short duration of effect. Blinatumomab might be useful in combinations to obtain even deeper response and remissions that are long enough to allow organisation of transplantation. Blinatumomab could thus find a place in a window period and serve as a bridge to SCT. Several factors should be considered for this approach, including the likelihood of achieving remission, organ toxic effects, and the time needed to screen, enroll, and treat patients before SCT. Finally, new therapeutic strategies might focus on exploiting targets governing stem-cell renewal and differentiation. An important issue in favour of combination therapy is that blinatumomab can target bulk leukaemia cells, but not the leukaemia stem cell. This supposition is supported by the short duration of effect with blinatumomab. Furthermore, the ability to target sanctuary sites remains a major challenge.

Many drugs have become available that have the potential to change the standard of care for adult patients with ALL. Combination of several agents targeting more than one antigenic determinant, gene mutation, or signal transduction pathway might be the most effective strategy, and could hold the promise of substantial benefit, and could represent a targeted solution similar to the total therapy approach pioneered by Don Pinkel in the 1960s with chemotherapeutic agents.

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I declare no competing interests.

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IBIS-I tamoxifen update: maturity brings questions

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The International Breast cancer Intervention Study (IBIS-I) is a randomised, placebo-controlled chemoprevention clinical trial of the effects of tamoxifen in a population of women at high risk of developing breast cancer. Jack Cuzick and colleagues' report in *The Lancet Oncology*[1] is an important update of the IBIS-I trial. The achievement of such long-term follow-up (median 16 years), especially with more than 74% of participants remaining masked to randomisation, is commendable.

An ongoing reduction in the incidence of oestrogen receptor-positive breast cancer through 16 years' cumulative median follow-up after 5 years of tamoxifen use results in a very favourable number needed to treat of only 22 (95% CI 19–26) women receiving tamoxifen for 5 years to prevent one case of breast cancer in the next 20 years. The findings have clinical implications because many women could be spared the psychological and physical problems associated with a breast cancer diagnosis and related treatment.[2] The results build on those from eight other selective oestrogen receptor modulator chemoprevention trials that showed a reduction in breast cancer risk through 10 years' follow-up.[3] However, the slightly higher number of deaths from breast cancer in the tamoxifen group than in the placebo group, which persisted beyond 10 years' follow-up in IBIS-I, raises a series of questions.

In Cuzick and colleagues' IBIS-I update, 99 fewer breast cancers occurred in the tamoxifen group than in the placebo group (251 [7%] in 3579 *vs* 350 [10%] in 3575 respectively; hazard ratio [HR] 0·71 [95% CI 0·60–0·83], p<0·0001), but surprisingly, there were five more deaths from breast cancer in the tamoxifen group than in the placebo group (31 *vs* 26; odds ratio 1·19 [95% CI 0·68–2·10], p=0·8). After 10 years' follow-up, the discordance between the effect of tamoxifen on breast cancer incidence and deaths from breast cancer was more pronounced (18 deaths in the tamoxifen group *vs* nine with placebo; odds ratio 2·00 [95% CI 0·85–5·06], p=0·08]), although it is important to note that this was not significantly different. To resolve such


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Published Online
December 11, 2014
http://dx.doi.org/10.1016/S1470-2045(14)71184-2

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differences is not easy, since the authors state that the survival results could not be attributed to differing menopausal hormone therapy use or oestrogen receptor-negative disease.[1]

The IBIS-I trial was undertaken when determination of HER2 status was not possible. Since endocrine therapy is less effective in oestrogen receptor-positive, HER2-positive advanced breast cancer[4] than in oestrogen receptor-positive, HER2-negative disease, could a differential distribution of HER2-positive cases, under the influence of tamoxifen therapy, have affected the breast cancer survival findings? This important issue needs to be addressed.

The IBIS-I findings contrast with those from tamoxifen use in the adjuvant setting where, in women with early-stage oestrogen receptor-positive disease, at 15 years of follow-up after 5 years of tamoxifen use, congruence was recorded between tamoxifen's effect on breast cancer recurrence (relative risk [RR] 0·53 [SE 0·03]) and on deaths from the disease (RR 0·71 [SE 0·05]).[5]

Even in a trial that enrolled and randomly assigned 7154 women, the findings about deaths from breast cancer could represent the effect of chance alone in the small sample of 57 deaths that occurred. In this regard, although the authors[1] cite previous power calculations to indicate that more survival events are needed before definitive assessment, additional events would be unlikely to appreciably change the results since the trend is in the opposite direction and survival curves that cross are unlikely to become positive. Although the magnitude and even the existence of breast cancer overdiagnosis by screening remains controversial,[6,7] could tamoxifen treatment in IBIS-I have been selectively preventing breast cancers with extremely favourable prognoses? Additional follow-up of the other selective oestrogen receptor modulator prevention trials might address this issue.

