Cancer: The Road to Amiens

David J. Stewart, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX
Razelle Kurzrock, Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas M. D. Anderson Cancer Center, Houston, TX

"The Battle of Amiens, which began on 8 August 1918, was the opening phase of the Allied offensive...that ultimately led to the end of World War I. Allied forces advanced over seven miles on the first day, one of the greatest advances of the war."

"The importance of this offensive in tactical terms was that it...provided a further example of the effectiveness of shifting from stagnant trench warfare to mobile multifaceted warfare."1

THE PROBLEM

After impressive victories against hematologic and germ cell malignancies, the battle against common epithelial cancers has evolved into a grinding war of the trenches, where statistical victories with \( P < .05 \) are hailed as advances despite survival gains of mere weeks (Table 1).3-11 We feel that progress against cancer and most other diseases has been slowed substantially by the clinical research efficacy bar having been set too low and consequently the safety bar having been set too high. When little is to be gained, minimization of risks becomes paramount. Together these faulty efficacy and safety standards slow research progress while escalating costs.

Low efficacy bars benefit many stakeholders. Investigator careers are built on "positive" studies, statisticians become indispensable when advances are so small that only they can detect them, National Cancer Institute programs demonstrate that they help identify "active" new drugs, the US Food and Drug Administration demonstrates that it fosters safe access to "useful" new therapies, companies can market new agents, and providers can bill for new therapeutic options delivered. Drug sales yield advertising dollars to fuel publications and campaign dollars to fuel elections. Insurers simply pass on the higher costs by raising premiums. Almost everyone benefits. Unfortunately, the gain for patients is often exceptionally modest and at exorbitant cost.

One can come up with many reasons supporting the efficacy bar being set at its current level, but in our opinion a low efficacy bar has not served patients or society well. By encouraging investors and investigators to go for the (by comparison) easy money, we feel that it is a major direct impediment to investment in more meaningful progress, and that substantially raising the bar is the most important first step for speeding the pace of progress. Successful sports coaches know that raising the bar is one of the most powerful tools at their disposal to improve team performance. While the behaviors encouraged and permitted by a low bar hold back the entire team, good people will rise to a challenge. Past discussions with both colleagues and with pharmaceutical companies suggest to us that what they are seeking are not low, easy standards, but rather standards that are clearly defined.

Raising the efficacy bar may prove difficult. There are no conspiracies or villains. Large armies of dedicated people are fighting very hard in this war on cancer, but maladjusted research goals, governance, economics, politics, legalities, accepted clinical research practices, and dogma unintentionally impede progress. "Every system is perfectly designed to get exactly the results it gets."12 Space only permits us to present below a simplified overview of a few of several potential mechanisms for altering the current landscape.

