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Adjuvant and neoadjuvant cancer therapies: A historical review and a rational approach to understand outcomes

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ABSTRACT

Drug development in oncology usually establishes efficacy in metastatic disease before advancing a therapy to the adjuvant or neoadjuvant settings. Unfortunately, too often use in adjuvant or neoadjuvant settings fails to improve overall survival. Reasons for the modest benefits include the fact that in many cases surgery cures a majority of patients making it difficult to demonstrate gains. We begin by looking at the history of adjuvant and neoadjuvant therapies and the principles guiding their development. We summarize accepted adjuvant and neoadjuvant therapies in several cancers and tabulate their outcomes. Then, extending our work on the growth and regression rate constants of tumors and the fraction of cells killed we demonstrate that therapies developed in the metastatic setting primarily delay tumor growth rather than kill more cells and argue this is a likely explanation for poor outcomes in adjuvant or neoadjuvant settings. We suggest a rational approach for enhancing success.

Historical perspective of adjuvant therapy

Historically, some of the most interesting preclinical experiments that initially gave support to the concept of adjuvant chemotherapy were published in 1957 [1]. In a mouse model of breast adenocarcinoma the relation of tumor burden and treatment response was studied using 6-mercaptopurine. The authors found "an inverse relationship between the number of solid tumour cells and the chemotherapeutic response." Additionally, they demonstrated that when a larger and a smaller tumor were implanted into mice chemotherapy effectiveness increased when the larger tumor was surgically extirpated. Based on this simple observation in a preclinical model, the authors argued "the potential value of administering postoperative chemotherapy as an adjunct to surgery is readily apparent" and "offers hope for cure of the microscopic metastases and inadvertent tumour 'seeding' in the so-called operable and potentially curable group of cancer patients." Twenty years later, a landmark study in women who had undergone a radical mastectomy and were found to have histologically positive axillary lymph nodes demonstrated the value of postsurgical (adjuvant) chemotherapy in patients with breast cancer; and set the stage for subsequent adjuvant chemotherapy studies in this and other cancers [2].

After the initial evidence of the benefit of adjuvant therapy in breast cancer, attempts were made to expand this approach to others tumors. Drug combinations have been more commonly employed, because they often achieve better response rates or delay progression in the metastatic setting, even when survival is not improved [3-5].

Table 1 lists solid tumors in which adjuvant chemotherapy is generally recommended and for which Level I evidence exists. In most cases the benefit achieved has been small. In colorectal cancer, for example, the International Multicentre Pooled Analysis of Colon Cancer Trials found a 5% gain at 3 years from 6 months of adjuvant 5-Fluorouracil (5-FU) plus leucovorin [16]. The number needed-to-treat (NNT) provides information for assessing interventions in daily practice by establishing the number of patients that must be treated to prevent one bad outcome [17]. In the Table 1 examples, the number needed-to-treat in lung cancer is approximately 20, representing an absolute survival benefit of 5%—20 patients with stage II/III lung cancer must be treated in order to avoid 1 death at 5 years. By comparison, in breast cancer, adjuvant therapy is administered to larger numbers for lesser benefits. Commonly used guidelines, such as National Comprehensive

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Table 1
Source of support for selected adjuvant and neoadjuvant regimens used in solid tumors [3–15].

Tumor	Stage	Meta-analysis or Individual Study – Characteristics – [Number of patients]	Chemotherapy Regimens* Adjuvant / Neo-adjuvant [Duration]	Absolute OS benefit gain**	NNT ***
Breast	I, II, III	Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[6] – Individual patient-data meta-analysis – [101,000 in 123 studies]	Adjuvant regimens Taxane-based / Non-taxane-based Anthracycline-based / CMF Higher anthracycline / Lower anthracycline Poly-chemoRx / No chemoRx	10% at 10 years	10
Colon	II, III	International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT)[7] [1493]	Adjuvant 5-FU + Leucovorin [6 months / 6 cycles] No adjuvant therapy	5% gain at 3 years	20
Bladder	II, III	Advanced Bladder Cancer Meta-analysis Collaboration (ABCMC)[8] – Individual patient-data; invasive bladder cancer – [2688 in 10 trials]	Neo-Adjuvant Regimens: Single agent cisplatin or cisplatin with one or more of doxorubicin/epirubicin, methotrexate, and vinblastine One trial used carboplatin + methotrexate + vinblastine [2-4 cycles, every 2-4 weeks] + Local treament Local Treatment	5% gain at 5 years	20
Gastric	II, III	MAGIC[9] [503]	Pre- and post-operative chemotherapy Epirubicin + Cisplatin + 5-fluorouracil + Surgery Surgery alone	13% gain at 5 years	7.7
Sarcoma	I, II, III	Pervaiz et al[10] meta-analysis [1953 in 18 studies]	Adjuvant Ifosfamide + Doxorubicin + Local treatment Local treatment alone	11% gain at 5 years	9.1
NSCLC	II, III	LACE[3] [4584 in 5 studies]	Adjuvant cisplatin-based chemotherapy ± Radiotherapy ± Radiotherapy	5.4% gain at 5 years	18.5
Ovarian	IC, II	Cochrane Gynecological Cancer Group[11] [1227 in 5 studies]	Adjuvant platinum-based chemotherapy No adjuvant chemotherapy or placebo	HR 0.71	3.4
Pancreatic	I, II, III	CONKO-001[4] [368]	Adjuvant gemcitabine Observation	10.3% gain at 5 years	9.7
Melanoma	II, III	Eastern Cooperative Oncology Group (ECOG) 1684[12] [287]	Adjuvant high-dose Interferon alpha (IFN-α) Observation	11% gain at 5 years	9.1
Endometrial	III, IV*	Cochrane meta-analysis[5] [1269 in 4 studies]	Adjuvant combinations of cisplatin, doxorubicin, cyclophosphamide and paclitaxel Radiotherapy	HR 0.75	4
Rectal	II, III	Cochrane meta-analysis[13] [9,785 in 21 studies]	Adjuvant 5-FU-based chemotherapy Observation	HR 0.83	5.9
Prostate	I, II, III	Early Prostate Cancer (EPC)[14] [8113 in 3 trials]	Standard care + Adjuvant bicalutamide Standard care + placebo	HR 1.01 (NS)	
Head & Neck	III, IV	Spanish Head and Neck Cancer Group (TTCC)[15] [439]	Induction chemotherapy [cisplatin + 5-FU ± docetaxel] before concurrent chemoradiotherapy Concurrent chemoradiotherapy	HR 0.94 (NS)	

Abbreviations: NSCLC, Non-small cell lung cancer; 5-FU, 5-fluorouracil; NS, non-statistically significant, NNT, number needed to treat
*In each instance the experimental treatment is described on top and the control strategy on bottom.
**All results represent statistically significant findings unless NS (not significant) noted. Represent absolute benefit (gains) over control. When absolute gains not provided the relative benefit is described in hazard ratio (HR)
***NNT calculated according to the time points describing the absolute gain in the OS column, with longer time points the NNT usually increases; In meta-analyses, NNTs were calculated according to the results of the meta-analysis not from individual NNTs

Cancer Network (NCCN), recommend considering adjuvant therapies in small tumors over 0.6 cm in size in which the absolute estimate of benefit is in the range 1%–3% [18,19].

Breast cancer

Adjuvant and neoadjuvant paradigms

We will use the example of breast cancer to describe the effort invested and the steps taken over the years that led to currently recommended adjuvant and neoadjuvant therapies. We will not include hormonal treatment of localized breast cancer given excellent overviews have been published [20,21]. The narrative that follows summarizes the clinical evolution of adjuvant and neoadjuvant strategies to improve breast cancer outcomes and Table 2 catalogues preclinical studies that supported these efforts. While initial clinical studies relied on basic observations, over time the rationale came from previous clinical trials in the adjuvant, neoadjuvant, and metastatic setting, relying less on basic studies for support. That progress in neo-adjuvant and adjuvant therapies has been wanting begs the question of where we might be had we continued to look beyond minimally successful clinical outcomes for support.

Clinical trials adding adjuvant chemotherapy to standard mastectomy for "curable cancer" of the breast began in 1957 under the auspices of the "National Institutes of Health, Cancer Chemotherapy National Service Center." With the limitation of local therapies in the management of breast cancer already apparent, investigators had come to believe "that until cancer of the breast can be prevented or as therapy becomes available which is capable by nonsurgical means of destroying both primary and secondary tumours, systemic therapy as an adjunct to surgery affords the most likely means for escape from the plateau in which the prognosis and salvage rate of this disease has been ensnared for the last 30 or more years" [34]. Initially, investigators reasoned adjuvant chemotherapy could eliminate "cells dislodged into the blood and lymph during surgical manipulation" and designed a trial that administered thiotepa (triethylenethiophosphoramide) or placebo the day of and 2 successive days after operation. The choice of thiotepa was based on its effectiveness in palliation of breast cancer and the approach drew support from "laboratory observations relative to favourable effects of chemotherapeutic agents on disseminated tumour cells in experimental animals, as well as reports of the frequent presence of cancer cells in the circulating blood of patients with tumour" [22,23,34]. In the initial study, representatives from 23 institutions adopted "a common protocol" and enrolled a total of 826 "acceptable patients" between April 1958 and October 1961 [34]. Although 5-year survival rates for thiotepa and placebo were not statistically different, premenopausal women with 4 or more positive nodes appeared to derive benefit from thiotepa—with recurrence and survival rates improved and 5-year survival more than twice as great with thiotepa (57%) compared to placebo (24%). In a follow-up study comparing 5-FU to thiotepa as adjuncts to radical mastectomy, benefit was again observed with thiotepa in premenopausal women with 4 or more positive nodes but 5-FU was deemed unwarranted given severe toxicity and lack of efficacy. While not as successful as had been hoped, the authors emphasized the results did not "repudiate the concept of systemic adjuvant chemotherapy in the treatment of breast cancer" and ratified the value of prospective controlled trials [34].

By early 1970s overall cure rates remained essentially unchanged but views about adjuvant therapy had evolved. Investigators recognized some women would die despite apparent localized disease at the onset. The impact of nodal metastases on recurrence rates and survival had been established and led to recognition that in a majority disease was disseminated at diagnosis, and systemic approaches would be necessary [35]. The rationale for a combined modality approach utilizing "systemic treatments with chemotherapy, endocrine therapy, and immunotherapy at the time when local therapy is applied" had evolved and now sought to apply therapeutic regimens viewed as moderately effective in advanced disease, "at the time the tumor cell numbers are small, after removal of the primary" [36]. Postoperative oophorectomy or radiologic castration had delayed disease recurrence but failed to improve survival [37,38]. In addition, 8 trials using 9 single-agent regimens had provided conflicting data but were generally seen as failures [35,36]. Thinking short-term single-agent therapy used in practically all studies was the cause of treatment failure, investigators turned to combinations administered for longer periods of time (Table 3) [39,40]. Starting June 1973, the first patient was enrolled in a randomized study assessing the efficacy of adjuvant cyclophosphamide + methotrexate + 5-fluorouracil (CMF) therapy in the management of axillary node positive breast cancer [39]. The aim was to improve the disease-free period and eventually survival. A total of 386 women who had undergone a radical mastectomy and had histologically positive axillary nodes were randomized to either 12 monthly cycles of adjuvant CMF or no additional therapy. Three years after mastectomy 45.7% and 26.3% in the control and adjuvant CMF groups, respectively, had experienced a recurrence ($P < .0001$). This was an important achievement even though survival was not significantly different with the actuarial analysis of survival at 36 months demonstrating 21.4% and 10.4% of control and CMF-treated patients dead of cancer respectively ($P = .08$) [20].

