Systemic Therapy Dosing for Obese Adult Patients with Cancer

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Objectives

- Review common descriptors for body size used in literature
- Describe the unique pathophysiology of obesity in cancer risk and survival
- Discuss the ASCO 2021 guideline and supporting literature on dosing systemic therapy in obese adult patients with cancer

BMI Classification in Adults

BMI Classifications:

- Formula = [mass (kg)/height^2(m)]
- Confers risk of cardiovascular disease & DMII
- Pitfalls – does not differentiate between lean body mass and fat mass
- Collective classifications for White, Hispanic, Black populations
- Separate classification for Asian population (underestimated risks)

Classification	BMI (kg/m^2) White, Hispanic, Black	BMI (kg/m^2) Asian
Underweight	<18.5	
Normal weight	≥18.5 – 24.9	
Overweight	≥ 25 – 29.9	≥ 23 – 24.9
Obesity – Class I	30 – 34.9	Obesity: > 25
Obesity – Class II	35 – 39.9	
Obesity – Class III *(Previously referred to as morbidly obese)*	≥ 40	

https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Body Weight Descriptors and Dosing Formulas

<table>
<tr><th>Descriptor</th><th>Formula</th><th>Use</th></tr>
<tr><td>Actual Body Weight (ABW): Unit = kg</td><td>Current total body weight
• Weight-based dose = mg/kg</td><td>-Majority of pharmacotherapies</td></tr>
<tr><td>Ideal Body Weight (IBW): Unit = kg</td><td>• Males = 50 kg + 2.3 kg for each inch over 5 feet
• Females = 45.5 kg + 2.3 kg for each inch over 5 feet</td><td>-Some meds regardless of ABW
-Cockcroft Gault:
$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$ (x 0.85 if female)</td></tr>
<tr><td>Adjusted Body Weight (AjBW): Unit = kg</td><td>IBW + 0.4 (ABW – IBW)
IBW + 0.25 (ABW – IBW)
• AdjBW25 rarely used (i.e., SCT)</td><td>-Nutrition - calculating energy requirements; considers lean and fat mass
-Some medications (mostly antibiotics) when TBW >20% of IBW
-Cockcroft Gault for TBW >20% of IBW
-SCT: some conditioning regimens, stem cell collection (AdjIBW 25)</td></tr>
<tr><td>Body Surface Area (BSA): Unit = m^2</td><td>
<table>
<tr><th>Study</th><th>Population size</th><th>Formula</th></tr>
<tr><td>DuBois and DuBois (1916) [1]</td><td>9</td><td>$BSA\ (m^2) = 0.20247 \times height\ (m)^{0.725} \times weight\ (kg)^{0.425}$ or
$BSA\ (m^2) = 0.007184 \times height\ (cm)^{0.725} \times weight\ (kg)^{0.425}$</td></tr>
<tr><td>Boyd (1935) [2]</td><td>197</td><td>$BSA\ (m^2) = 0.0003207 \times height\ (cm)^{0.3} \times weight\ (g)^{(0.7285 - (0.0188 \times \log(g)))}$</td></tr>
<tr><td>Gehan and George (1970) [3]</td><td>401</td><td>$BSA\ (m^2) = 0.0235 \times height\ (cm)^{0.42246} \times weight\ (kg)^{0.51456}$</td></tr>
<tr><td>Haycock et al. (1978) [4]</td><td>81</td><td>$BSA\ (m^2) = 0.024265 \times height\ (cm)^{0.3964} \times weight\ (kg)^{0.5378}$</td></tr>
<tr><td>Mosteller (1987) [5]</td><td>na[a]</td><td>$BSA\ (m^2) = \sqrt{([height\ (cm) \times weight\ (kg)]/3{,}600)}$ or
$BSA\ (m^2) = \sqrt{([height\ (in) \times weight\ (lbs)]/3{,}131)}$</td></tr>
</table>
[a] This formula is a modification of the Gehan and George [3] formula.
This information has partly been derived from http://www.halls.md/body-surface-area/refs.htm
</td><td>-DuBois most common
-Cytotoxic agents
-Pitfalls:
• Formulas not developed for use in obese
• Do not consider body composition or individual metabolism and excretion
• Risk of high interpatient variability in PK/PD</td></tr>
</table>

Obesity and Cancer Risk

- International Agency for Research on Cancer (IARC) working group in 2016:
  - Reviewed 1000+ epidemiologic studies (excess body fat and cancer risk)
  - Absence of excess body fat significantly reduced risk of many cancers (Table 2)
  - Association with recurrence and survival:
    - Breast – increased BMI reduced survival
    - Other cancers - data sparse and inconsistent

- Globally, obesity attributes to 4-8% of all cancers
  - New cases in US (2011-2015): 4.7% men, 9.6% women
  - Proportions vary:
    - 48.8% of all liver/gallbladder
    - 49.2% endometrial
    - 30.6% of all adenocarcinomas

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)
Male breast cancer	Limited	NA
Fatal prostate cancer	Limited	NA
Diffuse large B-cell lymphoma	Limited	NA
Esophagus: squamous-cell carcinoma	Inadequate	NA
Gastric noncardia	Inadequate	NA
Extrahepatic biliary tract	Inadequate	NA
Lung	Inadequate	NA
Skin: cutaneous melanoma	Inadequate	NA
Testis	Inadequate	NA
Urinary bladder	Inadequate	NA
Brain or spinal cord: glioma	Inadequate	NA

Lauby-Secretan B. N Engl J Med. 2016;375(8):794-798.
Pati S. Cancers (Basel). 2023;15(2):485.

Impact of Obesity on Breast Cancer Risk and Survival

Risk of developing breast cancer:

- **Post-menopausal women:**
  - **HR+ subtype**: 52% increased risk vs normal weight; 86% increased risk with BMI ≥ 35 kg/m^2
    - Disease at diagnosis more likely to be aggressive, advanced, larger tumor size, LN+, regional/distant mets
  - **HR- subtype**: no increased risk

- **Pre-menopausal women:**
  - Reduced risk of breast cancer vs. normal weight

Overall survival worse in all subtypes:

- **HR+/HER2-** (HR=1.39, 95% CI 1.20-1.62, p <0.001)
- **HER2+** (HR=1.18, 95% CI 1.05-1.33, p=0.006)
- **TNBC** (HR=1.32, 95% CI 1.13-1.53, p <0.001)
- **Pre-menopausal** (RR = 1.75, 95% CI 1.26-2.41)
- **Post-menopausal** (RR = 1.34, 95% CI 1.18-1.53)

LeVee A. Cancers (Basel). 2023;15(9):2526.

Pathophysiology of Obesity in Cancer Development

- Adipose tissue dysfunction leads to increased circulating insulin and glucose, altered levels of adipokines and estrogen signaling, chronic inflammation
- Metabolic dysfunction and hyperinsulinemia → increased insulin-like growth factor-1 (IGF-1) → activates PI3K + MAPK → cancer cell proliferation and survival
- Dysfunction impairs chemotherapy efficacy, increases drug resistance, and reduces likelihood of pathological complete response
- Altered microbiome may also increase cancer risk and impair efficacy of treatment

