projector slides

Lead team presentation

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma – STA

1st Appraisal Committee meeting, 29 March 2017

Background and Clinical Effectiveness

Committee D

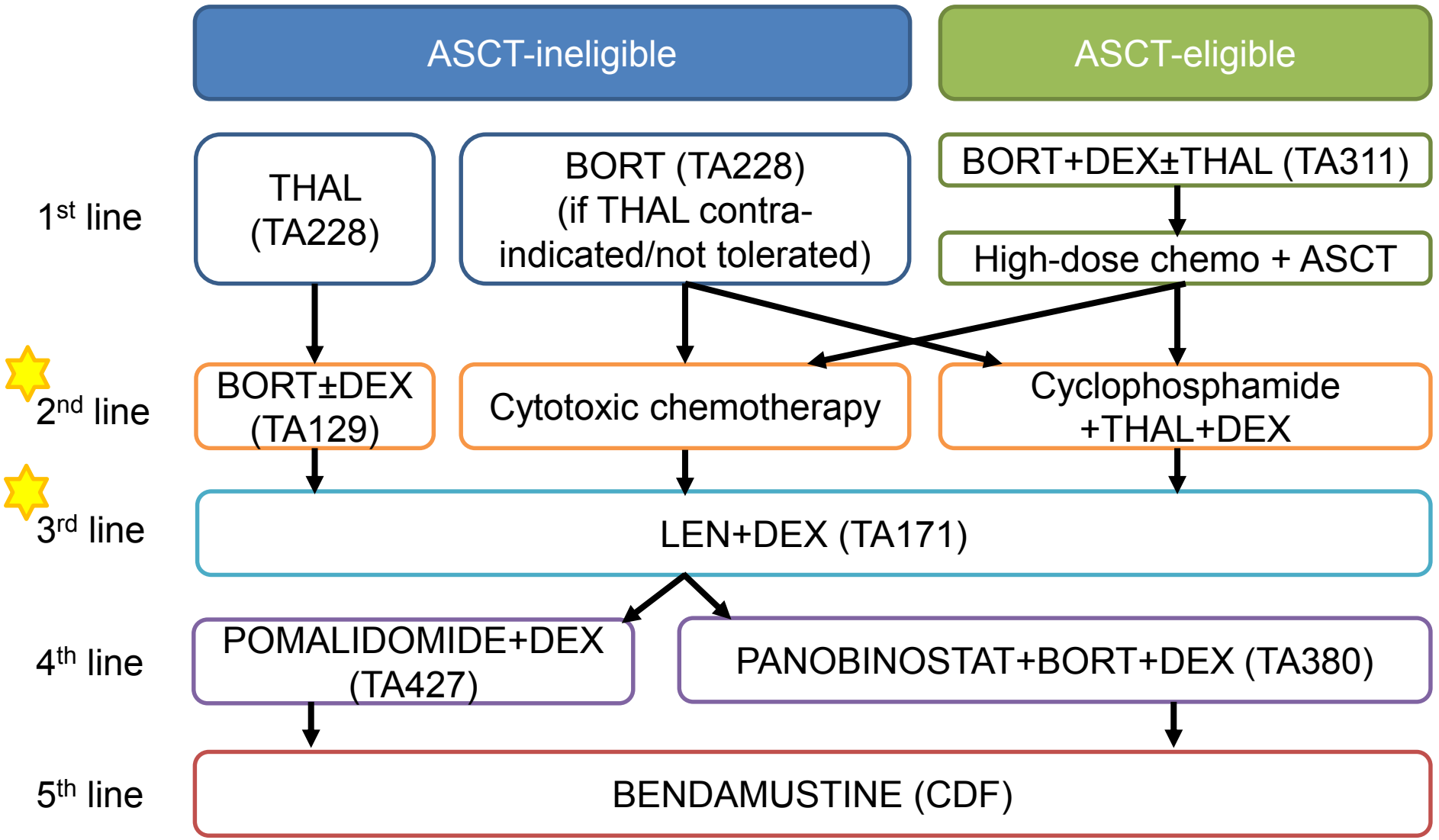
Lead team: Paula Ghaneh and Malcolm Oswald

ERG: Warwick Evidence

NICE technical team: Sophie Cooper, Raisa Sidhu

Company: Takeda

Treatment pathway: relapsed/refractory multiple myeloma



Ixazomib (Ninlaro)

