Integrating IV Iron into Cancer Care

An Expert Overview of Best Practices

Cancer-Related/Chemotherapy-Induced Anemia
Epidemiology

- **CRA**
  - Highly prevalent
    - Estimated to occur in >30% of patients with cancer, even prior to starting treatment
  - Positively correlated with advancing disease stage
  - Pathophysiologic take-home: *cancer = inflammation = increased hepcidin*
  - Detrimental to outcomes across the totality of the cancer care continuum
    - Disease progression, treatment response, morbidity, mortality, PROs
- **CIA**
  - Cytotoxic chemotherapy, myelosuppressive agents, radiation
  - Estimated to occur in >67% of patients after starting cancer treatment

Madeddu C, et al. *Front Physiol*. 2018; Gilreath JA, et al. *Am J Hematol*. 2014; Rodgers GM, et al. *Acta Haematol*. 2019.

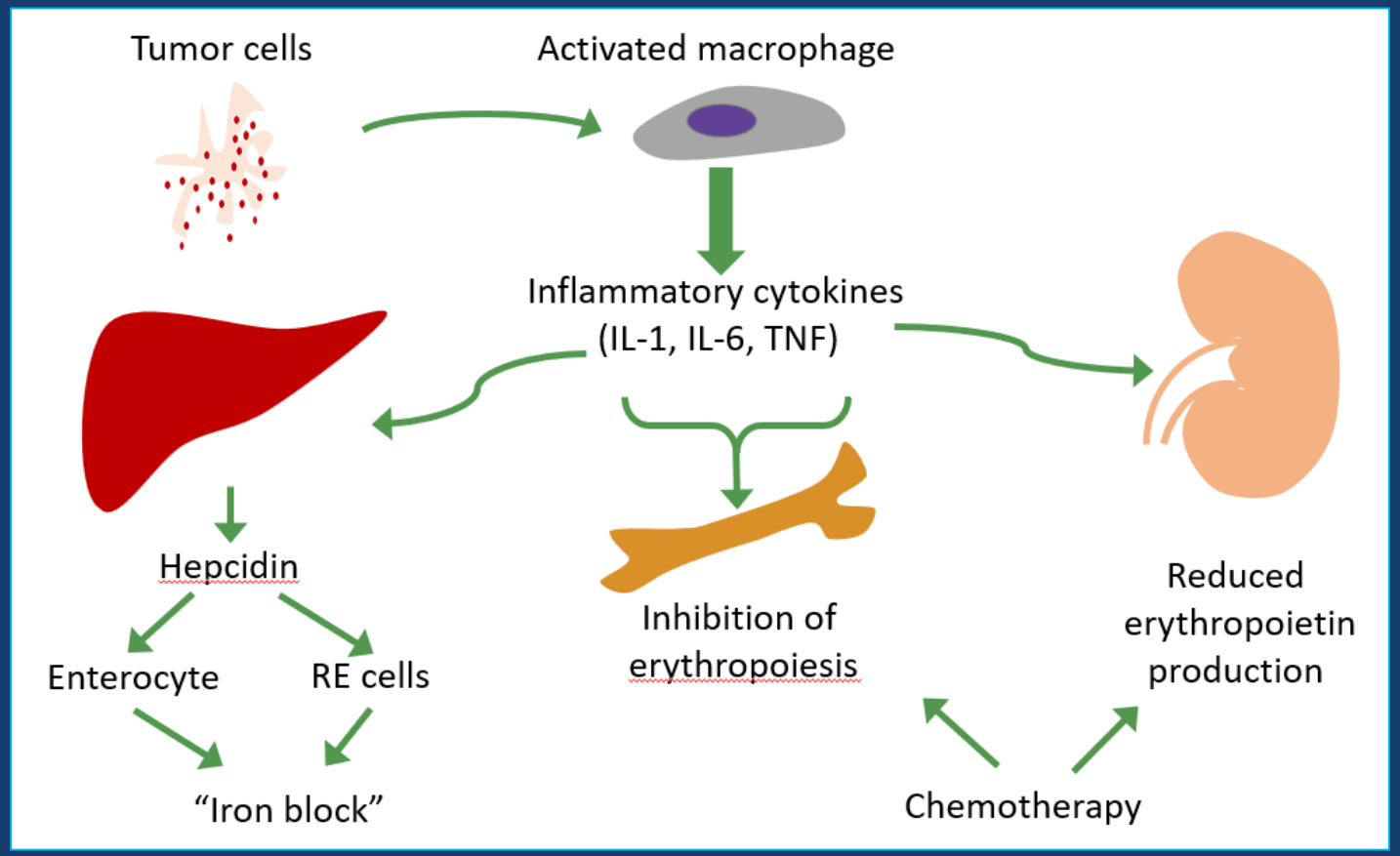
Cancer-Related/Chemotherapy-Induced Anemia

Understanding Multifaceted Etiologies

- Malignancy
  - Cancer is an intrinsically hyperinflammatory disease state
  - Increased inflammation = increased hepcidin
- Keystone cancer treatment modalities
  - Cytotoxic chemotherapy, myelosuppressive agents, radiation
  - All promote inflammatory processes and responses
- Blood loss (occult or otherwise)
- Nutritional derangement associated with disease/treatment
  - Iron deficiency eventually leads to iron-restricted erythropoiesis
- Chronic inflammatory comorbidities
  - Heart failure, IBD, CKD

Rodgers GM. *Expert Rev Hematol.* 2024; Madeddu C, et al. *Front Physiol*. 2018; Pagani A, et al.. *Front Physiol* 2019; Gilreath JA, et al. *Am J Hematol*. 2014.

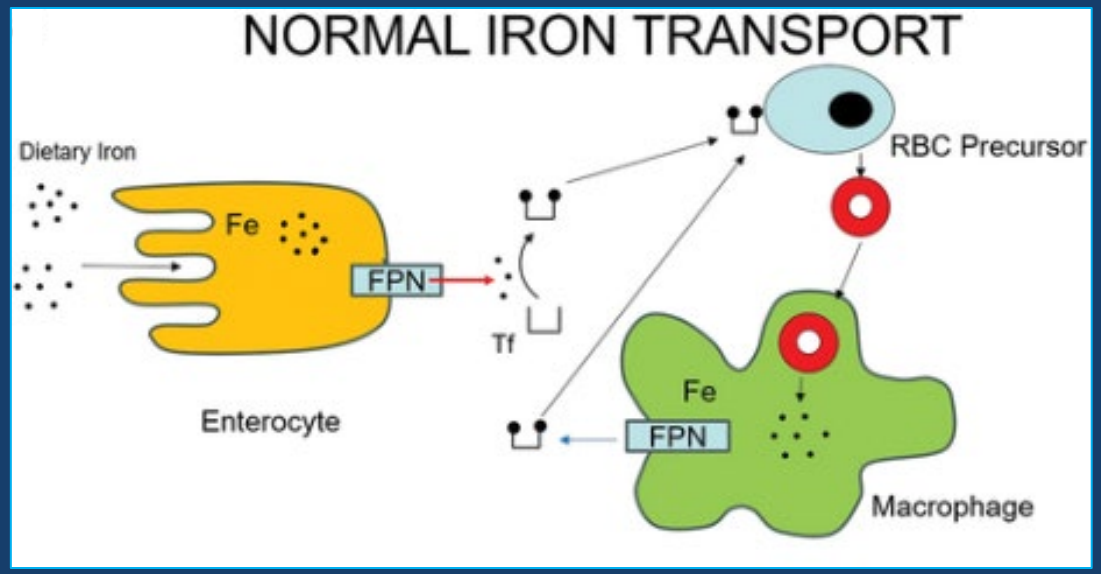
Functional Iron Deficiency (FID)
The Pathophysiologic Multi-Mechanism in Cancer