PHASE III TRIALS AIM TO FIND SMALL DIFFERENCES IN LARGE GROUPS, NOT LARGE DIFFERENCES IN SMALL GROUPS

To raise the efficacy bar, we must first better identify those patients who truly benefit from new treatments. There is a rapidly growing consensus among many clinical cancer researchers that treatments for individual patients should be much more personalized based on their tumor’s molecular characteristics, and we are at the earliest stages of seeing potential benefits from this approach (eg, selective use of trastuzumab versus breast cancers with high amplification of \( \text{HER2/neu} \) and erbitux in K-ras wild type colorectal cancers13). Currently, multi-million dollar randomized trials often accrue hundreds or thousands of largely unselected patients in the quest for statistical evidence of improved median survival. This “significant” improvement, which often measures less than 12 weeks, and may be as little as 11 days (Table 1) potentially represents substantial benefit in a subpopulation, but little or no benefit for most. Regrettably, the importance of the trial is judged far more by the size of the \( P \) value than by the absolute gain in survival. If a randomized study is positive, then the new therapy becomes a standard of care despite being minimally effective in a high proportion of patients to whom it will be applied. If it is negative, then a therapy may be discarded despite offering real benefit to a specific subpopulation of patients, as exemplified by gefitinib in non–small-cell lung cancer (NSCLC).14 Both consequences are unacceptable.
Furthermore, unless thousands of patients are enrolled, a drug that leads to dramatic responses, but only in 5% to 10% of patients, might be predicted to fail in randomized trials involving unselected patients, and hence may be abandoned without even reaching phase III testing. However, as advocated by an ever-increasing number of investigators, if we fully utilized modern tools that permitted us to better understand the molecular underpinnings of drug sensitivity, then a drug with even a 5% to 10% response rate in an unselected population might represent a major advance in a small subpopulation of patients who were predicted to benefit even though the drug did not have a meaningful impact on the population as a whole. Attention to this difficult but imminently achievable task is imperative since it may not be coincidental that most drugs tested in common cancers have not been coincidental that most drugs tested in common cancers have relatively low response rates. The same biologic reason may underlie a cancer being common and having low response rates: if multiple different molecular abnormalities can lead to a single type of cancer, then that cancer would be expected to occur frequently, only a minority of patients with that cancer would have a given molecular abnormality, and hence a new agent would yield only low response rates (since it would only impact the subset of tumors bearing the relevant target). For example, epidermal growth factor receptor (EGFR) mutations and K-ras mutations are each relatively uncommon and mutually exclusive precursors of NSCLC. EGFR inhibitors are active against NSCLCs with EGFR mutations, but generally inactive against those with K-ras mutations. If we properly select patients for sensitive mutations, a high proportion may benefit. It is time to stop investigating efficacy of drugs against tumors defined solely by histopathologic type and to instead investigate efficacy against tumors defined by a combination of histopathologic and molecular and genetic profiles, where the molecular and genetic profiles that prove to be of benefit may vary with both the tumor type and the drug under investigation. We may often find that our initial assumptions are wrong, but we should nevertheless be able to progressively narrow down the spectrum of patients targeted. The important factor is not the specifics of the type of profile that is investigated, but rather whether or not, at the end of the day, the profile can predict drug efficacy. While there has been some modest movement in this direction, it has been far too little.

One might also reasonably question whether it would be economically and technically feasible to develop agents where the expected benefit was limited to a small patient subpopulation. The development of imatinib in uncommon malignancies (chronic myelogenous leukemia and gastrointestinal stromal tumors) is an example arguing strongly that it is feasible.

Resources for clinical research are limited and large investments in one direction compromise our ability to pursue other directions. Therefore, instead of spending tens of millions of dollars on large randomized trials to identify miniscule average survival gains in large populations, limited resources would be better used to define molecular predictors that would identify a small proportion of patients with a relatively high probability of benefiting and that would permit pre-selection of patients for a drug. We believe that, with current molecular tools and the redirection of the multimillions that are typically spent on phase III trials, responders could be more reliably identified for many drugs. If this were done, high response rates might render a randomized trial unnecessary, unjustifiable or even unethical. Conversely, if it takes a large randomized trial to tell us whether we have made progress against metastatic cancer, we are aiming too low.

