

lesions to be turned into a mutation they need to be fixed through replication. Thus, a mutation occurring late in cancer development will only generate mutations in single daughter cells. This is in sharp contrast to high mutational rates caused by loss of mismatch repair or repeated exposure to UV or carcinogens at an early stage that increases mutation rates through hundreds rounds of replication (Figure 1). For example, a mismatch repair defect increases the mutation rate >100 fold [8], providing maybe ~1000 mutations instead of ~10 in each round of replication in the entire genome. This would, with over ~100 rounds of replication over many years, generate hundreds of thousands of mutations in each cancer cell as is the case of a mismatch repair defective cancer (Figure 1). A 10-fold increase in mutations in one round of replication is going to result in only a marginal increase in overall mutations (Figure 1).

3. *Non-dividing cancer cells do not mutate.* Most cells in established tumours are non-dividing and chemotherapy treatments trigger cell cycle checkpoints, lowering the amount of cycling cells. As new mutations require replication, the vast majority of cancer cells will not mutate following chemotherapy.
4. *The immune system primarily recognises clonal neo-antigens.* It has been demonstrated that cancers harbouring clonal neo-antigens (present in all cells) demonstrate highest survival and are likely to respond best to immunotherapy [3]. Furthermore, it has been demonstrated that cancer cells with new antigens escape and remain unrecognised if the cancer cells carrying the neo-antigen only make up a small proportion of the tumour [9]. For clonal neo-antigens to be generated, the mutations need to occur early in cancer evolution (Figure 1). Following chemotherapy, any mutation would be introduced in a single cancer cell and hence would likely go undetected by the immune system. Furthermore, even if such a cell could be recognised this is unlikely to generate any significant overall response, as there is no evidence of abscopal effects in this setting.

In conclusion, chemotherapy may potentially boost immunotherapy responses through the cGAS, STING or other pathways. However, for the above reasons it is unlikely that chemotherapy will introduce novel targetable neo-antigens in tumours.

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Making adjuvant therapy decisions with uncertain data

The purpose of adjuvant therapy—therapy given after the curative intent treatment of the primary cancer and in the absence of any measurable disease—is to reduce the risk of local and distant recurrence in order to reduce the complications of local failure (improve quality of life) and/or improve survival. This logic underlies the rational use for local therapies such as radiation, and systemic therapies such as chemo-, targeted- and immunotherapies. Recent trials in oncology highlight three issues in

adjuvant therapy. First, is it good enough to improve disease-free survival (DFS) if that does not translate into overall survival (OS)? Second, what magnitude of DFS should we pursue? And, third, how should we use adjuvant drugs in settings without randomized controlled trials (RCTs)?

Although the use of adjuvant therapies is common in a variety of malignancies—most notably in lung cancer, breast cancer and colorectal cancer—the evidence that their use improves overall survival is not always clear. Improving DFS from removal of primary tumor to development of relapse or death is sometimes considered to be a surrogate for overall survival; however, the

correlations are not always strong. For instance, the DFS in the adjuvant setting provides good correlation for OS in colon and lung cancers, but not breast [1]. In the absence of strong correlation, improving DFS without improving OS may offer a poor risk/benefit tradeoff to the patient, because unlike the metastatic setting, adjuvant therapy, by definition, cannot make people feel better. It is important to ask in settings with weak correlations whether other composite end points may be more robust. For instance, DFS in breast cancer includes local recurrence or ductal carcinoma *in situ*, and one wonders whether a composite of more severe events (distant metastasis or death) might function as a superior surrogate. Future research should test such claims.

In the absence of strong correlation to OS, the use of adjuvant therapy in this situation converts a person to a patient—i.e. adds a therapeutic burden that would not otherwise exist. For this reason, recommending adjuvant therapy ought to require us to have strong evidence that it is helping the patients. Indeed, if there is no improvement in OS, the patient might as well take the drug at the time of relapse when the motivation for treatment, and potential to improve symptoms, is stronger.