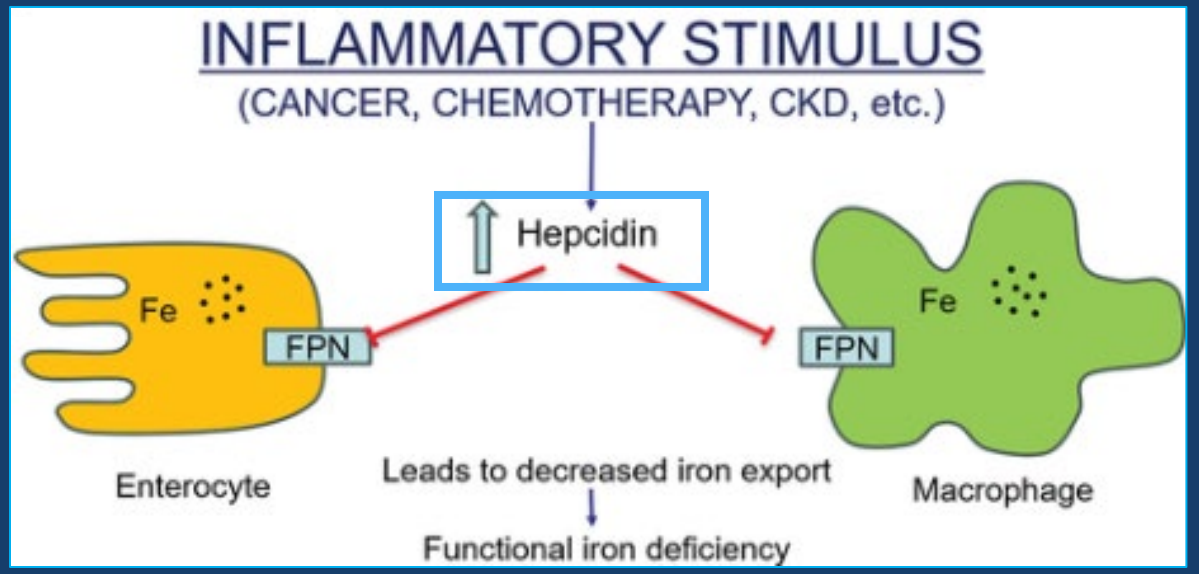


Rodgers GM. *Expert Rev Hematol.* 2024.

Functional Iron Deficiency (FID)

The Empiric Role of Hepcidin

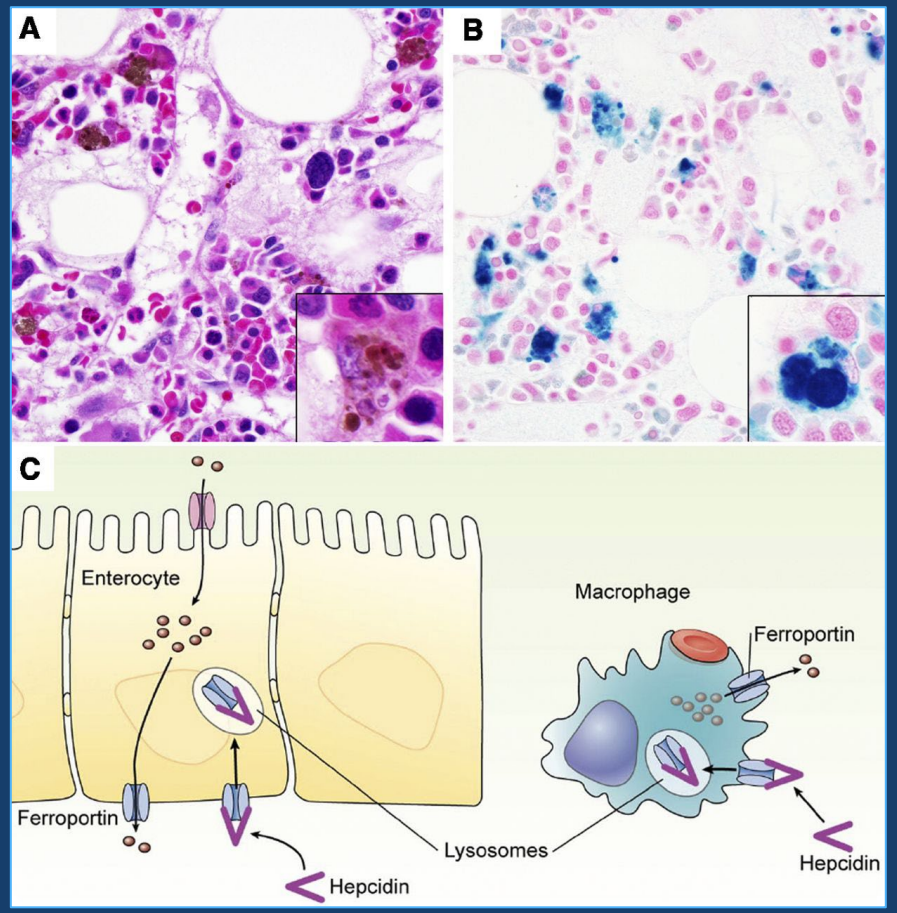




Pagani A, et al. *Front Physiol*. 2019; Rodgers GM. *Expert Rev Hematol*. 2024.

Functional Iron Deficiency (FID)

Inflammation-Driven Iron Sequestration

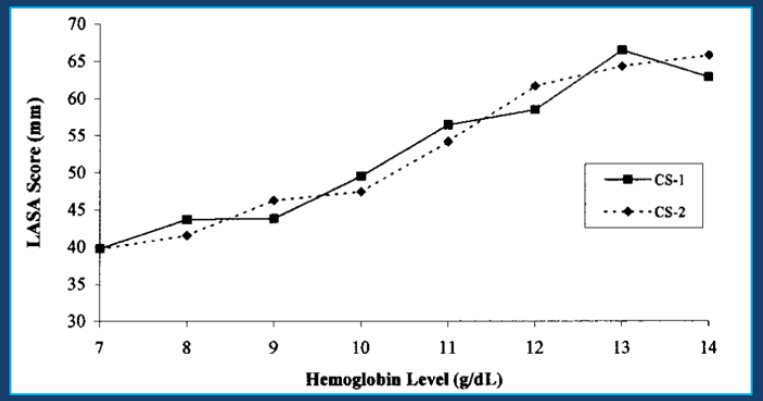


King RL, et al. *Blood*. 2014; Andrews NC. *Blood*. 2008.

The CRA/CIA Burden of Illness

Detriments in Clinical and Patient-Reported Outcomes (PROs)

- Clinical ramifications
  - Impaired cancer treatment-responsiveness
  - Increased risk of disease progression
  - Higher RBC transfusion burden, with inherent risks therein
  - *Independent risk factor for elevated cancer-related morbidity and mortality*
    - ~65% increased risk of cancer-related mortality in patients with CRA/CIA vs. cancer without anemia
- Deleterious effects on PROs
  - Reduced health-related quality of life across nearly all facets
    - Fatigue
    - Cognitive impairment
    - Diminished functional and exercise capacity
  - Hemoglobin level and QOL closely correlated