### Table 1. Selected Randomized Studies Supporting Drug Approval and/or Use in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Disease</th>
<th>Random Assignment</th>
<th>No. of Patients</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine³</td>
<td>Cytotoxic</td>
<td>Pancreatic cancer</td>
<td>Gemcitabine v fluorouracil</td>
<td>126</td>
<td>5.65 v 4.41 6 weeks .0025</td>
</tr>
<tr>
<td>Bevacizumab⁴</td>
<td>Anti-VEGF antibody</td>
<td>Colorectal cancer</td>
<td>Bevacizumab + FOLFOX4 v FOLFOX4</td>
<td>829</td>
<td>13.0 v 10.8 2.2 &lt; .05</td>
</tr>
<tr>
<td>Erlotinib⁵</td>
<td>EGFR inhibitor</td>
<td>Pancreatic cancer</td>
<td>Erlotinib + gemcitabine v gemcitabine + placebo</td>
<td>569</td>
<td>6.24 v 5.91 11 days .038</td>
</tr>
<tr>
<td>Bevacizumab⁶</td>
<td>Anti-VEGF antibody</td>
<td>Non–small-cell lung cancer</td>
<td>Bevacizumab/carboplatin/ paclitaxel v carboplatin/ paclitaxel</td>
<td>878</td>
<td>12.3 v 10.3 2 .013</td>
</tr>
<tr>
<td>Sorafenib⁷</td>
<td>VEGFR and Raf kinase inhibitor</td>
<td>Renal cancer</td>
<td>Sorafenib + supportive care v placebo + supportive care</td>
<td>902</td>
<td>4 v 2 2 &lt; .001</td>
</tr>
<tr>
<td>Temozolomide⁸</td>
<td>Cytotoxic</td>
<td>Glioblastoma multiforme</td>
<td>Temozolomide + radiation therapy v radiotherapy alone</td>
<td>573</td>
<td>14.6 v 12.1 2.5 &lt; .01</td>
</tr>
<tr>
<td>Docetaxel⁹</td>
<td>Cytotoxic</td>
<td>Prostate cancer</td>
<td>Docetaxel + prednisone v mitoxantrone + prednisone</td>
<td>1,005</td>
<td>18.9 v 16.5 2.4 .0094</td>
</tr>
<tr>
<td>Topotecan¹⁰</td>
<td>Cytotoxic</td>
<td>Cervical cancer</td>
<td>Topotecan + cisplatin v cisplatin alone</td>
<td>293</td>
<td>9.4 v 6.5 2.9 &lt; .05</td>
</tr>
<tr>
<td>Cetuximab¹¹</td>
<td>Anti-EGFR antibody</td>
<td>Colorectal cancer</td>
<td>Cetuximab + supportive care v supportive care</td>
<td>572</td>
<td>6.1 v 4.6 1.5 &lt; .05</td>
</tr>
</tbody>
</table>

**Abbreviations:** VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; FOLFOX4, fluorouracil/leucovorin/oxaliplatin; VEGFR, vascular endothelial growth factor receptor.
smaller, more focused phase III trials using prospective rather than retrospective assessments of profiles.

The current reliance on large randomized trials has played a role in trapping us in the current trench warfare situation. On the Western Front in World War I, the main objective of massive frontal attacks was to capture a trench a few hundred yards away. This led to expenditure of more than a million lives with very minimal gains. In March 1918, Germany’s General von Hutier implemented a new strategy. Instead of mounting a massive assault to try to capture nearby opposing trenches, he sent smaller units racing across and past the opposing trenches aiming for objectives far beyond them, leaving the trenches themselves to mop-up crews. With this approach in just 8 days he advanced 40 miles in a war that had for years been marked by advances of a few hundred yards. The Allies counterattacked, adapting the new high-mobility strategies of their enemy to launch the Battle of Amiens, the opening phase of the Hundred Days Offensive that culminated in Allied victory.1

Like amassed troops targeting only a nearby trench, large randomized trials aiming to increase survival by a few weeks are a huge expense likely to achieve only modest gains, because modest gains are precisely what they are aiming for. We instead need a plethora of highly mobile smaller trials each with the goal of achieving much more ambitious outcomes.

The successful strategy used in childhood acute lymphoblastic leukemia (ALL) of building on a series of small sequential advances to eventually achieve high cure rates has been proposed as a model for all cancers.19 However, this was not the strategy used in germ cell tumors or Hodgkin’s disease, where single new concepts led to large advances. In epithelial tumors this model has led to only modestly improved survival, and systemic therapies remain incapable of curing metastatic epithelial malignancies. Cancer and Leukemia Group B went from being unable to cure ALL to curing around 20% of patients over the course of just five trials.19 In leukemia, the goal was cure. Increased survival was not the primary goal, but instead was a byproduct of patients being cured. The ALL model has clearly not been translated effectively to metastatic epithelial malignancies.