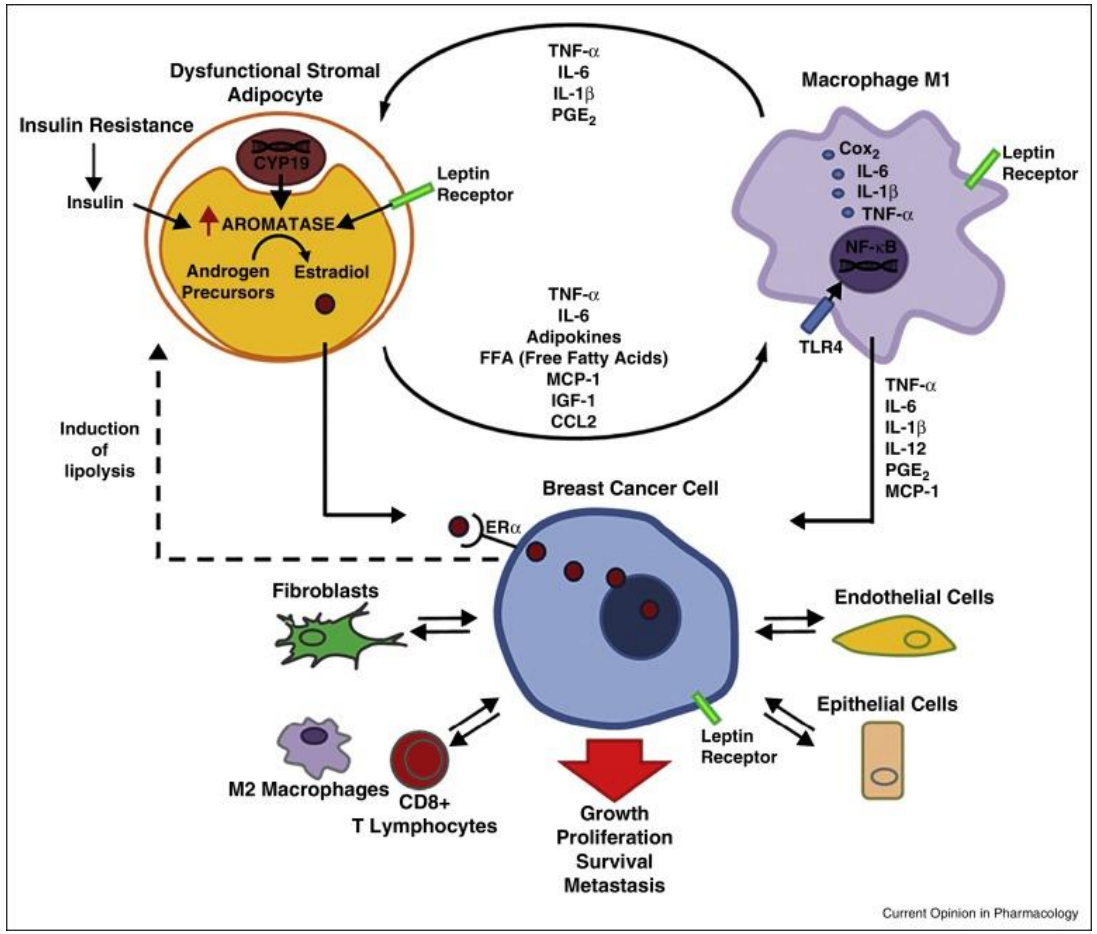


Figure 1 (Breast Cancer): Pro-inflammatory cytokines and adipokines recruitment and activation of immune cells, including macrophages, at the tumor site. Functional signaling between adipocytes and macrophages affects breast carcinogenesis and progression.

Lauby-Secretan B. N Engl J Med. 2016;375(8):794-798.
Crespi E. Curr Opin Pharmacol. 2016;31:114-122.

PK/PD in Obesity – Disparity in Studies

- BSA and BMI disregard differences in PK/PD that might occur in setting of obesity

Absorption:

- Accelerated gastric emptying/GI transit can decrease absorption and solubilization
- Increased fat proportion can reduce oral bioavailability of hydrophilic drugs
- Increased gastric pH impacts ionization

Distribution:

- Hydrophilic vs lipophilic drugs (considerations for protein binding)
- Vd changes not proportionate to TBW increase
- Less obese = more water in excess adipose and more distribution of hydrophilic drug
- Reduced expression of P-gp (*ACBC1*)

Metabolism (hepatic):

- Decreased: CYP 3A4, 2C19, hepatic glucuronidation
- Increased: CYP 1A2 (conflicting evidence), 2C9, 2D6, 2E1

Elimination (renal):

- Ideal parameters and formula up for debate
- Formula weight can vary (IBW/LBW, adjBW)
- TBW overestimates drug elimination

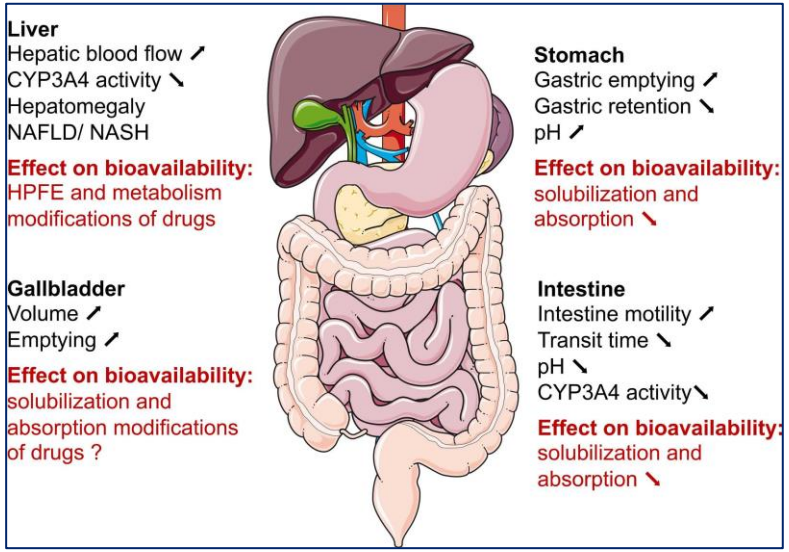


Fig. 1. Functional gastrointestinal modifications related to obesity leading to bioavailability changes.

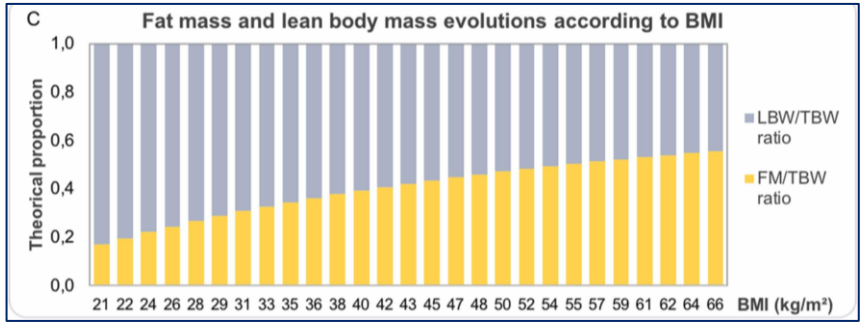


Fig. 3. Effect of obesity on evolution of the LBW and the FM and the LBW/FM proportion for man measuring 170 cm. (C) The FM/TBW ratio increases with obesity to the detriment of LBW/TBW ratio.

Zamboni WC. J Clin Pharmacol. 2023;63 Suppl 2:S85-S102.
Gouju J. Biomed Pharmacother. 2023;166:115281.
Vendelbo J. Pharmacogenomics. 2018;18(1):121-126.

PK/PD in Obesity – Disparity in Studies

- Uncertainties of impact on tumor biology and antitumor response
- Studies on obesity impact often only consider BMI (no evaluation of adiposity-related factors, inflammation, etc)
- Phase I data supporting drug target exposure, tumor response, and expected ADRs need further inclusion of obese patients, consistent definitions for obesity, and additional adiposity-related factors

Cytotoxic/narrow therapeutic index drugs	Immunotherapy	TKIs/oral agents
• Conflicting data on dosing even with same agents	• Many studies show improved survival with obesity • Reduction in clearance might boost efficacy of (i.e., reduced pembrolizumab clearance is associated with greater anti-tumor response)	• Impact on oral absorption due to alterations in GI physiology • Changes in pH can impact solubility • Changes in gastric emptying and intestinal transit times can affect rate and extent of absorption • Chronic inflammation may affect expression and activity of drug transporters and intestinal enzymes

Zamboni WC. J Clin Pharmacol. 2023;63 Suppl 2:S85-S102.

ASCO Guidelines on Antineoplastic Dosing in Obese Adults

ASCO Guideline – 2012 vs 2021

Original ASCO guideline published in 2012:

- Appropriate **Chemotherapy** Dosing for Obese Adult Patients with Cancer
- Authors identified that up to 40% of obese patients are underdosed (used IBW, adjBW, or capped BSA to 2.0 m^2)
- Concerns of toxicity and overdosing obese patients by using ABW were unfounded

ASCO released updated guideline in 2021:

- Appropriate **Systemic Therapy** Dosing for Obese Adult Patients with Cancer
- Purpose: expanded recommendations to include immunotherapy and targeted agents
- Process: systematic literature review, clinical experience, Multidisciplinary Expert Panel consensus

Griggs JJ. J Oncol Pract. 2012;8(4):e59-e61.
Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline – Antineoplastic Dosing in Obese Adults

	2012 Guideline for Obese Adults with Cancer
1	1.1) Use ABW when dosing cytotoxic chemotherapy regardless of obesity status 1.2) Use full weight-based chemo dosing for morbidly obese **Subject to appropriate considerations for comorbid conditions*
2	Do not dose reduce IV or PO chemo due to obesity **Data in breast cancer patients that reduced dose-intensity is associated with increased disease recurrence and mortality*
3	Use standard dose adjustments for obese patients experiencing toxicity
4	Consider fixed dosing only for select agents **Carboplatin, bleomycin, vincristine 2 mg in RCHOP/CVP* **It is not clear that fixed dosing is optimal for any other agents*
5	Use standard BSA formulas
6	Further research needed on role of PK and pharmacogenetics in obese patients

	2021 Guideline Update for Obese Adults with Cancer
1	Use full weight-based dosing of cytotoxic chemotherapy regardless of obesity status
2	Limit fixed dosing of chemotherapy to select agents (e.g., bleomycin) *Evidence remains limited that fixed-dosing strategies are equivalent to weight or BSA based dosing in terms of toxicity and efficacy
3	Use FDA approved dosing of checkpoint inhibitors
4	Use FDA approved dosing of targeted therapies
5	Use standard guidelines for dose reductions for high-grade toxicity
6	Standard formula for calculating BSA (no evidence to support other formulas)