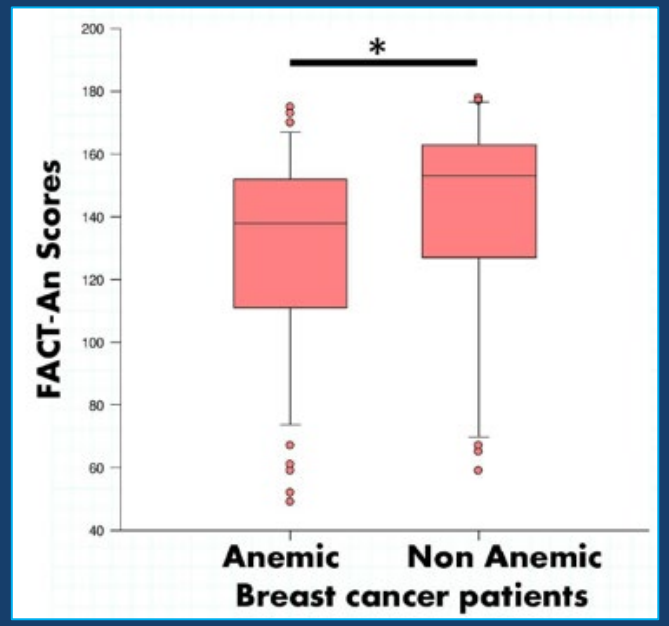


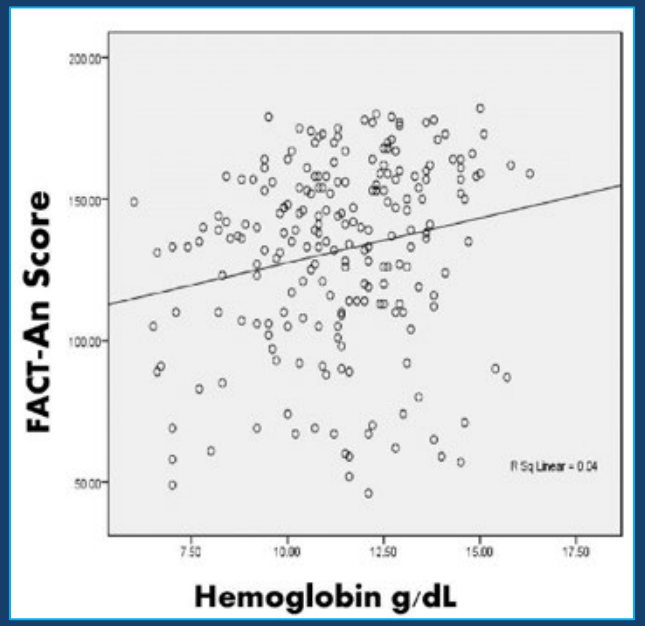
Rodgers GM. *Expert Rev Hematol.* 2024;; Gilreath JA, et al. *Am J Hematol*. 2014; Busti F, et al. *Pharmaceuticals*. 2018; Harper P, et al. *Oncology*. 2005; Crawford J, et al. *Cancer*. 2002; Kanuri G, et al. *PLoS One*. 2016; Gilreath J, et al. *Blood*. 2020.

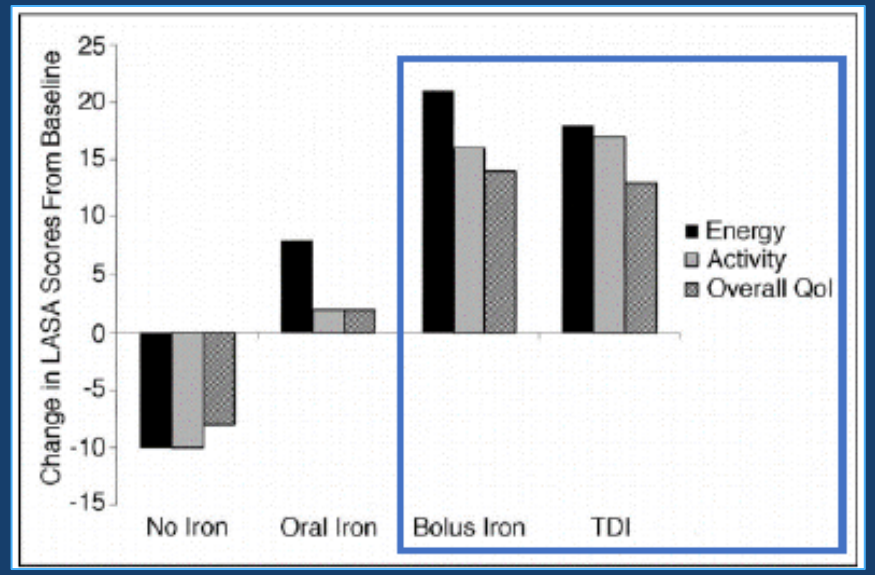
A Closer Look at QOL in CRA/CIA

Accentuating the Need for Effective Treatment

- Linear relationship between QOL and Hb level in patients with cancer
  - *Effective iron repletion and anemia correction = dramatically improved QOL*







Rodgers GM. *Expert Rev Hematol.* 2024;; Gilreath JA, et al. *Am J Hematol*. 2014; Busti F, et al. *Pharmaceuticals*. 2018; Kanuri G, et al. *PLoS One*. 2016; Auerbach M, et al. *J Clin Oncol*. 2004; Rodgers GM, et al. *Acta Haematol.* 2019.

Recognizing Iron Deficiency in Cancer Care

Cardinal Signs and Symptoms

Hallmark Manifestations	Common Presentations	Rare/Severe Features
• Fatigue • Dyspnea (especially upon exertion) • Headache • Paleness • Brain fog	• Dry skin • Brittle integument • Restless leg syndrome • Vertigo • Pica • Mood alterations • Alopecia • Angina	• Syncope • Spooning of nails • Hemodynamic instability

Gilreath JA, et al. *Am J Hematol*. 2014; Rodgers GM, et al. *Acta Haematol*. 2019; Lopez A, et al. *Lancet*. 2016; Friedman AJ, et al. *Obstet Gynecol Surv*. 2015; Rodgers GM. *Expert Rev Hematol*. 2024.

Understanding ID and IDA in Cancer
Diagnosis

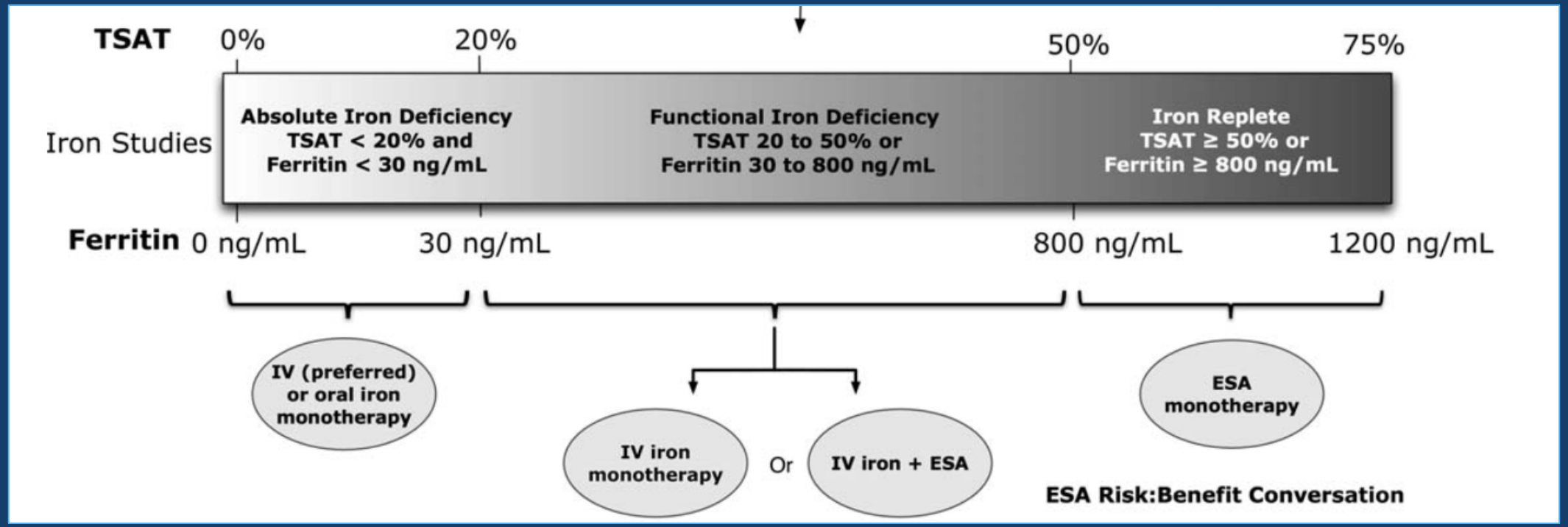
- Differentiating absolute ID (AID) and functional ID (FID)
  - AID
    - Iron storage pool AND functional pool are both depleted
    - Typical defining parameters:
      - TSAT <20%
      - Serum ferritin <100 ng/mL
  - FID (aka ‘anemia of inflammation’)
    - Iron storage pool is normal or elevated, but functional pool is depleted
    - Typical defining parameters:
      - TSAT <20%
      - Serum ferritin >100 ng/mL