With efficacy established but recognizing the importance of minimizing toxicity in a setting where the majority of patients may not be deriving benefit from the intervention, the need for 12 months of adjuvant therapy was examined by comparing a 6-month period of administration [41]. Looking at outcomes 5 years after mastectomy, neither relapse-free survival (CMF12: 59%; CMF6: 65.6%) nor overall survival (CMF12: 72.7%; CMF6: 76.9%) was significantly different. The authors concluded, "maximum tumour cytoreduction with CMF occurs within a relatively short period of time" and proposed "more intensive forms of treatment, utilizing non–cross-resistant combinations" to "improve (upon) the results achieved with a single multidrug regimen." In the 1980s non–cross-resistant combinations focused on the anthracyclines—doxorubicin and epirubicin—a drug class active in advanced disease [53,54]. In the adjuvant setting doxorubicin was initially added to melphalan (L-PAM) and 5-FU (designated L-PAM (melphalan) + adriamycin + 5-fluorouracil) or used as a single agent in different sequences with CMF [55,56]. Later both doxorubicin (5-fluorouracil (5-FU) + adriamycin + cyclophosphamide, i.e. CAF) and epirubicin (5-fluorouracil (5-FU) + epirubicin + cyclophosphamide, i.e. FEC) were substituted for methotrexate in the CMF regimen with at-best marginal benefits [57-59]. The evolution of adjuvant anthracycline trials realized by National Surgical Adjuvant Breast Program (NSABP) led to administration of AC (doxorubicin + cyclophosphamide) for shorter periods, an approach widely adopted in the United States because of convenience and tolerability [43,60,61]. It took a meta-analysis to demonstrate anthracycline-based combinations superior to CMF with absolute differences of ≈3% at 5 years and ≈4% at 10 years [62]. We discuss below, how gains in the metastatic setting might be achieved without much cell kill, the desired effect when therapies are employed in the adjuvant and neoadjuvant settings.

Dose intensity and incorporation of taxanes

Beginning in the late 1990s, a new paradigm emphasizing dose intensity and a kinetic model of cell death emerged and rapidly gained support, especially in the adjuvant setting [63-66].

Table 2
Key preclinical studies that provided support for adjuvant and neoadjuvant strategies.

Reference	Model and method	Result	Comment
Engell [1955] [22]	Patients with CRC; modified papanicolaou technique	Malignant cells found in venous drainage of 41/76 rectal cancer patients and 22/31 CRCs including 35% of G2, 78% of G3 and 100% of G4 tumors. Also found in PB of 3/65 operable cancer and 7/14 inoperable cancer	Often cited as first detection of CTCs and evidence this had to be addressed. Greater likelihood finding CTCs with larger more aggressive tumors possibly reflecting an assay sensitivity issue. Cells found equally in patients whose disease recurred from 6 mo to 4 yr as those who survived > 4 yr
Fisher and Turnbull [1955] [23]	25 CRC patients; Modified papanicolaou technique	Tumor cells recovered in blood 32% of cases examined	Cited as evidence of tumor dissemination that had to be addressed.
Cruz [1956] [24]	Rats/portal inoculation of Walker 256 carcinosarcoma	Nitrogen mustard prevented or diminished percentage "takes" when *given within one hour* after inoculation of cells	Studies that supported initial adjuvant approach that emphasized prevention of surgical dissemination
McDonald [1957] [25]	Rats/portal inoculation of Walker 256 carcinosarcoma	Thiotepa prevented/diminished percent "takes" when *given within one hour* after cell inoculation	Laboratory observations relative to favorable effects of chemotherapeutic agents on disseminated tumor cells in experimental animals
McDonald [1957] [26]	Rats/Portal inoculation of Walker 256 carcinosarcoma	As given, thiotepa slightly better than HN2. Both less effective with 220k *v* 110k inoculums; HN2 ineffective when given 48 h after surgery	Authors noted low percentage of CTCs that become tumors, ascribed this to host immunity, and suggested devoting efforts to enhancing immunity
Shapiro and Fugmann [1957] [27]	Mouse mammary adenocarcinoma 755	"Cures with 6-MP in 57%, 26% and 0% when therapy started 24 h, 8 d and 15 d after tumor implantation. "Age" effect ruled out by surgically reducing size of 15 d tumor and observing responses	Study to address why therapies worked in animals and not in humans and whether discrepancy due to tumor size. Preclinical observations showed proportion of cells killed by effective therapy inversely proportional to tumor size.
Morales [1957] [28]	Rats/portal inoculation of Walker 256 carcinosarcoma	HN2 given 48 h, 24 h and 6 h after inoculation reduced "takes" 5, 8 and 11%, respectively. Concluded must give drug at time of inoculation effect greatly diminished. Also 62% takes with 110k cells inoculated; only 31% with 220k	Sought to answer if giving chemotherapy over time (daily × 4) could reduce toxicity while exposing cells at "different stages of mitoses". Delaying chemotherapy diminished effects. Supported a peri-operative adjuvant treatment strategy
Martin and Fuggman [1960] [29]	2 mouse mammary adenocarcinoma, one mouse sarcoma, and one rat mammary adenocarcinoma	Less tumor amount led to greater chemotherapy effect in four tumors with four chemotherapy agents [6-MP, 6-AN, P and, N3TP]. Percent cures with surgery/surgery + chemotherapy: 17/71, 0/30, 45/81, 12/53, 2/48	Saw surgical excision as tool to optimize conditions for chemotherapy
Gunduz [1979] [30]	Transplantable C3H mammary tumor	Tumor growth rates similar whether growing alone or with second focus, but within 24 h of tumor removal, observed increased LI and decreased DT in residual focus	Increased proliferation in metastases after resection of primary tumor. Adjuvant strategy must impact residual tumor; not dislodged CTCs. Led to speculation surgery could have a pejorative impact on outcome by promoting growth of metastasis, and provided rationale for neoadjuvant chemotherapy
Fisher [1983] [31]	Transplantable C3H mammary tumor	Greater CY effect on the day of tumor removal than 3 d after, when the LI of metastases at peak. Least effective on 7 d after tumor excision, when the LI returned to preoperative level. Greatest effect when CY given prior to surgery	Preoperative CY resulted in maximal decrease of cancer cell proliferation rate and increased animal survival. Others also reported increase in LI following surgical removal and implicated change in immune system or increased corticosterone. These results provided biological rationale for adjuvant chemotherapy
Fisher [1989] [32]	Six different tumors [C3H, MXT_a, MXT_b, MC54, CD8, 3LL]	Increase in LI of distant tumor foci (metastases) with removal of each tumor type. Serum obtained from mice following removal of tumor increased the LI of tumor in recipient mice harboring same tumor and serum growth factor inferred	Authors concluded following primary tumor removal the behavior of metastatic deposits is affected by growth factor present in serum. Interestingly multiple serum injections did not further increase LI and speculated finite population likely in $G_{0/1}$ affected
Fisher [1989] [33]	Transplantable C3H mammary tumor	Administration of local or systemic CY, tamoxifen or Zoladex prior to primary tumor removal inhibited both the production of and the response to the putative serum factor	Argued evidence demonstrating increased proliferation of residual tumor and ability of treatment to blunt this with pre-removal therapy support testing neoadjuvant therapy clinically

CRC = colorectal carcinoma; PB = peripheral blood; CTCs = circulating tumor cells; 6-MP = 6-mercaptopurine; HN2 = nitrogen mustard; 6-AN = 6-aminonicotinamide; P = puromycin; N3TP = N-N'-N"-triethylenethiophosphoramide; LI = labeling index; DT = doubling time; CY = cyclophosphamide.

The thesis argued that a fixed cell kill achieved at shorter time intervals—a concept termed "dose density"—should improve therapy. Regrowth of resistant cells during and between cycles of chemotherapy was seen as a principal cause of failure and the strategy sought to suppress such growth with repetitive cycles of chemotherapy administered at shortened intertreatment intervals. Dose intensity, usually expressed as $mg/m^2/wk$ is commonly calculated by dividing the dose of drug given per surface area by the weeks of treatment, although, any time interval can be used. An increase in the dose intensity can be achieved by administering higher doses or by shortening the time between administrations; thus, the interval between chemotherapy administrations assumed importance. The availability of growth factors to stimulate medullary recovery made it possible to reduce treatment intervals. Thus, higher doses were explored in adjuvant regimens but mixed results indicated factors other than dose density were important [45-47]. For example the NSABP conducted a randomized trial (B-22) to determine if intensifying and either maintaining or increasing the total dose of cyclophosphamide in an adjuvant AC combination could improve outcomes. The investigators randomly assigned 2,305 women with primary breast cancer and positive axillary nodes to either 4 courses of standard adjuvant AC or one of two intensified regimens: the first, in which dose-intensification was achieved by administering the total cyclophosphamide dose in the first 2 cycles or the second in which in addition to dose-intensification, the total dose of cyclophosphamide was doubled.

Table 3
Representatives studies in the history of adjuvant treatment in breast cancer.