Conditional marketing authorisation (Nov 2016)	NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy
Mechanism of action	Proteasome inhibitor
Administration & dosage	Oral tablet, once a week on days 1, 8, and 15 of a 28-day cycle (with lenalidomide daily on days 1-21 of the cycle and dexamethasone on days 1, 8, 15, and 22 of cycle)
Duration of treatment	Until disease progression or unacceptable toxicity Treatment for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited
Cost	£6,336/cycle (3 tablets, list price) £10,778.48/cycle with LEN + DEX A confidential patient access scheme has been approved

Patient perspectives

- Living with multiple myeloma:
  - Incurable cancer that relapses
  - Few treatment options
  - Heavy burden on patients
  - Complications can include: severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system
  - In survey, patients said PFS was most important outcome
  - Emotionally and physically challenging for patients and carers
  - 5 year survival rate in England and Wales approx. 47%
- Ixazomib in combination with lenalidomide and dexamethasone:
  - Treats underlying disease, and prolongs life
  - Is innovative: first oral proteasome inhibitor
  - Adds to the limited options available, providing treatment choice for a cancer that is highly individual, evolving and potentially relapsing

Clinician perspectives

- Combination therapies, including novel agents, can “elicit frequent, rapid, and deep responses” but “disease-controlling effect lessens with each passing line of therapy in the majority of patients”
- Ixazomib in combination with lenalidomide and dexamethasone:
  - Provides rapid disease control, increased response and longer PFS compared with lenalidomide and dexamethasone
  - Use outside of clinical trials is limited in the UK
  - All-oral combination, so uptake is likely to be higher
  - Low-grade side-effects: requires monthly follow-up monitoring
  - Should be prescribed in secondary/tertiary care by specialists
  - Reasonable to expect local haematology departments to draw up clinical protocols
- The combination of proteasome inhibitor and an immunomodulatory drug is fast becoming standard of care for patients globally

	Final scope	Company submission and rationale for deviations
Pop.	People with relapsed or refractory multiple myeloma (RRMM) who have had at least 1 therapy	
Int.	Ixazomib in combination with lenalidomide and dexamethasone (IXA+LEN+DEX)	
Comp.	For people who have had ≥1 therapy: • BORT (±DEX) • BORT retreatment (±DEX) • LEN+DEX (subject to NICE appraisal) For people who have had ≥2 therapies: • LEN+DEX • Panobinostat+BORT+DEX	The company excluded: • BORT monotherapy because rarely used in practice • BORT retreatment because no longer available on CDF • LEN+DEX because no longer available on CDF and preliminary NICE guidance was negative • Panobinostat because predominantly used 4th line
Outcomes	• PFS, OS, response rates • Time to next treatment • AEs, quality of life	As per scope, except 'time to next treatment' was not collected in clinical trial