Labs	AID or AIDA	FID/FIDA/Anemia of Inflammation
TIBC	High	Low
TSAT	Low	Low
Serum Ferritin	Very low	Normal or High

AIDA, absolute iron deficiency anemia; FIDA, functional iron deficiency anemia

Gilreath JA, et al. *Am J Hematol*. 2014; Rodgers GM, et al. *Acta Haematol*. 2019; Rodgers GM. *Expert Rev Hematol*. 2024.

Informing CRA/CIA Treatment Strategies
Evaluating the TSAT/Ferritin Spectrum



Gilreath JA, et al. *Am J Hematol*. 2014.

Treating CRA/CIA
Establishing the Therapeutic Benefits of IV Iron

- Achieves rapid and effective iron repletion
- Next-generation IV iron products offer stark advantages over older formulations
  - Improved safety profile, with dramatic reductions in hypersensitivity risk
  - Total dose infusion (TDI) capacity, allowing for total repletion in a single dose
- ***IV iron pharmacodynamics can overcome functional iron deficiency in CRA/CIA***
  - Directly combats the deleterious effects of inflammation and elevated hepcidin
  - Saturates transferrin, loads macrophages, ultimately leading to upregulation of ferroportin
- Superior tolerability and adherence data vs. oral iron alternatives

Gilreath JA, et al. *Am J Hematol*. 2014; Rodgers GM, et al. *Acta Haematol*. 2019; Rodgers GM. *Expert Rev Hematol*. 2024.; Madeddu C, et al. *Front Physiol*. 2018.

IV Iron for CRA/CIA Management

Current FDA Labels

Iron Product	Dosing and Administration	Approved Indications	Common Adverse Drug Effects	Warnings
Low-Molecular-Weight Iron Dextran	• 100 mg daily via IV push over at least 2 minutes • Total dose is calculated based on iron deficit • May repeat daily	Iron deficiency (ID) in adult and pediatric patients 4 months of age and older for whom oral therapy is unsatisfactory or intolerable	Pruritis, abdominal pain, nausea, vomiting, diarrhea	**Black box**: risk for anaphylactic-type reactions, including fatalities
FMX	• 510 mg via IV infusion over at least 15 minutes • 2nd (510 mg) dose 3–8 days later	Iron deficiency anemia (IDA) in adult patients who have intolerance or unsatisfactory response to oral iron, or who have a diagnosis of CKD	Dizziness, hypotension, constipation, nausea	**Black box**: fatal and serious hypersensitivity reactions, including anaphylaxis
FDI	• For patient weighing ≥ 50 kg, give 1,000 mg (*single dose TDI*) over at least 20 minutes • For patients weighing <50 kg, give 20 mg/kg in a single dose	IDA in adult patients who have intolerance or unsatisfactory response to oral iron, or who have non–hemodialysis-dependent CKD	Nausea, injection site reactions, rash, hypotension	Hypersensitivity reactions, iron overload

FMX, ferumoxytol; FDI, ferric derisomaltose

FDA Prescribing Information.

IV Iron for CRA/CIA Management

Current FDA Labels

Iron Product	Dosing and Administration	Approved Indications	Common Adverse Drug Effects	Warnings
Iron Sucrose	• 100–400 mg, by setting • Doses may be repeated based on clinical response and iron indices	IDA in adult and pediatric patients (2 years of age and older) with CKD	Diarrhea, nausea, vomiting, headache, hypotension, pruritus	Hypersensitivity reactions, hypotension, iron overload
FCM	• For patients weighing ≥50 kg, may give 15 mg/kg up to 1,000 mg (*single-dose TDI*) or 750 mg infusion over at least 15 minutes • If 750 mg is given, may be repeated in 7 days, for a total dosage per course of 1,500 mg • For patients weighing <50 kg, give 15 mg/kg in 2 doses, separated by at least 7 days	IDA in patients 1 yo and older who have intolerance or unsatisfactory response to oral iron, and in adults who have non–dialysis-dependent CKD (NDD-CKD) ID in adult patients with heart failure and NYHA class II/III to improve exercise capacity	Nausea, hypertension, hypophosphatemia, flushing	Hypersensitivity reactions, symptomatic hypophosphatemia, hypertension
Sodium Ferric Gluconate	• 125 mg (adults) via IV infusion over 1 hour, per dialysis • 1.5 mg/kg in peds • Repeated weekly for up to 8 weeks	IDA in patients 6 years old and older who are receiving hemodialysis and supplemental EPO therapy for *CKD*	Chest pain, leg cramps, dizziness, dyspnea, nausea, vomiting, diarrhea	Hypersensitivity reactions, hypotension, iron overload, benzyl alcohol toxicity

FCM, ferric carboxymaltose

FDA Prescribing Information.

IV Iron for CRA/CIA Management
Evaluating the Evidence

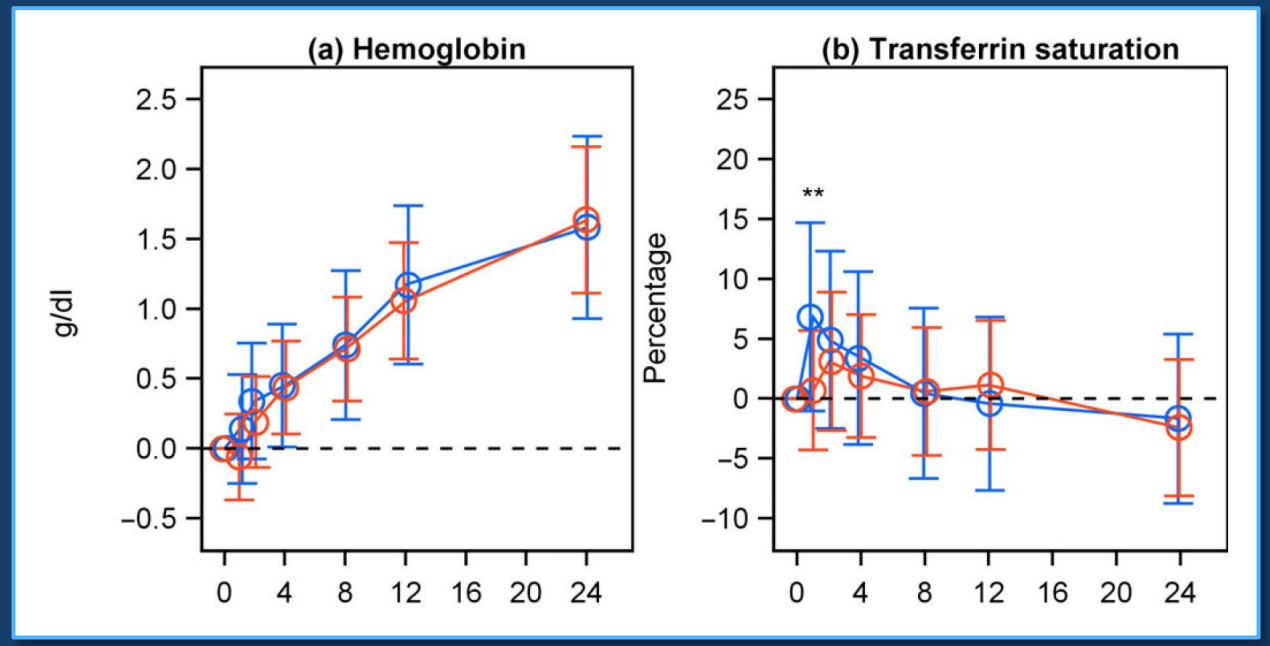
- IV iron has been extensively studied in CRA/CIA, ***including as monotherapy***
- Trials over the past 20 years have demonstrably revealed strong safety and efficacy
- Recent practice-changing studies:
  - **PROFOUND**
  - **IRON-CLAD**