**PRACTICALITIES**

Major practical issues face molecular-profile-based clinical research. The first is sample acquisition. Our experience running biopsy-based trials indicates that research tumor samples can be safely obtained from a majority of patients. While physicians may be reluctant to consider such biopsies, most patients gladly consent. Even if tumor is unavailable, blood is better than nothing, as there is increasing experience with blood-based biomarker and pharmacogenetic analyses that correlate with outcome.

The sequence of seeing a patient, discussing a study, arranging a biopsy and awaiting results to assess study eligibility is also too time-consuming. The alternative is that tumor and blood samples should be collected and broadly profiled as early as possible after diagnosis. The process then becomes finding the right study for a patient rather than finding the right patient for a study.

Sample acquisition and profiling are very expensive, but the profiling would be less expensive if done in centralized labs, and this broad profiling should be high priority for the National Cancer Institute and industry dollars freed up by our other suggestions.

Finally, there is pressure to use only CLIA-certified laboratory procedures for tests determining assignment of patients to study therapies. This is impractical for broad profiling. The option should be to use non-CLIA research laboratories initially to define the profiles of interest, and to require CLIA-certified procedures only for final validation and community adoption.

**USING RESISTANT TUMORS TO SCREEN FOR AGENTS THAT WILL ADD VALUE**

We should also preferentially target patients with highly resistant tumors in initial phase II trials. Over the past 25 years the strategy has been to instead preferentially target lightly pretreated patients to reduce the risk of missing “good drugs.” Consequently we ended up with many agents that probably killed similar tumor cell populations as the older drugs or were limited by the same resistance mechanisms, and positive phase II studies became negative phase III studies. What we really need are drugs that work against tumor cells that are resistant to other agents. Indeed, there are striking examples that demonstrate that hitting the right target can benefit patients with cancers resistant to conventional therapy, as happened with imatinib in gastrointestinal stromal tumors,20 EGFR inhibitors in NSCLC,21,22 and trastuzumab in breast cancers.23 The ability of a new drug to lead to further shrinkage of tumors that have either grown or stopped shrinking during standard therapy would suggest that it is capable of killing cells resistant to standard therapy, and that it may represent a potential therapeutic advance worthy of further study. We would argue that ability of a drug to give at least some tumor shrinkage in highly resistant tumors is more significant than a 20% partial response rate in lightly pretreated tumors.

Importantly, tumors growing or no longer shrinking on therapy may be different from tumors that progress after therapy discontinuation. As noted with a variety of malignancies, tumors regrowing after therapy completion may have reversion to partial sensitivity, either from reversal of resistance-inducing epigenetic changes that occurred while on therapy or from regrowth of sensitive clones that had been suppressed by therapy. Response to a new agent of tumors regrowing following cessation of therapy may not be as important as response of a demonstrably resistant tumor.

Shrinkage of resistant tumors with a new agent need not reach Response Evaluation Criteria in Solid Tumors Group (RECIST)24 or WHO25 partial response (PR) status to be interesting. RECIST and WHO criteria are based on the fact that old technologies (unlike modern scanning methods) required substantial shrinkage to ensure that tumors had actually shrunk.25 They discard useful information on lesser degrees of shrinkage, and there is no biologic basis for choosing a 30% reduction in tumor diameter or 50% reduction in products of diameters as a response cut point. We26 and others27 demonstrated the feasibility of reporting efficacy as a continuous variable (percent change in tumor size) rather than as response versus nonresponse. Positron emission tomography scanning or computed tomography tumor density changes may also be more relevant than RECIST for some malignancies.28 For resistant tumors, the important objective is evidence of tumor cell killing by the new therapy, not the achievement of PR status.
TUMOR SHRINKAGE VERSUS STABILITY