Study [yr]	Stage [number of patients]	Treatment arms	Results*	Comments
Bonadonna [40] [1977]	Positive axillary nodes [386]	CMF × 12 mo *v* Placebo	3y TFT: 26.3% *v* 45.7% (*P* < .0001) 3y OS: 89.6% *v* 78.6% (*P*=.08)	Pivotal trial of adjuvant therapy. Foundation for CMF and design of trials
Tancini [41] [1983]	Positive axillary nodes [466]	CMF × 6 mo *v* CMF × 12 mo	5y RFS: 65.6% *v* 59% (*P*=.17) 5y OS: 76.9% *v* 72.7% (*P*=.22)	Established 6 mo as duration of CMF treatment
Fisher [42]** [B11 trial, 1989]	Positive axillary nodes, ER 0–9 fmol [797]	PF *v* PAF	5y DFS: 44% *v* 51% (*P*=.007) 5y OS: 59% *v* 65% (*P*=.08)	One of the first to show anthracycline benefit in adjuvant setting
Fisher [43]*** [B15 trial, 1990]	Positive axillary nodes [2,194]	CMF × 6cy q28d *v* AC × 4cy q21d	3y DFS: 63% *v* 62% (NS; *P*=.5) 3y OS: 82% *v* 83% (NS; *P*=.8)	AC not inferior to CMF and duration of treatment was shorter
Bonadonna [44] [1995]	Positive axillary nodes [403]	Sequential: A × 4cy q3 wk →CMF × 8cy q3 wk *v* alternating: (CMF × 2cy q3 wk →A × 1cy q3 wk) × 4	10y RFS: 42% *v* 28% (*P*=.002) 10y OS: 58% *v* 44% (*P*=.002)	Doxorubicin intensity increased in the sequential regimen by ↓ in intervals without ↑ doxorubicin dose
Fisher [45] [B22 trial, 1997]	Positive axillary nodes [2,305]	A 60 × 4cy; C 600 × 4cy A 60 × 4cy; C 1200 × 2cy A 60 × 4cy; C 1200 × 4cy	5y DFS: 62% *v* 60% *v* 64% (NS) 5y OS: 78% *v* 77% *v* 77% (NS)	Cyclophosphamide intensification did not improve efficacy
French adjuvant study group [46] [2001]	Positive axillary nodes [565]	FEC50 *v* FEC100	5y DFS: 54.8% *v* 66.3% (*P*=.03) 5y OS: 65.3% *v* 77.4% (*P*=.007)	Epirubicin intensification improved both DFS and OS
Citron [47] [2003]	Positive axillary nodes [2,005]	4cyA→4cyT→4cyC q3w 4cyA→4cyT→4cyC q2w+F 4cyAC→4cyT q3w 4cyAC→4cyT q2w+F [+F = +Filgrastim]	Dose dense q2W + F *v* Standard q3w: 4y DFS: 82% *v* 75% (*P*=.01) 3y OS: RR 0.69 (*P*= .013) favors DD	Dose density improved outcome significantly. All arms received same drugs and # of cycles (similar cumulative doses)
Henderson [48] [2003]	Positive axillary nodes [3,121]	A60C × 4cy → ± T × 4cy A75C × 4cy → ± T × 4cy A90C × 4cy → ± T × 4cy	5y DFS (T *v* no T): 65% *v* 70% DFS HR (T / no T): 0.83; *P*=.0023 5y OS (T *v* no T): 77% *v* 80% OS HR (T / no T): 0.82; *P*=.006	Incremental benefit by adding taxol to an anthracycline regimen. A60 × 4cy→ T × 4cy recommended
Martin [49] [2005]	Positive axillary nodes [1,491]	TAC *v* FAC	5y DFS: 75% *v* 68% (*P*=.001) 5y OS: 81% *v* 87% (*P*=.008)	Adding docetaxel (T) to AC (TAC) improved DFS and OS over 5-FU (FAC) but with ↑ incidence of G3/4 and febrile neutropeinia
Roche [50] [2006]	Positive axillary nodes [1,999]	FEC × 6cy *v* FEC × 3cy → FEC-D × 3cy	5y DFS: 73.2% *v* 78.4% (*P*=.012) 5y OS: 86.7% *v* 90.7% (*P*=.017)	Incremental benefit by adding docetaxel (D) to an anthracycline regimen but with ↑ incidence febrile neutropeinia with docetaxel
Berry [51] (Meta-analysis) [2011]	15 Randomized Adjuvant Trials [6,120]	Control *v* HDC w/o stem cell support	RFS: HR 0.87 (*P* <.001); favors HDC OS: HR 0.94 (*P*=.13); no difference	HDC prolonged RFS but did not improve OS compared with standard treatment
Gianni [52] [HERA Trial, 2011]	Stage I to III [1,694]	Chemotherapy → Observation Chemotherapy→Trastuzumab1y Chemotherapy→Trastuzumab2y [Chemotherapy = Adjuvant, Neoadjuvant or both; Trastuzumab only adjuvant]	4y DFS: 72.2% *v* 78.6% (*P* <.0001) 4y OS: 89.3% *v* 87.7% (*P*=.11)	Largest clinical trial with trastuzumab in adjuvant setting. Crossover to trastuzumab was associated with improved outcomes compared to observation

CMF = cyclophosphamide + methotrexate + 5-fluorouracil; TAM = tamoxifen; PF = L-PAM (melphalan) + 5-fluorouracil; PAF = L-PAM (melphalan) + adriamycin + 5-fluorouracil; AC, adriamycin + cyclophosphamide; A = adriamycin; C = cyclophosphamide; cy = cycle; NS = not significant; FEC = 5-fluorouracil (5-FU) + epirubicin + cyclophosphamide; AC-P = adriamycin + cyclophosphamide + paclitaxel; FAC = 5-fluorouracil (5-FU) + adriamycin + cyclophosphamide; TAC = taxotere (docetaxel) + adriamycin + cyclophosphamide; FEC-D = 5-fluorouracil (5-FU) + epirubicin + cyclophosphamide + docetaxel; HDC = high dose chemotherapy; TFT = treatment failure time; OS = overall survival; RFS = relapse-free survival; DFS = disease-free survival.

* In every case the numbers are presented in same order as regimens are presented in previous column.

** This publication includes reports of 2 trials. A prior NSABP study identified cohorts of patients "who did or did not benefit from tamoxifen." Those with a tumor ER of 0 to 9 fmol cytosol protein deemed not to benefit from tamoxifen were assigned to B-11, while those whose ER was > 10 fmol were entered into the B-12 study. Results of the B-11 trial are described in the table.

*** A third arm used AC × 4 q21d → 6 mo later CMF × 3 q28d; it was not better and is not reported in the table.

The outcome of the NSABP B-22 trial was disappointing since there was no significant difference in disease-free survival (DFS, $P = .30$) or overall survival ($P = .95$) among the groups through 5 years; despite increased grade 4 toxicities in both groups receiving the "dose-intensified chemotherapy" [45]. However, in other trials, most notably a study conducted by the French Adjuvant Study Group, an improvement in both DFS and overall survival could be demonstrated with 100 mg/m^2 epirubicin over the standard 50 mg/m^2 dose [46]. Despite the mixed results and benefits that were modest, a consensus emerged that dose-dense administration could improve outcomes and this approach remains a treatment alternative in breast cancer [67]. Later, administration of higher chemotherapy doses followed by hematopoietic rescue with an autologous transplant was explored in high-risk breast cancer patients based on *in vitro* observations of steep dose-response curves for a majority of cytotoxic therapies [68]. Initially, its use rapidly expanded despite the lack of convincing evidence for a survival benefit. However, subsequent meta-analyses of individual patient data failed to demonstrate any survival benefit and even found harm from this strategy in the adjuvant and metastatic settings and its use was rapidly discontinued [51].

Finally, the taxanes were incorporated in adjuvant treatments, their use again supported by demonstrating activity in advanced disease [69]. Use of taxanes concurrently or sequentially with other chemotherapies increased recurrence-free and overall survivals and led to their widespread use [59,70–72].

HER2 as a therapeutic target

The foregoing adjuvant studies enrolled all women with breast cancer who had undergone a radical mastectomy and were found to have histologically positive axillary lymph nodes. However, an

approach that enrolled all patients changed with identification of HER2, a membrane protein expressed in 18%–20% of breast cancers [73] and with development of trastuzumab, a monoclonal antibody against the HER2 [75]. Able for a first time to target a defined subset, trastuzumab was moved to the adjuvant setting based on activity in metastatic breast cancer, originally demonstrated in a landmark study [74]. In the adjuvant setting, several trials demonstrated significantly reduced disease recurrence and improved survival in patients with stages I–III disease when trastuzumab was used with standard chemotherapy or as maintenance following an induction period of chemotherapy [75-78]. A 2012 Cochrane meta-analysis reported the hazard ratios (HRs) for disease-free and overall survival significantly favored trastuzumab-containing regimens (HR 0.60; $P < .00001$ and HR 0.66; $P < .00001$, respectively) [79]. Thus an agent aimed at an essential target improved overall survival without dose dense therapies. Current guidelines recommend administration of trastuzumab as an adjuvant for 1 year in patients with tumors more than 1 cm that express HER2. Some guidelines even recommend considering administration for tumors larger than 0.5 cm, a subset of patients with less clear benefit. Finally, pertuzumab, a second antibody targeting HER2 was shown to lead to better outcomes in the metastatic setting when added to trastuzumab compared to trastuzumab alone [80,81]. Although the study design was unbalanced and administered almost twice as much trastuzumab to women receiving pertuzumab, improvements in disease-free (HR 0.62; $P < .001$) and overall survival (HR 0.64; $P = .005$) led to the rapid incorporation of pertuzumab in an adjuvant regimen the outcome of which is pending.

Neoadjuvant strategies

Even as the adjuvant paradigm was being pursued, primary or neoadjuvant chemotherapy—administering systemic therapy before surgery usually to patients without evidence of metastatic disease—was also evolving (Table 4).

Early studies using a transplantable CH3 mammary tumor, had found removal of one tumor focus could affect a separate focus despite lack of evidence of an interaction relative to growth between the two foci (Table 2) [30-32]. Increased labeling and primer dependent DNA polymerase indices with a decrease in tumor doubling times indicated growth accelerated in the residual tumor. Since there was minimal change in DNA synthesis and cell cycle times, the authors concluded "the increase in growth following removal of the 'primary' tumour was probably not the result of a more rapid proliferation of the dividing cells but was more probably due to conversion of non-cycling tumour cells in G_0 phase into proliferation" [30]. Subsequent experiments in six different models [Table 2] characterized the effects of a putative serum growth factor responsible for the phenomenon [32]. The authors reported that administering serum from mice that had undergone resection of a tumor to a recipient with the same type of tumor increased the labeling index of the recipient's tumor. Because multiple injections did not further increase the labeling index, the authors concluded the data, suggested "there is a finite population of cells, most likely in the Go/G_1 phase, which are capable of responding to the stimulating factor" [32]. In turn this led to experiments using a murine mammary tumor that determined the preoperative administration of a single cyclophosphamide dose could prevent the augmentation of the labeling index in the recipient's tumor. The earlier studies had led to the conclusion that "for the most effective control of metastases the largest tolerable dose of chemotherapy would best be used at the time of or before primary tumour removal" and the results provided "a biological rationale for the use of perioperative adjuvant chemotherapy"—that is, neoadjuvant therapy [31]. The authors now argued that while there had been no rationale for comparing adjuvant and neoadjuvant approaches, the accumulating evidence now supported a comparison. They pointed out the experimental models indicated noncurative reduction of tumor cell burden increased the proliferation of residual tumor and this could be prevented by preoperative chemotherapy [31]. This approach was further supported by the argument that based on the somatic mutation theory, "resistant mutants arise spontaneously early in the natural history of cancers" and "(this) accounts for the invariable inverse relationship between cell number and curability by drugs and the greater effectiveness of combination chemotherapy over single agents" [103]. Additionally, it was envisioned, indeed evidence was emerging, that primary or neoadjuvant chemotherapy would bring benefits by reducing the size or extent of the cancer before any intervention making the ensuing procedure easier and more likely to succeed, and lowering local complications [104-106].