Publication	Patients	Product	Efficacy
Kim 2007	75	Iron sucrose	↑ Hb; ↓ RBC transfusions
Dangsuwan 2010	44	Iron sucrose	↑ Hb; ↓ RBC transfusions
Abdel-Razeq, 2013	25	Iron sucrose	↑ Hb
Athibovonsuk, 2013	64	Iron sucrose	↓ RBC transfusions
Steinmetz, 2013	577	FCM	↑ Hb
Hedenus, 2014	17	FCM	↑ Hb
Birgegard, 2016	**229**	**IIS/FDI**	**↑ Hb**
Vadhan-Raj, 2017	75	FMX	↑ Hb
Jang, 2020	92	FCM	↑ Hb
Makharadze, 2021	**244**	**FCM**	**↑ Hb and maintained Hb**

Gilreath JA, et al. *Am J Hematol*. 2014; Rodgers GM, et al. *Acta Haematol*. 2019; Rodgers GM. *Expert Rev Hematol*. 2024; Birgegard G, et al. *Pharmacotherapy*. 2016; Makharadze T, et al. *Am J Hematol*. 2021.

Treating CRA/CIA
PROFOUND – FDI

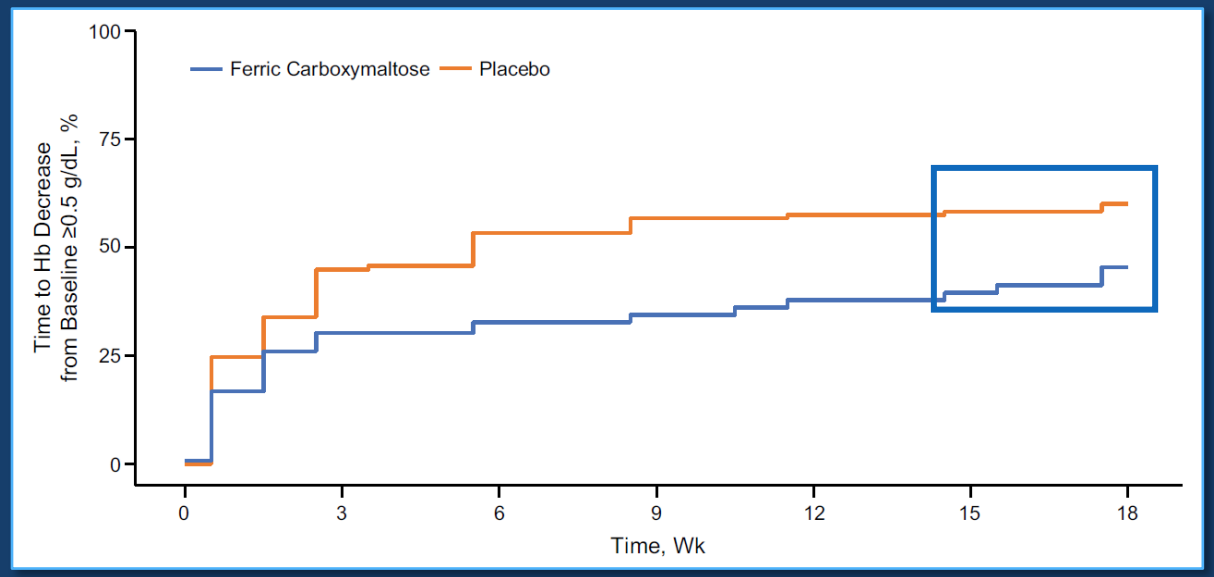
- FDI non-inferior to oral ferrous sulfate
  - Hb change from baseline to week 4 (P<0.001)
- FDI superior to oral ferrous sulfate
  - Time to Hb response at week 1 (P=0.03)
- Significant improvement in patient fatigue at study week 12 with FDI; no improvement with oral ferrous sulfate (*P*<0.001)
- FDI substantially better tolerated



Birgegard G, et al. *Pharmacotherapy*. 2016.

Treating CRA/CIA
IRON-CLAD – FCM

- FCM outperformed placebo
  - % of patients maintaining Hb level within 0.5 g/dL of baseline at study week 18
  - FCM = 50.8% vs. Placebo (35.3%)
  - *P*=0.01
- FCM achieved higher rise in Hb among patients with baseline Hb ≤9.9 g/dL
  - FCM = 1.08 g/dL vs. Placebo = 0.42 g/dL
  - *P*=0.01
- FCM well-tolerated and achieved ≥1 g/dL rise in Hb faster and more frequently than placebo
  - FCM = 71% vs. Placebo = 54% (*P*=0.01)
  - FCM = 43 days vs. Placebo = 85 days (*P*=0.001)



Makharadze T, et al. *Am J Hematol*. 2021.

IV Iron for CRA/CIA Management
Evaluating the Evidence

- IV iron has also been studied in CRA/CIA ***in combination with ESAs***
- General benefits consistently observed:
  - Enhanced response to ESAs
  - Allowance for lower ESA dosing
  - Decreased RBC transfusion burden

Publication	Patients	Product	Efficacy
Auerbach, 2004	157	LMW iron dextran	↑ ESA response
Hedenus, 2007	67	Iron sucrose	↑ ESA response; ↓ required ESA dose
Henry, 2007	187	Ferric gluconate	↑ ESA response
Bastit, 2008	396	Ferric gluconate/iron sucrose	↑ ESA response; ↓ RBC transfusions
Pedrazzoli, 2008	149	Ferric gluconate	↑ ESA response
Auerbach, 2010	243	LMW iron dextran	↑ ESA response
Steensma, 2011	502	Ferric gluconate	_
Steinmetz, 2013	73	FCM	↑ ESA response

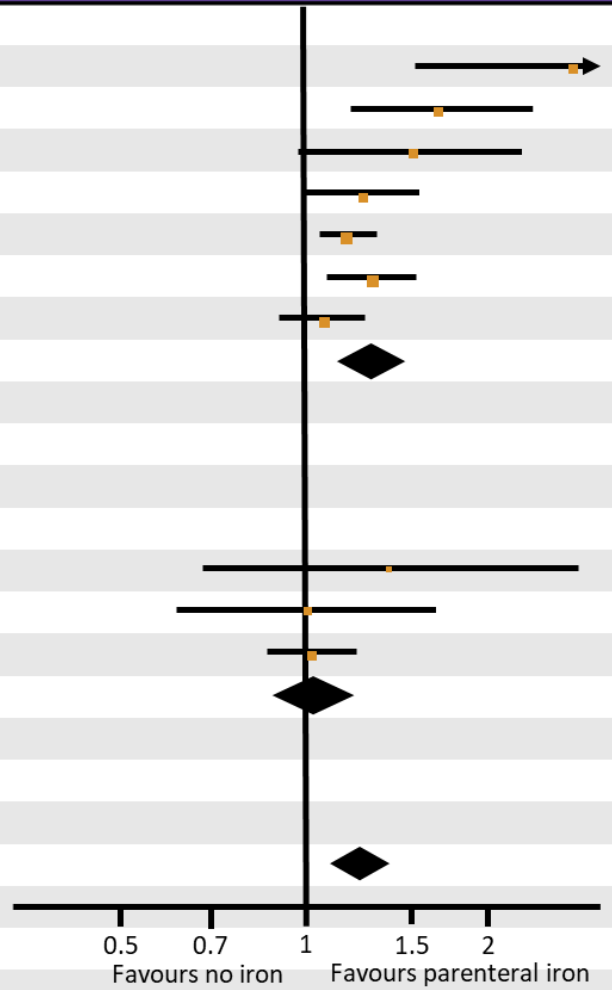
Rodgers GM, et al. *Acta Haematol*. 2019; Rodgers GM. *Expert Rev Hematol*. 2024.

