns stock in Genentech, Inc and Pfizer Inc. Dr. Mekhail has disclosed that he will reference unlabeled/unapproved uses of bevacizumab.

Hai T. Tran, PharmD, has received grant/research support from AstraZeneca, Genentech, Inc, Novartis Pharmaceuticals Corporation, and OSI Pharmaceuticals Inc; is a consultant for Genentech, Inc; and is on the speakers bureau of Genentech, Inc and Sanofi-Aventis. Dr. Tran has disclosed that he will not reference any unlabeled/unapproved uses of drugs or products in his presentation.

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This independent CE activity is supported by an educational grant from **Genentech, Inc** and **OSI Oncology.**

Chair

Hai T. Tran, PharmD

Assistant Professor
Pharmacology–Research Cancer Medicine and Pharmacy
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Hai T. Tran, PharmD is an assistant professor of Cancer Medicine & Pharmacology in the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas M. D. Anderson Cancer Center, in Houston, Texas. Dr. Tran holds a PharmD degree from the University of Kentucky, College of Pharmacy, in Lexington, Kentucky, and a BS from Temple University, School of Pharmacy, in Philadelphia, Pennsylvania. After completing his General Pharmacy Residency, he was a Post-Doctoral Fellow at the M. D. Anderson Cancer Center, where he also held a Post-Doctoral Residency in Oncology. Prior to becoming an assistant professor, Dr. Tran was a director in the Clinical and Translational Research Center Office of Research Administration-Clinical, in the Division of Cancer Medicine and Pharmacy, at the M. D. Anderson Cancer Center. In 1998, Dr Tran received an AACR/ASCO Methods in Clinical Cancer Research honor in Vail, Colorado. He continues to be actively involved in pharmaceutical and clinical research, and has authored dozens of publications. Dr. Tran is a peer-reviewer for several journals, including *Bone Marrow Transplantation, Pharmacology and Therapeutics,* and *Clinical Cancer Research*.

Faculty

Cathy Eng, MD

Assistant Professor
Department of Gastrointestinal Medical Oncology
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Cathy Eng, MD is an assistant professor in the Department of Gastrointestinal Medical Oncology at the University of Texas M. D. Anderson Cancer Center in Houston, Texas. After completing a BA in Psychobiology with an International Politics minor at New York University, New York, Dr. Eng was awarded an MD from Hahnemann University School of Medicine in Philadelphia, Pennsylvania. She completed her residency training in PGY-2 Diagnostic Radiology at St. Barnabas Medical Center in Livingston, New Jersey, and in internal medicine at Rush-Presbyterian St. Luke's Medical Center in Chicago, Illinois. She also completed a Hematology/Oncology fellowship at the University of Chicago Medical Center in Chicago, Illinois. Dr. Eng is board certified in internal medicine and medical oncology. Dr. Eng is highly involved in clinical research, primarily focusing on colorectal cancer, and is the principal investigator or co-investigator of numerous clinical trials. In recognition of her research accomplishments, Dr. Eng received the SWOG Young Investigator Award in 2005. She is an active member of SWOG's Gastrointestinal Committee, the ASCO Career Development Committee, the ASCO Scientific Program Committee Gastrointestinal Cancer-Colorectal/Liver track, and a liaison to the ASCO Health Services committee. Dr. Eng has authored dozens of peer-reviewed publications, abstracts, and book chapters. She is also a reviewer for almost a dozen publications including the *Journal of Clinical Oncology, Cancer,* and *Clinical Cancer Research.*

Faculty

Jon D. Herrington, PharmD, BCPS, BCOP

Hematology/Oncology Clinical Specialist
Department of Pharmacy
Scott & White Memorial Hospital
Temple, Texas