The use of combination chemotherapy prior to local therapy in the treatment of breast cancer was first reported in 1978 [107]. Treatment with 4 cycles of adriamycin plus vincristine (AV) resulted in some tumor shrinkage in 98/110 women with primary inoperable (T3b-T4) breast cancer with 81/98 (82.7%) in complete response (CR) after completion of radiotherapy (RT), a response status that lasted a median of 15 months and produced a 3-year survival of 52.8%. Subsequent studies reported comparable outcomes with respect to local control, patterns of recurrence, and survival with surgery as with RT after primary chemotherapy and underscored the investigators original conclusion that "to achieve a satisfactory control of T3b-T4 breast cancer a more aggressive and prolonged treatment is required" [108,109]. A similar treatment strategy in 52 patients with non-inflammatory breast cancer treated with 3 cycles of 5-fluorouracil (5-FU) + adriamycin + cyclophosphamide plus Bacillus Calmette-Guérin prior to local radiation or surgery followed by radiation achieved an objective response rate to chemotherapy of 82% with 40% actuarial 5-year survival [110].

Trials comparing the same regimen administered either pre- or postoperatively [88-90,110] demonstrated neoadjuvant therapy could be administered safely. Furthermore, although adjuvant therapy failed to improve recurrence-free and overall survival, other end points emerged as valuable, including improvements in breast conservation rates [88-90,104-106,110]. A higher response rate, for example, allowed for "down-staging," so that breast conservation became possible in cases where a mastectomy had been contemplated. In inflammatory breast cancer, characterized by extensive local involvement with lymphangitic spread and a high incidence of local recurrence, neoadjuvant approaches achieved high response rates and improved chances of successful surgery [111,112]. Additionally, for a first time the potential use of response, especially pathologic complete response (pCR) as a "short-term surrogate of outcome" was considered [89,90,113]. Indeed, as limitations of neoadjuvant therapies have become apparent, efficacy judged by pCR is increasingly advocated as a drug development endpoint, albeit with many caveats [113,114]. Although an attractive hypothesis, the value of pCR as a surrogate will have to be established. A large meta-analysis coordinated by the Food and Drug Administration (FDA) using data from 12 international trials with 11,955 patients found the survival of patients who attained a pCR was improved. However this pooled analysis failed to establish pCR as a valid surrogate endpoint for improved event free survival and overall survival [115]. And more recently, adjuvant trastuzumab with lapatinib, a tyrosine kinase inhibitor targeting both HER1 and HER2, failed to achieve better disease-free and overall survivals, despite robust evidence in phase II and III trials showing marked increases in pCR with this combination given as adjuvant therapy [102,116]. Some of this discordance is likely due to differences in outcomes between women whose tumors are hormone-receptor positive and those with hormone-receptor negative tumors—not

Table 4
Representative studies in the history of neoadjuvant treatment in breast cancer.

Study [yr]	Stage [number of patients]	Treatment arms	Results	Comments
DeLena [82] [1978]	T3b-T4 [110]	• AV chemotherapy	At the end of RT, 81/98 (82.7%) patients with some tumor shrinkage from AV classified in CR. Median duration of CR was 15 mo; 3-yr survival 52.8%	Authors concluded a more aggressive and prolonged treatment is required to achieve satisfactory control of T3b-T4 breast cancer.
DeLena [83] [1981]	Locally advanced breast cancer [132]	• AV chemotherapy + mastectomy • AV chemotherapy + radiotherapy	Higher complete remission rate after mastectomy (100%) compared to radiotherapy (60%), but total response rate at end of combined modality identical (75%)	Failed to indicate surgery improved overall results including local control, over radiotherapy in a combined modality setting
Hortobagyi [84] [1983]	Locally advanced primary breast cancer (T3, T4/N2, N3) [52]	• FAC + immunotherapy with Bacillus Calmette-Guerin (BCG) + simple mastectomy and/or radiotherapy + adjuvant chemotherapy	F49/52 (94%) rendered free of clinically detectable disease. Median disease-free interval 24 mo; 40% free of disease, off all therapy at 5 yr	Despite good tolerance, treatment compliance was poor
Swain [85] [1987]	III, IV [76]	• CAMF • CAMF Tamoxifen Premarin Hormonal synchronization attempted with tamoxifen and premarin	PR: 96%; CR: 49% [62% CR negative biopsies] TTP: 35.3 [IIIA] and 34.2 [IIIB]. 24 relapses: 5 loco-regional; 4 loco-regional + distant; 15 distant	Early trial of NeoAdj CTX with attempt at hormonal synchronization. Highlighted problem of inflammatory breast cancer
Bonadonna [86] [1990]	Operable tumors >3 cm [165]	Five cohorts: [1] 3cy CMF; [2] 4cy CMF; [3] 3cy FAC; [4] 4cy FAC; [5] 3cy FEC	81% of tumors shrank to <3cm allowing breast conservative surgery; pathologic CR (pCR) in 7 patients	Full-dose NeoAdj CTX, with conservative surgery/radiation effective and safe. Reported increased RR in HR(-) tumors
Mauriac [87] [1991]	Operable tumors >3 cm [272]	• EVM→MTV→Surgery • Surgery→EVM→MTV	CR: 33%; HR(−) tumors more likely to be treated conservatively (77% *v* 52%); More local recurrences in NeoAdj CTX arm. RFS: No difference (P=.5) OS: NeoAdj CTX better (P=.04)	Patient with CR were treated with radiation without surgery. HR(-) tumors had higher response rate (P=.003).
Scholl [88] [1994]	T2-T3/N0-N1 Premenopausal [414]	• NeoAdj FAC→RT ±Surgery • RT ± Surgery→FAC	5y DFI: 59% *v* 55% (P=.4) 5y OS: 86% *v* 78% (P=.039) 5y Metastases: 73% *v* 64% (P=.09)	Reason for OS advantage with Neoadj uncertain. Possibilities: (1) early initiation CTX; (2) slightly more aggressive treatment
Fisher (B-18) [89,90] [1998]	T1-3/N0-1/M0 operable tumors [1,523]	• NeoAdj AC→Surgery • Surgery→Adj AC	cCR: 36% cCR (pCR 26% of cCR) 12% more lumpectomies in NeoAdj CTX group; 175% more in women with tumors >5.1 cm	1st large randomized NeoAdj trial. Authors concluded Neoadj CTX: (a) is as effective as Adj CTX; (b) permits more lumpectomies; (c) is appropriate for certain patients with stages I/II disease; (4) gives insight into breast cancer biology; and (5) should be considered for initial management of tumors judged too large for lumpectomy
Smith [91] [2002]	Large (≥3 cm) or locally advanced (T3/T4/TxN2) [162]	• 4cy CVAP→4cy CVAP • 4cy CVAP→4cy Doc	cRR: 66% *v* 94% (P=.001) pCR 16% *v* 34% (P=.04)	NeoAdj study demonstrating doceatxel substantially increased response rates
Rastogi (B-27) [92] [2006]	T1c-3/N0-1/M0 or T1-3/N1/M0 [2,411]	• AC→Surgery [1] • AC→Doc→Surgery [2] • AC→Surgery→Doc [3]	cRR [1+3] *v* [2]: 86% *v* 91% (P <.001) pCR [1+3] *v* [2]: 13% *v* 26% (P <.001) OS and DFS no difference across all arms	Largest trial of Neoadj CTX. Together with B-18, the B-27 study demonstrated that NeoAdj is equivalent to Adj therapy. Adding NeoAdj taxanes to AC improves response, but not OS
Untch [93] [2009]	Tumors ≥3 cm or inflammatory [668]	• E + Ptx • Dose-dense E→Ptx	pCR: 10% *v* 18% (P=.008) 5y DFS: 59% *v* 70% (P=.011) 5y OS: 77% *v* 83% (P=.041)	Demonstrated dose-dense strategy in NeoAdj setting improves results. But subgroup of inflammatory tumors no benefit
Giann1 [94] (NOAH) [2010]	HER2+ T3N1/T4/TN2-3/T + ipsilateral supraclavicular nodes [235]	• 3cy AT→4cy Ptx→3cy CMF→Surgery • 3cy ATH→4 cy Ptx + Her→3cy CMF + Her→Surgery→Her after surgery for total 1 year	3y EFS: 56% *v* 71% (P=.013) 3y OS: 79% *v* 87% (P=.114)	First randomized comparison of Her *v* placebo in NeoAdj setting. Addition of NeoAdj/Adj Her to chemotherapy beneficial for HER2-positive locally advanced or inflammatory breast cancer
Untch [95] (TECHNO) [2011]	HER-2(+) tumors ≥2 cm or HER-2(+) inflammatory tumors [217]	• 4cy EC→4cy Ptx + Her→Her after surgery for total 1 yr	pCR: 38.7% DFS: 77.9% OS: 89.4%	Early study incorporating Her in NeoAdj CTX. Improved outcome with pCR

(*continued on next page*)

Table 4 (*continued*)

Study [yr]	Stage [number of patients]	Treatment arms	Results	Comments
Gianni [96] NeoSphere [2012]	HER2-positive, operable (T2-3/N0-1/M0), locally advanced (T2-3/N2-3/M0 or T4a-c/any N/M0), or inflammatory (T4d/any N/M0) [417]	• 4cy Her + Doc • 4cy Her + Per + Doc • 4cy Her + Per • 4cy Per + Doc	pCR: 29% pCR: 45.8% pCR: 16.8% pCR: 24%	Exploratory study examining four different regimens. Significant improvement in pCR in patients receiving Her Per Doc
Untch [97] (GeparQuinto) [2012]	cT3/4, HR(-), HR(+)/cN+/cT2, HR(+)/pN_{SLN}/cT1 [620]	• 4cy EC→4cy Doc + Her • 4cy EC→4cy Doc + Lap	pCR: 30.7% *v* 22.7% (*P* = .04)	Direct comparison between Her *v* Lap in the NeoAdj setting demonstrated superiority of Her
von Minckwitz [98] (GeparTrio) [2013]	Tumors ≥2 cm [2,072]	TAC responders: • Total 6cy TAC *v* • Total 8cy TAC TAC nonresponders: • + Additional 4cy TAC • + Additional 4cy NX	TAC responders: DFS TAC8 better than TAC6 (HR 0.78; *P* = .026); OS NS TAC nonresponders: DFS NX better than TAC (HR 0.059; *P* = .001); OS NS	Exploratory study of "response-guided" NeoAdj CTX. Response assessed after 2 initial cy of TAC. Effective in HR(+) but not in HR(-) tumors
Robidoux [99] (B-41) [2013]	Tumors ≥2 cm HER-2 positive [529]	• 4cy AC→4cy Ptx Her • 4cy AC→4cy Ptx Lap • 4cy AC→4cy Ptx Her Lap	pCR 52.5% pCR 53.2% pCR 62% (*P*=.095)	No difference in the rate of pCR using Lap, Her or Lap + Her.
Schneeweis [100] TRYPHAENA [2013]	Locally advanced, or inflammatory [225]	• 3cy FEC + Her + Per→3cy Doc + Her + Per • 3cy FEC→3cy Doc + Her + Per • 6cy Doc + Carboplatin + Her	pCR in breast: 61.6% pCR in breast: 57.3% pCR in breast: 66.2%	Primary goal of study evaluate cardiac safety. Per + Her and standard CTX resulted in low rates of symptomatic LVSD. pCR rate higher in patients with HR(-) than HR(+) tumors
Von Minckwitz [101] [2014]	Tumors ≥4 cm HER2 (-) [1,948]	• 4cy EC→4cy Doc • 4cy EC Bev→4cy Doc + Bev	3y DFS:81.5% *v* 80% (*P*=.78) 3y OS: 88.7% *v* 90.7% (*P*=.657)	Bev increased pCR but not DFS or OS. Patients with TNBC similarly showed no improvement in DFS or OS with Bev
de Azambuja [102] NeoALTTO [2014]	HER-2 (+) tumors ≥2 cm [455]	• 6 wk Lap→12 wk Ptx + Lap • 6 wk Her→12 wk Ptx + Her • 6 wk Her + Lap→12 wk Ptx + Her + Lap	pCR 29.5% *v* 24.7% *v* 51.3% (*P*=.0001) 3y EFS: 76% *v* 78% *v* 84% (*P*=.33) 3y OS: 90% *v* 93% *v* 95% (*P*=.19)	Despite significant increase in the rate of pCR with Her/Lap no increase in DFS or OS. Confirmed longer EFS and OS with than without pCR