IV Iron for CRA/CIA Management
Evaluating the Evidence

- Large-scale systematic reviews and meta-analyses corroborate the clinical utility of IV iron in CRA/CIA established in monotherapy and combination trials
  - Petrelli F, et al. *J Cancer Res Clin Oncol.* 2012.
  - Gafter-Gvili A, et al. *Acta Oncol.* 2013.
  - Mhaskar R, et al. *Cochrane Database Syst Rev*. 2016.

Rodgers GM. *Expert Rev Hematol.* 2024; Petrelli F, et al. *J Cancer Res Oncol.* 2012; Gafter-Gvili A, et al. *Acta Oncol*. 2013; Mhaskar R, et al. *Cochrane Database Rev.* 2016.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.1.1 Parenteral iron vs no iron							
Auerbach 2004	53	78	9	36	3.1%	2.72 (1.51–4.88)	2004
Hedenus 2007	29	33	18	34	7.1%	1.66 (1.18–2.34)	2007
Henry 2007a	32	60	21	59	5.3%	1.50 (0.99–2.27)	2007
Pedrazzoli 2008	56	73	47	76	12.1%	1.24 (1.00–1.54)	2008
Bastit 2008	172	200	143	196	19.0%	1.18 (1.06–1.31)	2008
Auerbach 2010	95	116	77	122	15.3%	1.30 (1.11–1.52)	2010
Steensma 2011	114	164	106	163	15.9%	1.07 (0.92–1.24)	2011
Subtotal (95% CI)		724		686	77.9%	1.29 (1.13–1.48)	
Total events	551		421				
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.10$; df = 6 (P=0.01); $I^2 = 63\%$							
Test for overall effect: Z = 3.82 (P=0.0001)							
3.1.2 Oral iron vs no iron							
Auerbach 2004	15	43	9	36	2.2%	1.40 (0.69–2.80)	2004
Henry 2007a	22	61	21	59	4.3%	1.01 (0.63–1.64)	2007
Steensma 2011	109	163	106	163	15.6%	1.03 (0.88–1.20)	2011
Subtotal (95% CI)		267		258	22.1%	1.04 (0.90–1.20)	
Total events	146		136				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$; df = 2 (P=0.69); $I^2 = 0\%$							
Test for overall effect: Z = 0.54 (P=0.59)							
Total (95% CI)		991		944	100.0%	1.23 (1.10–1.38)	
Total events	697		557				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.07$; df = 9 (P=0.02); $I^2 = 55\%$							
Test for overall effect: Z = 3.71 (P=0.0002)							
Test for subgroup differences: $Chi^2 = 4.75$; df = 1 (P=0.03); $I^2 = 79.0\%$							



Petrelli F, et al. *J Cancer Res Oncol.* 2012.

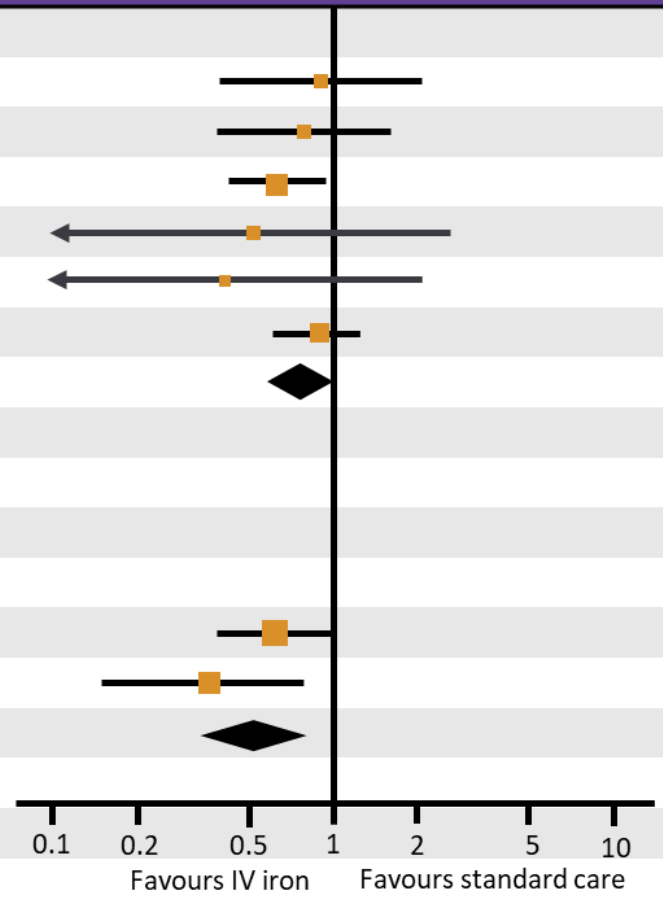
IV Iron for CRA/CIA Management

Petrelli 2012 – Data Conclusions

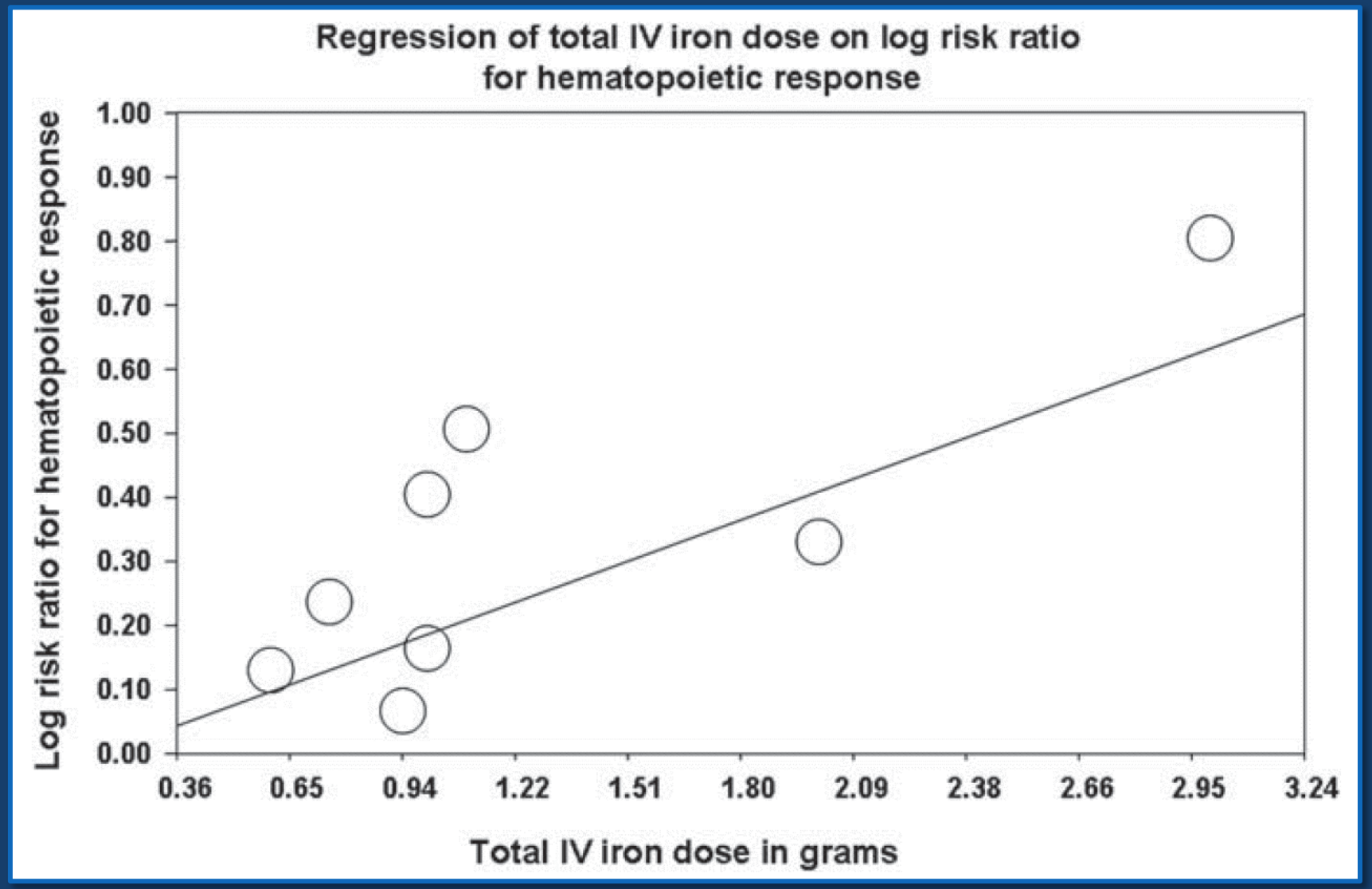
- IV iron reduced RBC transfusion burden by 23% vs. ESA monotherapy
- IV iron improved hematopoietic response by 29% vs. ESA monotherapy
- IV iron markedly outperformed oral iron in the setting of CRA/CIA
  - Oral iron did not outpace ESA monotherapy with respect to hematopoietic response rate or transfusion burden (no statistical significance)
  - IV iron achieved these improvements faster and with greater magnitude
- **Real-world IV iron ramifications**:
  - Tangible clinical utility
  - Improvement in patient-reported outcomes (PROs), including quality of life
  - Amelioration of health economic burden