Jon D. Herrington, PharmD, BCPS, BCOP is a Hematology/Oncology Clinical Pharmacy Specialist at Scott & White Memorial Hospital and Clinic in Temple, Texas. He is also the Hematology/Oncology Specialty Residency Program Director and an active member of the Blood and Marrow Transplant Program at the same institution. Dr. Herrington is a highly experienced, Board Certified Pharmacotherapy Specialist and Oncology Pharmacy Specialist. After receiving his BS in Pharmacy, Dr. Herrington completed a doctor of pharmacy degree from the St. Louis College of Pharmacy, in St. Louis, Missouri. He then completed a Pharmacy Practice residency and a Hematology/Oncology Specialty Residency at the Lucille P. Markey Cancer Center of the University of Kentucky Chandler Medical Center in Lexington, Kentucky. Dr. Herrington has a lengthy and varied publication record in general clinical pharmacy and oncology clinical research. He is a reviewer for *Pharmacotherapy* and the *American Journal of Health-System Pharmacy.*

Faculty

Tarek Mekhail, MD, MSc, FRCSI, FRCSEd

Director, Lung Cancer Medical Oncology Program
Hematology/Medical Oncology
The Cleveland Clinic Foundation
Cleveland, Ohio

Tarek Mekhail, MD, MSc, FRCSI, FRCSEd is the Director, Lung Cancer Medical Oncology Program and Hardis Chair in Oncology Research, Taussig Cancer Center, at The Cleveland Clinic Foundation, in Cleveland, Ohio. His clinical interests focus on aero-digestive malignancies and the development of novel agents. Dr. Mekhail is board certified in hematology, medical oncology, and internal medicine. He holds an MD from Cairo University in Egypt. Dr. Mekhail received his advanced medical training in Ireland where he was awarded a Master Degree (MSc.) in ENT and Head and Neck Surgery, a Fellowship of The Royal College of Surgeons in Ireland (FRCSI), and a Fellowship of The Royal College of Surgeons of Edinburgh (FRCSEd). He completed his post-graduate training at the Cleveland Clinic Foundation with an internal medicine residency and a hematology and medical oncology fellowship. Dr. Mekhail is a member of the SWOG Lung and Lung Biology committees, and the Hematology and Oncology Fellowship Committee. He has published more than 30 peer-reviewed articles and authored numerous abstracts, presentations, and book chapters. Dr. Mekhail received a SWOG Young Investigator Award in 2000 and the Teacher of the Year Award, Hematology/Medical Oncology Program in 2003-2004 and 2004-2005.

Unraveling the Molecular Basis of Cancer

Hai T. Tran, PharmD

Cancer is a complex disease that is slowly surpassing heart disease as the leading cause of deaths in the United States. In 2006, it is estimated that almost 840,000 Americans will die from cancer, with the respiratory-related cancers accounting for 59% of the cases.[1,2] There are many identified causes of cancer, including exposures to chemicals (eg, hydrocarbons, asbestos, and tobacco), radiation, viruses (both DNA and RNA types), and cellular oncogenes.[3,4]

Over the last 30 years, one of the major areas of oncology research has been to identify the molecular differences between normal host cells and cancerous cells. Researchers are discovering the complexity of the signaling networks that regulate various biochemical processes and the difficulties that arise when attempting to block some of these critical pathways. Other critical areas of research include: understanding the processes involved in the transformation of a normal cell to a malignant cell, identifying the various genes that are altered, and understanding how cell cycle and associated proteins control cellular death or apoptosis.

Standard cytotoxic agents, which usually target more rapidly proliferating cells, have been the mainstay of cancer therapeutic interventions, and they have done so with varying degrees of success. Newer therapeutic strategies have turned towards the inhibition of specific growth factors and cellular pathways necessary for tumor survival, growth, and metastasis. Examples of agents with novel therapeutic targets include: decitabine (a demethylating agent), bortezomib (a proteasome inhibition), bevacizumab (an anti-vascular endothelial growth factor [VEGF] monoclonal antibody), interferon alfa and beta, sunitinib (a multitargeted agent), trastuzumab (an anti-HER-2 monoclonal antibody), cetuximab (an anti-epidermal growth factor [EGFR] monoclonal antibody) and erlotinib (an EGFR tyrosine kinase inhibitor). These are some of the first- and second-generation targeted agents that have been approved for specific indications. Many more agents are currently under clinical investigation. The key to maximizing the potential of these novel agents will be to optimize their use in combinations with other targeted agents and with standard cytotoxic agents.