NeoAdj = neoadjuvant (induction, primary, or preoperative) chemotherapy; Adj = adjuvant (postoperative) chemotherapy; CTX = chemotherapy; S = surgery; cy = cycles; HR, hormone receptor [estrogen/progesterone]; RT = radiation therapy; NS = difference not significant; pCR = pathologic complete response; cCR = clinical complete response; cPR = clinical partial response; AV = Adriamycin [doxorubicin] + vincristine; CAMF: cyclophosphamide + adriamycin (doxorubicin) + methotrexate + 5-fluorouracil (5-FU); CAMFTPL: cyclophosphamide + adriamycin (doxorubicin) + methotrexate + 5-fluorouracil (5-FU) + tamoxifen + premarin + leucovorin; CMF = cyclophosphamide + methotrexate + 5-fluorouracil; FAC = 5-fluorouracil (5-FU) + Adriamycin [doxorubicin] + cyclophosphamide; FEC = 5-fluorouracil (5-FU) + epirubicin + cyclophosphamide; EVM = epirubicin + vincristine + methotrexate; MTV = mitomycin C + thiotepa + vindesine; CVAP = cyclophosphamide + vincristine + doxorubicin + prednisolone; Doc = docetaxel (taxotere); Ptx = paclitaxel (taxol); AC = adriamycin + cyclophosphamide; EPtx = epirubicin + paclitaxel; E = epirubicin; AT = doxorubicin + paclitaxel; CMF = cyclophosphamide + methotrexate + 5-fluorouracil; Her = herceptin = trastuzumab; TAC = docetaxel + doxorubicin + cyclophosphamide; NX = vinorelbine (navelbine) + capecitabine (xeloda); EC = epirubicin + cyclophosphamide; Lap = lapatinib; Bev = bevacizumab; Per = pertuzumab; LVSD = left ventricular systolic dysfunction; OS = overall survival; RFS = relapse-free survival; DFS = disease-free survival; TTP = time to progression; EFS = event free survival.

Table 5
Representatives studies in the history of adjuvant treatment in colon cancer.

Study [Yr]	Stage [number of patients]	Treatment arms	Results	Comments
Wolmark [117] [1988]	Dukes B, C [1,166]	• Observation • MOF × 8 cycles • BCG	5y DFS: 51% *v* 58% ($P=.02$) 5y OS: 59% *v* 67% ($P=.05$)	First large scale trial to show benefit of adjuvant treatment in CRC
Laurie [118] [1989]	Dukes B, C [401]	• Observation • 5-FU + levamisole	Reduction in recurrence 45% ($P=.003$) Reduction in death 13% ($P=.03$)	First trial to describe benefit of 5-FU + levamisole
Moertel [119] [1990]	Dukes B, C [1,296]	• Observation • 5-FU + levamisole	3½y RFS: 56% *v* 47% ($P<.0001$) 3½y OS: 55% *v* 71% ($P=.0064$)	Second trial to describe benefit of 5-FU + levamisole
Wolmark [120] [1993]	Dukes B, C [1,081}	• MOF • 5-FU + leucovorin	3y DFS: 64% *v* 73% ($P=.0004$) 3y OS: 77% *v* 84% ($P=.003$)	First NSABP trial to show benefit of modulating 5-FU with leucovorin in adjuvant setting
SAKK [121] [1995]	Localized tumors [533]	• Observation • Intraportal 5-FU + mitomycin	5y DFS: 48% *v* 57% ($P=.051$) 5y OS: 55% *v* 66% ($P=.026$)	Efficacy of a local strategy in the adjuvant setting
Andre [122,129] [2004, 2009]	II, III [2,246]	• 5-FU + leucovorin • FOLFOX	5y DFS: 67.4% *v* 73.3% ($P=.003$) 6y OS: 68.7% *v* 72.9% ($P=.023$)	Efficacy of adding oxaliplatin mainly in stage III disease
Twelves [123] [2005]	III [1,987]	• 5-FU + leucovorin • Capecitabine	3y DFS: 60.6% *v* 64.2 ($P=.12$) 5y OS: 77.6% *v* 81.3% ($P=.05$)	Noninferiority of oral capecitabine over 5-FU + leucovorin
Saltz [124] [2007]	III [1,264]	• 5-FU + leucovorin • 5-FU + leucovorin + irinotecan	5y DFS: 62% *v* 59% ($P=.85$) 5y OS: 71% *v* 68% ($P=.74$)	No benefit to adding irinotecan in adjuvant setting

MOF = mustard (semustine) + oncovin (vincristine) + 5-fluorouracil (5-FU); BCG = Bacillus Calmette-Guéri; 5-FU = 5-fluorouracil; FOLFOX, 5-FU + leucovorin + oxaliplatin; DFS = disease-free survival; OS = overall survival; RFS = relapse-free survival.

surprisingly two distinct entities [114]. Women with hormone-receptor negative tumors have better responses to chemotherapy but those with hormone-receptor positive tumors survive longer (Table 3) [114,115]. It is increasingly clear that neoadjuvant trials should address these two patient populations separately.

Colorectal cancer

Adjuvant therapies

Unlike the history of adjuvant therapies in breast cancer, in colorectal cancer adjuvant therapies did not focus on dose-dense or dose intensive approaches. Instead the paradigms that guided adjuvant strategies included the use of immunostimulants (Bacillus Calmette-Guérin) or immunomodulators (levamisole) exploiting multiagent regimens established in the metastatic setting (Table 5). Additionally, greater emphasis has often been given to identifying those most likely to benefit from such therapies; specifically, patients with surgical presentations that seem confined (stage I/II) have generally not been considered candidates (QUASAR Trial (Quick and Simple and Reliable)), such that some therapies are tested only in patients with more advanced disease presentations.

Survival in patients with stage I disease exceeds 90% and these patients are never considered candidates for adjuvant therapy. Al-

Table 6
Adjuvant trials of "molecular targeted agents" and immunotherapy in solid tumors.

Tumor [yr]	Study	Stage[number of patients]	Treatment arms	Results
Breast [2013]	Goss [135] (TEACH)	I to III [3,161]	Chemotherapy + Placebo *v* Chemotherapy + Lapatinib	4y DFS: 83% *v* 87% (HR 0.83; NS) 4y OS: 94% both arms (HR 0.99; NS)
Breast [2013]	Cameron [136] (BEATRICE)	I, II, II (TN) [2,591]	Chemotherapy + Bevacizumab *v* Chemotherapy	3y IDFS: 83.7% *v* 82.7% (HR 0.87; NS) 3y OS: 93% *v* 92% (HR 0.84; NS)
Breast [2014]	Piccart [137] (ALTTO)	I to III [6,281]	Chemotherapy + Trastuzumab + Lapatinib *v* Chemotherapy + Trastuzumab	4y DFS: 88% *v* 86% (HR 0.84; NS) 4y OS: 95% *v* 94% (HR 0.91; NS)
Colon [2012]	Alberts [130] (N0147)	III [2,686]	Chemotherapy + Cetuximab *v* Chemotherapy	3y DFS: 71.5% *v* 74.6% (HR 1.21; NS)* 3y OS: 85.6% *v* 87.3% (HR 1.25 NS)*
Colon [2013]	Allegra [131] (NSABP-08)	II, III [2,673]	Chemotherapy + Bevacizumab *v* Chemotherapy	3y DFS: 77.9% *v* 75.1% at (HR 0.93; NS) 5y OS: 82.5% *v* 80.7% at (HR 0.95; NS)
Colon [2014]	Taieb [138] (PETACC-8)	III (exon 2 WT tumors) [2,559]	Chemotherapy + Cetuximab *v* Chemotherapy	3y DFS: 75% *v* 78% (HR 1.05; NS)* 3y OS: 88.3% *v* 90.5% (HR 1.09 NS)*
GIST [2009]	Dematteo [139] (ACOSOG Z9001)	Completely resected GIST ≥3 cm	Imatinib** *v* Placebo	1y RFS: 98% *v* 83% (HR 0.35; $P < .0001$) OS: (HR 0.66; NS)
NSCLC [2014]	Kelly [140] (RADIANT)	I, II, IIIA [973]	Erlotinib *v* Placebo	Median DFS: 50.5 m *v* 48.2 m (HR 0.9; NS) Median OS: Not reached (HR 1.13; NS)
HCC [2014]	Bruix [141] (STORM)	Resected or ablated [1,114]	Sorafenib *v* Placebo	Median TTR: 38.6 m *v* 35.8 m (HR 0.89; NS) Median OS: Not reached (HR 0.995; NS)
High-risk RCC [2106]	Haas [142]	Completely resected, pathological stage ≥ high-grade T1b	Sunitinib or Sorafenib *v* Placebo	Median DFS Sunitinib: 5.8 y *v* 6.6 y (HR 1.02; NS) Median DFS Sorafenib: 6.1 y *v* 6.6 y (HR 0.97; NS)
High-risk RCC [2016]	Ravaud [143]	≥tumor stage 3, regional lymph-node metastasis, or both	Sunitinib *v* Placebo	Median DFS: 6.8 y *v* 5.6 y (HR 0.76; $P = .03$)
High-risk RCC [2017]	Motzer [144]	pT2 high grade or ≥pT3 including N1 [1,538]	Pazopanib *v* Placebo	3y DFS: 67% *v* 64% [600 mg group] 3y DFS: 66% *v* 56% [800 mg group] (HR, 0.86; $P = .16$ NS)
Melanoma [2017]	Weber [145]	III [906]	Nivolumab *v* Ipilimumab	1y RFS: 70.5% *v* 60.8% (HR 0.65; $P < .001$)
Melanoma [2018]	Eggermont [146,147]	III [1019]	Pembrolizumab *v* Observation	1y RFS: 75.4% *v* 61% (HR 0.57; $P < .001$)

DFS = disease free survival; HR = hazard ratio; NS = nonsignificant; OS = overall survival; IDFS = invasive disease free survival; RFS = recurrence free survival; TTR = time to recurrence; RCC = renal cell carcinoma.
* Results Wild-Type *KRAS* patient population.
** Only targeted agent recommended for use in the adjuvant setting.

though the QUASAR trial [125] showed a statistically significant benefit for all patients with stage II colon cancer, absolute improvements were small and because most patients have a low recurrence risk, adjuvant chemotherapy is not routinely recommended for most patients with low-risk stage II colon cancer. Its use can be considered for patients with high-risk stage II defined as (1) inadequately sampled nodes (<12); (2) T4 lesions; (3) perforation; (4) poorly differentiated histology; or (5) lymphovascular invasion [126]. Adjuvant therapy however is given to patients with stage III colon cancer usually as systemic combination chemotherapy [127,128]. Combinations of oxaliplatin with bolus or infusional fluorouracil/leucovorin (FOLFOX 4 or FLOX) or oral capecitabine (CAPEOX) have become the standard based on improved disease-free and overall survivals compared with fluorouracil/leucovorin [122,123]. Trials assessing irinotecan, bevacizumab and cetuximab have all been negative or in the case of bevacizumab possibly detrimental [124,130-132].