Petrelli F, et al. *J Cancer Res Oncol.* 2012.

Study or Subcategory	IV Iron n/N	Standard Care n/N	Risk Ratio (fixed) 95% CI	Weight %	Risk Ratio (fixed) 95% CI
01 Trials of CIA with ESA					
Auerbach 2004	9/78	10/79		7.64	0.91 (0.39–2.12)
Henry 2007	11/63	14/63		10.77	0.79 (0.39–1.60)
Bastit 2008a	32/200	49/196		38.07	0.64 (0.43–0.95)
Beguin 2008	2/50	4/52		3.02	0.52 (0.10–2.71)
Pedrazzoli 2008	2/73	5/76		3.77	0.42 (0.08–2.08)
Auerbach 2010	42/116	49/122		36.74	0.90 (0.65–1.25)
Subtotal (95% CI)	580	588		100.00	0.76 (0.61–0.95)
Total events	98	131			
Test for heterogeneity: $Chi^2 = 2.70$; df = 5 (P=0.75); $I^2 = 0\%$					
Test for overall effect: Z = 2.38 (P=0.02)					
02 Trials of CIA without ESA					
Kim 2007	12/30	29/46		62.37	0.62 (0.38–1.01)
Dangsuwan 2010	5/22	14/22		37.63	0.36 (0.16–0.82)
Subtotal (95% CI)	52	67		100.00	0.52 (0.34–0.80)
Total events	17	43			
Test for heterogeneity: $Chi^2 = 1.28$; df = 1 (P=0.26); $I^2 = 21.9\%$					
Test for overall effect: Z = 3.02 (P=0.002)					



Gafter-Gvili A, et al. *Acta Oncol.* 2013.



Gafter-Gvili A, et al. *Acta Oncol.* 2013.

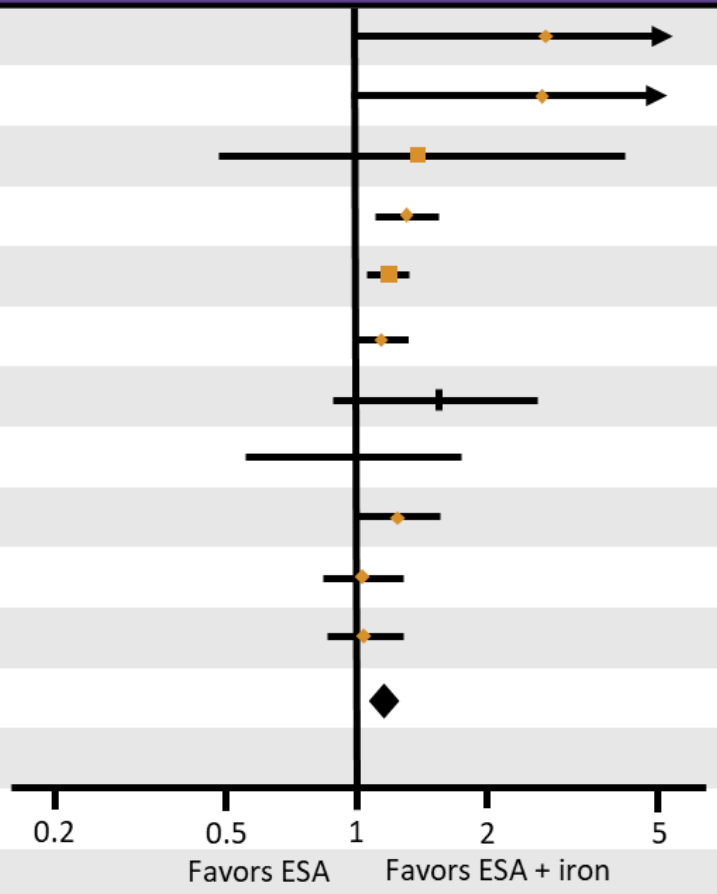
IV Iron for CRA/CIA Management

Gafter-Gvili 2013 – Data Conclusions

- IV iron improved hematopoietic response rate in combination ESA trials
- IV iron decreased RBC transfusion burden irrespective of concomitant ESA use
- IV iron was well-tolerated, with no significantly increased risk for toxicity

Gafter-Gvili A, et al. *Acta Oncol.* 2013.

Study or subgroup	ESA + Iron n/N	ESA n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Auerbach 2004 (1)	28/41	3/12		0.54%	2.73 (1–7.44)
Auerbach 2004 (2)	25/37	3/12		0.54%	2.7 (0.99–7.38)
Auerbach 2004 (3)	15/43	3/12		0.48%	1.4 (0.48–4.03)
Auerbach 2010	95/116	77/122		15.9%	1.3 (1.11–1.52)
Bastit 2008	172/200	143/196		28.64%	1.18 (1.06–1.31)
Beguin 2008	46/50	42/52		16.6%	1.14 (0.97–1.33)
Henry 2007 (1)	32/60	10/29		1.73%	1.55 (0.89–2.69)
Henry 2007 (2)	22/61	11/30		1.6%	0.98 (0.55–1.75)
Pedrazzoli 2008	56/73	47/76		9.8%	1.24 (1–1.54)
Steensma 2011 (1)	112/164	53/81		12.27%	1.04 (0.86–1.26)
Steensma 2011 (2)	109/163	53/82		11.9%	1.03 (0.85–1.26)
Total (95% CI)	1008	704		100%	1.17 (1.09–1.26)
Total events:	712	445			
Heterogeneity: $Tau^2=0$; $Chi^2=11.8$, df=10 ($P=0.3$); $I^2=15.27\%$					
Test for overall effect: Z=4.24 ($P<0.0001$)					



Mhaskar R, et al. *Cochrane Database Syst Rev.* 2016.