The recent FDA approval of the first vaccine against human papillomavirus (HPV) is making way for the prevention of one of the main causes of cervical cancer. The hope is that cervical cancer might be one of the first to be removed from the list of malignancies that affect humans. Cancer therapy is an evolving paradigm. The future of anticancer therapy rests on understanding cancer at the molecular level, taking advantage of current available anticancer agents, and testing novel agents.

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How Do Targeted Therapies Work?

Jon D. Herrington, *PharmD, BCPS, BCOP*

Over the past 10 years, the growth of new specific targeted agents has expanded. From the development of rituximab to that of multitargeted tyrosine kinase inhibitors (TKIs), these agents have revolutionized the treatment of specific malignancies. Unlike the nonspecific chemotherapy agents, which use a shotgun approach that harms both normal and malignant cells, these newer therapies have a more specific targeted mechanism of action, which attempts to minimize damage to normal cells.

The main advantage of traditional chemotherapy agents is that they have recognized cytotoxic activity in certain malignancies. Disadvantages include their mechanism of selectivity (which targets rapidly dividing cells regardless of their malignant status), minimal efficacy in advanced disease, and significant toxicities. Targeted therapies have the advantage of a higher degree of selectivity to certain molecular targets that are more specific to the malignant state and the associated decreased toxicity to normal cells. Disadvantages include unknowns surrounding their clinical use in combination with other agents, challenges to optimizing regimens, the need to identify potential long-term effects, and higher costs.

Currently available classes of targeted agents include monoclonal antibodies and TKIs. Monoclonal antibodies (MoAbs)—bioengineered with murine, chimeric (murine/human), humanized, or fully-human molecular make-up—exert their mechanism of action by binding to the extracellular domain of a targeted TK receptor or by binding to circulating ligands for transmembrane receptors.[1] For example, the recombinant humanized MoAb cetuximab and the fully-human recombinant MoAb panitumumab both bind to the epidermal-growth factor receptor (EGFR). Bevacizumab, another recombinant humanized MoAb, binds to vascular endothelial growth factor (VEGF), a ligand of VEGFR, leading to disruption of intracellular signals that stimulate angiogenesis.

Small molecule TKIs include those agents that target the TK domain of single or multiple molecules in order to disrupt the neoplastic transformation, invasion, growth and metastases and/or angiogenesis.[2] Single-action TKIs include erlotinib and gefitinib, which compete for ATP in the intracellular domain of EGFR. Current multitargeted TKIs include imatinib, dasatinib, sunitinib, and sorafenib. These agents selectively inhibit a variety of TKs on malignant cells and normal cells. For example, imatinib occupies the ATP pocket of the Bcr-abl kinase, thus inhibiting the phosphorylation of the substrate. In addition to inhibiting the intracellular kinase Bcr-abl, imatinib also inhibits the membrane TKs, platelet-derived growth factor receptor (PDGFR), found on pericytes, and Kit. Newer TKIs are active against a variety of membrane-bound TKs and intracellular kinases acting downstream in various signaling pathways. One such drug, sorafenib, is an effective inhibitor of the membrane TKs, VEGFR, PDGFR, Kit, Ftl3 and the downstream intracellular kinase, Raf.

Binding of MoAbs and TKIs to their targets in malignant cells is expected to lead to cell cycle arrest; potentiation of apoptosis; inhibition of angiogenesis, cell invasion, and metastases; and augmentation of antineoplastic effects from chemotherapy and radiation therapy.[1] An increased understanding of cancer cell biology has led to important advances in targeted therapy with the use of MoAbs and TKIs. One fertile area of research is uncovering the mechanisms of resistance to TKIs and developing agents and regimens that can circumvent these mechanisms.[2]

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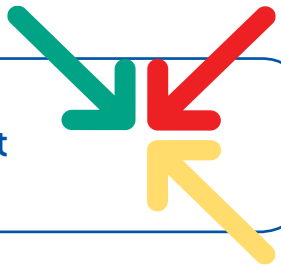


Clinical Update: Efficacy and Safety of Targeted Therapies

Cathy Eng, MD

Over the past 4 years we have seen an abundance of advancements in the three most common malignancies in the United States, lung, breast, and colorectal cancers. The breakthroughs made in these malignancies provide the impetus for further analysis in less-common malignancies, such as renal cell carcinoma.