While tumor shrinkage less than PR is of interest in resistant tumors, and while patients with stable disease survived as long as those with PR in some studies,29 the recently espoused concept30 that success in cancer treatment can be defined as converting cancer to a chronic disease with long-term stability, even in the absence of tumor shrinkage, may not play out favorably. Unlike cancer, other chronic diseases like diabetes and atherosclerosis are not plagued by evolving mutations and metastases. With infections, treatment with an agent that suppresses growth but does not eradicate the infection ultimately leads to resistance. We would generally not be happy just keeping tuberculosis (TB) stable and we should not be happy just keeping cancer stable either. With cancer as with TB, the objective has to be cell killing and eventual eradication, since both develop resistance over time. The fact that tumor eradication has proven difficult does not justify aiming lower.

NEED FOR A HIGHER STANDARD FOR LIGHTLY PRETREATED PATIENTS

While we should use the ability to benefit those with resistant disease as an important criterion for selecting agents that one subsequently tested in lightly pretreated patients (in order to minimize the probability of ending up with new agents that simply do the same thing that older agents can do), studying lightly pretreated patients would also need to be an option to allay the competing concern that a drug which constituted a major advance in chemotherapy-naive patients would be missed if tested only in highly resistant disease with accumulated mutations. There is no question that a good agent will generally be more effective in lightly pretreated than in heavily pretreated populations. However, if tested in lightly pretreated patients, one should raise the bar and expect substantially greater efficacy than typically seen with conventional agents when studying lightly pretreated patients. Regardless of the prior treatment status of the study participants, the major objective should remain the identification of those most likely to benefit by using molecular markers to progressively narrow down the population as studies progressed.

One might argue that having different standards for lightly pretreated than for heavily pretreated patients could introduce a new degree of complexity to trial design that is impractical. In fact, this is very straightforward. Already in standard phase II and III trials, one generally defines ab initio the level of efficacy that one would need to see in order to designate that a drug is worthy of further study, and this level of activity does vary among studies. Hence, rather than increasing study complexity, we are simply stating that the bar must be placed higher, particularly for trials in lightly-pretreated patients.

BENCHMARK FOR RANDOMIZED TRIALS

While randomized trials may not always be needed to confirm a new agent’s efficacy in resistant disease, or where the responders can be selected so well that response rates are very high, they may be warranted in less resistant populations. However, when randomized trials are done in patients with metastatic disease, progression-free survival (PFS) should generally be used rather than overall survival (OS) because of the potential confounding effect of subsequent therapies on OS. While there are many examples of improved PFS not translating into improved OS, this simply means that we need to do a better job of understanding what happens to patients after tumor progresses, and does not negate the importance of PFS as an end point. Furthermore, we feel one should aim at least for the greater of a 6-month absolute increase or 50% relative increase in PFS in such trials since this will only be achieved if investigators first identify those most likely to benefit from the new therapy and since targeting a large increase in PFS substantially reduces the number of patients required for adequate statistical power. If one does successfully identify the population most likely to benefit and is thereby able to reduce trial size by concentrating on this population, this in turn will consume fewer research resources, potentially freeing more resources for assessment of factors predicting efficacy. Advances in tumor molecular profiling should be used to identify small groups with large gains from a new therapy. We must avoid the temptation of using them with the objective of trying to tease out a small population with only a small gain. The ultimate goal of the exercise must be salvaging patients, not salvaging borderline drugs.

Randomized trials may also be valuable where cure is possible (eg, with adjuvant therapy), and some of the most important advances in oncology have been in the adjuvant setting. Improving cure rates of common cancers even slightly can translate into thousands of lives saved. However, while change in hazard ratio or median survival is often the primary end point of these trials, the proportion of patients cured is instead actually the most important outcome in adjuvant trials. In a few studies, specific analytic methodologies such as mixture distribution analysis31 or nonlinear mixed effects modeling32 have been used to help define the proportion of patients cured. We have also recently experimented with nonlinear regression analysis of exponential decay survival curves,33 which can define percentage of patients potentially cured while also providing the survival half-life for the group that are not cured.