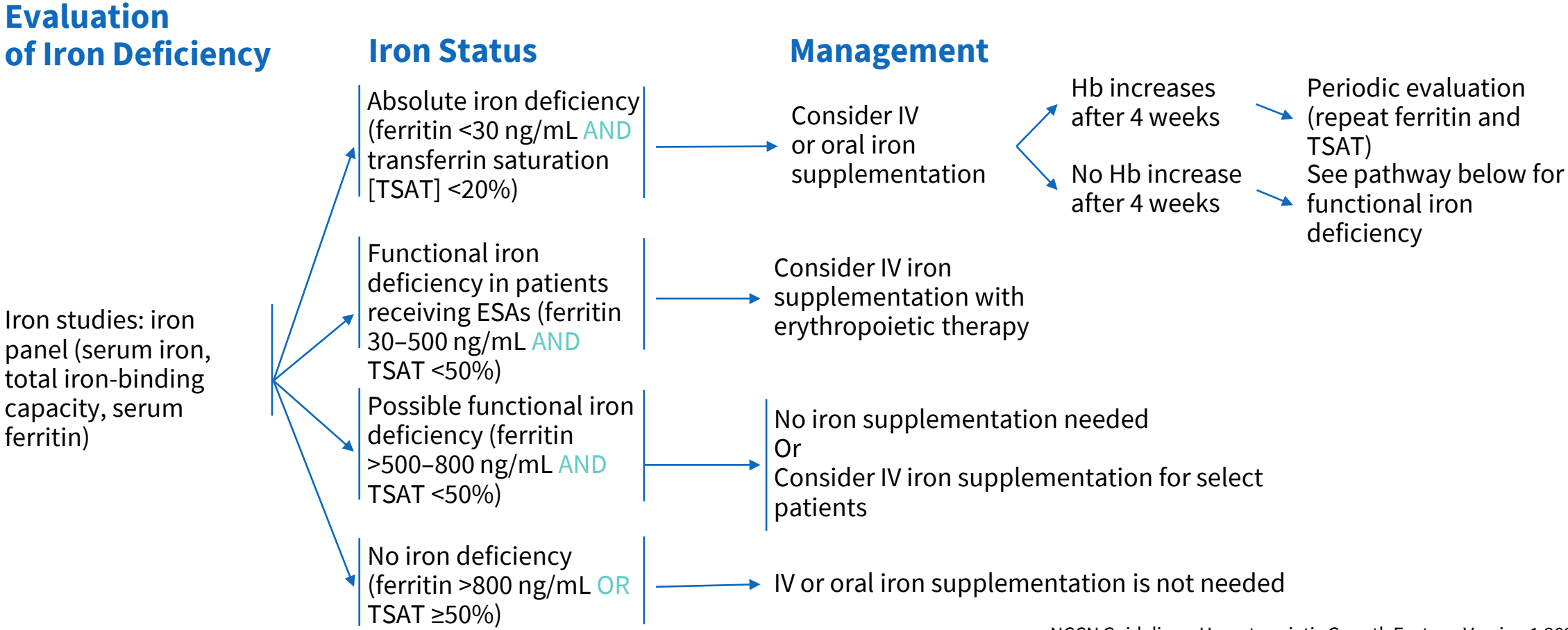
IV Iron for CRA/CIA Management
Mhaskar 2016 – Data Conclusions

- IV iron improved hematopoeitic response rate in combination with ESAs vs. ESA monotherapy (and oral iron did not)
- IV iron significantly reduced RBC transfusion requirements (RR, 1.20; *P*<0.00001)
- IV iron was well-tolerated across 8 randomized controlled trials
  - Comprising >2,000 patients with CRA/CIA

Mhaskar R, et al. *Cochrane Database Syst Rev.* 2016.

IV Iron for CRA/CIA Management

Expert Consensus Guidelines – NCCN



NCCN Guidelines. Hematopoietic Growth Factors. Version 1.2025.

IV Iron for CRA/CIA Management

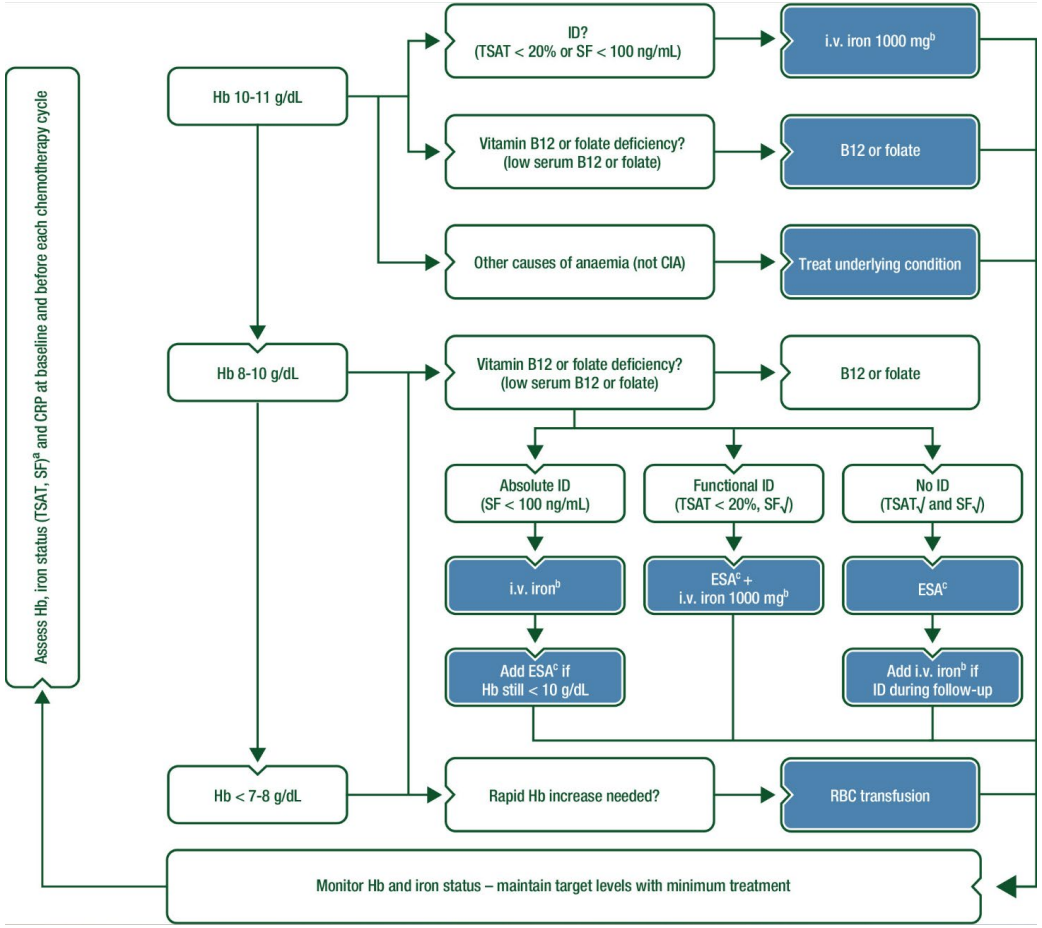
Expert Consensus Guidelines – ASCO/ASH

- **Consensus Recommendations:**
  - Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency
  - ESAs may be offered to patients with CIA whose treatment is not for curative intent if Hb <10 g/dL
  - With the exception of patients with MDS, ESAs should not be offered to most cancer patients with non-chemotherapy associated anemia
  - RBC transfusion remains a therapeutic option

Bohlius J, et al. *J Clin Oncol.* 2019.

IV Iron for CRA/CIA Management

Expert Consensus Guidelines – ESMO



Aapro M, et al. *Ann Oncol*. 2018.