In IBIS-I, tamoxifen was less effective in reducing breast cancer risk in women who used menopausal hormone therapy than in those who did not use hormone therapy.[1] Menopausal hormone therapy[8] and tamoxifen[3,5] can both affect breast cancer and other chronic diseases, and their combined effect on most of these illness is unknown. In the Women's Health Initiative randomised trials, oestrogen plus progestin, in the form of conjugated equine oestrogen, increases breast cancer incidence and deaths from breast cancer, whereas oestrogen alone reduces breast cancer incidence and deaths.[9] Additionally, these hormone therapy regimens also have effects on other cancers.[9] Future IBIS-I subgroup analyses should separate the effects of these two hormone therapy regimens.

Overall survival is a reasonable endpoint for advanced breast cancer and adjuvant trials. In prevention trials that incorporate analyses after long-term follow-up, an increasingly larger proportion of deaths from other causes occur, years or decades after interventions are stopped. In the current IBIS-I report, only 57 (15%) of 389 total deaths were related to breast cancer. Alternative endpoints should be considered for future chemoprevention trials, especially for those that enrol older participants similar to those entered in IBIS-I.

At present, despite positive findings in terms of their effect on breast cancer incidence, the use of selective oestrogen receptor modulators for breast cancer chemoprevention in clinical practice is very infrequent.[10] The discordance between tamoxifen's effects on breast cancer incidence and outcome noted in the IBIS-I update could merely represent the effects of chance alone, or alternatively might indicate that tamoxifen mainly decreases the incidence of cancers with a very favourable prognosis, increases cancers with unfavourable outcomes, or both. How these alternative ideas are viewed will determine the effect of the IBIS-I update on breast cancer chemoprevention practice in the clinic.

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I have received consulting fees or honoraria from Novartis, Amgen, and Genomic Health; fees for participation in review activities for Pfizer and Novo Nordisk; payment for lectures from Novartis; and payment for educational activities from Educational Concepts Group.

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Towards effective adjuvant treatment for urothelial cancer

Data for the efficacy of adjuvant chemotherapy in urothelial cancer comes from prematurely closed trials with poor accrual that have not yielded definitive conclusions about benefit. Yet, the potential activity reported in these trials has been promising enough to encourage investigators to pursue assessment of this treatment. In *The Lancet Oncology*, Cora Sternberg and colleagues[1] report the results of the EORTC 30994 trial, which compared immediate versus deferred cisplatin-based combination chemotherapy after radical cystectomy in patients with urothelial carcinoma of the bladder. They found no significant difference in the study's primary endpoint of overall survival between immediate and deferred chemotherapy (hazard ratio [HR] 0·78, adjusted 95% CI 0·56–1·08; p=0·13), but immediate chemotherapy did significantly increase 5-year progression-free survival (HR 0·54, 95% CI 0·4–0·73; p<0·0001).

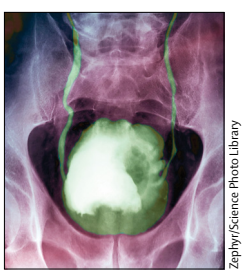
Some might argue against the relevance of this study, since neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is the proven standard for the treatment of muscle-invasive bladder cancer.[2] Although these recommendations were made more than a decade ago, neoadjuvant therapy remains highly underused. The inherent toxicity associated with cisplatin-based therapy in the typical urothelial cancer population of elderly and frail patients ensures that it is unlikely to be given to a substantial proportion of patients. Therefore, recommendations about adjuvant chemotherapy will remain highly relevant either until a non-toxic curative therapy is discovered, or until the patients who truly benefit from these potentially toxic regimens can be accurately identified.

Efforts to improve chemotherapy for urothelial cancer date back to the 1980s, when adjuvant CISCA (cisplatin, cyclophosphamide, and doxorubicin) was reported to have cured a higher proportion of patients with bladder cancer than did surgery alone.[3] MVAC arrived soon after with compelling evidence supporting the use of this combination in patients with pathological T3b or worse disease at surgery,[4] yet insufficient numbers of patients or design flaws prevented definitive confirmation of a survival benefit. Additional trials of gemcitabine cisplatin have been limited by similar problems.[5]

Other chemotherapy combinations for urothelial cancer, including those with higher doses of ifosfamide,[6] have been assessed in the perioperative setting, but have not surpassed the outcomes achieved with MVAC. Even high-dose MVAC,[7] which is administered every 2 weeks, has not improved survival outcomes, although the improved toxicity profile has supported its use. One potential exception is adjuvant gemcitabine, paclitaxel, and cisplatin, which was reported to improve survival in a recent abstract.[8] Perhaps final results from this trial will yield the definitive conclusions that investigators seek.

Results of Sternberg and colleagues' study[1] suggest that adjuvant chemotherapy might benefit patients with node-negative disease. However, most patients in this trial did not have adequate lymph-node dissection, so this finding should be interpreted with caution. An alternative conclusion is that patients with inadequate lymph-node dissection might be more likely to benefit from adjuvant chemotherapy. Also, many of these patients might have been characterised as node-positive if more lymph nodes had been removed. Clearly, additional studies are needed to confirm this finding.

In view of the absence of definitive success with this trial, and admittedly most other trials of adjuvant chemotherapy for bladder cancer reported so far, it seems unlikely that using a similar framework to design



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Published Online
December 11, 2014
http://dx.doi.org/10.1016/S1470-2045(14)71187-8

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