Decision problem summary: comparators

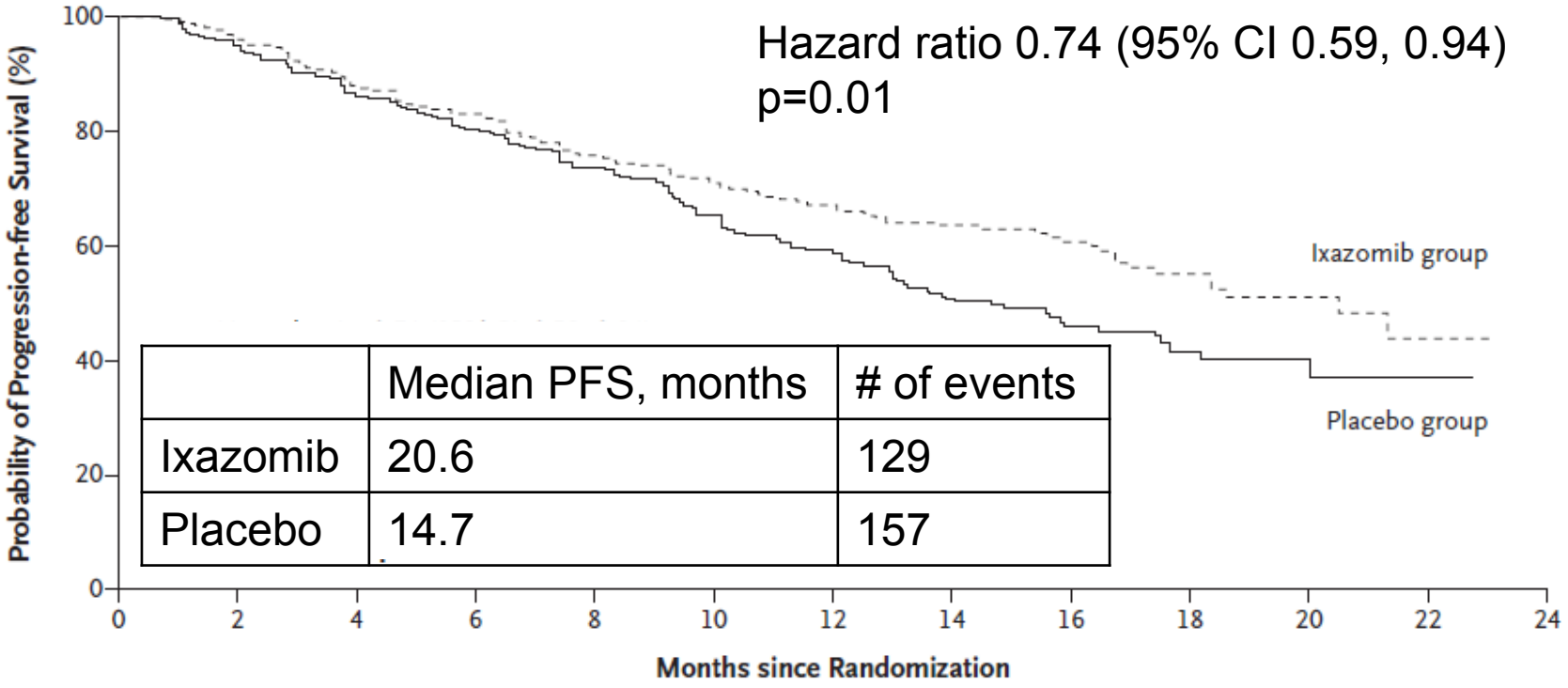
IXA+LEN+DEX positioning	**Comparator**
For people who have had 1st line THAL	BORT+DEX
For people who have had 2 therapies	LEN+DEX

Pending, so committee may be unable to make a recommendation		
For people who have had 1st line BORT	Cyclophosphamide+THAL+DEX (CTd)	Comparators not in scope so company did not provide analyses; will be provided the opportunity to submit evidence on this comparison (if available)
	Cytotoxic chemotherapy	
	LEN+DEX (subject to ongoing NICE part review of TA171)	

1 randomised controlled trial: TOURMALINE-MM1 (TMM1) trial

Design	Phase III double-blind randomised controlled trial
Status	Ongoing, 2 interim analyses at ~15 and ~23 months follow up
Sites	147 sites in 26 countries including 9 in the UK (n=21)
Population	Adults with relapsed and/or refractory multiple myeloma (RRMM) • received 1-3 prior lines of therapy • measurable disease • ECOG performance status 0–2
Randomisation stratified by	• Number of prior therapies: 1 (n=425) vs. 2 or 3 (n=297) • Previous proteasome inhibitor exposure: naïve vs. exposed • International Staging System disease stage: I or II vs. III
Intervention	IXA+LEN+DEX (n=360)
Comparator	LEN+DEX (n=362)
Primary endpoint	Progression-free survival (PFS)
HRQoL	Assessed every 4 weeks until progression and every 12 weeks post-progression using EQ-5D, EORTC QLQ-C30 and MY-20