In rectal cancer, either neoadjuvant or adjuvant chemoradiotherapy can be employed for patients with full thickness musculari involvement (T3), adjacent structure invasion (T4), and/or regional node involvement (N1/N2) since similar DFS and overall survival outcomes have been reported [133–136]. Adjuvant chemotherapy is offered to patients who have undergone preoperative chemoradiotherapy. When a sphincter-sparing operation is contemplated preoperative chemoradiotherapy is favored as it may make it more technically feasible compared to an up-front surgical approach. Novel strategies using chemotherapy alone for induction or preceding or after short course radiation and surgery are undergoing evaluation.

Solid tumors

Targeted agents in adjuvant and neoadjuvant setting

While the agents in Table 1 would be classed as "cytotoxic," the availability of an increasing number of "targeted therapies" has led to their evaluation in the adjuvant setting. As with "cytotoxic agents" demonstration of activity in the metastatic setting has preceded evaluation in adjuvant and neoadjuvant studies. Unfortunately, as shown in Table 6 with the exception of imatinib, used in gastrointestinal stromal tumors (GIST) to inhibit the proto-oncogene cKIT commonly mutated in these tumors, and possibly sunitinib in high-risk renal cell cancer, where disparate results have been achieved, all other studies have failed to demonstrate a benefit to patients [131,137,141,142]. In colorectal cancer, non-small cell lung cancer, and hepatocellular carcinoma, the addition of the targeted agent has not improved outcomes and in colorectal cancer, bevacizumab actually resulted in a worse outcome [132].

Evaluating adjuvant and neoadjuvant strategies

Although gains have been achieved with a myriad of adjuvant and neoadjuvant strategies, the magnitude of the benefit has often been smaller than hoped. Explanations suggested include inadequate doses or inadequate combinations of agents, problems in study designs and the emergence of treatment resistant cells [125]. Alternately one could argue the paradigm followed—administering therapies demonstrated to improve outcomes in the metastatic setting—may be wrong. DeVita in 1983 cautioned that in the design of future chemotherapy adjuvant trials "drugs that produce partial responses in patients with clinically evident disease should not necessarily be expected to produce better results (cures) in the adjuvant setting" [103]. Amongst the obstacle he envisioned, were inherent drug-resistance as described by the Goldie-Coldman hypothesis, an influential view at the time. He argued that "mutation toward resistance is mass related, (and) patients with large masses of cancer prior to debulking already have a high likelihood of having developed at least one and probably more than one resistant cell line. If these lines have metastasized widely prior to reductive surgery, reducing the mass, while it may improve response to chemotherapy, will not likely improve curability unless the resistant lines in large tumour masses have little propensity to metastasize" [103]. Visionary in its prediction, the reason for failure still eludes us.

In the sections that follow, we discuss a possible explanation for why moving therapies to the adjuvant and neoadjuvant setting have so often failed or have achieved only very modest gains; and why often the gains in survival are less than gains in DFS. Extending our work on the growth and regression rate constants of tumors and the fraction of cells killed [148-152] we posit an explanation for the poor outcomes in the neoadjuvant and adjuvant settings and suggest a rational approach for reducing failures and enhancing success.

Box 1. Kinetic analysis of tumors where regression and growth are occurring simultaneously.

Estimate of concomitant growth and regression rates of a tumor when therapy is administered can be obtained using the equations that follow. In the majority of cases, Eq. (1) provides an acceptable fit to the data and is advantageous as it contains only two undetermined parameters, g and d.

$$\mathbf{f(t)=exp(-d\cdot t)+exp(g\cdot t)-1} \quad (1)$$

Where **f** represents **f**old-change in tumor quantity at time t after therapy is administered, **d** is rate of regression or **d**ecay, and **g** is rate of tumor **g**rowth.

With more robust data sets the fraction of tumor sensitive to therapy can be included in the equation, and its value determined [86]. In these cases the equation is:

$$\mathbf{f(t)=\emptyset\cdot exp(-d\cdot t)+(1-\emptyset)\cdot exp(g\cdot t)} \quad (2)$$

where **d** is rate of regression or **d**ecay of the fraction **Ø** of the tumor sensitive to the therapy, while **g** is rate of **g**rowth of the tumor fraction (**1 – Ø**) that is resistant, or more accurately relatively resistant, to the therapy.

When the data show a continuous decrease from the start, and only the regression parameter **d** differs significantly from zero with $P < .1$, the growth rate constant is eliminated and Eq. (1) is simplified as follows,

$$\mathbf{f(t)=exp(-d\cdot t)} \quad (3)$$

or when tumor measurements show a continuous increase, and only the growth parameter **g** differs significantly from zero with $P < .1$, the decay constant is eliminated, and Eq. (1) is simplified as follows,

$$\mathbf{f(t)=exp(g\cdot t)} \quad (4)$$

Finally, we have defined the **Ø** index as:

$$\frac{\text{Cases for which the Ø equation (Eq.2) was statistically preferred} \pm \text{Cases where no regrowth was found}}{\text{Total number of cases}}$$

We include the cases where no regrowth was found because those cases represent an entirely sensitive tumor. Note that the **Ø** index does not establish the fraction of tumor sensitive to therapy (**Ø**), but rather is a construct that gives insight into the value of **Ø** and more importantly can be uniformly applied allowing for comparisons to be made

Tumor growth and regression constants

With metastatic tumors we have previously shown that outcomes are a result of concurrent effects of therapies on the rates

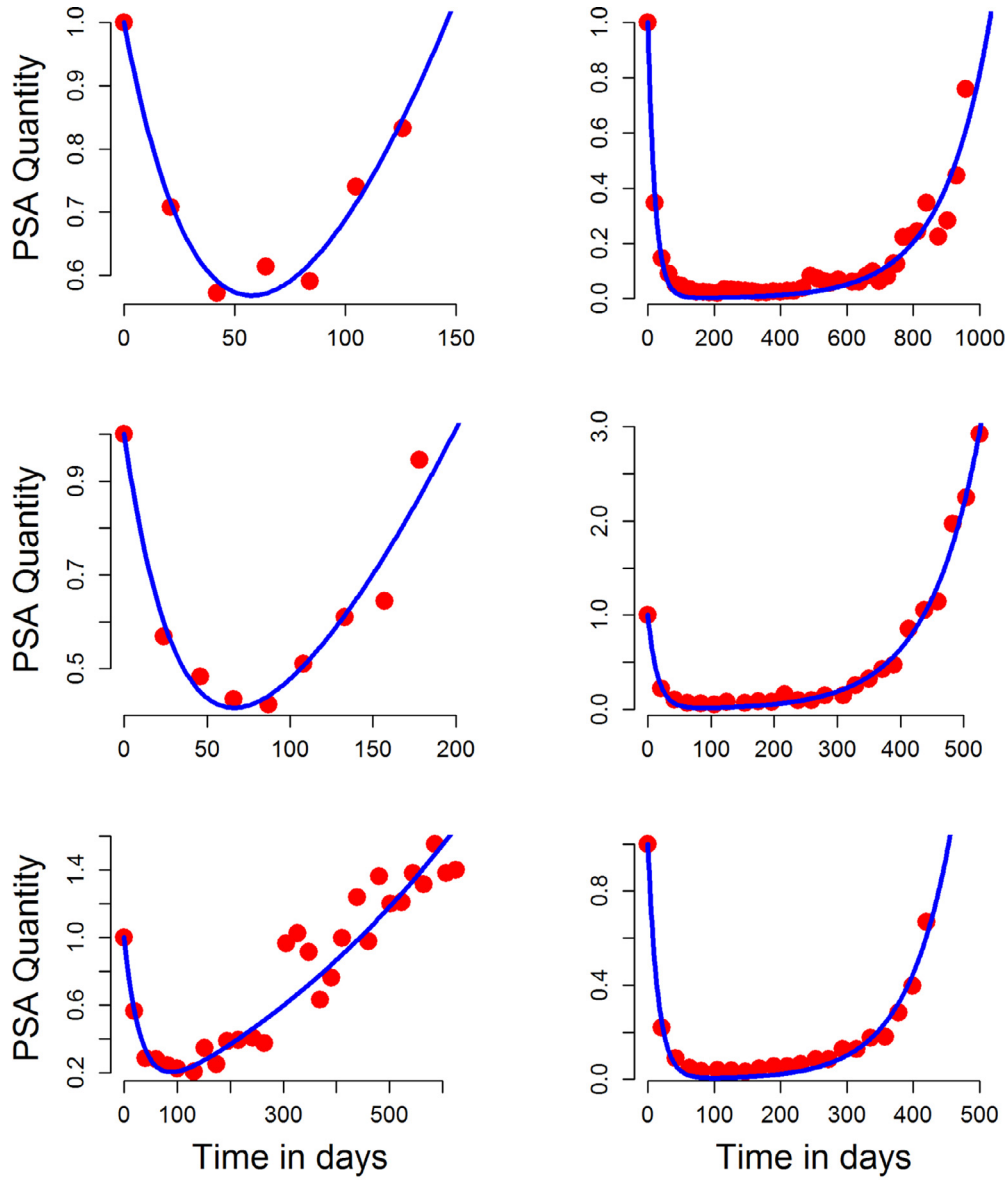

Fig. 1. Six tumor growth curves. Data from 6 representative cases of patients with CRPC treated with ATTP. The solid points are, on the *y*-axis, the ratio of the PSA signal at the time given on the *x*-axis (in days) to its value at study entry. The solid lines are the predicted values from the best-fit regressions using the equations in Box 1.

of tumor regression (***d***) and growth (***g***), and the fraction of tumor killed by the drug (***Ø***) [148-152]. Fig. 1 depicts 6 examples in patients with castration refractory prostate cancer (CRPC) treated with bevacizumab, docetaxel, thalidomide, and prednisone (ATTP) [153]. PSA values are normalized to 1.0 at time zero. The solid lines in each panel represent the best fit of equations we use to model tumor growth. In the left-hand panels PSA values drop to no less than one-fifth the initial value, followed by rises in PSA. In the right-hand panels, PSA values show deeper, longer lasting responses to the therapy.