The correlation between DFS and OS that has been documented in the cited umbrella review is applicable only to the class of drugs studied and cannot be extrapolated to other class [1]. Because the mechanism of action of cytotoxic agents, targeted drugs and immunotherapies are different, any correlation achieved between DFS and OS with cytotoxics may not be translatable to targeted drugs or immunotherapies in the same setting. This is best exemplified by good correlation with OS with cytotoxic chemotherapies for NSCLC, but trials with targeted agents such gefitinib showing mixed results in biomarker subgroups (DFS benefit, but no OS benefit) [2].

Recent approvals have shown that OS benefits have become not only unnecessary but that a DFS benefit itself from a drug can be very marginal and yet the drug can receive approval. Neratinib has received FDA approval for use in HER2+ breast cancer patients as an adjuvant drug post trastuzumab for 1 year [3]. With 1 year of a drug as toxic and expensive as neratinib, the only recorded benefit is in invasive DFS by a mere 2.3% at 2 years [4]. Here, the placebo group patients had a 2 year invasive DFS of 91.9%. In a similar study of adjuvant pertuzumab, the 3-year invasive DFS were 94.1% versus 93.2% in the pertuzumab and placebo groups, respectively [5]. Thus, it seems nearly 92% patients will remain disease free without any additional therapy. Pertuzumab is also associated with increased diarrhea and cardiotoxicity that has to be taken into account. For the extra 1% prevention of relapse/death (again not mortality), is it justified to ask all patients an extra year of therapy with all the toxicities and cost?

Consider also the use of sunitinib as adjuvant therapy after surgical resection of high-risk renal cell cancer. Two randomized trials have assessed this agent. Both fail to show OS benefit and one of two trials had a DFS benefit, although the DFS benefit was also lost when the two trials were pooled together [6]. Quality of life for patients on adjuvant sunitinib was worse [7]. However, the overall survival curves—extending to 7 years of follow-up—were superimposable [8]. Again, despite the FDA approval, one might question the role of such an adjuvant therapy where quality of life is worsened with no effect on survival and disputed effect on DFS.

We believe that adjuvant trials in oncology must satisfy certain criteria to be meaningful to patients. The adjuvant trials should (i) first target the patients at highest risk of relapse; (ii) utilize the primary end point of OS (unless DFS is validated in that setting for the given class of agent); (iii) universally measure quality of life (iv) and be powered to detect clinically meaningful differences in outcome, but not overpowered to detect the significance of marginal differences.

As a corollary, in the absence of clear randomized trial data that an adjuvant therapy improves outcomes in that setting, caution must be warranted.

Table 1 depicts eight examples where adjuvant therapy is widely used and recommended by professional societies in the absence of randomized controlled trial data supporting its use. Notably, many of these examples are cytotoxics or are supported by retrospective observational studies. The uniting thread in all of these examples, however, is the lack of benefit in prospective randomized controlled trials.

Consider this alongside [supplementary Table S1](#), available at *Annals of Oncology* online. [Supplementary Table S1](#), available at *Annals of Oncology* online shows several examples of drugs which were highly promising and successful in the metastatic setting, which were unable to be translated in to the adjuvant setting. Notably, we find targeted therapies, angiogenesis inhibitors, cytotoxic and other drugs, suggesting all classes of medication may fail.

Finally, consider [supplementary Table S2](#), available at *Annals of Oncology* online. [Supplementary Table S2](#), available at *Annals of Oncology* online shows many examples of adjuvant therapies which are successful in appropriate patient populations, but are not successful when expanded to populations at lower clinical risk. Most notably, in early-stage non-small-cell lung cancer, the latest meta-analysis failed to show survival benefits in stage IA patients. In stage I colorectal cancer and much of stage II colorectal cancer, NCCN and ASCO guidelines recommend against therapy and several randomized controlled trials have failed to show clear and convincing benefits. In the setting of breast cancer, low risk node-negative breast cancer is not an indication for adjuvant chemotherapy.