TMM1 results: first interim analysis PFS



Hazard ratio 0.74 (95% CI 0.59, 0.94)
p=0.01

	Median PFS, months	# of events
Ixazomib	20.6	129
Placebo	14.7	157

No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

N Engl J Med. 2016 Apr 28;374(17):1621-34

TMM1 results: first interim analysis

	IXA+LEN+DEX	LEN+DEX	HR or OR (95% CI)
PFS: n; median, months			
ITT population	**129; 20.6**	**157; 14.7**	**HR: 0.74 (0.59, 0.94) p=0.012**
1 prior therapy	80; 20.6	88; 16.6	HR: 0.88 (0.65, 1.20)
2–3 prior therapies	**49; NE**	**69; 12.9**	**HR: 0.58 (0.40, 0.84) p<0.05**
OS: n; median, months			
ITT population	51; NE	56; NE	HR: 0.90 (0.62, 1.32)
1 prior therapy	31; NE	26; NE	HR: 1.24 (0.74, 2.10)
2–3 prior therapies	20; NE	30; NE	HR: 0.62 (0.35, 1.09)
ORR: n (%)			
ITT population	**282 (78.3)**	**259 (71.5)**	**OR: 1.44 (1.03, 2.03) p=0.04**
1 prior therapy	163 (76.9)	159 (74.6)	OR: 1.13 (0.72, 1.77)
2–3 prior therapies	**119 (80.4)**	**100 (67.1)**	**OR: 2.03 (1.19, 3.45) p<0.05**

Bold red denotes statistically significant differences. HR, hazard ratio; NE, not estimable; OR, odds ratio

TMM1 results: second interim analysis

	IXA+LEN+DEX	LEN+DEX	HR or OR (95% CI)
PFS: n; median, months (ERG highlight ITT results no longer significant)			
ITT population	177; 20	195; 15.9	HR: 0.82 (0.67, 1.0)
1 prior therapy	109; 18.7	112; 17.6	HR: 0.99 (0.76, 1.29)
2–3 prior therapies	**68; 22.0**	**83; 13.0**	**HR: 0.62 (0.45, 0.86)**
OS: n (%); median, months (ERG emphasise data too immature)			
ITT population	81 (23); NE	90 (25); NE	HR: 0.87 (0.64, 1.18) p=0.359
1 prior therapy	48; NE	45; NE	HR: 1.11 (0.74, 1.66)
2–3 prior therapies	33; NE	45; NE	HR: 0.65 (0.41, 1.02)
ORR: n (%) (ERG highlight ITT results no longer significant)			
ITT population	283 (78.6)	265 (73.2)	OR: 1.35 (0.96, 1.91)
1 prior therapy	164 (77.4)	166 (77.9)	OR: 0.97 (0.61, 1.53)
2–3 prior therapies	**119 (80.4)**	**99 (66.4)**	**OR: 2.09 (1.23, 3.56)**

Bold red denotes statistically significant differences. HR, hazard ratio; NE, not estimable; OR, odds ratio

Extracts from European Public Assessment Report (EPAR)

After initially recommending against granting a marketing authorisation, the CHMP re-evaluated the data, concluding:

- "the primary endpoint [PFS] was met … However, updated efficacy data from a second interim analysis … showed a reduced difference in effect between arms" [acknowledging that this is only a sensitivity analysis]
- "recently approved drugs for multiple myeloma have shown improvements in median in PFS in the range of 4 to 6 months; 5.9 months improvement … is considered clinically relevant."
- "the median OS is not evaluable yet and the data is considered immature in this respect."
- "there is some uncertainty about the magnitude of the treatment effect …[which] seems acceptable given the favourable toxicity profile, and considering that ixazomib is the first agent to allow oral triple combination therapy"

ERG comments: benefit of IXA+LEN+DEX after 2–3 prior therapies may be driven by benefit in people with 3 prior therapies

		OS (1st interim analysis)		OS (2nd interim analysis)	
Prior tx	**n**	**HR**	**95% CI**	**HR**	**95% CI**
2–3	297	0.62	(0.35, 1.09)	0.65	(0.41, 1.02)
1	441	1.210	(0.727, 2.017)	1.092	(0.732, 1.629)
2	208	0.770	(0.382, 1.553)	0.725	(0.419, 1.256)
3	73	0.318	(0.100, 1.017)	0.455	(0.181, 1.146)

		PFS (1st interim analysis)		ORR (1st interim analysis)	
Prior tx	**n**	**HR**	**95% CI**	**HR**	**95% CI**
2–3	297	0.58	(0.40, 0.84)		
1	441	0.832	(0.616, 1.123)	1.214	(0.785, 1.880)
2	208	0.749	(0.484, 1.161)	1.658	(0.873, 3.149)
3	73	0.366	(0.169, 0.791)	2.890	(0.983, 8.495)

Company network meta-analysis (NMA) IXA+LEN+DEX vs. BORT+DEX

- Insufficient evidence to create networks specifically for 1 prior therapy; company used data for whole population (≥1 prior therapy)