We have explored the ability of the equations in Box 1 to accurately estimate concomitant growth (***g***) and regression (***d***) rates and the fraction of tumor sensitive to therapy (***Ø***). Thus, in Fig. 1, for example, the estimated values of ***Ø*** are 0.71, 0.84, and 0.84 for the data sets on the left (leaving 29%, 16% and 16% of tumor capable of regrowing) and 0.990, 0.995, and 0.999 for those on the right (1%, 0.5%, and 0.1% capable of regrowing).

Growth kinetics

Informing on how drugs work

For a trial as a whole, one can determine median values of ***g***, ***d***, and ***Ø*** and thus establish whether gains, if any, observed with a therapy have occurred because of effects on ***g***, ***d*** or ***Ø***, or some combination. Fig. 2 shows results of a study in metastatic renal tumors [154,155]. The upper and lower panels depict results with sunitinib and interferon alfa, respectively. The solid downward lines depict regression of tumor sensitive to the therapy and start at ***Ø***, the fraction of tumor sensitive to treatment. Note that sunitinib (upper) kills a slightly greater fraction of tumor than interferon (lower), 63% as compared with 50%; and that the rate of tumor regrowth is slower with sunitinib.

Not uncommonly, an experimental arm in a randomized trial achieves a higher overall response rate (ORR) and extension in PFS, both statistically significant, with a prolongation in overall survival

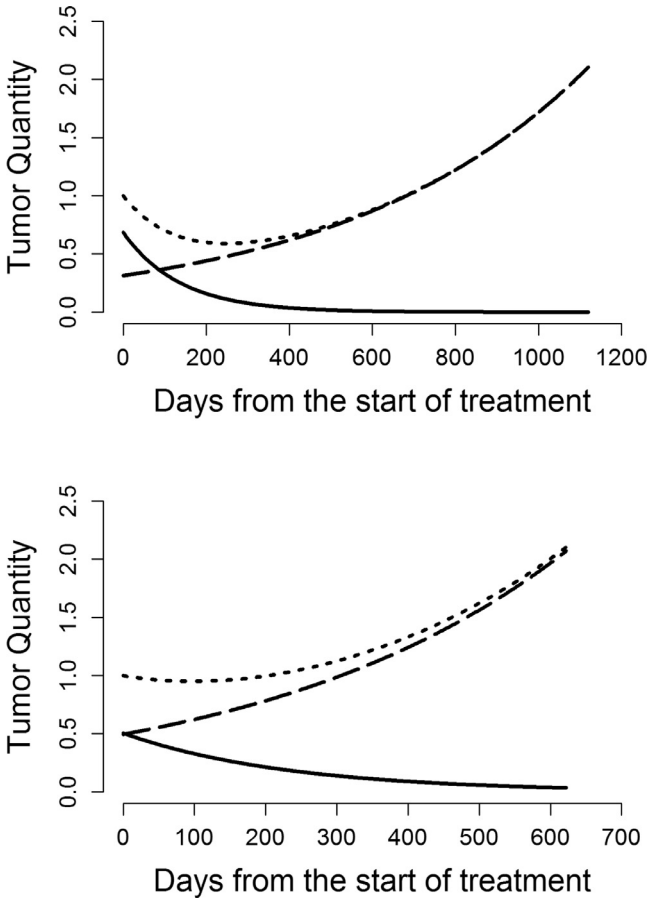

Fig. 2. Deconvoluting overall tumor progression into the decay and growth curves. The upper and lower panels depict results with sunitinib and interferon alfa, respectively. Tumor quantity relative to study entry data is given on the *y*-axis, time in days on the *x*-axis. Four of the curves (2 in each panel) that originate at the *y*-axis begin at values that depend on ***Ø***, the fraction of tumor sensitive to the administered therapy. The solid downward lines depict regression of tumor sensitive to the therapy and start at ***Ø***. The dashed upward lines depict growth of that fraction of tumor insensitive to drug starting at **1 – *Ø***. In each panel, the sum of the solid and dashed curves is the descending and then rising dotted line representing actual tumor measurements obtained in the study. Sunitinib kills a slightly greater fraction of tumor than interferon—63% versus 50%—as shown by the higher starting point on the *y*-axis for the solid line; and the rate of tumor regrowth is slower with sunitinib (note *x*-axes are different). Median ***g*** and ***d*** values were estimated from the analysis using Eq. (1) and tumor measurement data in the 2 separate arms of the trial and this was used to plot the projected outcomes. Eq. (2) was then fitted to these curves and the appropriate ***g***, ***d***, and ***Ø*** parameters extracted.

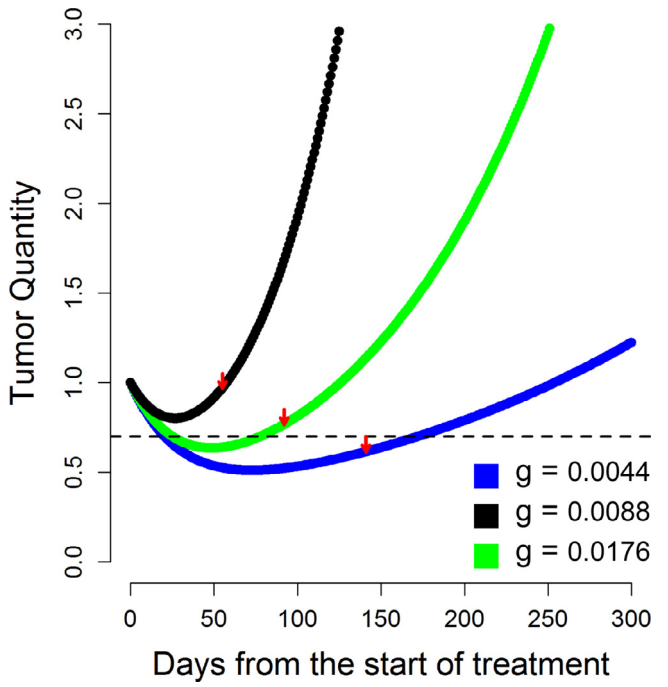

Fig. 3. How ***g***, ***d***, and ***Ø*** interact in determining the profile of a tumor progression. The lowest curve is the prediction obtained with the median ***g***, ***d***, and ***Ø*** parameters from fitting Eq. (2) to the curve obtained using the median ***g*** and ***d*** parameters when using Eq. (1) on a trial of thalidomide plus docetaxel in CRPC patients. In the successive upward curves, the ***g***- ***d***- and ***Ø***-based prediction is made keeping both ***d*** and ***Ø*** constant but increasing the value of ***g*** by 2 and 4-fold. Predicted tumor quantity relative to the size at study entry is given on the *y*-axis, time in days on the *x*-axis. Values for ***d*** (0.0332/d) and ***Ø*** (0.673) are the same for all 3 curves. The lowest curve has a ***g*** value of 0.0044/d, and the 2 above it have ***g*** values of 0.0088/d and 0.0176/d. The nadirs from lowest to highest are 0.510, 0.635, and 0.800; while PFS values (20% above nadir and indicated by downward pointing red arrows) are 54.5, 91.5, and 140.5 days. (Color version of figure is available online.)

that is statistically insignificant [143]. Often higher ORRs are seen as evidence of greater fractional cell kill. However, this need not be the case and indeed we would argue is often not the case. While a higher response rate indeed indicates a higher percentage of patients achieved sufficient reduction in tumor size to qualify as an "objective response," this reduction in tumor size does not necessarily mean a greater fraction of tumor cells were killed. Such an effect can be observed if the experimental therapy has a greater effect on the growth rate constant without any effect on ***Ø***. An example of this is shown in Fig. 3, which presents theoretical curves based on our analysis of thalidomide plus docetaxel in CRPC patients. The lowest curve is based on the median values of the ***g***, ***d***, and ***Ø*** parameters found for thalidomide plus docetaxel and for this exercise will be considered the results one would observe in a single patient (in this case a patient with rate constants and a ***Ø*** value equal to the median of the group as a whole, ***d*** = 0.0332/d, ***g*** = 0.0044/d, and ***Ø*** = 0.673). The two curves above this lowest curve are computed for hypothetical cases in which both ***Ø*** and ***d*** are held constant while ***g*** is doubled successively. The figure shows in these examples, each of which could represent a patient, how only the tumors represented by the lower two curves would be scored as having a response (nadirs 51% and 63.5%), while the third example (nadir 80%) would not. Thus, one can readily see a greater response rate can be achieved by a greater reduction in the growth rate constant of the resistant fraction, without killing any more cells. In effect, slowing the growth rate constant allows decay of the sensitive fraction to manifest more fully, before the quantity of resistant cells becomes sufficient to be seen clinically as tumor growth. Thus a higher response rate need not mean a larger ***Ø***. Therapies that achieve a greater fractional cell kill (right hand panels of Fig. 1) we will refer to as "***Ø*** therapies," while those that primarily impact the rate of tumor growth we will refer to as "***g*** therapies." In general, data for ***Ø*** therapies are well-fitted by Eq. (2), while ***g*** therapies are well-fitted by Eq. (1).

*Optimal **Ø** therapies*

Before arguing why only ***Ø*** therapies can be expected to perform well in the neoadjuvant and adjuvant settings, let us clarify the term "resistant" fraction. We would argue "relative resistance" is a better term. While not sensitive enough to be killed by the therapy, the surviving (relatively resistant) fraction is slowed to variable extents during therapy, delaying progression and resulting in better outcomes. For example, one can envision DNA damage insufficient to kill slowing progression as cells slow to repair DNA. Referring to Fig. 3 one can see where progression is scored—20% above nadir—occurs earlier with each doubling of ***g***, with progres-

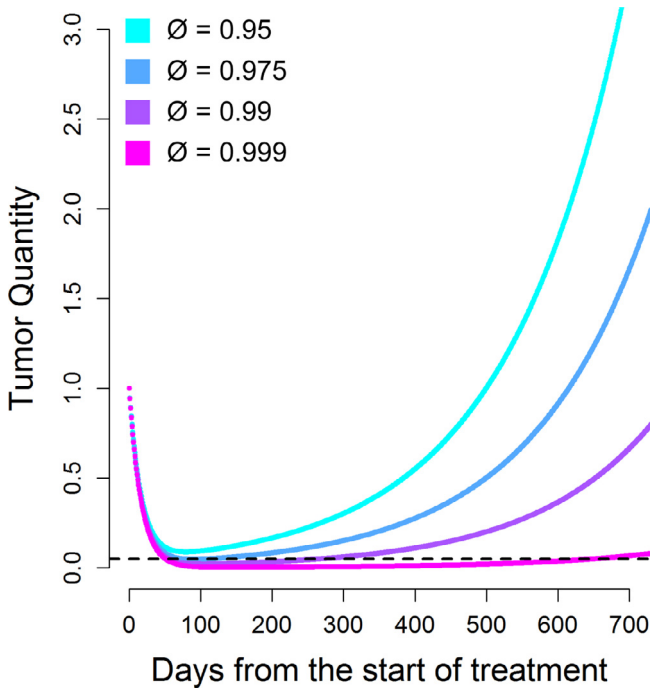

Fig. 4. The importance of **Ø** even at high levels of fractional cell kill. Graphs demonstrating the tumor quantity as a fraction of initial as **Ø** increases from 0.95 to 0.999. In drawing all graphs we used **g** (0.006/d) and **d** (0.06/d) values in the range of those in the studies described in this manuscript. The graphs demonstrate the marked effect, even small changes in **Ø**, at these very high levels can have on the tumor quantity.