Griggs JJ. J Oncol Pract. 2012;8(4):e59-e61.
Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline Update – Systematic Literature Review in Obese Patients with Cancer

- Highest quality data available from RCTs, meta-analysis, cohort studies, all with n ≥ 25
- Systemic interventions: chemotherapy, targeted therapies, immunotherapy
- Primary outcomes: efficacy, toxicity
- Dates: 1/1/10 to 3/27/20
- Excluded SCT population
- 532 studies pulled → 101 examined in detail → 60 met eligibility criteria for guideline

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline – Recommendation 1

Use full weight-based dosing of cytotoxic chemotherapy

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Moderate

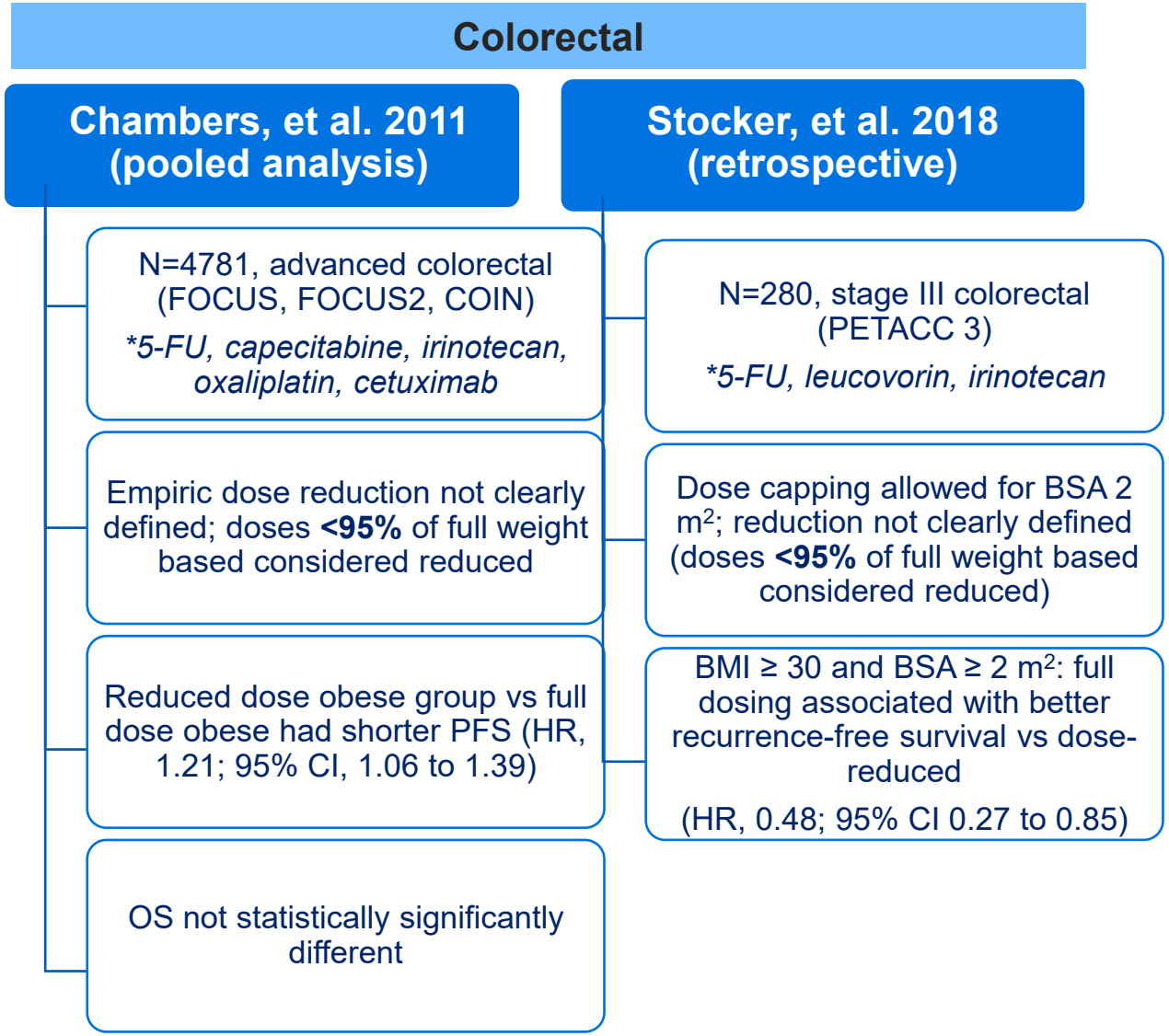
Evaluation of Full Weight-based Dosing of Cytotoxic Chemotherapy

Studies:	10 retrospective, 1 meta-analysis of observational studies
Dosing:	Uncapped, dosed by body size
Cancer types:	Breast, gynecologic, NHL, HL, advanced colorectal, GBM, or any (meta-analysis of solid tumors including breast, 1 study AML s/p autoSCT)
Ages:	Adults, though 1 early breast cancer study focused on ≥65 yo
Results:	All but 1 study showed no significant difference in toxicity with full dose chemotherapy

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline – Recommendation 1 (Efficacy Evaluation)

- 5 studies in solid tumor patients assessed efficacy of full dose vs. reduced dosed cytotoxic chemotherapy
  - In 3 studies initial dose reduction was associated with worse outcomes in at least 1 subset of patients with obesity



Chambers P. Ann Oncol. 2012;23:748-753.
Stocker G. Eur J Cancer. 2018;99:49-57.

ASCO Guideline – Recommendation 1 (Efficacy Evaluation)

Prostate

Wu, et al. 2015 (retrospective)

- N=333, metastatic prostate
  **docetaxel*
- 115 (34.5%) docetaxel initial empiric dose reduction of >10%
- Dose reduction at 1st dose **(<90%** of full weight-based dose) vs full dose had significantly shorter PFS and OS (18.2m vs 22.4m; p=0.001)

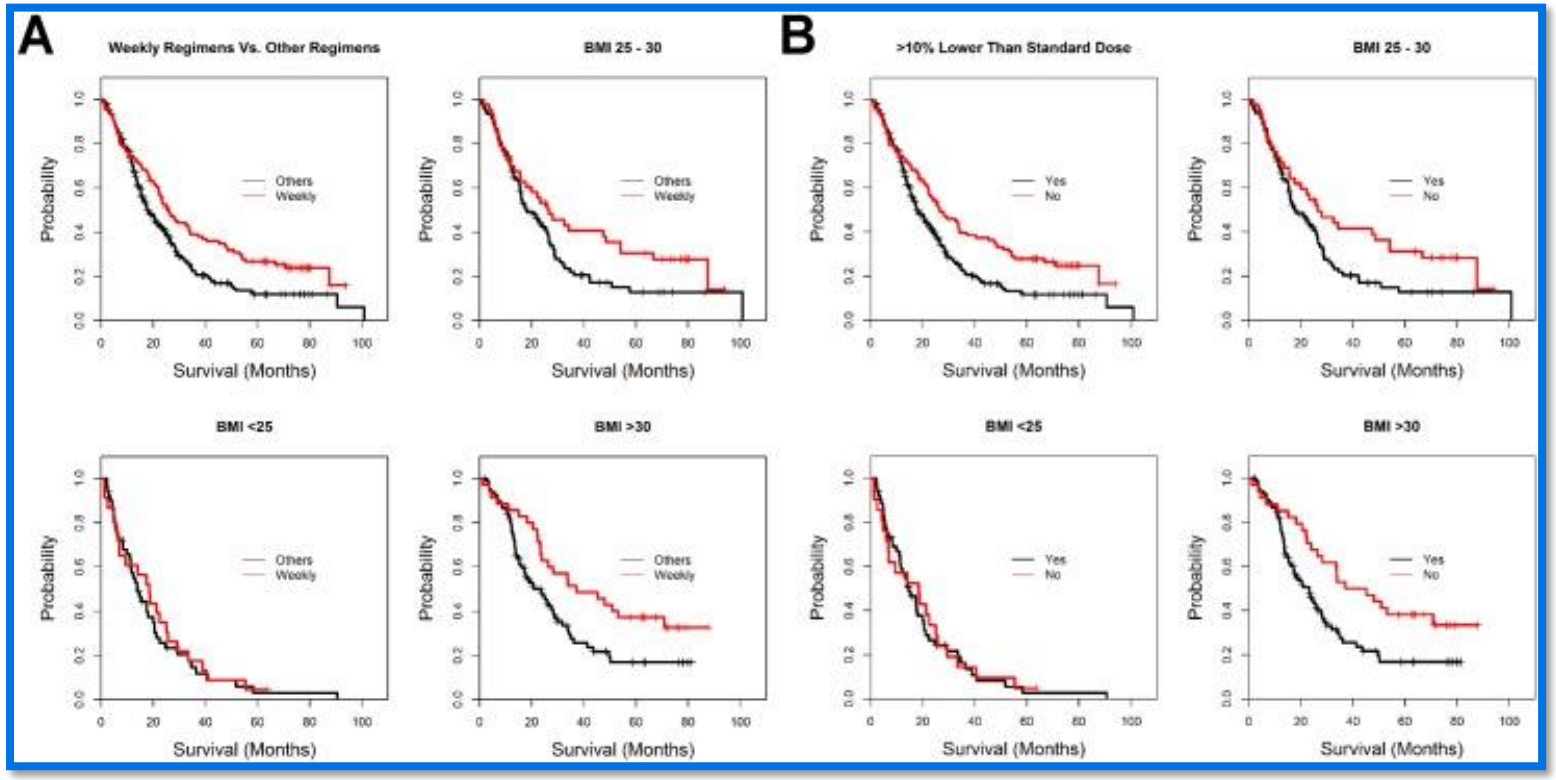


Fig 4. Overall survival of metastatic prostate cancer patients starting docetaxel treatment

Wu W. PLoS One. 2015;10(3):e0122047.

