Web appendix

Plain English Summary

When a new medication is considered effective and safe enough to start being given to patients, we do not always know how best to use it. There may still be questions about its optimal dose, schedule and duration, and its place within the whole treatment plan, which may include surgery, radiation or other medications. Pharmaceutical companies do not usually conduct much research into these issues, leaving academic and clinical researchers to find answers to these questions.

Finding out the optimal use of a cancer medication for patients requires several investigations. Perhaps a lower dose is good enough, sparing patients the extra harm and saving the health system the extra cost resulting from higher doses. Or perhaps a different administration schedule is better than the current one.

Cancer treatments are complex and costly, and because they evolve rapidly, we must prioritise and define carefully the questions most relevant to patients, oncologists and health systems. We can achieve this most effectively with input and support from patients, healthcare payers and funders (government or charities). This article groups all these questions aiming to determine the optimal use of drugs and provides guidance to help academics plan and successfully conduct clinical trials addressing those questions.

Supplementary Table 1: inclusion in guidelines and on the drug label of the examples from Table 1

'Less drug' questions	Example with PICO details	Guidelines (consulted Dec 24)	Label change (EMA)
1.1 Drug omission			
Complete drug or regimen omission	SIOP WT 2001[8] P: Stage 2-3 intermediate risk Wilms' tumours I: Vincristine/Dactinomycin D C: Vincristine/Dactinomycin/Doxorubicin O: 2-year EFS	UK: yes (CCLG) No ESMO guidelines NCCN: yes recommended, but paper not directly cited	No but labelled indications very broad ("Wilm's tumour")
Response- or biomarker-driven drug or regimen omission	DYNAMIC[9] P: Resected stage 2 colorectal cancer I: ctDNA adjuvant chemotherapy C: Standard adjuvant chemotherapy O: RFS	UK: from 2020 (NICE), guidelines preceding trial results ESMO: from 2020, guidelines preceding trial results NCCN: results discussed but not recommended by panel	No but relevance of updating product information questionable
1.2. Stopping/Breaks			
Shorter duration or early stopping	PERSEPHONE[10] P: Early HER2+ breast cancer I: Adjuvant trastuzumab for 6 months C: Adjuvant trastuzumab for 12 months O: DFS	UK: from 2018 (NICE), no mention of duration ESMO: not recommended, but discussed as an option in resource-constrained setting NCCN: not recommended, but discussed ("Considering the conflicting results between PERSEPHONE and PHARE [...], the NCCN panel recommends up to one year of HER2-targeted therapy with trastuzumab")	No
Treatment break vs continuous treatment until progression	STAR[11] P: Advanced renal cell carcinoma I: Sunitinib or pazopanib 24 weeks then break(s) C: Sunitinib or pazopanib continuously O: OS & QALYs (co-primary)	UK: guidelines in production (NICE) ESMO: yes ("treatment breaks from VEGFR TKI therapy do not appear to have any detrimental effect on efficacy [I, C]"). NCCN: no, not mentioned.	No

Individualised adaptive schedule	ANZADAPT (NCT05393791) P: Metastatic castration-resistant prostate cancer I: Adaptive abiraterone or enzalutamide C: Continuous abiraterone or enzalutamide O: Time to treatment failure	N/A (ongoing trial)	N/A (ongoing trial)
1.3. Same duration, less drug			
Lower dose	DEDICATION-1[12] P: Advanced NSCLC with no driver mutation I: 300mg Q6W pembrolizumab C: 400mg Q6W or 150-200 mg Q3W pembrolizumab O: OS	N/A (ongoing trial)	N/A (ongoing trial)
Lower dose with booster (food or drug)	Szmulewitz et al[13] P: metastatic castration-resistant prostate cancer I: 250mg abiraterone with low-fat meal C: 1000mg abiraterone fasting O: PSA at 12 weeks	UK: no, not mentioned ESMO: not recommended but discussed ("Low-dose abiraterone taken with food appeared to have similar activity to standard dose abiraterone under fasting conditions; however, this has not been tested in phase III trials.") NCCN: mentioned as an option ("The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast").	No
Same standard dose but longer intervals	CALGB 70604[14] P: Patients with bone metastases (prostate, breast or MM) I: Zoledronate every 12 weeks for 2 years C: Zoledronate every 4 weeks for 2 years O: % of patients with ≥ 1 skeletal-related events at 2 years	UK: no mention of bisphosphonate exact schedule (prostate), no mention (breast, from 2017), no mention (MM, from 2016) NCCN: yes recommended for prostate ("every-12-week dosing of zoledronic acid is recommended for symptomatic SRE reduction when indicated"), breast ("The NCCN Panel	No

		recommends an optimal dosing of every 12 weeks"), no clear recommendation for MM ("The frequency of dosing (monthly vs. every 3 months) would depend on the individual patient criteria, response to therapy, and agent used") ESMO: neither mentioned nor recommended for prostate and MM, an option for breast ("zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments")	
1.4. Neoadjuvant			
Full neoadjuvant	INTERLACE[15] P: Patients with locally-advanced cervical cancer I: induction chemotherapy (weekly paclitaxel and carboplatin) and CRT C: CRT O: PFS and OS	Trial results published in Oct 2024 UK: no from 2020 (BGCS), guidelines preceding trial results ESMO: no, from 2017, guidelines preceding trial results NCCN: not mentioned, guidelines preceding trial results	No, but paclitaxel and carboplatin have been used off-label in cervical cancer for decades despite widespread use
Neoadjuvant with response-guided adjuvant treatment	NADINA[16] P: Stage 3 melanoma I: 2 Q3W cycles of neoadjuvant ipilimumab (80mg) + nivolumab (240mg) followed by response-based adjuvant treatment C: Adjuvant nivolumab (12 cycles of 480mg Q4W) O: EFS	Trial results published in June 2024 UK: no (from 2015, update in 2022), guidelines preceding trial results ESMO: yes ("For patients with resectable stage III melanoma and pathologically proven, clinically or radiologically detectable LN metastasis, neoadjuvant nivolumab/ipilimumab [ESMOMCBS v1.1 score: A; not EMA or FDA approved] followed by surgery should be offered.") NCCN: yes, mentioned as an option though "The optimal regimen and duration for neoadjuvant systemic therapy is not well established"	No