The fundamental concept that "angiogenesis" is involved in endothelial cell growth and tumor survival was coined by Judah Folkman in 1971.[1] A primary mediator of angiogenesis is the vascular endothelial growth factor (VEGF) family, which is composed of several different glycoproteins (PIGF, VEGF-A, VEGF-B, VEGF-C, and VEGF-D) that bind various receptors (VEGFR 1-3 and neuropilin). Neuropilin is unique in lacking an intracellular tyrosine kinase domain and appears to enhance the activity of VEGFR-1 and 2.[2] It was not until 2004 that the biological agent, bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor-A (VEGF-A, aka vascular permeability factor) was approved in the treatment of metastatic colorectal cancer (CRC).[3] Its approval has brought to fruition the theory of antiangiogenesis treatment for patients with cancer. However, bevacizumab selectively blocks only one part of the VEGF family, specifically VEGF-A. Furthermore, the VEGF family is only one of several key pathways with a role in carcinogenesis.

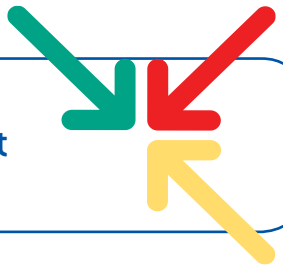
Bevacizumab is currently approved in the front-line and second-line treatment (if bevacizumab treatment naive) of metastatic CRC. It appears to be most efficacious in combination with systemic chemotherapy based on its minimal response and time to progression when provided as a single agent.[4] Two phase III studies have been conducted with bevacizumab in combination with chemotherapy in the patients with treatment-naive stage IIIb/IV non–small-cell lung carcinoma (NSCLC)[5] and in patients with recurrent metastatic breast cancer.[6]

The epidermal growth factor receptor (EGFR) is overexpressed in several malignancies (including NSCLC and colorectal, pancreatic and ovarian cancers), and is associated with an increased risk of tumor cell survival, growth, and risk of metastases. The chimeric, anti-EGFR monoclonal antibody, cetuximab, was first approved for treatment of patients with metastatic CRC, who were previously exposed to irinotecan or intolerant to irinotecan, resulting in overcoming resistance to irinotecan. It is currently being evaluated in the front-line and second-line setting (without prior irinotecan exposure); final results are pending. Cetuximab has efficacy not only in combination with systemic chemotherapy and as a single agent, but also as a radiation sensitizer and is currently approved in the treatment of patients with locally advanced, unresectable head and neck squamous cell carcinoma.[7] The fully human monoclonal antibody panitumumab recently received approval for the treatment of patients with EGFR-positive refractory metastatic CRC (after treatment with fluoropyrimidine-, irinotecan-, and oxaliplatin-based therapy), based on results of a phase III trial that compared best supportive care with best supportive care plus panitumumab.[8]

Another promising biologic agent in the treatment of metastatic breast cancer is the dual tyrosine kinase inhibitor of ErbB1/ErbB2, lapatinib. Lapatinib given in combination with capecitabine demonstrated improved time to progression compared with capecitabine monotherapy in a heavily pretreated patients.[9] Results of this clinical study with lapatinib further exemplify the additive role of biologics when given in conjunction with systemic chemotherapy.

Sunitinib and sorafenib are other recently approved agents that have stimulated a great deal of interest. Both have very different mechanisms of action (ie, targeting the VEGF versus the Raf/ras MAP kinase pathways, respectively), yet both clearly demonstrate the progress made in the treatment of advanced renal cell carcinoma.[10-12]

Increased use of the biologic agents will likely continue to reveal potential treatment-related toxicities requiring all patients and healthcare workers to be familiar with the potential side effects to prevent any unnecessary morbidity and mortality. As progress continues in the development of biologic agents, greater knowledge regarding the mechanism and interaction of existing pathways will likely be used in the development of even more effective biologic agents and regimens. Of great need is to develop ways to distinguish among patients who are or are not likely to respond to currently available cytotoxic and biologic agents. This will help minimize exposure of patients to unnecessary toxicities. Studies in genomics and proteomics are currently under way to address these very issues.