CALGB study 8541

- N=1,572, stage II breast cancer, regional LN+
- Randomized to 3 dose levels adjuvant cyclophosphamide, doxorubicin, fluorouracil
- BMI ≥ 27.3 obese, BMI ≥ 32.3 very obese
- Dose “reduced” if <95% of full ABW dose

		Treatment Arm (mg/m^2)		
Variable	**Day**	**600/60/600 x4C**	**400/40/400 x6C**	**300/30/300 x4C**
Cyc	1	600	400	300
Doxo	1	60	40	30
5-Fu	1,8	600	400	600
# 28-day cycles		4	6	4
No. patients		502	496	499
BMI ≥ 27.3		194 (39%)	208 (42%)	190 (38%)

Cyc: Cyclophosphamide, Doxo: Doxorubicin, 5-Fu: Fluorouracil

Results:

- N=1,435 evaluated: 40% obese, 17% very obese
- Obese full dose had similar toxicity vs non-obese in all arms
- BMI ≥ 27.3, toxicity during C1 dosed by ABW vs <95% of ABW:
  - ≥G3 heme tox in 600/60/600 group (47% vs 29%, p=0.04)
  - No other significant differences in heme or non-heme ADRs
- Overall risk of death or treatment failure for all obese:
  - Full ABW dose: 1.02 (95% CI 0.83-1.26)
  - ABW vs reduced dose: 0.73 (95% CI 0.53-1.00)
  - Obese, dose-reduced, had worse FFS in all arms

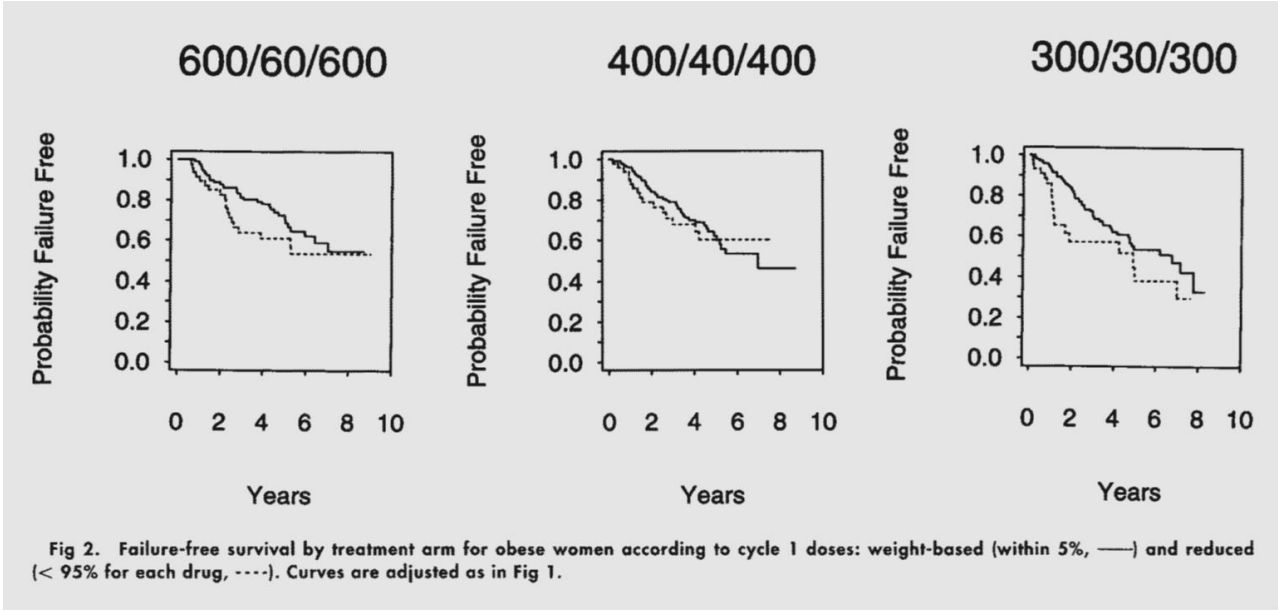


Fig 2. Failure-free survival by treatment arm for obese women according to cycle 1 doses: weight-based (within 5%, ——) and reduced (< 95% for each drug, ----). Curves are adjusted as in Fig 1.

Rosner GL. J Clin Oncol. 1996;14(11):3000-8.

ASCO Guideline – Recommendation 1 (Efficacy Cont. & Toxicity Evaluation)

- **2 studies did not report significant associations with 1st cycle dose reduction and efficacy**
  - GAIN Study, Furlanetto, et al. 2016: no significant difference in OS with dose reduction vs full dose
  - Aparicio, et al. 2018: pooled analysis, 5 trials, first-line treatment for metastatic colorectal cancer
    - First-cycle dose reductions more common in obese patients vs normal-weight patients
    - OS (HR, 1.28; 95% CI, 0.88-1.87) and PFS (HR, 1.03; 95% CI, 0.74-1.45) were not significantly different despite dose reductions

- **Toxicity Evaluation of Full Dose Chemo:**
  - In 10 out of 11 studies toxicity was not significantly worse amongst obese patients that received full dose
    - GAIN Study – reported increased toxicity in obese patients receiving full dose, intense dose-dense chemotherapy
    - Potentially increased risk of cardiotoxicity with anthracyclines and HER2 agents (unclear clinical implications)

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

GAIN Study - Furlanetto, et al. 2016

Design:

- Phase III, randomized, adjuvant trial comparing 2 different dose dense regimens (iddETC vs EC-TX)
- N=2,990 (mITT group), high-risk, early BC, treated 2004-2008
- Supportive care (iddETC and EC): peg-filgrastim D2/cycle, ciprofloxacin 500 mg/d
- Initial dosing: ABW or BSA capped at 2.0 m^2 per provider discretion

	Weeks		
	Week 1 - 6	**Week 1 - 6**	**Week 1- 6**
Arm 1 (iddETC)	Epi 150 mg/m^2 q2wk x3C *(~92 mg/m^2 doxo equiv)*	Pac 225 mg/m^2 q2wk x3C	Cyc 2500 mg/m^2 q2wk x3C

	Weeks	
	Week 1 – 8	**Week 1 - 10**
Arm 2 (EC-TX)	Epi 112.5 mg/m^2 q2wk x4C *(~68 mg/m2 doxo equiv)* +Cyc 600 mg/m^2 q2wk x4C	Pac 67.5 mg/m^2 qwk x10C +Cape 2000 mg/m^2, D1-14 q3wk

Epi: Epirubicin, Doxo: Doxorubicin, Pac: Paclitaxel, Cyc: Cyclophosphamide, Cape: Capecitabine

Furlanetto J. Ann Oncol. 2016;27(11):2053-2059.

Furlanetto, et al. 2016

GAIN Study

Amended for safety concerns:

- Used adjBW in Dubois formula for obese or capped at 2 m^2
- Cyc in ETC arm reduced for all patients (2500 mg/m^2 to 2000 mg/m^2)

Results:

- Obese group (BMI ≥ 30; range: 30.0-52.7), n=555 (18%):
- iddETC, n=307 (unadjusted dose, n=95; adjusted dose, n=212)
- EC-TX, n=248 (unadjusted dose, n=78; adjusted dose, n=170)
  - Total unadjusted BSA dosing in obese, n=173 (31%); adjusted, n=382 (69%)
  - Adjustments: 382 (69%) utilized IBW instead or capped BSA to 2.0 m^2

Outcome	Non-obese	Obese-unadjusted	Obese-adjusted	P-value
5-year DFS	81% (CI 79%-83%)	82% (CI 75%-87%)	81% (CI 76%-84%)	P=0.761
5-year OS	90% (CI 88%-91%)	86% (CI 80%-91%)	88% (CI 84%-91%)	P=0.143
DFS adjusted vs unadjusted	N/A	HR=0.95 (CI 0.68-1.31)	HR=1.01 (CI 0.81-1.31)	O-Unadj, p=0.738 O-Adj, p=0.943
OS adjusted vs unadjusted	N/A	HR=1.23 (CI 0.83-1.78)	HR=1.01 (CI 0.78-1.41)	O-Unadj, p=0.313 O-Adj, p=0.772
Neutropenic Fever	8.4%	14.7%	6.3%	-NO vs O-Unadj, p=0.008 -O-Unadj vs O-Adj, p=0.003
TCP G3/4	5.2%	9.4%	2.9%	-NO vs O-Unadj, p=0.034 -O-Unadj vs O-Adj, p=0.002
VTE	9.3%	17.3%	9.9%	-NO vs O-Unadj, p=0.001 -O-Unadj vs O-Adj, p=0.017

NO: Non-obese, O-Adj: Obese-adjusted, O-Unadj: Obese-unadjusted

Furlanetto J. Ann Oncol. 2016;27(11):2053-2059.