INAPPROPRIATELY HIGH SAFETY BARS MARKEDLY SLOW PROGRESS

As noted earlier, if efficacy bars are low then safety bars must be high to make treatment “worth it.” When we talk of a high safety bar, we are not talking necessarily about the degree of toxicity to which patients are exposed, but rather the bureaucratic load associated with dealing with that toxicity. High safety bars dramatically slow progress. For example, animal toxicology and efficacy studies are poorly validated, add little to safety of anticancer agents, and do not predict well for either toxicity or antitumor activity in humans. The requirement for such animal studies delays entry of new agents into clinical trials, decreases the number of agents that can be tested clinically, and escalates costs. The only preclinical toxicology data actually needed before initiation of a phase I trial in patients with advanced malignancies are the mouse LD10 (to permit selection of a reasonably safe phase I starting dose) and an assessment of interactions of the agent with the cytochrome p450 system (to permit reasonably safe use in patients receiving other drugs). One can always go back to animal species later to further investigate unexpected toxicities seen in early clinical trials.

The low efficacy bar/high safety bar paradigm has also led to an increasing obsession with not allowing any deviation from the protocol, despite there being little evidence that this rigidity ultimately
improves safety. While deliberate falsification of data should be dealt with harshly, there should be greater flexibility in clinical trial conduct. In the past, protocols were regarded as guides for study conduct, and the principal investigator had substantial latitude in permitting deviations that would be in the patient’s best interests. However, in recent years, purportedly in order to protect patient safety, protocols have come to be regarded as legally binding documents rather than as guides. When physicians are forced to very rigidly follow preconceived protocols rather than their clinical judgment, safety may be lowered. Turning protocols into legally binding documents also slows trials by requiring repeated delays while formal amendments are written, reviewed, and approved. Patient quality of life can also be unnecessarily adversely impacted by regulations which outline exactly what day each and every test and procedure must be done. Furthermore, as the demands for compliance escalate, even patient refusal to undergo procedures they do not want are now, at times, being designated “major protocol violations.” Since such violations reflect poorly on the investigator and research personnel, this may increase study compliance, but it is not in the best interest of the patient, nor does it follow the basic tenet of creating a research environment where respect for patient autonomy is paramount. In addition, this type of rigidity does not reflect standard clinical practice and may make the protocol a poorer predictor for how a new drug will ultimately perform. The important thing is what was actually done and what were the results? This is more important than trying to adhere in minute detail to an original plan, especially in the context of treating patients with complex illnesses such as cancer. While an appropriate degree of order and cautious, thoughtful interpretation of results are very important to the conduct of sound clinical research, we feel that the current unthinking rigidity governing clinical research is detrimental.

The current regulatory burden in the conduct of clinical trials is to the war on cancer what World War I mud was to trench warfare. The thigh-deep, sticky Flanders mud jammed rifles, entrapped vehicles, weighed down massively caked clothing, pulled like glue at legs and boots, and swallowed and drowned those who stumbled and fell.34 This regulatory burden is onerous, misguided, and expensive, with little value added. For example, one author’s (D.J.S.) department receives around 600 external serious adverse event (SAE) reports per month for agents that it is studying clinically. A single event may generate a dozen or more SAE reports (one for the original event, one for each follow-up, and a separate copy of each of these for each protocol using the agent). In addition to the SAE reports being highly repetitive, the overwhelming majority report events that are more likely related to tumor progression or comorbidity, are well-known toxicities of the agent, or are irrelevant for other reasons. Despite this, purportedly to raise the safety bar, each copy of each form received required a separate document be prepared, submitted, reviewed, corrected (to properly conform to the shifting regulatory interpretation du jour) and resubmitted to the institutional review board (IRB). This does not improve patient safety but does magnify research costs and investigator frustration. Similarly, Humphreys et al35 documented that 16.8% of the total costs of an eight-site observational trial were devoted to IRB interactions, despite no visible effect on human subject protection, and the essential procedures of their study never changed substantially despite exchanges of more than 15,000 pages of material.