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Present and Future Role of Targeted Therapies in Cancer Care

Tarek Mekhail, MD, MSc, FRCSI, FRCSEd

The drug development paradigm in cancer therapeutics has evolved into a much more systematic approach than what was previously used to identify cytotoxic agents. This approach involves extensive preclinical experimentation to identify and characterize suitable therapeutic targets, evaluation of preclinical activity, and clinical assessment. One of the most valuable new therapeutic targets is the HER2/ErB2 family of receptors that includes the epidermal growth factor receptor (EGFR).[1,2] Commercially available agents that target EGFR include the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib, and the monoclonal antibodies cetuximab and panitumumab. Another successful new target for anticancer agents is the process of angiogenesis, which is a key step in tumor growth and metastasis.[3,4] In particular, the vascular endothelial growth factor (VEGF) pathway became a truly validated target through the success of the anti-VEGF monoclonal antibody bevacizumab, which has FDA-approved indications in both colorectal cancer and lung cancer.

The future of targeted therapies depends on optimizing their use in combination with each other and with cytotoxic agents, the development of new multitargeted drugs that attack more than key signaling pathways to fight the potential of developing drug resistance, and the development and validation of clinical and molecular markers of response to direct therapeutic selection for individual patients. Clinical trials have begun to hint at the tantalizing potential of combination targeted therapies, for example with bevacizumab and erlotinib,[5] and the potential of multitargeted TKIs.[6] Analysis of data from the National Cancer Institute of Canada Clinical Trials Group Study BR.21 has provided additional support that smoking history may have some usefulness as a clinical marker for response to erlotinib treatment.[7] Examples of molecular markers for response include EGFR mutation status by gene sequencing, EGFR gene copy number as determined by fluorescence in situ hybridization, and EGFR protein expression by immunohistochemistry. Clearly, none of these are ready for prime time in the clinic.

A fascinating story on the impact of targeted therapies in cancer treatment is the recent advances in the treatment of renal cell carcinoma (RCC). An understanding of the molecular mechanisms of RCC tumor development was critical to the development of new effective agents.[8] The multitargeted TKIs sorafenib[9] and sunitinib[10] recently earned FDA-approved indications in RCC, the first new drugs approved for RCC in decades.

All of these agents have side effects that tend to be mild to moderate, but include rarer, possibly life-threatening toxicities. These are not the typical side effects (eg, severe nausea/vomiting, neutropenia) associated to chemotherapy that gave a bad name to medical oncologists. The new side effects include hypertension and skin toxicities that are common to anti-EGFR agents, and infrequent bleeding episodes associated with anti-VEGF agents.

The future of cancer care rests on achieving a better understanding of the mechanism of action of currently available and new agents, overcoming evolving drug resistance, learning how to use these agents in combination, applying these agents to the treatment of earlier stages of disease, and developing individualized treatment approach. Our ultimate goal continues to be cure, and now we have additional tools to judiciously offer our patients.

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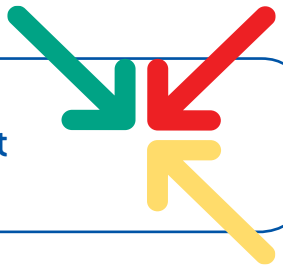

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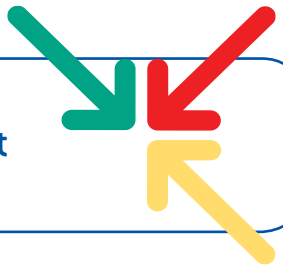

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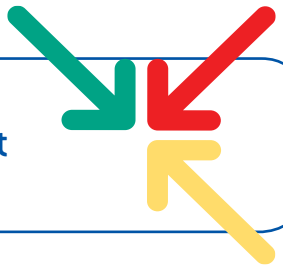

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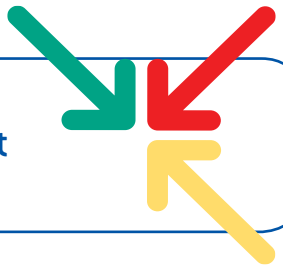

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