ASCO Guideline – Recommendation 1

Cardiotoxicity with Anthracyclines & HER2 Therapies

Guenancia C, et al. 2016

- **Design:**
  - Meta-analysis,15 studies, prospective & retrospective, localized and metastatic breast cancer, N=8745
  - Evaluated proportion of patients with cardiotoxicity divided by total number that received anthracyclines and/or trastuzumab
  - Pooled effects by weight status: normal weight, overweight (BMI 25-29.9), obese (BMI ≥30)
  - Subgroup analysis by treatment: anthracycline only vs. trastuzumab +/- anthracyclines

- **Results:**
  - 91% of patients included received both trastuzumab and anthracycline
  - Mean rate of cardiotoxicity:
    - Whole group = 17% (95% CI 11-25)
    - Anthracycline only = 20% (95% CI 5-43)
    - Trastuzumab +/- anthracycline 16% (95% CI 10-24).
  - Overweight or obese (BMI >25) more likely to develop cardiotoxicity after anthracyclines or sequentially + trastuzumab (OR, 1.38; 95% CI, 1.06 to 1.80).
  - Obesity was not a risk factor for cardiotoxicity with trastuzumab alone

- **Considerations:**
  - Recovery not reported per BMI, cumulative doxorubicin dose, other risk factors, symptomatic vs asymptomatic toxicity
  - Not all studies defined the regimen received, if patients had cardiac dysfunction at baseline, and definition of cardiotoxicity varied between studies
  - Additional monitoring of cardiotoxicity in obese patients may be warranted
  - Data does not provide recommendation for dose reduction or capping

Guenancia C. J Clin Oncol. 2016;34(26):3157-3165.

ASCO Guideline – Recommendation 1

Full Weight-Based Dose Dense AC in Obese Patients

Lomma, et al. 2023

- **Design:** Retrospective study (data collected prospectively) over 14-year period
- **Regimen:** ddAC (Doxo 60 mg/m^2, Cyc 600 mg/m^2) q14d x4C → Pac 175 mg/m^2 q14d x4C
  - ABW used for BSA dosing in all patients
- **Inclusion:** non-metastatic breast, normal cardiac function, received ≥ 1C ddAC as NAC or AC
- **Exclusion:** discontinued ddAC for reason other than chemo-related tox
- **Methods:**
  - Collected comorbidities (DM, IHD, HTN, chronic autoimmune conditions, immunosuppressants), dose intensity, GCSF use
  - Primary outcomes: surgical complications, RT complications, chemo AEs obese vs. non-obese
  - Groupings: obese (BMI ≥30) vs non-obese (BMI <30), molecular subtypes (TNBC, HR+/HER2- or HER2+), dose intensity (adequate, inadequate for 1, inadequate for both)

ddAC: dose-dense doxorubicin and cyclophosphamide, AC: adjuvant chemotherapy, NAC: neoadjuvant chemotherapy

Lomma C. Clin Breast Cancer. 2023;23(5):491-499.

ASCO Guideline – Recommendation 1

Full Weight-Based Dose Dense AC in Obese Patients

Lomma, et al. 2023

- **Results:**
  - N=280; obese, n=55 (20%); non-obese, n=225 (80%)
  - Characteristics balanced between obese and non-obese (comorbidities, tumor size, nodal status, grading, stage) except for HER2 status (52 [23.1%] non-obese, 7 [12.7%] obese)
  - **Toxicities:**
    - Obese patients experienced higher incidence G≥2 RT related skin toxicity (OR 3.24 [95% CI 1.23-8.49], p=0.017)
    - Symptomatic EF declines: 3 non-obese/HER2+ patients (recovered to >50% EF in all and determined to be anti-HER2 therapy related); 0 cases in obese
  - **Dose Intensity**: adequate in 95% of total population; similar distribution between obese and non-obese
    - Anthracycline cumulative dosing mg/m^2: obese, median 239.7 (range 195-248); non-obese, median 240.1 (range 204-274)
  - **Survival & Complications**: no significant difference in odds of death, survival, recurrence, or post-operative complications between obese and non-obese patients

Critique of Literature

Considerations:

- Large amount of efficacy data in obese patients receiving full dose chemotherapy
- Empiric dose reductions in obese patients can negatively impact survival
- Toxicity with full ABW dosing is generally manageable
- Contradictory data exists:
  - Survival data in obese vs. non-obese receiving ABW dosing (DFS, PFS, OS), with phase of treatment (NAC, AC, metastatic), disease risk, staging, and cytotoxic regimens (epirubin or doxorobucin, cyclophosphamide, and taxane)

Critique of study designs:

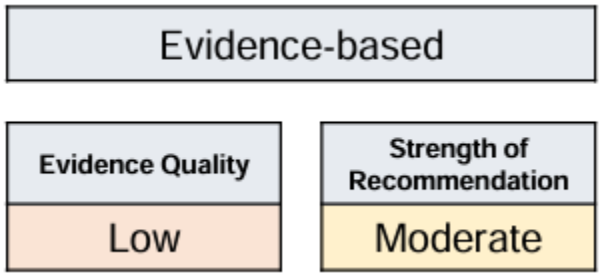
- Most data retrospective and much data now well described (regimens received, grading, resolution of toxicity)
- Prospective studies do not compare empiric dose reduction to full weight-based with adequate number of subjects
- Treatment related mortality between obese and non-obese not routinely evaluated

Clinical Interpretation:

- Limited evidence to suggest that using ABW increases toxicity, however, data is available showing that underdosing is associated with inferior outcomes → overall supports full weight-based dosing
- Further PK/PD analysis is needed
- Consider nature of toxicity (i.e., cardiotoxicity timing, reversibility, mortality) and prognosis

ASCO Guideline – Recommendation 2

Limit fixed dosing



ASCO Guideline – Recommendation 2

Evaluation of Fixed Dosing with Cytotoxic Chemotherapy

Fixed Dose

- Dose independent of weight or BSA

Clinical Interpretation

- Fixed dosing should be avoided in the absence of data supporting its equivalence or superiority

Exception

- Bleomycin
  - *Note – 2012 guideline included carboplatin and vincristine (2 mg)*

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline – Recommendation 2

Fixed Dosing vs Weight-Based Capecitabine

de Man, et al. 2019

- **Design**: retrospective, single-site
- **Goal**: standardize dose to reduce prescribing errors, prep, and costs
- **Cancer types**: colorectal, breast, gastric, or "other"
- **Fixed vs BSA-dosing**: Cape mono, Cape + RT, CapeOx, ECC, EOX

- **Results:**
  - N=2,319; fixed dose, n=1,126; BSA-based dosing, n=1,193
  - No sig. difference in incidence of Cape related toxicity between fixed-dose and BSA-dose cohort (diarrhea, HFS, neutropenia)
    - **Cape MONO**:
      - Fixed-dose - lower incidence HFS ≥G2 (22% vs 33%, p=0.026)
      - BSA-dose - higher incidence neutropenia ≥G2 (14% vs 6%, p=0.005)
    - **Cape TRIPLET:**
      - Fixed-dose - higher incidence neutropenia ≥G2 (82% vs 61%, p=0.003) and more DC d/t tox (37% vs 23%, p=0.043)
  - **Efficacy** - assessed in colorectal and gastric cancer: no statistical difference in PFS or DFS identified

Treatment	Schedule	Fixed dose (mg/day)*	BSA-dosed dose (mg/ m²/day/)*
CAPE + RT			
Capecitabine	Continuous**	3,000	1,650
CAPOX			
Capecitabine	D1-14 (Q3W)	3,500	2,000
Oxaliplatin	D1 (Q3W)		130
MONO			
Capecitabine	D1-14 (Q3W)	3,500 (BC) 4,000 (CRC)	2,000
TRIPLET			
ECC			
Capecitabine	D1-14 (Q3W)	3,500	2,000
Epirubicin	D1 (Q3W)		50
Cisplatin	D1 (Q3W)		60
EOX			
Capecitabine	D1-21 (Q3W)	3,500	2,000
Epirubicin	D1 (Q3W)		50
Oxaliplatin	D1 (Q3W)		130
DOC			
Capecitabine	D1-14 (Q3W)	***	1,700
Docetaxel	D1 (Q3W)		50
Oxaliplatin	D1 (Q3W)		100

de Man FM. Ther Adv Med Oncol. 2019;15:11.