Large amounts of valuable research nurse time are also spent completing deviation reports and answering numerous queries from sponsors and compliance personnel, and numerous lab reports must be individually signed by investigators. The details of the clinical trials methodology reflect a system in which the real objective is reduction of legal and regulatory risk rather than enhancement of safety or increasing cancer cure rates. Dr Greg Koski (former director of the US Office for Human Research Protection) noted that IRBs are “more focused on protecting themselves from the regulatory hammer than on protecting human subjects from harm, to the detriment of the clinical research process.”36 Others noted that “the IRB system is being overwhelmed by a focus on procedures and documentation at the expense of thoughtful consideration.”37

“A good manager does things right. A good leader does the right thing.”38 Currently in clinical research, management trumps leadership. We now have a massive machine managing research but have lost sight of our goal. The solution is not to further strengthen a myriad of labyrinthine rules by which research is managed. The solution instead is to establish a few key guideposts by which we are led. Stricter compliance with policies, procedures, and regulations will not win the war on cancer. The most effective leaders and managers are those who cut through the plethora of rules that do not add value and get things done rather than becoming bogged down in a managerial morass.39 The most effective businesses are those in which well-trained workers are given substantial independence with respect to how they reach clearly defined goals rather than being required to follow detailed procedural cookbooks.40 The most effective nations are those in which freedom of thought and action supersedes rigidity and dogma.41

Cancer is a terrible disease. Progress to date has been slow, tedious, and too limited. We feel that we now have the knowledge to potentially change the landscape for patients with cancer. However, the objectives, methods, and regulation of clinical trials need to change so that we can rapidly move drugs from the lab into the clinic, and then define those drugs that are effective and those patients who are most likely to benefit.

**Authors’ Disclosures of Potential Conflicts of Interest**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “C” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None Consultant or Advisory Role: David J. Stewart, GlaxoSmithKline (C); Liquidia Technologies (C); McKinsey & Co (C); Adherex (C); Cowen and Co (C); Easton Associates (C); Medacorp (C); Nektar Therapeutics (C); Yung Shin Pharmaceuticals (C); Pierre Fabre (C); Methylenic Inc (C); Univalor (C); Medicanova, Inc (C); Weyth (C); Human Genome Sciences (C); AstraZeneca (C); LC Diagnostics; Razelle Kurzrock, Centocor Inc (C); Maxygen (C); AstraZeneca (C)

**Stock Ownership:** None Honoraria:
Sophie Raworth presents live from Amiens Cathedral in France to commemorate the centenary of the battle that changed the course of the First World War. 08 Aug 2018. Share this with Facebook. Share this with Messenger. Share this with Twitter. Share this with Email. Share this with Facebook. ThinkLab | Infectious Disease. 1. Cancer: The Road to Amiens. Journal of Clinical Oncology 182d 1 tweets. Vivek Subbiah, MD 182d ago. Cancer: The Road to Amiens ascopubs.org/doi/full/10.12â€¡ @Dr_R_Kurzrock. 0. However, the current pre-Amiens paradigm in cancer research points us toward a much larger clinical trial than is required. Like the stagnant trench warfare strategy, large clinical trials hamper progress toward victory in the war against cancer. Therefore, we cheer the initiative of Stewart and Kurzrock. 1. The author(s) indicated no potential conflicts of interest. REFERENCES. 1. Stewart DJ, Kurzrock R: Cancer: The road to Amiens. J Clin Oncol. 27:328-333, 2009. Journal of clinical oncology correspondence. VOLUME 27 Ä¡ NUMBER 18 Ä¡ JUNE 20 2009. 3062 © 2009 by American Society of Clinical Oncology Journal of Clinical Oncology, Vol 27, No 18 (June 20), 2009: pp 3062-3069. Downloaded from jco.ascopubs.org on April 8, 2013.