Supplementary Table 2: inclusion in guidelines and on the drug label of the examples from Table 2

'Similar amount' (≈) questions	Example with PICO details	Guidelines (consulted Dec 24)	Label change (EMA)
2.1 Sequence			
Sequencing	Khalaf et al [17] P: Metastatic castration-resistant prostate cancer I: Enzalutamide then abiraterone (at progression) C: Abiraterone then enzalutamide (at progression) O: Time to second PSA progression	UK: no ESMO: mentioned but not recommended: "the use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended NCCN: mentioned but not recommended because "after abiraterone or enzalutamide, data suggest that giving the alternate novel hormone therapy may not be the optimal strategy"	No
Alternating drugs/regimen	ROPETAR[18] P: Advanced renal cell carcinoma I: 8-week rotation of pazopanib and everolimus C: Pazopanib then everolimus (at progression) O: 1-year PFS	UK: guidelines in production (NICE) ESMO: no mention NCCN: no mention	N/A (negative)
2.2 Timing			
Different timing of administration	OBELICS[19] P: Advanced colorectal cancer I: Bevacizumab 4 days before FOLFOX or CAPOX C: Bevacizumab on day 1 of FOLFOX or CAPOX O: ORR	UK: no (NICE) from 2021 ESMO: no NCCN: no	No
Neoadjuvant initiation of (otherwise) adjuvant treatment	SWOG1801[20] P: Stage IIIB to IVC resectable melanoma I: pembrolizumab 3 neoadjuvant + 15 adjuvant cycles C: pembrolizumab 18 adjuvant cycles O: EFS	UK: no (from 2015, update in 2022), guidelines preceding trial results ESMO: yes, "Neoadjuvant plus adjuvant pembrolizumab is also recommended for these patients [II, A; not EMA or FDA approved]"	No

		NCCN: yes, mentioned as an option though "The optimal regimen and duration for neoadjuvant systemic therapy is not well established"	
2.3 Frequency			
Lower dose but shorter interval	ICON8[21] P: Stage IC-IV epithelial ovarian cancer I: either Q3W Carboplatin (AUC5/6) + Q1W Paclitaxel 80mg/m^2 or Q1W Carboplatin (AUC2) + Q1W Paclitaxel 80mg/m^2 C: Q3W Carboplatin (AUC5/6) + Q3W Paclitaxel 175mg/m^2 O: OS & PFS (co-primary)	UK: results discussed but not recommended – in line with results (BGCS 2024) ESMO: results discussed but not recommended – in line with results NCCN: both interventional regimen mentioned as possible options	N/A (negative)
Change in cycles pace	RESTORE[22] P: Advanced renal cell carcinoma I: sunitinib 50mg QD 2 weeks on, 1 week off (2/1) C: sunitinib 50mg QD 4 weeks on, 2 weeks off (4/2) O: pick the winner on FFS	UK: in production (NICE) ESMO: no mention NCCN: no mention	No
Higher dose but longer interval	Cetuximab CEGOG[23] → not powered for formal comparison P: KRASwt metastatic colorectal cancer I: FOLFOX4 Q2W + cetuximab 500mg/m^2 Q2W C: FOLFOX4 Q2W + cetuximab 250mg/m^2 Q1W O: ORR	UK: no ESMO: no NCCN: yes, cetuximab 500mg/m^2 Q2W preferred over 250mg/m^2 Q1W (though no direct reference to this study)	No
2.4 Individualised dose			
Therapeutic drug monitoring	CAINTA[24] P: Metastatic castration-resistant prostate cancer I: Cabazitaxel 25 mg/m^2 Q3W	UK: no mention ESMO: not mentioned NCCN: not mentioned	No

	C: Therapeutic Drug Monitoring of Cabazitaxel Q3W O: Clinical Feasibility Rate		

Supplementary Table 3: inclusion in guidelines and on the drug label of the examples from Table 3

'More drug' questions	**Example with PICO details**	**Guidelines (consulted Dec 24)**	**Label change**
Longer duration	GEINO 14-01[25] P: Glioblastoma I: 12 months of temozolomide C: 6 months of temozolomide O: PFS at 6 months	UK: no (NICE) EANO: results mentioned to recommend against longer duration (link) NCCN: results mentioned to recommend against longer duration	N/A (negative)
Higher Dose	High Dose Imatinib GIST[26,27] P: Advanced or metastatic GIST I: Imatinib 400mg BD C: Imatinib 400mg QD O: PFS	UK: yes 400mg is recommended except in patients with KIT exon 9 variants who should receive 800mg (link) ESMO: yes 400mg is recommended except in patients with KIT exon 9 variants who should receive 800mg NCCN: yes 400mg QD is recommended. 800mg is mentioned as an option for patients with KIT exon 9 variants.	N/A (negative though escalation to 800mg is already included on label as an option)
Response- or biomarker-driven treatment intensification	RESORT trial[28] P: Low–Tumour Burden Follicular Lymphoma I: Maintenance rituximab C: Retreatment rituximab O: OS	UK: not mentioned (BSH) ESMO: mentioned, recommended against maintenance NCCN: yes, recommended against maintenance	N/A (negative though maintenance is already included on label as an option)