Fixed-dose SC vs Weight-Based IV Trastuzumab

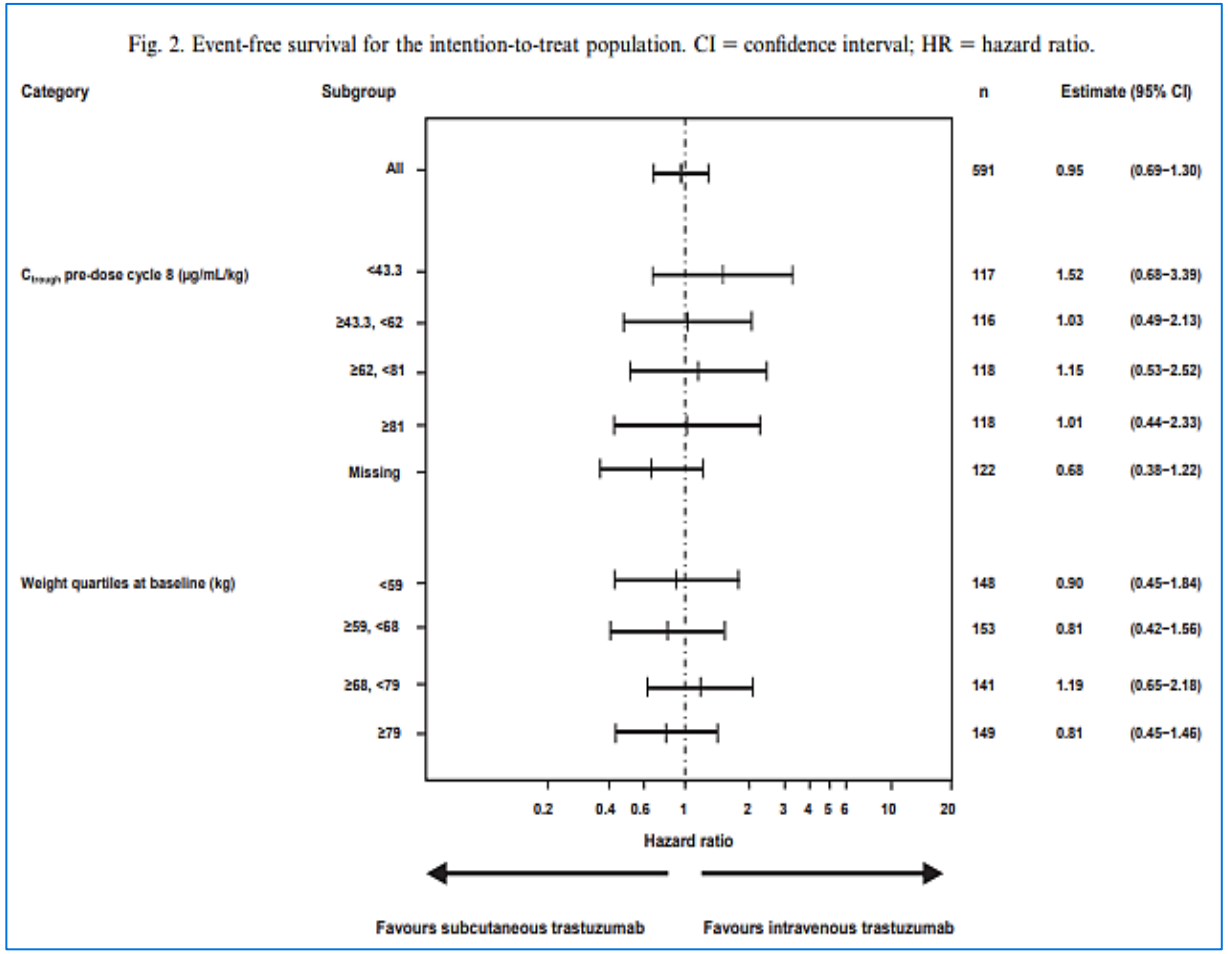
HannaH study, 2016:

- **Design:** Phase III, non-inferiority study, IV or SC trastuzumab in HER2+ early BC, 2 years of follow-up

- **Regimen:**
  - NAC docetaxel x4C → 5-FU/Epi/Cyc x4C
  - Randomized to concomitant SC or IV trastuzumab q3 wk:
    - **Arm 1** - Fixed dose SC: 600 mg SC
    - **Arm 2** - Weight-based IV: 8 mg/kg load, 6 mg/kg maintenance IV
  - Post-op continued trastuzumab per randomization x1 year

- **Outcomes:**
  - Assessed C_{trough} pre-dose cycle 8, pCR, EFS
  - Baseline weight quartiles in kg (<59; ≥59,<68, ≥68,<79; ≥79)

- **Results:**
  - Baseline BW (kg): SC median, 68 (range 39-136); IV median, 66.2 (range 42-137.1)
  - C_{trough} pre-dose cycle 8 similar for all weight quartiles
  - **3y EFS**: 76% SC, 73% IV in ITT (HR=0.95 [95% CI 0.69-1.3])
  - **3y OS**: 92% SC, 90% IV (HR=0.76 [95% CI 0.44-1.32])
  - **tpCR** associated with reduced risk of EFS event: SC, HR=0.38 (95% CI 0.22-0.65), IV HR=0.32 (95% CI 0.18-0.60)
  - No significant difference in outcomes between quartiles
  - SC considered non-inferior to IV



Jackisch C. Eur J Cancer.2016;62:62-75.

PK of SC and IV Trastuzumab in Obese Patients

Gonzalez Garcia, et al. 2020

- **Background:**
  - HannaH trial established that T-SC fixed dose was non-inferior to IV at steady state
  - Concern that with BMI ≥ 30 that plasma concentration may be below 20 ug/mL (established target concentration for efficacy)
- **Aim:**
  - Compared initial minimum plasma concentration after fixed dose SC vs IV weight-based dosing in obese
- **Study design:**
  - Observational, prospective, single-center study, patients with HER2+ non-metastatic breast cancer
  - **Dosing:** SC 600 mg q3 wks vs IV 8 mg/kg load → 6 mg/kg IV q3 wks
  - Trough assessed prior to dose #2
- **Results:**
  - N=50; IV, n=16 (32%); SC, n=34 (68%)
  - Average BMI 28 kg/m^2 (range 19-42)
  - Proportion of patients reaching C_{min} ≥20 μg/mL after first dose higher with IV vs SC
- **Implications:**
  - Unclear – trough subtherapeutic though HannaH study supports efficacy

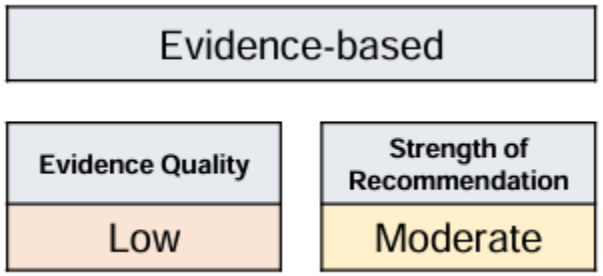
Table 2. Patients Who Reach a C_{min} ≥20 μg/mL After the First Administration of the Drug According to BMI and Dosification Strategy.

Dosification Strategy	BMI	Patients With C_{min} ≥20 μg/mL, n (%)	*P* Value
T-SC	BMI ≤30 kg/m^2 (n = 24)	21 (87.5%)	*P* < 0.001
	BMI > 30 kg/m^2 (n = 8)	2 (20.0%)	
T-IV	BMI ≤30 kg/m^2 (n = 10)	9 (90.0%)	*P* = 0.63
	BMI > 30 kg/m^2 (n = 6)	6 (100.0%)	

Gonzalez Garcia, et al. Ann Pharmacother. 2020;54(8):775-779.