Even for drugs that have a demonstrated survival advantage in metastatic setting, judgment is required when used as adjuvant therapy. For example, ipilimumab improves overall survival both as a primary therapy in metastatic melanoma and as adjuvant therapy after surgical resection of melanoma. However, the benefit of adjuvant ipilimumab shows just a 10% better 5-year recurrence-free survival rate, which means we would be subjecting 100% of patients to the burden of treatment to benefit 10% of them [9]. Because the efficacy of the drug in metastatic setting when this has already been used as adjuvant therapy is unknown, this would mean that we might jeopardize 90% of patients the opportunity to benefit from the same drug when they relapse. Notably, this concern would not arise if post-protocol use of ipilimumab in the control arm (upon relapse) were higher.

We believe [supplementary Tables S1 and S2](#), available at *Annals of Oncology* online provide further caution that simply because a drug is active or successful in the metastatic setting, it may not be in the adjuvant setting. The biological challenge to improve outcomes in the adjuvant space is arguably higher, and reflected by the fact that all drugs approved in the adjuvant

Table 1. Adjuvant treatment without positive RCT

| Setting | Drug | Class | Rationale | Evidence of use | Annual incidence | 5-Year survival | Reference |
|--|-------------------------------------|----------------|---|------------------------|------------------|---|--|
| Adenocarcinoma | Mitotane | Cytotoxic | Effective in metastatic setting | NCCN, Uptodate | 0.72 per million | 38.60% | 18973179 |
| Neuroendocrine tumors—gastro-intestinal, carcinoid and large cell lung | Cisplatin+etoposide | Cytotoxic | Similar to small-cell lung cancer | NCCN, Uptodate, NANTES | 2 per 100 000 | 78.2% for localized | 12569593 |
| Small-cell lung cancer completely resected | Cisplatin+etoposide | Cytotoxic | OS has improved significantly compared with historical data | NCCN, Uptodate | 10 per 100 000 | 10% for limited stage | 25822850 and 17008692 |
| Cholangiocarcinoma | 5FU, gemcitabine-based regimens | Cytotoxic | Effective in metastatic setting | NCCN, ESMO guidelines | 1.18 per 100 000 | Localized: 15% intrahepatic, 30% extrahepatic | American Cancer Statistics and PMID 27000463 |
| Bladder cancer | GC or MVAC | Cytotoxic | Effective in neoadjuvant setting | NCCN, Uptodate | 20.1 per 100 000 | 70.2% for localized | SEER data |
| Uterine leiomyosarcoma | Doxorubicin, docetaxel, gemcitabine | Cytotoxic | ?? | Uptodate | 0.36 per 100 000 | 76, 60, 45% stage I, II, III | 28209496 |
| Sarcoma | Various | Cytotoxic | Mixed results in trials | NCCN, ESMO guidelines | 0.9 per 100 000 | 67.5% overall | SEER data |
| Breast cancer | Zoledronic acid | Bisphosphonate | Meta-analysis shows benefit | ASCO recommends | 1.25 per 100 000 | 98.8% for localized | SEER data |
| Small bowel adenocarcinoma | 5FU, oxaliplatin | Cytotoxic | Extrapolation of colon cancer | PMID 19106677 | 2.2 per 100 000 | 66.9% overall | SEER data |

setting are effective in the metastatic setting, though the reverse is far from true. Moreover, [supplementary Tables S1 and S2](#), available at *Annals of Oncology* online also suggest that merely because a regimen is successful in a cancer type, does not mean it is beneficial in all risk categories. In many tumor types, there is a clear tipping point where adjuvant therapies fail or are even harmful. For these reasons, the use of adjuvant therapy must be subject to careful shared decision-making, and ideally trials conducted to provide clarity.

In the absence of randomized controlled trials showing improved survival, quality of life or improvement in a validated surrogate, only the potential harms of adjuvant therapy are certain. Harms include both the adverse effects of treatments, including downstream adverse effects. One such example is the use of anthracycline chemotherapy in breast cancer, which carries late toxicity risks of second malignancy including treatment-related MDS and leukemia. Harms also include treatment burden; financial, logistical and adverse effects of treatment are all significant burdens placed on patients. These burdens are only justified if treatments show benefits later on, in terms of overall survival or significant local benefits that improve quality of life. This is no small bar to meet, and the history of oncology is replete with examples where many experts believed that highly promising therapies would be successful in the adjuvant setting, but were ultimately unsuccessful.

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