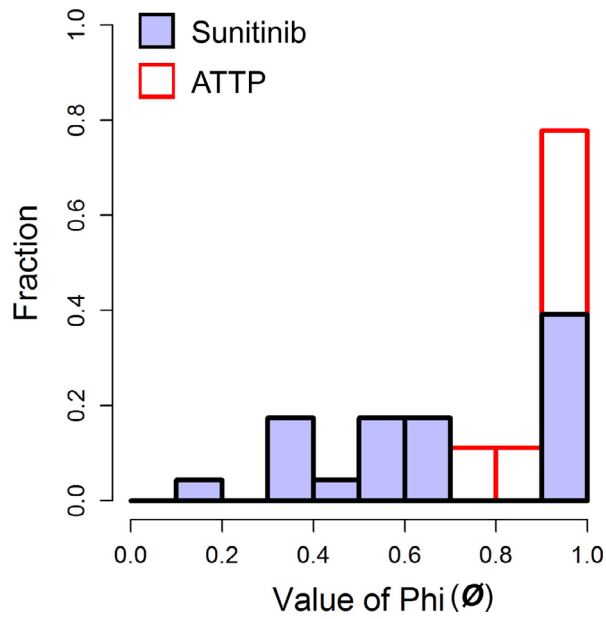

Fig. 5. Histograms of the **Ø** values extracted from the ATTP/CRPC and the interferon/sunitinib renal cancer study. For 36 of the 59 CRPC cases treated with the **Ø** therapy, ATTP, Eq. (2) gave valid values for the ***g***, ***d***, and **Ø** parameters. By comparison, in 24 of the 375 cases in the sunitinib arm of the interferon/sunitinib renal study, although primarily a ***g*** therapy, Eq. (2) yielded valid ***g***, ***d***, and **Ø** values. The orange bars show the distribution of **Ø** values for the ATTP study. The teal bars the distribution for the interferon/sunitinib study. The *y*-axis shows the number of cases in either study having the **Ø** value on the *x*-axis. (Color version of figure is available online.)

sion scored at 54.5, 91.5, and 140.5 days for the fastest, intermediate, and original ***g*** values, respectively. This analysis demonstrates that although the fraction of tumor killed by therapy (**Ø**) did not change, not only a higher response rate, but also greater efficacy—as assessed by time to progression—can be achieved with incremental decreases in ***g***. One can thus see how in the metastatic setting where death is often only a few months away, and survival and not cure is the endpoint and basis for regulatory approval, ***g*** therapies that slow growth of the relatively resistant fraction conferring only months of advantage can be considered "successful."

However, in the neoadjuvant and adjuvant settings, therapy is administered for a brief period of time before and/or following surgery or radiation. Here, a ***g*** therapy that slows growth of the relatively resistant fraction while administered, will only marginally prolong survival, which might occur years later. Such marginal delays will confer neither statistical, nor clinically meaningful benefit. However, **Ø** therapies that kill larger tumor fractions may do so even during short administration times and in the setting of microscopic tumor could, in principle, eradicate the remaining tumor.

This argument might become clearer on looking at Fig. 4. The curves depicted are drawn using ***g*** (0.006/d) and ***d*** (0.06/d) values in the range of those observed in the studies described herein. The value of **Ø** is varied from 0.95 to 0.999 and shows the marked effect even small incremental changes have on outcome emphasizing the need when moving to the neoadjuvant and adjuvant settings of using therapies with optimal **Ø**. We would note that in the neoadjuvant setting, reduction in tumor growth rate with a ***g*** therapy might appear at the time of surgery (pCR) to have conferred an advantage, but because the fraction of tumor killed has not increased, such a therapy will not prolong survival.

Given the high failure rate of neoadjuvant and adjuvant trials and their costs we would argue if the goal of such a therapy is to eradicate microscopic disease, success will be achieved with **Ø** therapies. Unfortunately, our current paradigm of success for metastatic disease is not to cure, but to prolong survival a few months, and not surprisingly these are ***g*** therapies.

Discriminating therapies using clinical trial data

How can one determine whether a histology/therapy combination is best described as a **Ø** or ***g*** therapy? Table 7 summarizes data from almost 3,000 patients with various combinations of histologies and therapies [153-162]. Individual patient data has been fitted to the equation in Box 1 that gave the statistically best fit. Insight into whether a therapy is primarily a **Ø** or a ***g*** therapy can be gleaned from the percent of cases for which one can determine a value for **Ø** and by looking at the **Ø** index.

With the therapy/histology pair ATTP/CRPC [153], for example, a valid estimate of **Ø** could be obtained in many cases, and we determined the **Ø** index as 0.51. Similarly we determined **Ø** indices of 0.41 and 0.44 for multiple myeloma treated with bortezomib, with or without pegylated liposomal doxorubicin [161]. These three therapies should perhaps be defined as **Ø** therapies. However, for most of the therapies, **Ø** indices are low and the term ***g*** therapy might be more appropriate. Two such contrasting patterns are depicted as histograms in Fig. 5. CRPC treated with ATTP is shown as an example of a **Ø** therapy with data from 36/59 patients well-fitted by Eq. (2), and most with high **Ø** values. By comparison, renal cell carcinoma treated with sunitinib is shown as an example of a ***g*** dominant therapy with only 24/375 well-fitted by Eq. (2), the majority of cases being well-fitted by Eq. (1) [154,155]. Also the values of **Ø** in many of the renal cell carcinomas are low, as compared to those treated with ATTP. Indeed, if there are some statistically valid **Ø** cases for a dataset that is intrinsically ***g-dominant***, most **Ø** values so obtained are well below the values of 0.9 and above found for a typical **Ø** therapy/histology combination. Finally, we would stress we see **Ø** indices as most valu-

Table 7
The Ø index for various histology/therapy combinations.

Histology	Number	Therapy	Ø index*	Reference
Prostate	10	Thalidomide	0.13	(Dahut, 04) [96]
Prostate	46	Thalidomide + docetaxel	0.30	(Dahut, 04) [96]
Prostate	36	Ketoconazole	0.21	(Figg, 05) [95]
Prostate	36	Ketoconazole + alendronate	0.21	(Figg, 05) [95]
Prostate	59	ATTP	0.51	(Ning, 10) [90]
Prostate	46	ARTP	0.31	–
Renal	39	Placebo	0.04	(Yang, 03) [98]
Renal	94	Avastin	0.08	(Yang, 03) [98]
Renal	373	Interferon	0.18	(Motzer, 07) [91]
Renal	374	Sunitinib	0.24	(Motzer, 07) [91]
Renal	77	Ixabepilone	0.23	(Huang, 10) [97]
Breast	346	Capecitabine	0.21	(Thomas, 07) [94]
Breast	352	Capecitabine + Ixabepilone	0.21	(Thomas, 07) [94]
Multiple myeloma	322	Bortezomib	0.41	(Orlowski, 07) [99]
Multiple myeloma	323	Bortezomib + Pegylated liposomal doxorubicin	0.44	(Orlowski, 07) [99]
Medullary thyroid carcinoma	99	Placebo	0.03	(Wells, 12) [100]
Medullary thyroid carcinoma	231	Vandetanib	0.37	(Wells, 12) [100]

* The Ø index is defined as (the sum of cases for which the Ø equation [Eq. (2)] was statistically preferred + cases where no regrowth was found)/total number of cases.

able when comparing the ***Ø*** indices of two therapies—an experimental and standard therapy—rather than in absolute terms, since such comparisons can discern whether the experimental therapy has achieved a greater amount of cell kill, or ***Ø***.

Therapy setting success and failures

Given the above, it is not surprising drugs fail when "moved up front" to the neoadjuvant and adjuvant settings. With metastatic cancer as the proving ground, ***g*** therapies affecting growth and not fractional cell kill have emerged as our most common therapies. But, as we have just seen, one can ascertain whether a new therapy is better considered as a ***Ø*** or ***g*** therapy, and in this way more rationally decide its potential in the neoadjuvant and adjuvant settings. Indeed, we would argue new combinations or "add-ons" should be tried as neoadjuvant or adjuvant therapies only if they impact ***Ø***.

Interestingly, in the metastatic setting where continuation of effective therapies beyond accepted definitions of progression are increasingly being examined and advocated, the converse of the adjuvant paradigm often applies [163,164]. While obviously a highly effective ***Ø*** therapy that eradicates all cancer cells is ideal, realistically a ***g*** therapy is more likely to be identified and in the metastatic setting continuing such a ***g*** therapy beyond generally accepted progression endpoints might be beneficial. This benefit occurs if ***g*** indeed remains constant, an observation that we have documented occurs often in the metastatic setting [152,165].

Conclusions

We have summarized adjuvant and neoadjuvant therapies and highlighted the development of breast and colorectal therapies to provide the reader a perspective of how investigators have viewed this intervention that still offers much hope going forward. That the results have been less than expected may reflect the difficulty of treating cancer in general, but it is hoped that newer therapies and newer strategies will improve outcomes. We believe most cancer therapies fail in the neoadjuvant and adjuvant settings because they are developed in the metastatic setting as ***g*** therapies that impact the growth rate constant and prolong survival without increasing fractional cell kill. That therapies identified in the metastatic setting are primarily ***g*** *therapies* is likely a consequence of trial designs looking to prolong survival by a few months. It is important to recognize that a ***g*** therapy ratified as effective in the metastatic setting might result in a higher ORR, as a consequence of its growth retardant properties, not greater cell kill. In deciding which therapies to move forward to the neoadjuvant and adjuvant settings, one must look for therapies with a substantial impact on ***Ø***, not necessarily on ***g***. Development of better ***Ø*** therapies that kill a greater fraction of tumors will result in greater success in the neoadjuvant and adjuvant settings and hopefully cure more patients of their cancer at the point when they have the lowest tumor burden.

Conflicts of interest

None.

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