ASCO Guideline – Recommendation 3

Use FDA-approved dosing for immunotherapy



ASCO Guideline – Recommendation 3

Evaluation of dosing of immunotherapy

Cortellini, et al. 2020

Design:

- Multicenter, retrospective observational study, adult patients, n=1,070
- **Cancer type**: Advanced NSCLC, melanoma, RCC
- **Treatment**: pembrolizumab (25.1%), nivolumab (70.7%), atezolizumab (2.5%)
- Overweight, n=416 (38.9%), obese, n=130 (12.1%)

Results:

- **mPFS:** underweight (1.9 m), normal-weight (4.4 m), overweight (11 m), obese (12.9 m); BMI affect p<0.0001
- **mOS:** underweight (3.3m), normal-weight (8m), overweight (26.6m), obese (NR); BMI affect p<0.0001
- **Any irAE:** underweight (13.6%), normal-weight (13%), overweight (61.5%), obese (71.5%); BMI affect p<0.0001

Conclusion: overweight and obese patients had improved survival and increased toxicity vs non-obese

Xu, et al. 2019

Design:

- Meta-analysis, 16 retrospective studies, n=4,090
- **Cancer type**: solid tumors (NSCLC, melanoma, RCC)
- **Treatment:** ipilimumab, nivolumab, pembrolizumab

Results:

- **OS high BMI vs low BMI:** (HR=0.72, 95% CI: 0.51–1.02; p = 0.06)
- **PFS high BMI improved vs low BMI:** (HR=0.67, 95% CI: 0.48–0.95; p = 0.02)
- **BMI > 30:** correlated with significantly better OS (HR = 0.64; 95%CI: 0.43–0.96; p= 0.03).

Conclusion: patients with BMI >30 had improved survival vs. non-obese

Cortellini A. Eur J Cancer. 2020;128:17-26.
Xu H. Int Immunopharmacol. 2019;74:105-

ASCO Guideline – Recommendation 3

FDA Approved Dosing of Immunotherapy

Nivolumab and pembrolizumab flat dosing based on equivalent PK:

- **Nivolumab flat dose PK:**
  - Zhao X, et al 2017: melanoma, NSCLC, RCC; included obese patients
    - Median exposure and distribution similar between 240 mg IV q2wk and 3 mg/kg q2wk
- **Pembrolizumab flat dose PK**:
  - Freshwater, et al 2018: head and neck, NSCLC, CRC, urothelial; included high weight >90kg

Immunotherapy data in breast:

- **KEYNOTE-522:** BMI, obesity, high-weight not mentioned in original study
  - **MSK KN522 experience** (ddAC/CbT sequencing + pembrolizumab):
    - Median BMI all patients, 26 (range: 17.1-45.8)

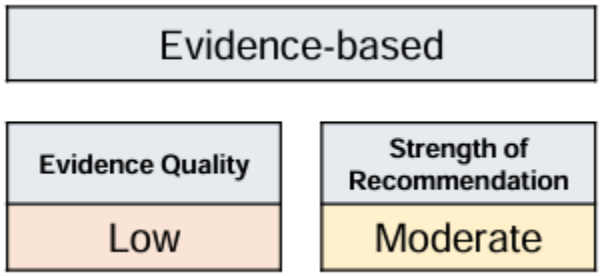
Clinical Interpretation:

- Wider therapeutic window and distribution in blood plasma and ECF which correlates less with body size characteristics
- Improved efficacy in obesity theorized to be related to increased expression of PD-L1 via elevated levels of leptin
- Data supports continuation of full weight-based or evidence-based flat dosing of immunotherapy in obese patients

Zhao X. Ann Oncol. 2017;28(8):2002-2008.
Freshwater T. J Immunother Cancer. 2017;16(5):3.
Mai N. NPJ Breast Cancer. 2024;10(1):39.

ASCO Guideline – Recommendation 4

Use FDA-approved dosing for targeted therapies



ASCO Guideline – Recommendation 4

Efficacy of FDA Approved Dosing of Targeted Therapies

- Pooled analysis 2018 – metastatic melanoma, n=1,918:
  - Patients classified by BMI normal, overweight, or obese [(BMI ≥30), n=513 (27%)]
  - Trials have no mention of dose capping or reductions based on weight or BMI

Improved Efficacy:
2 cohorts from RCTs with targeted tx (dabrafenib/trametinib, n=599; vemurafenib/cobimetinib, n=240)

Obesity associated with improved:
- **PFS** (HR 0.72 [0.57-0.97)
- **OS** (HR 0.60 [0.45-0.79])

Improved Efficacy:
2 cohorts with immunotherapy (RCT ipilimumab/dacarbazine, n=207; retrospective with pembrolizumab, nivolumab, or atezolizumab, n=331)

Obesity associated with improved:
- **PFS** (HR 0.75 [0.56-1.00])
- **OS** (HR 0.64 [0.47-0.86])

No Difference in Efficacy:
2 cohorts with chemotherapy (2 RCT dacarbazine, n=320, n=221):

No association for improved PFS or OS

McQuade JL. Lancet Oncol.2018;19(3):310-322.

PARP Inhibitors

Improved Toxicity with Niraparib:

- **Design:** ENGOT-OV16/NOVA, RCT trial, in recurrent, platinum sensitive, ovarian, fallopian tube, or primary peritoneal cancer
- **Regimen**: niraparib maintenance (300 mg/day) following CR or PR with last platinum regimen
- **Results**:
  - Whole population (n=533):
    - Dose interruptions in >80%
    - Dose reductions in 73%
  - Weight categories based on quartiles at baseline
    - Dose reductions & DC due to TEAEs per quartile:
      - Lowest weight quartile (<58kg): 51% & 10%
      - Highest weight quartile (≥77 kg): 33% & 1%
  - PFS amongst those dose reduced to 200 mg or 100 mg was consistent with 300 mg (full dosing)
  - Overall full dose better tolerated in patients with higher weight
- Implications
  - Package insert starting dose modified: < 77 kg or PLT <150k = 200 mg/day; ≥ 77 kg or PLT ≥ 150k = 300 mg/day

Berek JS. Ann Oncol. 2019;20(5):859.

PARP Inhibitors

Rucaparib:

- Population based PK used data from 4 studies (ovarian, other solids)
- BMI range included obese patients
- Did not differentiate between obese and non-obese
- Report no clinically relevant effects based on weight
- Clinical studies did not stratify by weight or BMI

Olaparib:

- Retrospective analysis of pilot study in ovarian cancer
- Assessed heme tox in normal BMI vs excess-weight patients
- N=38, 2 groups: 1) Normal BMI (18.5-24.9), 2) Excess-weight (BMI ≥25)
- Dose/kg-adjusted C_{trough} higher in excess-weight (204.17 ± 172.10 ng/mL/mg/kg) vs normal BMI (159.32 ± 150.82 ng/mL/mg/kg); p=0.372

Variable	Study 1014 (n=30)	Study 10 (n=123	ARIEL2 (n=300)	All studies (n=453)
Weight, median (range), kg	67 (47-119)	68 (41-133)	70 (46-171)	69 (41-171)
BMI, median (range), kg/m^2	25 (18-39)	26 (18-52)	27 (17-59)	27 (17-59)

Group	Anemia (%)	Neutropenia (%)
Normal BMI	G1: 42.86	G1: 21.43 G2: 7.14
Excess-weight	G1:41.67 G2: 4.17 G3: 8.33	G1: 20.83 G2: 4.17

Green ML. Cancer Chemother Pharmacol. 2022;89(5):671-682.
Stanislawiak-Rudowicz J. Rep Pract Oncol Radiother. 2024;29(1):113-121.

ASCO Guideline – Recommendation 4

EGFR TKIs

- Gefitinib and osimertinib studied in patients with advanced melanoma harboring EGFR mutations
  - Standard dosing regardless of body size: Gefitinib 250 mg/day, osimertinib 80 mg/day
  - Efficacy and toxicity did not significantly differ between low and high BSA groups

Gefitinib, n=103 *Retrospective cohort study *BSA affect on efficacy in NSCLC (IIIB/IV, EFGR+)			
Outcome	BSA ≥ 1.45 m^2	BSA < 1.45 m^2	P value
RR	60%	69.8%	P=0.20
Median Survival Time	24.7 m	26.2 m	P=0.78

Osimertinib, n=47 *Prospective observational study *BSA & BMI affect on efficacy in NSCLC (IIIB/IV, T790M+)			
Outcome	BSA ≥ 1.5 m^2 BMI ≥ 21.5	BSA < 1.5 m^2 BMI <21.5	P value
ORR	56% 54.1%	59.1% 60.8%	P=0.83 p=0.64
mPFS	7.6 m 7.6 m	9.1 m 7.6 m	P=0.69 P=0.38

Igawa S. Cancer Chemother Pharmacol. 2014;74(5):939-46.
Ono T. Thorac Cancer. 2019;10(4):880-889.