Outcome	**Hazard ratio (HR) or odds ratio (OR) for IXA+LEN+DEX vs. BORT+DEX**
Progression-free survival (PFS)	HR 0.72 (95% CrI 0.41, 1.19)
Overall survival (OS)	HR 0.31 (95% CrI 0.13, 0.65)
Overall response rate (ORR)	OR 0.88 (95% CrI 0.35, 1.85)
Best overall response (BoR) of very good partial response (VGPR) or better	OR 3.82 (95% CrI 1.32, 8.93)
Discontinuation due to AEs	OR 2.58 (95% CrI 0.81, 6.32)

ERG comments on company NMA

High level of heterogeneity across the studies, relating to:

- number of prior therapies
- previous myeloma treatments (1st line treatment is an effect modifier)
- dosages of dexamethasone

Not appropriate to use Montefusco study in the PFS network:

- Montefusco included cyclophosphamide in the intervention and comparator arms; might change relative effect of LEN+DEX
- Montefusco was non-randomised and poor quality
- Company could have used alternative studies which reported TTP, which is a good proxy for PFS

Large survival benefit for IXA+LEN+DEX vs. BORT+DEX implausible

- Results for OS contrasted PFS (usually these correlate in myeloma)
- An error in the NMA inputs in OS network explains the overestimation of OS for IXA+LEN+DEX vs. BORT+DEX
  - APEX trial reported HR for death of 0.57 for BORT vs. DEX
  - company applied the HR of 0.57 for death to DEX vs. BORT

Results of the ERG exploratory NMA: people with ≥1 prior therapy

ERG exploratory NMA made the following changes to company NMA:

- corrected the error in the OS network
- excluded the Montefusco study from PFS network
- included alternative sources of PFS outcomes
- used TTP as a proxy for PFS where relevant
- excluded studies of poor methodological quality.

	ERG NMA	**Company NMA**
Hazard ratio for IXA+LEN+DEX vs. BORT+DEX		
PFS	0.75 (95% CI 0.41, 1.38)	0.72 (95% CrI 0.41, 1.19)
OS	0.91 (95% CI 0.43, 1.92)	0.31 (95% CrI 0.13, 0.65)
Hazard ratio for BORT+DEX vs. LEN+DEX		
PFS	0.98 (95% CI 0.56, 1.71)	1.06 (95% CrI 0.61, 1.85)
OS	0.99 (95% CI 0.54, 1.83)	3.11 (95% CrI 1.52, 6.35)

Key clinical issues

- Does the company's placement of ixazomib (restricted to 2nd and 3rd line) reflect its anticipated use in clinical practice?
- Have all relevant comparators been included?
  - Is panobinostat used 3rd line?
  - What are the current established treatment options in England for people who have received 1st-line BORT (either as induction before ASCT, or in people ineligible for ASCT)?
- Does IXA+LEN+DEX improve clinical outcomes — including PFS, OS and response rates — compared with LEN+DEX?
  - Are these benefits maintained long-term?
  - Are there any subgroups in whom IXA+LEN+DEX is more effective? For example, based on number of prior therapies
- In the network meta-analysis, is it appropriate to:
  - use the Montefusco study? (as in the company NMA)
  - use TTP as a proxy for PFS? (as in the ERG exploratory NMA)
- Does IXA+LEN+DEX improve clinical outcomes compared with BORT+DEX?

Back up slides

Results of the ERG exploratory NMA: people with 1 prior therapy only

- ERG did an additional exploratory NMA in people with 1 prior therapy only
  - company said insufficient evidence to make a network for this population
- Results suggested IXA-LEN-DEX is less effective in the 1 prior therapy only subgroup (second line) than in the overall population
- ERG considered the results of its exploratory NMA for OS in people with 1 prior therapy only to be questionable, because:
  - the NMA used a limited number of small, heterogeneous studies which provided estimates with wide confidence intervals
  - hazard ratios for other treatment comparisons were not plausible

	Hazard ratio for IXA+LEN+DEX vs. BORT+DEX	
	≥1 prior therapy	**1 prior therapy only**
Progression-free survival	0.75 (95% CI 0.41, 1.38)	0.90 (95% CI 0.41, 1.96)
Overall survival	0.91 (95% CI 0.43, 1.92)	2.16 (95%CI 0.74, 6.36)
Overall response rate		0.77 (95%CI 0.27, 2.23)