ASCO Guideline – Recommendation 4

Other Targeted Agents

Ado-trastuzumab emtansine (T-DM1):

- **Lee, et al. 2020: retrospective chart review**
  - N=119: obese, n=44; non-obese, n=75
  - Composite outcome of treatment modifications due to toxicity significantly higher in obese vs non-obese (45% vs 25%, p=0.024)
  - Treatment delays higher in obese vs non-obese (36% vs 16%, p=0.011)
  - All-grade AEs with higher incidence in obese vs non-obese: LVEF decrease (11% vs 5%), bilirubin increase (32% vs 12%), TCP (61% vs 55%), and peripheral neuropathy (34% vs 27%)

Abemaciclib (CDK4/6 Inhibitor)

- **Franzoi, et al. 2021: Monarch 2 & 3 pooled analysis**
  - N=1,138: abemaciclib + ET, n=757; placebo + ET, n=381
  - No difference in PFS between BMI categories in either group (p=0.07)
  - Abemaciclib + ET group:
    - Higher ORR in normal and/or underweight vs overweight and/or obese patients (49.4% vs 41.6%, OR=0.73, 95% CI 0.54-0.99)
    - Higher neutropenia frequency in normal and/or underweight vs overweight and/or obese (51.0% vs 40.4%, p=0.004)

Alpelisib (PI3K)

- **Alaklabi, et al. 2022: retrospective**
  - N=27; mean BMI=26.82 though 24 patients reported as not having obesity
  - BMI did not have a significant effect on responses (p=0.966)

Lee A. J Oncol Pharm Pract. 2022;28(1):49-54.
Franzoi MA. J Natl Cancer Inst. 2021;113(4):462-470.
Alaklabi S. Front Oncol. 2022:12:1012391.

Adjuvant Endocrine Therapy

Concern for impaired efficacy:

- Obesity associated with increased breast adipose tissue → increased aromatase activity → increased estrogen production
- Patients with BMI > 35 vs < 25 have estradiol levels nearly 3 times as high
- Given historical data, concern for reduced effectiveness with ET in general especially with flat dosing
- Many studies have shown contradictory findings

MOA of ET might guide decisions:

- Tamoxifen binds to estrogen receptors
- Aromatase inhibits block aromatization of estrogens from androgens (potentially higher aromatase activity in obesity)

Future Guidance:

- Final results pending from, “Impact of Obesity on the Efficacy of ET with AIs in Postmenopausal Patients With Early Breast Cancer”
  - RCT: Tamoxifen 20 mg/d or AIs (letrozole 2.5 mg/d, anastrozole 1 mg/d, or exemestane 25 mg/d) x5y

Adjuvant Endocrine Therapy

Study	Population	Treatment	Outcomes with BMI >30	95% CI
Danish Breast Cancer Cooperative	-Early breast -Broad pop. -N=18k w/BMI -Median f/u 7.1y	-Chemo SOC at time (CMF, ECF; docetaxel; trastuzumab) -ET (tamoxifen or AI)	**BMI >30 vs normal:** -Increased risk of distant metastasis -Breast cancer-related death -At 10y: Increased risk of death with chemo -At 10y: Increased risk of death with ET	 HR=1.46 (1.11-1.92), **p=0.007** HR=1.38 (1.11-1.71), **p=0.003** HR=1.77 (1.37-2.29), **p=0.02** HR=1.57 (1.09-2.26), **p=0.02**
ATAC	-Post-menopausal -Early breast -Broad pop. -N=5,172	Randomized: -Anastrozole -Tamoxifen -Anastrozole/tamoxifen	**BMI >35 vs normal:** -Increased risk of recurrence -Increased risk of distant recurrence -Tamoxifen equally effective all BMIs; BMI >35 -Anastrozole less effective with BMI >30	 HR=1.39 (1.06-1.82), **p=0.03** HR=1.46 (1.07-1.61), **p=0.01** HR=1.18 (0.90-1.84), p=0.54 HR=1.53 (1.01-2.23), **p=0.01**
ABCSG-12	-Pre-menopausal -Early breast -Broad pop. -N=1,803	Randomized: -OAS + tamoxifen -OAS + anastrozole -w/w/o ZA	**BMI >25 vs normal:** -DFS with tamoxifen -OS with tamoxifen -Risk of recurrence with anastrozole -Risk of death with anastrozole	 HR=0.94 (0.60-1.64), p=0.76 HR=0.83 (0.35-1.93), p=0.65 HR=1.60 (1.06-2.41), **p=0.02** HR=2.14 (1.17-3.92), **p=0.01**
BIG 1-98	-Post-menopausal -Early breast -Broad pop. -N=4,760	Randomized: -Tamoxifen -Letrozole	**BMI >30 vs normal:** -OS with letrozole -OS with tamoxifen -Distant recurrence–free interval with letrozole -Distant recurrence–free interval with tamoxifen	 HR=1.22 (0.93-1.60) HR=1.18 (0.91-1.52) HR=1.21 (0.88-1.66) HR=1.11 (0.82-1.50), p=0.92

ASCO Guideline – Recommendation 5

Use standard dose reductions for high-grade toxicities

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Insufficient	Weak

ASCO Guideline - Recommendation 5

Use standard guidelines for dose reductions for high-grade toxicity

- Not addressed in the literature
- Excess toxicity may be due to reduced drug elimination of agent(s)
- Obesity should not affect degree of dose modification due to toxicity

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.

ASCO Guideline – Recommendation 6

Use standard formulas for calculating BSA

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Moderate

ASCO Guideline - Recommendation 6

Use standard formula for calculating BSA in obese patients

- DuBois and Mosteller equations most frequently used for BSA
- Data from CDC analyzed differences in Mosteller and DuBois calculations
  - Mosteller provided higher dose vs DuBois especially for patients in the 50^{th}-95^{th} percentile for height and weight
- Current formulas result in noticeable differences (10%) in BSA at the extremes for weight and/or height
- There is no data that one formula should be used over another

Griggs JJ. J Clin Oncol. 2021;39(18):2037-2048.
Fancher KM. J Oncol Pharm Pract. 2016;22(5):690-5.

Future Directions

- **Precision Medicine Initiatives:**
  - Many studies already underway
  - Goal to individualize dosing for agents with high PK/PD variability and low therapeutic index
  - Develop dosing strategies that move beyond BSA and BMI
  - Considerations for tumor microenvironment (i.e., obesity paradox), adipose tissue biology, and body composition (can vary between different tumor subtypes)
  - Considerations for response, toxicity, mortality
  - ASCO Obesity Initiative – cancer prevention to survivorship

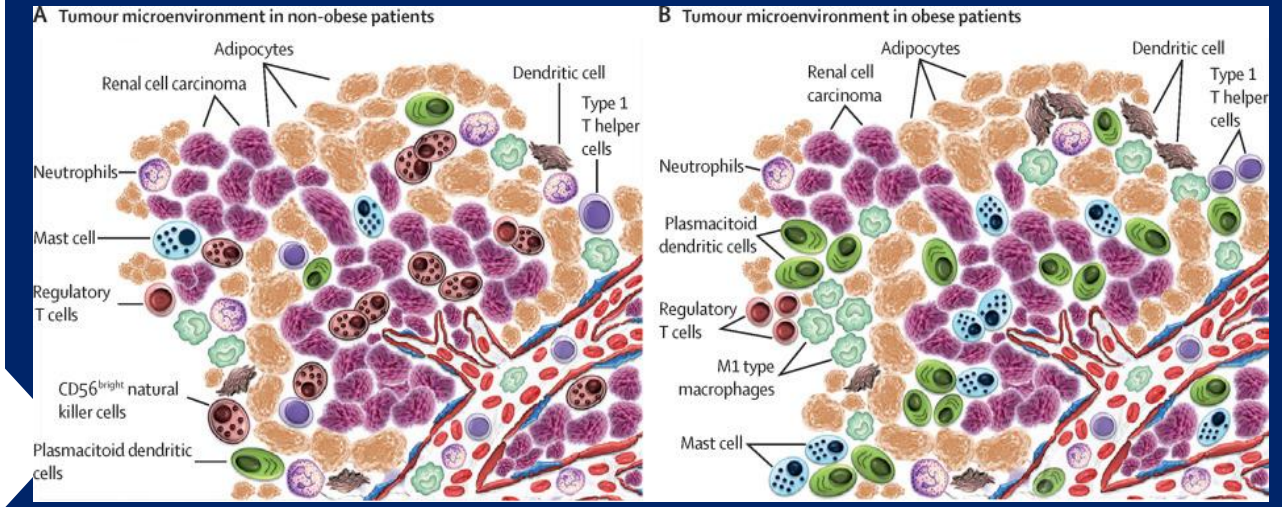


Figure. Perinephric tumor microenvironment in non-obese vs obese patients with renal cell carcinoma
(A) Non-obese patients. (B) Obese patients.

Rossi T. Front Med (Lausanne). 2021; 8:725346. doi:10.3389/fmed.2021.725346.
Santoni M. Lancet Oncol. 2020;21(2):194-196
Modi N. NPJ Breast Cancer. 2021;7(1):30.
Ligibel J. J Clin Oncol. 2016;34(35):4256-4260.

Conclusions

- Use of current body weight descriptors and formulas can lead to high interpatient PK/PD variability stressing the importance of additional research in this area
- Despite some contradictory data, evidence supports the use of full weight-based dosing of cytotoxic chemotherapy
- Until more data is available, FDA approved dosing of immunotherapy and targeted therapies should be utilized for obese patients

Questions?